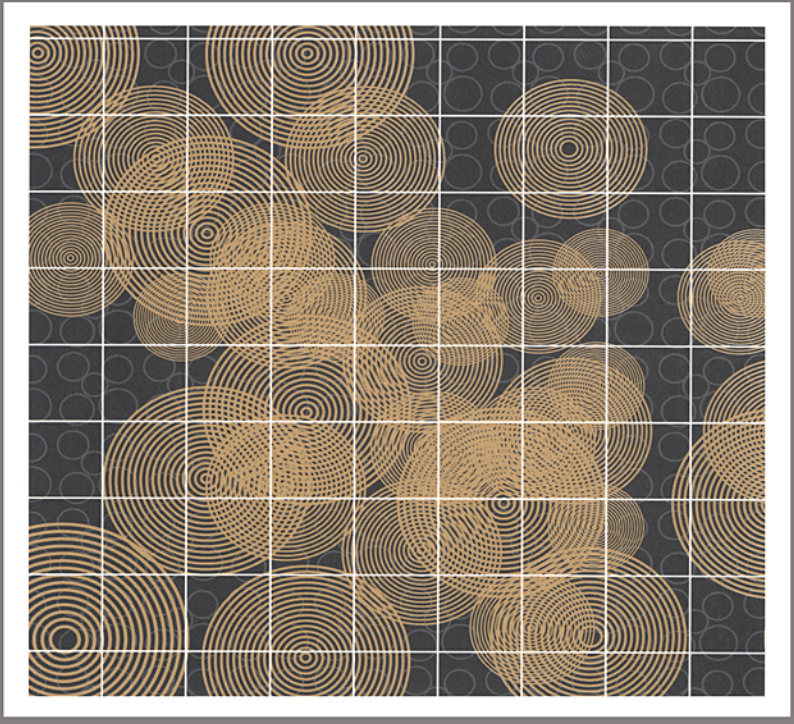
ELLIS HORWOOD SERIES IN
FOOD SCIENCE AND TECHNOLOGY

EPIDEMIOLOGY OF DIET AND CANCER

editors
Michael J. Hill, Attilio Giacosa
and Christine P. J. Caygill



EPIDEMIOLOGY OF DIET AND CANCER

ELLIS HORWOOD SERIES IN FOOD SCIENCE, MANAGEMENT AND TECHNOLOGY

Ali and Robinson	**TRADITIONAL FERMENTED FOODS**
Bourgeois, Mescle and Zucca	**FOOD MICROBIOLOGY:** Volumes 1 & 2
Cheng	**FOOD MACHINERY:** For the Production of Cereal Foods, Snack Foods and Confectionery
Dennis and Stringer	**CHILLED FOODS:** A Comprehensive Guide
Fellows	**FOOD PROCESSING TECHNOLOGY:** Principles and Practice
Girard	**TECHNOLOGY OF MEAT AND MEAT PRODUCTS**
Grandison and Lewis	**SEPARATION PROCESSES:** Principles and Applications
Grandison, Lewis and Wilbey	**DAIRY TECHNOLOGY**
Harrigan	**MICROBIOLOGY OF CHILLED AND FROZEN FOOD**
Henderson and Grootveld	**FOOD IRRADIATION:** Molecular and Medical Implications
Hill	**EPIDEMIOLOGY OF DIET AND CANCER**
Lewis	**PRACTICAL PROPERTIES OF FOOD AND FOOD PROCESSING SYSTEMS**
Morton and Lenges	**EDUCATION AND TRAINING IN FOOD SCIENCE:** A Changing Scene
Niranjan and de Alwis	**FOOD PROCESS MODELLING:** Relating Food Process, Design, Food Safety and Quality
Watson	**SAFETY OF CHEMICALS IN FOOD:** Chemical Contaminants

Watson	**FOOD SCIENCE REVIEWS:** Volume 1 Food Hygiene and Safety
Watson and Meah	**FOOD SCIENCE REVIEWS:** Volume 2 Chemical Migration from Food Packaging
Wiese, Jackson, Wiese and Davis	**FOOD CONTAINER CORROSION**

EPIDEMIOLOGY OF DIET AND CANCER

Edited by
MICHAEL J.HILL, D. Sc., FRCPath
Chairman
European Cancer Prevention Organisation
Andover, Hampshire
ATTILIO GIACOSA
ECP Scientific Coordinator
National Institute for Cancer Research
Genoa
and
CHRISTINE P J CAYGILL
PHLS-CDSC, Colindale
London

ELLIS HORWOOD

NEW YORK LONDON TORONTO SYDNEY TOKYO
SINGAPORE

First published 1994 by
Ellis Horwood Limited
Market Cross House, Cooper Street
Chichester
West Sussex, PO19 1EB
A division of
Simon & Schuster International Group

This edition published in the Taylor & Francis e-Library, 2005.

Library of Congress Cataloging-in-Publication Data

Available from the publisher

British Library Cataloguing in Publication Data
A catalogue record for this book is available from the British Library

ISBN 0-203-16892-5 Master e-book ISBN

ISBN 0-203-26422-3 (Adobe eReader Format)
ISBN 0-13-031998-8 (hbk)

1 2 3 4 5 97 96 95 94

Contributors

L Borsa
Istituto di Ricerche Farmacologische “Maria Negri’
Via Eritrea 62
20157 Milano
Italy

C P J Caygill
PHLS Communicable Diseases Surveillance Centre
61 Colindale Avenue
London NW9 5HT
UK

B D’Avanzo
Istituto di Ricerche Farmacologische “Maria Negri
Via Eritrea 62
20157 Milano
Italy

R Filiberti
National Institute for Cancer Research
Viale Benedetto XV, 10
16132 Genova
Italy

S Franceschi
Epidemiology Unit
Aviano Cancer Centre
Via Pedemontana Occ
33081 Aviano (PN)
Italy

M Gerber
Groupe d’Epidemiologie Metabolique
Epidaure-CRLC
Montpellier
France

A Giacosa

National Institute for Cancer Research
Viale Benedetto XV, 10
16132 Geneva
Italy

M J Hill
European Cancer Prevention Organization
41 London Street
Andover
Hants SP10 2NJ
UK

T Hirayama
Institute of Preventive Oncology
1–2 Ichgaya-Sadohara
Shinjuku-ku
Tokyo 162
Japan

C La Vecchia
Istituto di Ricerche Farmacologische “Maria Negri
Via Eritrea 62
20157 Milano
Italy

F Levi
Registre Vaudois des Tumeurs
Inst Universitaire de Medecine Social et Preventive
Lausanne
Switzerland

F Lucchini
Istituto di Ricerche Fannacologische “Maria Negri”
Via Eritrea 62
20157 Milano
Italy

F Merlo
National Institute for Cancer Research
Viale Benedetto XV, 10
16132 Geneva
Italy

E Negri
Istituto di Ricerche Fannacologische “Maria Negri”
Via Eritrea 62
20157 Milano
Italy

J D Potter

Division of Epidemiology
University of Minnesota
1300 South Second Street
Minneapolis
Minnesota 55454
USA

G Reggiardo
National Institute for Cancer Research
Viale Benedetto XV, 10
16132 Geneva
Italy

S Richardson
Groupe d'Epidemiologie Metabolique
Epidaure-CRLC
Montpellier
France

A Tavani
Istituto di Ricerche Farmacologische "Maria Negri
Via Eritrea 62
20157 Milano
Italy

G Varela
Department of Nutrition
Universidad Complutense
Cuidad Universitaria
28040 Madrid
Spain

P Visconti
National Institute for Cancer Research
Viale Benedetto XV, 10
16132 Genova
Italy

Table of contents

Preface

The European Cancer Prevention Organization (ECP) was established in 1981 to utilize the favourable situation in Europe for studying cancer causes and control. So what is this *favourable situation in Europe*? The first aspect is the wide range in incidence in most of the common cancer sites and the quality of cancer registration that makes this information reliable. In studies of cancer causation it is usual to start by comparing populations with greatly differing risks of the disease. Europe provides a perfect setting for such multinational concerted action studies.

The second aspect is the wide range in exposure to putative carcinogens or promoters of carcinogenesis (*eg* industrial pollutants, UV radiation, diet and dietary carcinogens, exogenous hormones). Again, this provides an ideal situation for study of the role of specific agents in human carcinogenesis.

The third requirement needed if we are to be able to use Europe as the setting for multinational studies of cancer causation is that a spirit of cooperation and enquiry should be generally ambient. In Europe in general medical services are good by world standards, making the countries of Europe comparable. In addition, medical services are directed to patient care rather than market forces making a more suitable environment for research.

Although the range in cancer incidence and carcinogen exposure are well recognized they are surprisingly poorly documented. For that reason, ECP has begun the task of collecting and collating the relevant data. Diet is accepted to be as important as tobacco as a contributor to cancer risk and, in this volume, we have attempted to demonstrate the wide regional variations within Europe and within some European countries in cancer risk and in diet pattern. Within Europe the major variables considered for both diet and cancer risk are (a) regional; (b) temporal; (c) urban-rural and (d) socioeconomic status.

We are grateful to the many cancer registries who provided us with data, to the Ministry of Agriculture, Fisheries and Food (MAFF) library and to the IST library for allowing us access to their material, and to our many colleagues who assisted us in producing this volume. We would like to thank the Kellogg Company of Great Britain for a grant which enabled us to collect and collate the data. In particular we would like to thank Theresa Gallagher for her hard work in preparing the manuscript in camera ready form for publication.

1
General background of diet and cancer
M J Hill

1.1
INTRODUCTION

It is generally accepted that diet is a major cause of human cancer and various attempts have been made to quantitate the risk. Wynder and Gori (1977), based on some crude calculations, estimated that up to 40% of cancers were caused by dietary factors. This was followed later by a more sophisticated analysis of the evidence by Doll and Peto (1981) which reached essentially the same conclusion.

Part of this risk is inevitable and unavoidable; the fact that 30–40% of cancers are caused by dietary factors does not mean that all of these can be prevented by adoption of a suitable diet. Whereas smoking-related cancers can be avoided by giving up smoking we do not have the option of giving up eating. Nevertheless, it is certain that some of the diet-related cancers can be avoided by the adoption of a suitable diet and this is likely to be achievable without losing palatability—the joy of eating. For example, the Mediterranean diet is associated with a low risk of *fat-related* cancers but relatively high risk of the alcohol-related cancers. Provided that alcohol is not responsible for the protective effects, a considerable decrease in cancer risk should be achievable simply by adopting a more Mediterranean style diet but combined with a north European level of abstemiousness from alcohol.

Table 1.1 lists the main diet-related cancers and they fall into 3 broad classes. The first, and most widely discussed in the media, comprises the *fat-related* cancers and includes the large bowel, breast, endometrium, ovary and prostate. It can be seen from Table 1.2 that this group includes some of the commonest cancers in European populations. The second class comprises the *alcohol-related* cancers and includes the upper digestive tract (oropharynx and oesophagus) and liver. The third class is associated with poor nutrition and includes the oesophagus and stomach. Table 1.2 lists the most important cancers (in terms of prevalence) in some European countries, and shows that cancers of the large bowel, stomach, breast and prostate are

Table 1.1—Cancer sites for which diet is a major aetiological agent

Site	Type of diet implicated
Oropharynx	Alcohol
Oesophagus	Alcohol (Europe)
	Poor nutrition (Asia)
Stomach	Low intake of fresh vegetables
	High intake of starchy roots
Colon/rectum	Meat and animal fat; low cereals and vegetables
Breast (post-menopausal)	High animal fat
Endometrium	High fat and energy
Prostate	High fat and energy
Liver	Alcohol; mycotoxins

Table 1.2—Data on ranking of cancer mortality within countries

Country	Oes	Stom	Int		Panc	Breast	Uterus	Ovary	Prost	Lung	Liver
M	M	M	F	M	F	F	F	M	M	M	
Belgium	10	2	3	2	5	1	4	5	4	1	13
Denmark	10	4	2	2	5	1	4	5	3	1	14
England & Wales	10	3	2	3	5	1	5	4	4	1	17
Germany	9	3	2	2	5	1	4	5	4	1	16
Finland	12	2	4	3	5	1	7	5	3	1	11
France	5	6	2	2	8	1	3	4	4	1	13
Greece	12	2	3	2	8	1	5	9	4	1	14
Hungary	13	2	3	2	5	1	3	7	4	1	6
Italy	10	2	3	2	8	1	4	7	4	1	11
Netherlands	11	3	2	2	5	1	5	3	4	1	18
Norway	13	4	3	2	5	1	4	3	2	1	15
Poland	11	2	3	4	6	1	2	7	4	1	5
Portugal	5	1	3	3	6	1	4	8	4	2	14
Spain	9	2	4	3	11	1	4	10	3	1	5
Sweden	12	4	3	2	5	1	5	3	2	1	11
Yugoslavia	11	2	3	4	7	1	3	6	4	1	5

amongst the commonest in Europe but that there are wide regional differences in their relative importance (with fat related cancers being more important in the north and west, alcohol-related in the south and poor or simple nutrition in the east).

Although a relation between diet and cancer has been discussed for 2,000 years (for example, Galen stated that *cancer is caused by black bile and can be prevented by avoiding cabbage, walnuts, pickled food and by not drinking wine*

or vinegar the earliest systematic studies were delayed until this century. Stocks carried out a series of studies in North Wales on diet and gastrointestinal cancer; his techniques were a good example to others of how to conduct such studies but were marred by the inclusion of cancers of the stomach and large bowel as a single group (Stocks and Karn, 1933).

The first stage in studying cancer epidemiology is to distinguish between genetic and environmental factors. The environmental effects must then be divided into those caused by the physical environment and those caused by culture. Finally, the cultural effects need to be segregated into those due to diet and those caused by other aspects of culture.

1.2 EVIDENCE FOR A ROLE FOR DIET IN CANCER CAUSATION

Epidemiological studies can be divided into population (or ecological) correlations, case-control studies and prospective (or cohort) studies.

1.2.1 Population studies

The incidence of most cancers shows major geographical variations. For example colorectal cancer is much more common in North America, western Europe and Australasia than in Africa, Asia and the Andean countries of South and Central America. Gastric cancer is much more common in Asia and the Andean countries than in North America, Western Europe and Australasia. Liver cancer is common in Eastern Asia and in parts of Africa. Oesophageal cancer has its maximum incidence in a broad band across Asia stretching from east of the Caspian sea through China and Southern USSR to Japan. Within Europe there is a relatively high incidence of cancers of the breast, large bowel, endometrium and ovary in western Europe whilst in southern Europe there tends to be a high incidence of cancers of the oesophagus, stomach and liver.

The simplest and cheapest type of epidemiological investigation of diet and cancer is to correlate the cancer incidence in a group of populations with the dietary intake of these same populations. In general, the cancer incidence or mortality data comes from compilations of registry data such as those published by Segi (1975–1984) or by the IARC (*eg* Muir *et al*, 1988). The diet data are usually taken from the tables published by the Food and Agriculture Organization (FAO), a United Nations body which publishes tables of average amounts of food purchased in shops per person per week in easily comparable form. Such a study was carried out by Armstrong and Doll (1975) using data from 23 countries to relate dietary factors to the incidence and mortality of cancers of various sites. Their observations are summarized in Table 1.3.

Table 1.3—Correlation coefficients of total fat intake with cancer risk in 23 populations (Armstrong and Doll, 1975)

Cancer Site	Cancer incidence		Cancer mortality	
M	F	M	F	
Colon	0.74	0.78*	0.85	0.81
Rectum	0.76*	0.60*	0.74*	0.64*
Breast	–	0.79*	–	0.89*
Ovary	–	0.53*	–	0.79*
Prostate	–	–	0.74*	–

*Fat was the dietary component most highly correlated with cancer risk.

Many such studies have been done before and since that of Armstrong and Doll. For example Table 1.4 lists some of the ecological studies of diet and colorectal cancer; a similar Table could be produced for breast cancer and it would have the same level of unanimity of type and strength of observation. However, this is mainly because all of the studies use essentially the same data set with variations only in which countries are included or omitted and in the type of analysis carried out. The observations have many major weaknesses the most important of which are:

(a) The diet data are *soft* because they are expressed as mean intakes (when perhaps extreme intakes are more important), only include food purchases and take no account of home-grown food or *food-for-free* picked wild (*eg* many types of berries and other fruit and nuts) or of food wastage. They are therefore not food consumption data.
(b) The Cancer Registry data often apply to a relatively small region of a country which rarely corresponds to the population covered by the nutrition data.
(c) The populations differ in many respects other than diet (*eg* race, climate, sunlight, industrial pollution).

Some of these problems can be overcome, still within the format of population studies. For example, numerous studies of migrants have been made, the assumption being that most migrants and all of their offspring take on the culture of their new home. Comparison of cancer incidence rates in Japanese living in Japan, those who had migrated to the United States and the American born offspring of such migrants have demonstrated (Buell and Dunn, 1965; Haenszel and Kurihara, 1968) that the incidence of gastric, colorectal and breast cancer in the American-born Japanese (*ie* the offspring of migrants) was similar to that in their American homeland and contrasted with that in Japan. The incidence of colorectal cancer in Japanese migrants to the United States is similar to that of their new homeland whilst the incidence of

Table 1.4—Ecological studies of diet and colorectal cancer

Reference	Number of populations	Observation
Wynder *et al*, 1967	2	Association with fat intake
Gregory *et al*, 1967	28	Association with meat, fat and animal protein
Drasar *et al*, 1973	37	Association with meat, fat and animal protein
Armstrong and Doll, 1975	23	Association with meat, fat and animal protein
Enstrom, 1977	47	Beer associated with rectal cancer
Liu *et al*, 1979		Fat, fibre (protective) cholesterol
Eyssen and Bright-See, 1984		Fat, meat, fibre (protective)

gastric cancer is similar to that in their birth place whilst that of breast cancer is between the two (Table 1.5). These results have been interpreted as meaning that (a) the difference in incidence between Japan and the United States in these cancers is due to environmental and not genetic/racial factors, since the incidence of the cancers in the US born Japanese is similar to that in US born Americans; (b) the environmental factors act throughout life in colorectal cancer but mainly in early life in gastric cancer. Similar studies of migrants (all with similar results) have been carried out on colorectal cancer in Polish migrants to the US (Staszewski and Haenszel, 1965) or to Australia (Staszewski *et al*, 1971), various of foreign born residents in the United States (Haenszel, 1961) and Indian migrants to London (McKeague *et al*, 1989). Finally, Haenszel and Dawson (1965) studied colorectal cancer incidence in migrants within the United States.

The studies of migrants overcome the problems of controlling for racial/genetic factors but still leave the effects of non-dietary environmental factors uncontrolled. These problems can be overcome in part by studying groups with distinct cultures within a particular area in which the physical environment is similar for all groups. Examples of such groups that can be compared in this way are the various religious subgroups living in Bombay, the racial groups in Johannesburg, religious groups in California. These studies again show that for certain cancers (*eg* stomach, colorectum, breast) incidences vary between cultures with, for example, vegetarian groups tending to have lower incidences than omnivorous groups of cancer of the colon and breast.

Table 1.5—The incidence of cancer in Japanese people living in Japan, or who were born in Japan but who have migrated to the United States, or who are the offspring of migrants to the US (*ie* US born)

	Japanese persons			US citizens
	Japanese born living in Japan	Japanese born living in US	US born living in US	
Colorectal cancer	+	+++	+++	+++
Gastric cancer	+++	+++	+	+
Breast cancer	+	++	+++	+++

All of these types of study suggest that the conclusions drawn from the geographical studies are, in fact, valid and not due to confounding factors such as racial factors, the climate and other geographical factors, air pollution etc. The main conclusions are that, from the migrant studies, the geographical variations are not due to racial differences in sensitivity to carcinogens but to levels of carcinogen exposure. Further, the level of carcinogen exposure is determined not by the physical environment but by the lifestyle of the population concerned. The correlations with dietary components are so great that it is impossible to reach any other conclusion than that diet is an important contributor to the risk of cancers of the gastrointestinal tract (oropharynx, oesophagus, stomach, large bowel), the hormone-related cancers (breast, prostate, endometrium and ovary) and of some other digestive organs (*eg* pancreas, kidney).

Nevertheless, they still have the problem that they compare the mean diets of populations rather than the actual diets of individuals.

1.2.2
Case-control studies

Case-control studies have major advantages over the population studies, including the opportunity to control for the various possible confounding factors such as race and non-dietary environmental factors. The diet history of cancer cases can be compared with that of suitable chosen controls matched for age, sex, area of residence and whichever other factors are thought to need to be controlled for. Ideally, cases and controls should be interviewed *blind* but this is often not possible. This type of study has two major problems with regard to determining the diet of the patients. The first is that the symptoms of many cancers have a profound effect on eating patterns. This is particularly true of cancers of the gastrointestinal tract where foods which aggravate the early symptoms are left out of the diet, often subconsciously. To obviate these difficulties it is usual to try to identify a presymptomatic period and to determine the diet for that period; this requires the use of diet recall which is notoriously unreliable. The second major problem is that for some cancers the migrant studies

indicate that the key effects occur in early adulthood and this, too, requires the use of diet-recall techniques.

Examination of the literature makes it clear that the shortcomings of diet recall greatly outweigh those seen with the ecological studies. Table 1.6 illustrates the

Table 1.6—Results of case-control studies on this relation between diet and cancer of the large bowel and of the breast

Colorectal cancer	Fat	Jain *et al*, 1980
		Miller *et al*, 1983
		Pernu, 1960
	Meat	Haenszel *et al*, 1973
		Jain *et al*, 1980
	Fish (protective)	Haenszel *et al*, 1973
		Kune *et al*, 1987
	Fish (causal)	Graham *et al*, 1978
	Fibre (protective)	Modan *et al*, 1975
		Kune *et al*, 1987
	Fibre (causal)	Haenszel *et al*, 1973
		Potter *et al*, 1982
	Vitamins A and C (protective)	Bjelke, 1974
	Vitamin A (causal)	Tuyns *et al*, 1987
	Alcohol	Enstrom, 1977
Breast cancer	Fat	Miller et *al*, 1983
		Tonioli, 1989
	Meat	Lubin *et al*, 1986
	Fibre (protection)	Lubin *et al*, 1986
	Fruit/vegetables	Phillips, 1975 (protect)
	Milk/dairy products	Tonioli, 1989
		Lubin *et al*, 1986

diversity of dietary items correlated with the risks of, for example, cancer of the colon and of the breast. Some of these give results in agreement with those from the international correlations whilst others do not. This has resulted in great confusion in the field of diet and cancer because of the faith of epidemiologists in the case-control technique.

One way in which epidemiologists have been able to make some sense of the data is by examining the proportion of studies which show a particular correlation. An example is the work of Boutron *et al* (1991) with respect to diet and colorectal cancer (Table 1.7); another example is found in Chapter 17 of this book, in which the protective effect of fruit and vegetables against a variety of cancer is reported.

Table 1.7—Analysis by Boutron *et al* of the case-control studies of diet and colorectal cancer

Item	Proportion of studies showing an association with colorectal cancer	
Total or saturated fat	10/15	positive association
	5/15	no relation
Protein	7/12	positive association
	5/12	no relation
Meat	9/15	positive association
Fish	4/8	protective effect
	1/8	positive association
Fibre	10/19	protective effect
	7/19	no effect
	2/19	positive association
Vegetables	13/16	protective effect
Fruit	1/6	protective effect
	5/6	no effect

In conclusion, the contribution of case-control studies to our understanding of the relation between diet and cancer has been disappointing because of the difficulty of determining past diet. Nevertheless, an important contribution has come from the pooled analysis of groups of studies.

Current diet can be determined relatively accurately and this suggests that the way forward is to carry out prospective studies of large cohorts in whom the diet can be determined accurately at recruitment and long before the onset of symptoms.

1.2.3 Prospective or cohort studies

In prospective studies a large cohort of healthy adults is recruited and followed for sufficient years to yield a significant number of cancer cases. The cohorts need to be large because in the United Kingdom a population of 10,000 persons aged 50–75 followed for 10 years would be expected to yield only 100 cases of colorectal cancer. A similar sized cohort of women would yield more breast cancers (because the risk of breast cancer in women is higher than that of colon cancer) but all other cancer of interest are much less common and so would yield fewer cases. The diet of all persons is determined at recruitment using the relatively accurate methods that are available for determining the current diet of healthy adults. When the number of cases is sufficient to permit analysis the diet of those who have developed the cancer of interest can be compared with that of the rest of the cohort who have not developed the disease. Alternatively a set of

carefully chosen controls matched for age, sex and whatever else is thought necessary can be selected from the cohort for comparison with the cases. This gives a case-control study *nested* within a cohort study and has the combined strengths of the prospective approach (with its more accurate diet data) and the case-control methodology (with its ability to control for extraneous effects. The problems with prospective studies are the costs of diet evaluation (10,000 diet determinations need to be made when a maximum of only 300–500 are likely to be used in a nested study), the costs of follow-up (usually relatively modest compared to the cost of diet determination) and the time before a result is available (usually 7–10 years at least). In consequence only a small number of such studies have been made.

The most important such study is that carried out by Hirayama in Japan and described in Chapter 2 of this book. A cohort of more than 250,000 persons had their diet determined in 1950 and have been followed since that time! In consequence very large numbers of cases of even the relatively less common cancers are available for analysis. No more need be said at this stage (since the information is in Chapter 2). Smaller cohorts of American nurses have been assembled for study of cancers of the colon and of the breast by Willett *et al* (1990); the results are summarized in Table 1.8. The results on colon cancer are in good agreement with those from the population studies, and show strong correlations with intakes of fat and meat and inverse correlations with dietary fibre and cereals; correlations with animal fat were very much stronger than those with vegetable fat and those with red meat were much stronger than with white meat.

Table 1.8—The results of cohort studies carried out by Willett *et al* on diet and cancer of the colon and of the breast

Colon cancer	Meat>low meat
	Red meat>poultry
	Animal fat>vegetable fat
	Fibre protective
	Fish protective
Breast cancer	Fat not associated

1.2.4 Conclusions from epidemiology

Conclusions from the epidemiology, overall, are that for a range of cancers of the digestive tract and hormone-related cancers:

(a) Migrant studies show that the geographical variations in incidence are not due to familial/genetic factors but to environmental factors that operate

throughout life for some cancers (*eg* colorectal) and only in early life for other sites (*eg* stomach).

(b) Comparison of populations living within an area (*eg* religious groups in Bombay or in California or in New York; racial groups living in Johannesburg etc) show that the risk of these cancers is not determined by geography but by culture.

(c) The cultural item most strongly linked to these cancers is diet and this is manifest from comparisons of populations and from prospective cohort studies. For very good reasons the case-control studies are less helpful in demonstrating the link between diet and cancer.

1.3
COMPLEXITY OF THE PROBLEM

A major reason why the relationship between diet and cancer is less than clear is the complexity of the problem, particularly from the cancer side. This complexity is due to the differences in aetiology between different histological types of cancer at a given site, between subsites within a target organ and between the various stages in the carcinogenesis process.

1.3.1
Multiple histological types

All published studies of diet and gastric cancer have treated the disease as a single entity, yet Lauren (1965) showed that there are two histological types of gastric cancer—the so-called *intestinal* and *diffuse* types. The latter of these has been shown to be related to the genetic and not to environmental factors (Lehtola, 1978) and yet accounts for about a third of gastric cancer cases. Inclusion of such cases in epidemiological studies inevitably causes confusion but to date no study has excluded them. Oesophageal cancer has historically been squamous cell and this histological type is known to be related to tobacco and alcohol consumption (Tuyns, 1993). However, recently there has been a big increase in the proportion of adenocarcinoma of the oesophagus (Powell *et al*, 1987; 1992). In some studies these account for more than 40% of all oesophageal cancers (Johnston *et al*, 1991) and yet we know nothing of their epidemiology (except that, unlike squamous cell carcinoma, they are *not* related to smoking or to alcohol).

Pre- and post-menopausal breast cancer do not differ in histological type (both being usually adenocarcinomas) and yet the epidemiology of the two differ markedly (as first noted by Clemmenson, 1948) with the post-menopausal disease being much more strongly correlated with diet. Yet still many epidemiological studies group the two types together for correlation with diet etc.

1.3.2
Subsites within a target organ

In general all gastric cancers are grouped together in epidemiological studies but there is growing evidence that cancers of the cardia have an epidemiology much more similar to that of adenocarcinoma of the oesophagus than to antral carcinoma (Table 1.9).

Table 1.9—Epidemiology of squamous cell carcinoma of the oesophagus and adenocarcinoma of the oesophagus, gastric cardia and antrum

	Oesophagus		Stomach	
	Squamous cell	Adenocarcinoma	Cardia	Antrum
Ratio M/F	2	4	4	2
Subsite	upper	lower		
Social class assoc	lower	higher	higher	lower
Temporal changes	decreasing	increasing	increasing	decreasing

It has long been recognized that within the large bowel, carcinomas of the rectum and of the colon have distinct epidemiologies and aetiologies (*eg* Haenszel and Correa, 1973; Berg and Howell, 1974). More recently it has been realized that there are differences also in the epidemiology of cancer of the proximal and of the distal colon (Jensen, 1984; Faivre *et al*, 1985) as illustrated in Table 1.10.

Table 1.10—The epidemiology of cancer of the proximal colon, distal colon and rectum

Aetiological agent	Proximal colon	Distal colon	Rectum
Smoking	+	−	−
Alcohol	−	+	++
Biliary or small bowel surgery	+	−	−
Familial factors	+	−	−
Geographical variation	+	+++	+

Within other cancer sites there are clear differences between subsites but with much less definitive information than for the stomach and colon. Oesophageal cancer can be subdivided into those in the upper, middle or lower third. Upper oesophageal cancers are related to alcohol intake whilst those of the lower third are thought to be more related to gastric reflux. Within the biliary tract the factors associated with cancer of the gallbladder (gallstones, bacterial infection, gastric surgery) differ from those associated with bile duct cancer (*eg* colitis, parasitic infection). Within pancreatic cancers the aetiology of periampullary tumours differ from that of cancer of the body of the pancreas.

1.3.3
Stages in carcinogenesis

Cancer in most sites is almost certainly a multi-stage process and there is evidence that the factors responsible for the individual stages differ. This will be considered in more detail later in this book in other sections but will be discussed briefly here.

In colorectal cancer the sequence of events is (a) normal mucosa to small adenoma, (b) small adenoma grows to a large size, (c) severity of epithelial dysplasia within the adenoma increases from mild through moderate to severe, (d) severe dysplasia is irreversible and progresses to carcinoma. Data from Faivre (1992) have shown that smoking is strongly associated only with the adenoma formation stage and that alcohol is principally associated with the adenoma growth stage. It is likely that the dietary factors associated with colorectal cancer are implicated in the adenoma growth and progression of dysplasia stages rather than in adenoma formation. This is suggested by the relative strength of the relation to recent rather than to past diet; if this is so then the dietary correlations would be much stronger if control patients with small adenomas were used. This will be discussed in more detail later.

In gastric cancer of the intestinal type there is a histopathological sequence from normal mucosa to chronic atrophic gastritis to intestinal metaplasia, through increasingly severe dysplasia to cancer. The later stages appear to be strongly associated with the formation of N-nitroso compounds in the gastric milieu. In contrast the early stages are associated with poor nutrition and perhaps with *H.pylori* infection. Study of the relation between diet and the individual stages would certainly give stronger correlations than study of the overall process with its built-in confounding factors. Table 1.11 summarizes information on the stages of gastric and colorectal cancer and their relation to diet or other aetiological agents.

1.3.4
The rate-limiting step

In a multistep process A → B → C → D the rate at which the individual steps proceed will vary (whether we are considering a biochemical process, a car assembly line, production and packaging of biscuits etc) and the factors controlling those rates will also vary from step to step. Let us assume that the rate of step A → B and of C → D is fast but that B → C is slow; the rate at which D is formed from A will be entirely dependent on the rate of step B →C. There are other consequences which allow us to identify easily the rate-limiting step. Since the rate of formation of B is much faster than its conversion to C, the amount of B will build up rapidly. In contrast since the rate of conversion of C to D is faster than the formation of C from B, there will be very little of C detectable (since it disappears as soon as it is formed). The rate-limiting step is

therefore readily identified by the large excess of substrate and the small amount of product present in the system.

Table 1.11—Factors associated with different stages in gastric and colorectal cancer

Cancer	Stage	Associated factors
Stomach	Atrophic gastritis	*H.pylori*, poor diet
	Intestinal metaplasia	Vitamin C (protective)
	Dysplasia	Endogenous N-nitroso compounds
Colon	Adenoma formation	Genetic factors
		Smoking
		Diet
	Adenoma growth	High meat/fat, low fibre diet
	Dysplasia	Faecal bile acids
		Hormonal factors

This has implications, too, for factors responsible for the individual stages. Those factors which may speed or slow the rate of conversion of A → B or of C → D will not affect the overall rate of formation of D unless they make the rate of the step slower than that of step B → C (in which case *it* will then become the rate-limiting step). Factors affecting the rate of B → C, in contrast, will directly affect the rate of formation of D (by modifying supply of the amount of substrate for the final fast stage). Indeed the rate of formation of D will largely be controlled by the factors controlling the rate of B → C.

An example of this, to be discussed in more detail later in Chapter 3, is to be found in colorectal carcinogenesis, where the histopathological sequence is from normal mucosa (N) to small adenoma (SA) to large adenoma (LA) through increasingly severe dysplasia (D) to carcinoma (CA). The lifetime risk of adenomas is 50% for men and 30% for women, and so the first stage, N → SA, is simple. A high proportion of large adenomas already contain dysplasia of a severity that can be classified as pre-cancer, and so the stage LA → D occurs at high frequency. Further, the development of severe dysplasia is irreversible and inevitably progresses to cancer; the step D → CA cannot be rate-limiting either. However, although the prevalence of adenomas is high that of large adenomas with only mild dysplasia is relatively small and clearly the rate-limited step is SA → LA. The relationship between diet and colorectal cancer seen in epidemiology is in fact that between diet and adenoma growth.

The concept of the rate-limiting step and its implications for our understanding of carcinogenesis have still to be fully appreciated.

1.4 CONCLUSIONS

There is a large body of evidence that diet is important in the aetiology of cancer at many sites, principally the digestive tract—the hormone-related cancer. However, it is becoming clear that the relationships are not all in the same directions with some cancer sites associated with dietary excess (*eg* colon, breast) and some with poor nutrition (*eg* oesophagus, stomach), whilst others are associated with alcohol intake (*eg* liver, oropharynx, oesophagus).

The relationship between diet and cancer risk is relatively clear for only a small number of sites (*eg* endometrium), and this lack of clarity is partly due to the complexity of cancer and partly to the difficulties associated with diet assessment. Clearly we need much more understanding of the histopathogenesis of cancer at all sites; this will enable us to study in detail the causation of individual stages of carcinogenesis and to remove some of the confusion caused by the multi-stage nature of carcinogenesis. In addition, the epidemiologists need to take into account not only the multi-stage nature of the disease but also the multiple histological types of cancer, each of which may have a different aetiology.

REFERENCES

Armstrong B, Doll R (1975). Environmental factors and the incidence and mortality from cancer in different countries with special reference to dietary practice. *Int J Cancer* **15:** 617–31.

Berg J, Howell M (1974). The geographic pathology of bowel cancer. *Cancer* **34:** 807–14.

Bjelke E (1974). Epidemiological studies of cancer of the stomach, colon and rectum; with special emphasis on the role of diet. *Scand J Gastroenterol* **9 (Suppl 31):** 1–235.

Boutron MC, Wilpart M, Faivre J (1991). Diet and colorectal cancer. *Eur J Cancer Prev* **l (Suppl 1):** 13–20.

Buell P, Dunn J E (1965). Cancer mortality amongst Japanese Issii and Nissei of California. *Cancer* **18:** 656–64.

Clemmenson J (1948). Carcinoma of the breast. Results from statistical research. *Br J Radiol* **21:** 583–90.

Doll R, Peto R (1981). The causes of cancer: quantitative estimates of avoidable risks of cancer in the United States today. *JNCI* **66:** 1191–1308.

Drasar BS, Irving D (1973). Environmental factors and cancer of the colon and breast. *Br J Cancer* **27:** 168–72.

Enstrom JE (1977). Colorectal cancer and beer drinking. *Br J Cancer* **35:** 674–83.

Eyssen GE, Bright-See E (1984). Dietary factors in colon cancer: international relaitonships. *Nutr Cancer* **6:** 160–70.

Faivre J (1992). Diet and colorectal cancer. In *Public Education on diet and Cancer* (eds Benito E, Giacosa A, Hill M); Kluwer, Lancaster, pp. 53–68.

Faivre J, Boutron MC, Hillon P *et al* (1985). Epidemiology of colorectal cancer. In *Diet and Human Carcinogenesis* (eds Joossens J, Hill M, Geboers J); Excerpta Medica, Amsterdam, pp. 123–36.

Gregor O, Toman R, Prusova F (1969). Gastrointestinal cancer and nutrition. *Gut* **10:** 1031–4.

Graham S, Dayal H, Swanson M, Mittelman A, Wilkinson G (1978). Diet in the epidemiology of cancer of the colon and rectum. *JNCI* **61:** 709–14.

Haenszel W (1961). Cancer mortality among the foreign born in the US. *JNCI* **26:** 37–132.

Haenszel W, Berg JW, Kurihara M, Locke F (1973). Large bowel cancer in Hawaiian Japanese. *JNCI* **51:** 1765–99.

Haenszel W, Correa P (1973). Cancer of the large intestine: epidemiological findings. *Dis Col Rectum* **16:** 371–7.

Haenszel W, Correa P (1982). Epidemiology of large bowel cancer. In *Epidemiology of Cancer of the Digestive Tract* (eds Correa P, Haenszel W); Martinus Nijhoff, Amsterdam, pp. 85–126.

Haenszel W, Dawson E (1965). A note on mortality from cancer of the colon and rectum in the United States. *Cancer* **18:** 265–72.

Haenszel W, Kurihara M (1968). Mortality from cancer and other diseases among Japanese in the United States. *JNCI* **40:** 43–68.

Jain M, Cook GM, Davis FG, Grace MG, Howe GR, Miller AB (1980). A case-control study of diet and colorectal cancer. *Int J Cancer* **26:** 757–68.

Jensen OM (1984). Different age and sex relationship for cancer of subsites of the large bowel. *Br J Cancer* **50:** 525–9.

Johnston BJ, Reed PI (1991). Changing pattern of oesophageal cancer in a general hospital in the UK. *Eur J Cancer Prev* **1:** 23–6.

Kune S, Kune GA, Watson LF (1987). Case-control study of dietary etiological factors: the Melbourne colorectal cancer study. *Nutr Cancer* **7:** 21–42.

Lauren P (1965). The two histological main types of gastric carcinoma: diffuse and so-called intestinal type. *Acta Path Mic Scand* **64:** 31–49.

Lehtola J (1978). Family study of gastric carcinoma; with special reference to histological types. *Scand J Gastroenterol* **13(Suppl 50):** 1–54.

Levi F, Maisonneuve P, Filiberti R *et al* (1989). Cancer incidence and mortality in Europe. *Med Soc Prev* **34(Suppl 2)**.

Liu K, Moss M, Persky V *et al* (1979). Dietary cholesterol, fat and fibre and colon cancer mortality. *Lancet* **ii:** 782–5.

Lubin F, Wax Y, Modan B (1986). Role of fat, animal protein and dietary fiber in breast cancer etiology. A case control study. *JNCI* **77:** 605–11.

McKeague P, Adelstein AM, Marmot M *et al* (1989). Diet and faecal steroid profiles in South Asian population with a low colon cancer rate. *Am J Clin Nutr* **50:** 151–4.

Miller AB, Howe GR, Jain M, Craib KJP, Harrison L (1983). Food items and food groups as risk factors in a case control study of diet and colo-rectal cancer. *Int J Cancer* **32:** 155–61.

Modan B, Barrel V, Lubin F, Modan M, Greenberg RA, Graham S (1975). Low fiber intake as an etiologic factor in cancer of the colon. *JNCI* **55:** 15–18.

Muir C, Waterhouse J, Mack T *et al* (1988). Cancer Incidence in five Continents. IARC, Lyon.

Pernu J (1960). An epidemiological study of cancer of the digestive organs and respiratory system. *Ann Med Intern Fenn* **49:** 1–117.

Philips RL (1975). Role of life style and dietary habits in risk of cancer among Seventh Day Adventists. *Cancer Res* **35:** 3513–22.

Potter JD, MacMichael AJ, Hartshorne JM (1982). Alcohol and beer consumption in relation to cancers of the bowel and lung: an extended correlation analysis. *J Chronic Dis* **35:** 833–42.

Powell J, McConkey C (1992). The rising trend in oesophageal adenocarcinoma and gastric cardia. *Eur J Cancer Prev* **1:** 265–70.

Powell J, Robertson J, McConkey C (1987). Increasing incidence of oesophageal carcinoma: in which sites and which histological types? *Br J Cancer* **55:** 346–7.

Segi M (1975–1984). Age adjusted death rates for cancer for selected sites in 51 countries in 1970–79.

Staszewski J, Haenszel W (1965). Cancer mortality among the Polish born in the US. *JNCI* **35:** 291–7.

Staszewski J, McCall M, Stenhouse N (1971). Cancer mortality in 1962–6 among Polish migrants to Australia. *Br J Cancer* **25:** 599–610.

Stocks P, Karn NIN (1933). Cooperative study of habits, home life, dietary and family histories of 450 cancer patients and an equal number of control patients. *Ann Eugen* **5:** 237–51.

Tonioli P, riboli E, Protta F, Charrel M, Cappa A (1989). Calorie-providing nutrients and risk of breast cancer. *JNCI* **81:** 278–86.

Tuyns AJ (1993). Oesophageal cancer. Prospects for primary prevention. *Eur J Cancer Prev* **2(Suppl 3):** in press.

Tuyns AJ, Haelterman M, Kaaks R (1987). Colorectal cancer and the intake of nutrients: oligosaccharides are a risk factor, fats are not. A case-control study in Belgium. *Nutr Cancer* **10:** 185–96.

Willett WC, Stampfer MJ, Colditz J *et al* (1990). Relation of meat, fat and fiber intake to the risk of colon cancer in a prospective study among women. *New Eng J Med* **323:** 1664–72.

Wynder EL, Gori G (1977). Contribution of the environment to cancer incidence: an epidemiological exercise. *JNCI* **58:** 825–32.

Wynder EL, Shigematsu T (1967). Environmental factors of cancer of the colon and rectum. *Cancer* **20:** 1520–61.

2
Japanese studies on diet and cancer
T Hirayama

2.1
INTRODUCTION

Diet is now believed to be crucial in modulating risks for cancer at selected sites. In humans, evidence for this idea has been obtained mostly by correlation studies and case-control studies conducted in many countries. Much stronger evidence was obtained by a census population based large scale cohort study conducted in Japan, which provided direct estimates of the risk for developing cancer with different frequencies of consumption of various foods (Hirayama, 1990a). A cohort study, or a population prospective study, is believed to be one of the best methods for confirming existing hypotheses as well as for generating new hypotheses regarding any key issue of health including diet and cancer. The subjective bias in obtaining dietary information is far less than in case-control studies, as the interview is carried out prior to the start of follow-up and therefore in most cases prior to onset of the disease. In addition, the study provides precious information on the relationship between diet and cancer and other diseases, covering the entire spectrum of mortality. The data obtained may also serve as an example of the usefulness of such studies in exploring the association between diet and cancer.

2.2
MATERIAL AND METHODS

In order to observe the effect of diet on mortality, a large-scale census population-based prospective cohort study of cancer and other major causes of death was conducted from 1 October to 31 December 1965. A total of 265,118 adults (122,261 men, 142,857 women) aged 40 years and over, *ie* 94.8% of the census population in the study areas (29 health centre districts in 6 prefectures in Japan) were interviewed using a questionnaire including questions on such items as smoking, drinking, diet, occupation, marital status and reproductive history (Hirayma, 1990a).

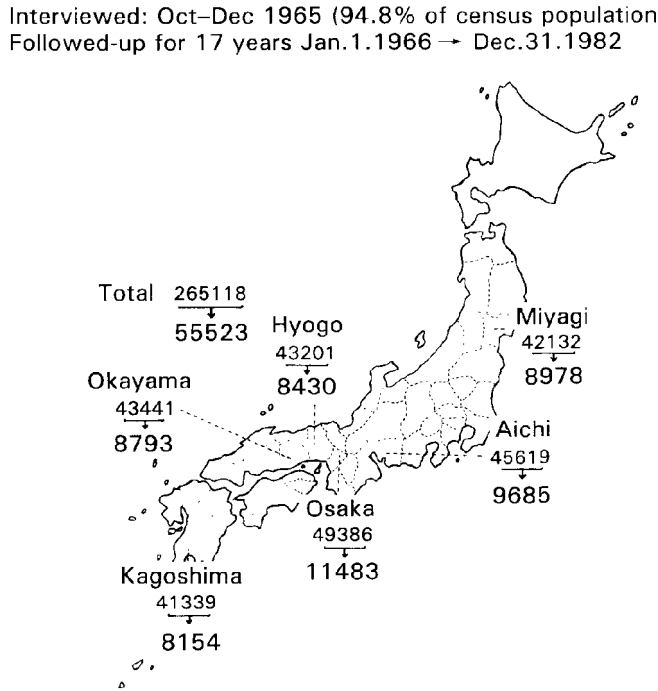


Fig. 2.1—Census-population based prospective cohort study

Successful implementation of the programmes for surveying and following-up such a large population over many years was ensured by full utilization of the existing system of public health surveillance composed of an administrative network (prefecture—health centre—city, town and village—neighbourhood unit); budgetary support was provided by a Grant-in-Aid from the Ministry of Health and Welfare of Japan. Six prefectures (Miyagi, Aichi, Osaka, Hyogo, Okayama, Kagoshima) were selected as study areas (Fig. 2.1).

2.2.1 Interviews

Two kinds of interviews were carried out—one with all cohort members in 1965 and a second in a randomly selected subpopulation of 3% of the cohort in 1971. In the first survey, a questionnaire was administered on smoking, drinking and dietary habits, including some questions on medical history. In the second survey, a slightly extended questionnaire was used, designed to assess changes in habits that had occurred over time. The two questionnaires are given in Appendix 1.

The study was conducted during home visits by public health nurses and midwives from each health centre, an average of 50 per health centre or about 1,

500 in total, who were trained to conduct the interview in a standardized way. The interviews were usually conducted immediately after a home visit by a census taker. The questionnaire was simple and straightforward, as shown in questionnaire Form 1 (Appendix 1). Printed guidelines for interviewers were provided, and tapes were used to demonstrate model inquiries. Examples of guidelines are as follows: (a) Area numbers, household numbers and individual number must be recorded as identification items for each person in addition to name, sex, date of birth and detailed address, (b) For items regarding diet, current habits throughout the year should be elicited and not seasonal peculiarities, (c) Criteria for frequency of consumption are as follows: daily—four or five times or more a week; rare—one to three times a month; occasional—in between; none—two to three times a year (such as at festivals).

2.2.2
Response rates

Response rates among census population of 1 October 1965 in target districts in Miyagi, Aichi, Osaka, Hyogo, Okayama and Kagoshima prefecture were 99.8%, 91.3%, 93.8%, 95.3%, 99.2% respectively.

Such high response rates were also observed in each health centre districts and also in subunit study areas. Among those responding, inquiries regarding frequency of consumption were answered by 99.2% for meat, by 99.5% for fish, by 95.8% for milk, by 99.2% for green-yellow vegetables, by 99.5% for soybean paste soup, by 99.2% for cigarette smoking, and by 98.0% for alcohol drinking. Inquiries regarding amounts consumed were answered by 91.6% of daily consumers for milk, by 89.6% for rice or wheat, and by 95.3 % for cigarette smoking.

2.2.3
Comparisons between first and second interview

Although life-styles can vary with time, they are usually surprisingly stable individually. To determine the reliability of responses in the interview and the extent of changes in selected life-style factors, a second survey was conducted in 1971, six years after the initial survey. A comparison of the results of the two surveys for 7,507 individuals, selected by use of random number tables, out of the original population (Fig. 2.2) showed that the rate of agreement concerning daily consumption in the two categories *daily consumption* and *non-consumption* was quite high: 94.2% for smoking, 79.1% for alcohol drinking, 86.1% for meat consumption, 68.5% for fish consumption and 67.5% for consumption of green-yellow vegetables. The rates of exact agreement (daily/daily, occasional/occasional, rare/rare and none/none) were 84.3, 57.6, 63.3, 60.4 and 65.5% respectively. All of these concordance rates were found to be significantly different from what could be expected by change alone.

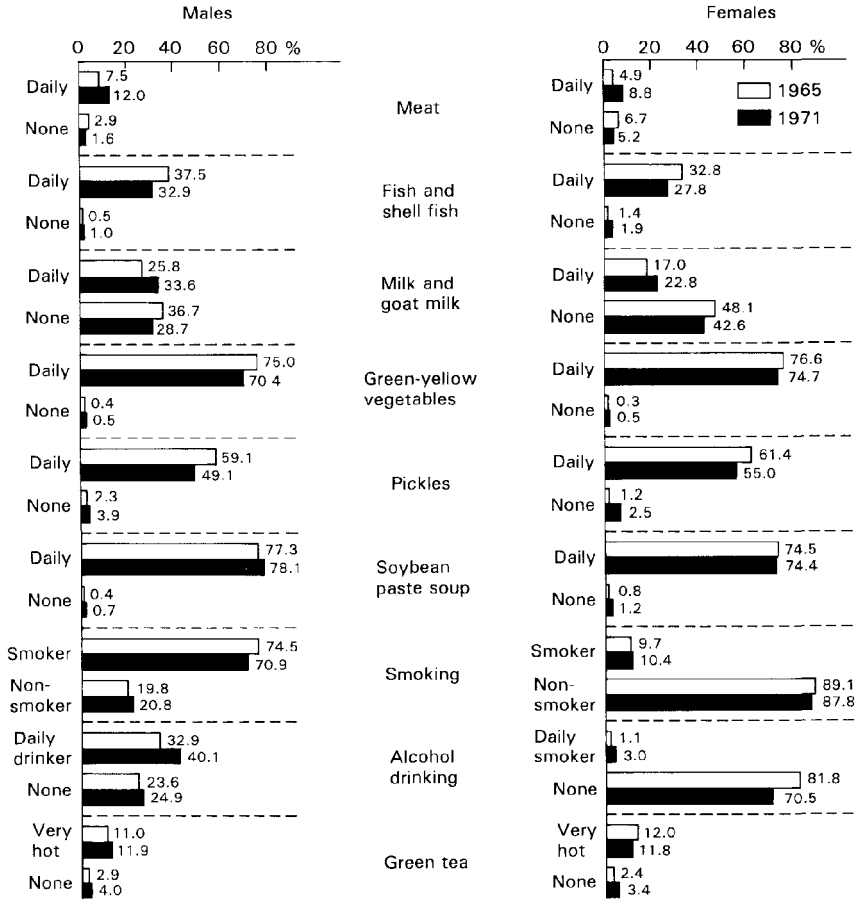


Fig. 2.2—Comparison of lifestyle variable studied in 1965 and 1971

The policy of one-time assessment of risk factors was therefore adopted for practical purposes and information regarding risk factors obtained at the initial survey was used mostly in this study.

2.2.4
Record linkage and data processing

The study subjects were followed up for 17 years by establishing a record-linkage system between the risk factor records obtained by interview in 1965 and in 1971, and a current residence list obtained by a specially planned annual census and death certificates.

Original risk factor records for each individual in the study were assembled at the central office in the Epidemiology Division, National Cancer Center

Research Institute, Tokyo and filed systematically by residence and by date of birth, which facilitated matching of death certificates (and/or cancer registry records) with individual records. Name cards with individual records, name cards with address and key numbers were also used to help matching when necessary. The time required for manual matching was usually several seconds. Data processing and analyses were done by computer.

2.2.5
Statistical methods

For the total of 265,118 persons included in the study, person-years and numbers of deaths due to selected causes of death were calculated in categories of age, sex and life styles. Age- and sex-specific mortality rates, defined as the weighted average of separate age- and sex-specific rates, were calculated for cancers at selected sites and for other causes of death by each life style variable. The weights applied corresponded to the actual age distribution of the population in each of the years 1966 to 1982. Age-specific mortality rates are presented as rates per 100,000 per year.

In order to compare mortality rates between subgroups defined by certain exposures (*eg* smoking), the ratios of standardized mortality rates for these subgroups were calculated.

In general, internal comparisons were used, *eg* mortality rates in exposed persons were compared with those in unexposed persons within the study population. The ratio of these rates is referred to as the relative risk. The 90 % confidence intervals for the relative risks were calculated using standard techniques as described by Breslow and Day (1987). To detect monotone dose-response relationships, a one degree of freedom chi^2 test for trend was calculated where appropriate.

Most of the analyses were based on univariate methods; however, to account for confounding and interaction, logistic regression analysis and matched group analysis were also used and the results of this analysis were compared with those of the univariate analysis. Techniques for fitting multiplicative models to grouped cohort data (Breslow and Day, 1987) were applied.

2.3
RESULTS OF THE STUDY

2.3.1
Comparison of the effect of each lifestyle component and mortality by cause of death

Using data from 17 years follow-up, the relative risks, *ie* the ratio of sex- and age-standardized mortality rates for daily *vs* non-daily consumers, with 90%

confidence limits, were calculated for all causes of death and for 43 selected causes of death, according to frequency of consumption of meat, fish, milk, green-yellow vegetables and soybean paste soup in addition to cigarette smoking and alcohol drinking.

Of the life style risk factors studied, daily cigarette smoking and daily alcohol drinking significantly increased the risk of dying from 29 (65.9%) and 18 (40.9%) of 44 possible causes of death, respectively. Thus cigarette smoking was identified as the most important risk factor for cancer and for other causes of death.

Of the life style risk factors studied, on the other hand, daily consumption of green-yellow vegetables and fish were identified as being most important by reducing the risk of dying from 15 (34.1%) and 14 (31.8%) of 44 causes of death, respectively. Therefore in the following overview of diet-cancer association, special emphasis will be put on the role of consumption of green-yellow vegetables and fish.

Before showing epidemiological evidence of the role of such dietary factors alcohol-cancer association will be mentioned briefly (Hirayama, 1989). Alcohol consumption is occasionally regarded as a part of diet as it serves as a considerable source of calories in the case of daily drinkers. Our large scale cohort study clearly revealed that daily alcohol consumption was associated with the following diseases: cancer of the mouth (*rr* to non-drinkers 2.3), pharynx (2.4), oesophagus (2.3), stomach (0.9), proximal colon (1.0), sigmoid colon (5.4), rectum (1.4), liver (1.2), pancreas (1.0) and liver cirrhosis (1.7). Thus, the closest association with daily drinking of alcohol was observed for cancer of the sigmoid colon. A close association with consumption of hard liquor was also observed for prostate cancer. A sharp increase in the mortality of cancers of the sigmoid colon and prostate in recent years in Japan is therefore interpreted as strongly influenced by a sharp increase in alcohol consumption which has been taking place in Japan.

Other noteworthy epidemiological characteristics are the interaction of alcohol drinking with cigarette smoking observed clearly for cancers of mouth, pharynx, oesophagus and liver. In case of cancers of the sigmoid colon and prostate no such tendency of interaction with cigarette smoking was observed.

2.4
DIET AND CANCER

Seventeen years of follow-up (1966–1982) revealed close associations between dietary habits and risks for cancers at selected sites. Consumption of green-yellow vegetables, meat, fish and cereals were considered to represent typical dietary components in Japan.

2.4.1
Green-yellow vegetables (GYV)

GYV are defined as those that contain 0.6 mg or more carotene per 100 g of edible parts and include carrots, spinach, green peppers, Italian broccoli, pumpkin, turnip leaves, green lettuce, chives, leeks (green), asparagus (green), chicory and parsley. According to the annual national nutrition survey in 1987 on 7,000 randomly selected households and 20,000 family members, GYV provide 56.0% of total vitamin A, 5.8% of vitamin B_1, 9.3% of total vitamin B_2, 22.8% of total vitamin C, 6.5% of total calcium and 11.0% of total iron intake daily in Japan. GYV are thus an important source of ß-carotene, vitamins A and C and selected minerals; they are also one of the major sources of dietary fibre in the Japanese diet.

GYV are thus rich in ß-carotene (vitamin A), vitamin C, minerals such as calcium and iron and dietary fibre. In addition to having a high nutritional value, our study strongly indicates that they lower the risk for cancers at many sites, heart disease and many other causes of death probably due to the scavenging effects of ß-carotene and vitamin C on oxygen radicals. Therefore, increased consumption of GYV has been strongly recommended in recent years, not only by experts in nutrition but also by epidemiologists including the author (Hirayama, 1979, 1982, 1986).

2.4.1.1
Effect of GYV consumption on mortality from each cause of death

As shown in Table 2.1, the less frequently GYV were consumed, the higher the risk of most causes of death in men and in women compared to daily consumers. Sex- and age-standardized mortality ratios for cancers at all sites, for stomach cancer and for colon cancer increased significantly with decreased frequency of GYV consumption (Fig. 2.3A). Relative risks for cancers at all sites compared to daily consumers were 1.04 for occasional consumers, 1.13 for rare consumers and 1.28 for non-consumers (chi^2 for trend=9.97; one tail P=0.0008). For stomach cancer, the corresponding relative risks were 1.08, 1.16 and 1.50 (chi^2 for trend=9.92; P=0.0008) and those for colon cancer were 1.17, 1.24 and 1.89 (chi^2=3.81, P=0.025).

A significant association with the frequency of GYV consumption was also observed for cancer of the uterine cervix in daily smokers, where the relative risk compared to daily consumers was 1.42 for occasional and 2.35 for rare/non-consumers (chi^2 for trend=4.68; P=0.015). RR for prostatic cancer at age below 74 were 1.4 in GYV occasional consumers and 1.82 in rare or non-consumers compared to daily consumers (chi^2=3.46, P=0.031).

These results clearly indicate that daily consumption of GYV lowers considerably the risk for a variety of diseases. As shown in Fig. 2.3B, 2.3C,

2.3D, 2.3E this tendency was clear for all causes of death, heart disease, cancers at all sites and cancer of the stomach for each sex and for each age group.

2.4.1.2
Effect of GYV consumption by smoking habits

An analysis stratified by smoking habits revealed a greater risk-lowering effect of daily consumption of GYV in heavy smokers than in nonsmokers. The results of this analysis for cancer of the lung in men and for cancer of the cervix are shown in Fig. 2.4A and 2.4B. In each case, a clear dose-response relationship was observed between the amount of smoking and the cancer risk. When compared to nonsmokers consuming GYV daily, smokers of 25 or more cigarettes daily who ate GYV rarely or never had a 3.12 (90% confidence interval, 2.43–4.07) times higher risk for cancers at all sites and a 12.35 (8.25–19. 90) times higher risk for cancer of the lung. For cancer of the cervix uteri, the risk was 3.79 (2.03–9.25) times higher in rare or non-consumers of GYV who smoked 10 or more cigarettes daily compared to nonsmokers

Table 2.1—Relative risks[a] (and 90% confidence intervals) for major causes of death by frequency of consumption of green-yellow vegetables

Cause of death	Consumption of green-yellow vegetables				*chi*^{2} for trend
daily	occasional	rare	none		
Males					
Person-years	1,219,864	434,085	36.636	5,403	
All causes		1.04(1.02–1. 07)	1.12(1.05–1. 19)	1.38(1.20–1. 59)	−5.030
Cerebrovascular disease		1.02(0.98–1. 07)	1.00(0.89–1. 13)	1.20(0.90–1. 61)	−1.011
Subarachnoid haemorrhage		1.14(0.89–1. 48)	1.58(0.83–3. 00)	1.33(0.22–7. 98)	−1.380
Ischaemic heart disease		1.11(1.02–1. 20)	0.95(0.74–1. 22)	0.98(0.52–1. 87)	−1.465
Other heart disease		1.11(1.02–1. 20)	1.16(0.92–1. 46)	1.70(1.02–2. 74)	−2.623
Hypertensive heart disease		1.03(0.88–1. 21)	1.35(0.89–2. 05)	1.58(0.59–4. 23)	−1.082
Ulcer of stomach		1.17(0.99–1. 39)	0.60(0.30–1. 20)	0.80(0.17–3. 80)	−0.252
Liver cirrhosis		1.04(0.91–1. 19)	1.88(1.40–2. 51)	1.51(0.66–3. 48)	−2.329
Asthma		0.84(0.68–1. 04)	1.48(0.90–2. 43)	–	0.435

Cause of death	Consumption of green-yellow vegetables				chi^2 for trend
daily	occasional	rare	none		
Aneurysm		0.76(0.46–1.25)	2.41(1.02–5.67)	–	−0.309
Peripheral vascular disease		0.47(0.20–1.14)	1.26(0.21–7.51)	–	0.902

Cause of death	Consumption of green-yellow vegetables				chi^2 for trend
daily	occasional	rare	none		
Cancers at all sites		1.04(1.00–1.08)	1.11(0.99–1.25)	1.32(1.00–1.73)	−2.301
Ca buccal/ pharynx		0.69(0.44–1.08)	1.89(0.80–4.47)	–	0.388
Ca oesophagus		0.87(0.72–1.05	1.19(0.73–1.96)	3.48(1.72–7.04)	−0.207
Ca stomach		1.06(1.00–1.13)	1.12(0.93–1.35)	1.47(0.97–2.23)	−2.073
Ca intestine		1.18(0.94–1.48)	1.08(0.53–2.17)	1.14(0.20–6.55)	−1.148
Ca rectum		0.97(0.78–1.20)	1.19(0.67–2.14)	–	−0.052
Ca bile duct/ gall bladder		0.96(0.75–1.23)	1.13(0.57–2.26)	1.16(0.20–6.69)	−0.065
Ca liver		1.11(0.97–1.27)	1.42(1.00–2.01)	0.87(0.28–2.73)	−1.715
Ca pancreas		0.93(0.77–1.13)	0.66(0.33–1.31)	2.03(0.75–5.53)	0.473
Ca larynx		0.75(0.48–1.18)	0.52(0.10–2.67)	–	1.172
Ca lung		1.17(1.07–1.29)	1.25(0.95–1.65)	1.28(0.64–2.56)	−2.966
Ca prostate		1.08(0.82–1.42)	0.97(0.41–2.29)	–	−0.351
Ca kidney		0.81(0.48–1.36)	–	–	0.663
Ca bladder		0.97(0.73–1.29)	0.99(0.42–2.43)	–	0.139

Cause of death	Consumption of green-yellow vegetables			chi^2 for trend
daily	occasional	rare	none	
Females				

Cause of death	Consumption of green-yellow vegetables				chi^2 for trend
daily	occasional	rare	none		
Person-years	1,578,790	503,326	37,064	5,895	
All causes		1.03(1.01–1.06)	1.08(0.99–1.17)	1.08(0.88–1.32)	−2.595
Cerebrovascular disease		0.92(0.88–0.97)	0.82(0.69–0.97)	0.72(0.46–1.13)	3.481
Subarachnoid haemorrhage		0.88(0.69–1.12)	0.82(0.36–1.85)	–	0.931
Ischaemic heart disease		1.06(0.96–1.18)	1.28(0.94–1.73)	1.44(0.71–2.92)	−1.581
Other heart disease		1.12(1.03–1.22)	1.13(0.86–1.48)	1.69(0.97–2.93)	−2.530
Hypertensive heart disease		0.92(0.79–1.08)	1.13(0.70–1.82)	0.98(0.28–3.50)	0.425
Ulcer of stomach		0.94(0.70–1.25)	0.58(0.18–1.85)	–	0.717
Liver cirrhosis		1.16(0.96–1.39)	0.86(0.44–1.69)	–	0.945
Asthma		0.96(0.71–1.29)	0.65(0.20–2.10)	–	0.528
Aneurysm		1.35(0.79–2.30)	–	–	−0.992
Peripheral vascular disease		0.40(0.08–2.15)	–	–	0.915

Cause of death	Consumption of green-yellow vegetables				chi^2 for trend
daily	occasional	rare	none		
Cancers at all sites		1.05(1.00–1.10)	1.15(0.99–1.35)	1.22(0.84–1.76)	−2.178
Ca buccal/ pharynx		0.70(0.35–1.38)	4.01(1.59–10.08)	–	−0.591
Ca oesophagus		0.97(0.70–1.34)	1.16(0.44–3.03)	2.93(0.70–12.30)	−0.207
Ca stomach		1.11(1.02–1.22)	1.23(0.94–1.61)	1.62(0.91–2.89)	−2.522
Ca intestine		1.16(0.94–1.43)	1.31(0.70–2.47)	1.90(0.57–6.92)	−1.598
Ca rectum		0.95(0.74–1.21)	0.45(0.14–1.41)	–	0.865

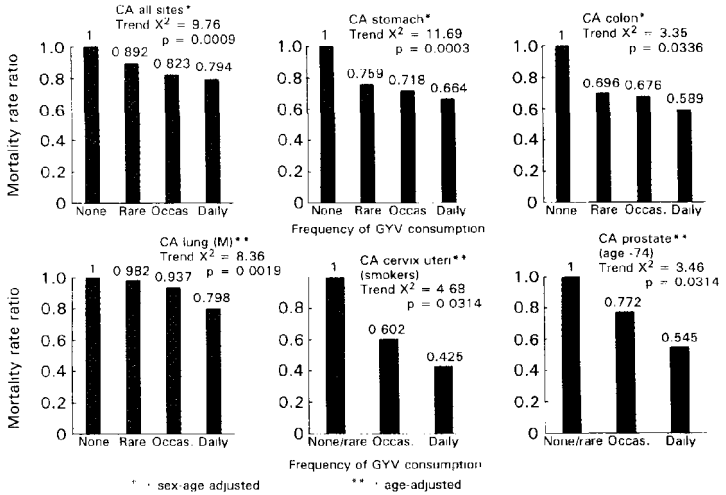


Fig. 2.3A—Mortality rate ratio for cancer of selected sites by frequency of green-yellow vegetable consumption (cohort study, 1966–82, Japan)

Cause of death	Consumption of green-yellow vegetables			*chi*^{2} for trend
daily	occasional	rare	none	
Ca bile duct/ gall bladder		0.91(0.72–1. 15)	1.35(0.72–2. 53)	–	0.190
Ca liver		1.07(0.89–1. 27)	1.00(0.56–1. 80)	–	−0.508
Ca pancreas		0.87(0.68–1. 11)	1.00(0.48–2. 11)	1.36(0.28–6. 60)	0.698
Ca larynx		2.29(1.09–4. 79)	–	–	−1.826
Ca lung		1.22(1.03–1. 44)	0.25(0.08–0. 75)	0.87(0.18–4. 24)	−0.532
Ca breast		0.95(0.74–1. 23)	0.96(0.42–2. 20)	1.32(0.23–7. 64)	0.177
Ca cervix		0.98(0.83–1. 15)	1.69(1.13–2. 52)	–	−0.797
Ca ovary		1.13(0.78–1. 63)	0.61(0.19–1. 98)	–	−0.483
Ca kidney		0.82(0.41–1. 65)	–	–	0.488
Ca bladder		0.83(0.51–1. 34)	2.29(0.88–5. 93)	9.65(3.67–25.35)	−1.376

[a]Reference category is daily consumers.

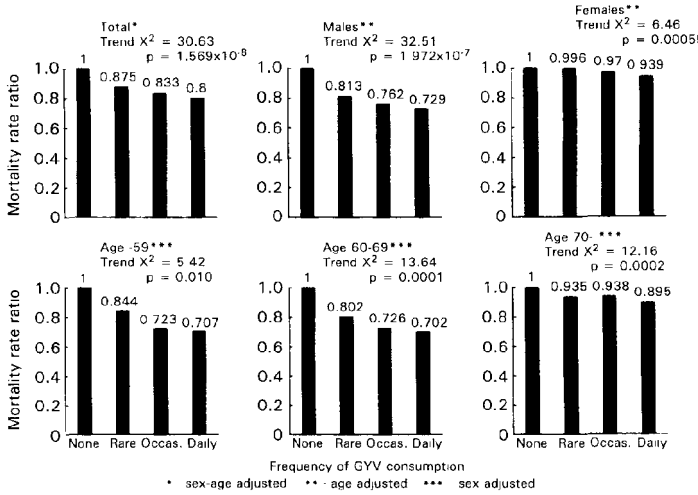


Fig. 2.3B—Mortality rate ratio for all causes of death by frequency of green-yellow vegetable consumption (cohort study, 1966–82, Japan)

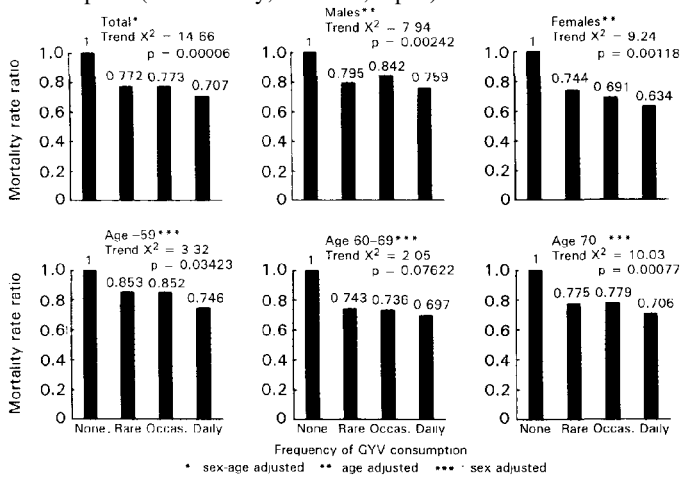


Fig. 2.3C—Mortality rate ratio for heart diseases by frequency of green-yellow vegetable consumption (cohort study, 1966–82, Japan)

consuming GYV daily. These relative risks were observed to be much lower when GYV were consumed daily even in such heavy smokers, *rr* in daily GYV consumers for lung cancer and for cervical cancer being 7.15 (or 58% of 12.35) and 1.11 (or 29% of 3.79) respectively.

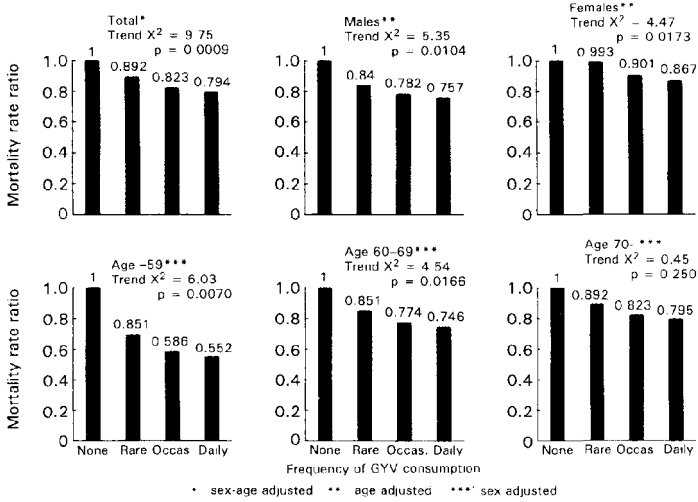


Fig. 2.3D—Mortality rate ratio for cancer of all sites by frequency of green-yellow vegetable consumption (cohort study, 1966–82, Japan)

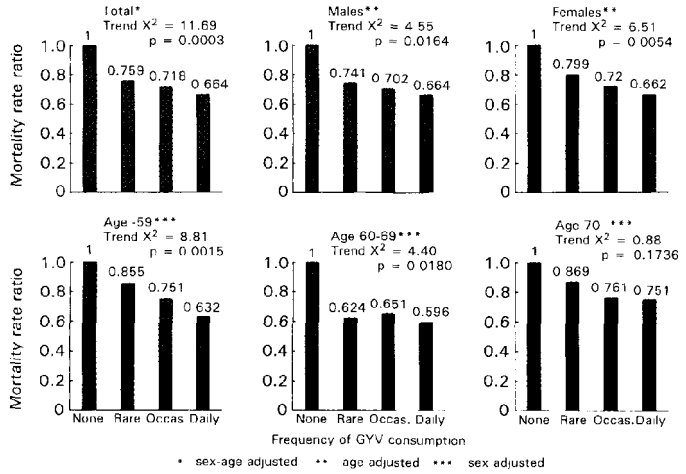


Fig. 2.3E—Mortality rate ratio for cancer of the stomach by frequency of green-yellow vegetable consumption (cohort study, 1966–82, Japan)

2.4.1.3
Effect of GYV consumption on lung cancer risk after smoking cessation

Lung cancer mortality in smokers approached that of nonsmokers more rapidly after smoking cessation in daily GYV consumers than in non-daily consumers. In daily GYV consumers, the risk approached the levels of nonsmokers within four years after smoking cessation. In contrast, in non-daily GYV consumers the risk

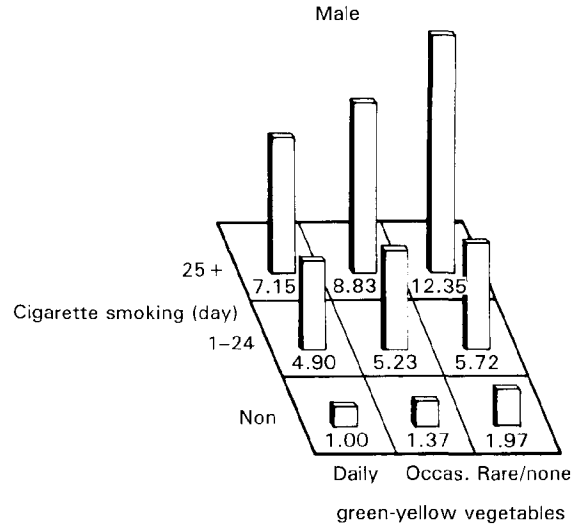


Fig. 2.4A—Relative risks for cancer of the lung in relation to frequency of green-yellow vegetables and the number of cigarettes smoked per day.

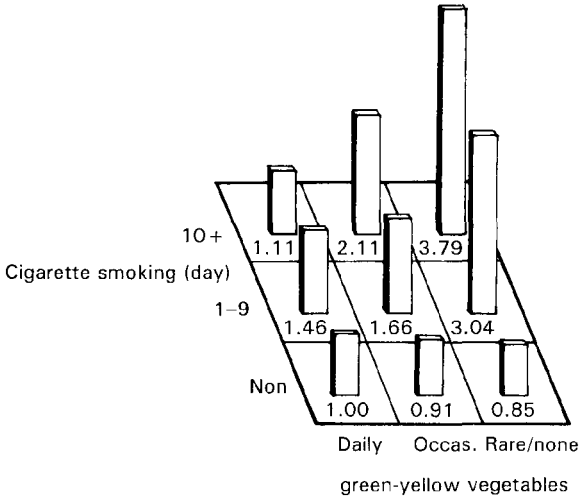


Fig. 2.4B—Relative risks for cancer of the cervix uteri in relation to frequency of green-yellow vegetables and the number of cigarettes smoked per day.

remained twice as high as that of nonsmokers even five years or more after smoking cessation.

Among daily GYV consumers, the relative risks in comparison with current smokers were 0.30 for ex-smokers within four years, 0.30 for ex-smokers within five years or longer and 0.21 for nonsmokers; while for non-daily GYV

consumers the corresponding relative risks were 0.87 for ex-smokers within four years, 0.51 for exsmokers within five years or longer and 0.26 for nonsmokers. Thus, daily intake of GYV appears to enhance the effect of smoking cessation.

2.4.1.4 Effect of GYV consumption on lung cancer risk due to passive smoking

Nonsmoking women with smoking husbands were observed to have a significantly higher risk of lung cancer than those with nonsmoking husbands (Hirayama, 1981). It is noteworthy that those who ate GYV daily had a significantly reduced risk due to passive smoking; the age- and occupation-standardized lung cancer relative risks compared to that of nonsmoking women with nonsmoking husbands were 1.92 for women with ex-smoking husbands or husbands smoking 1–19 cigarettes daily and 2.38 in women with husbands smoking 20 or more cigarettes daily in non-daily GYV intakers, and 1.20 (or 0. 63 of 1.92) and 1.63 (or 0.68 of 2.38) in daily GYV intakers, respectively (both increases in trend were statistically significant [Mantel-extension chi^2 being 2.07 and 2.49 and two-tailed P being 0.038 and 0.013, respectively]) (Fig. 2.5). Thus, GYV daily consumption appeared to lower lung cancer risk due to both active and passive smoking.

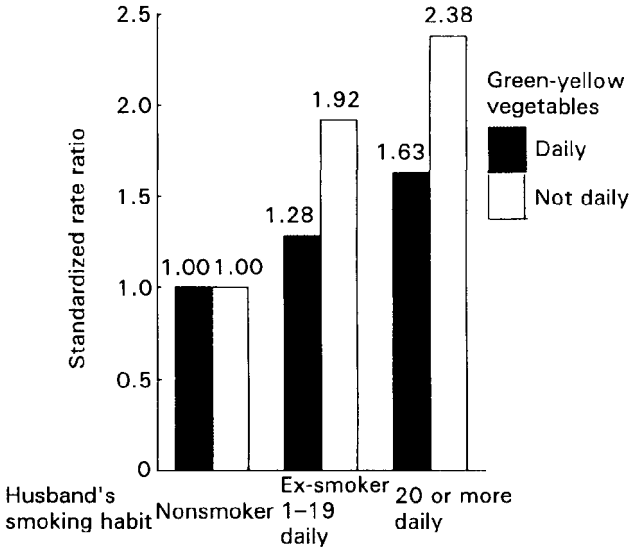
2.4.1.5 Effect of GYV combination on the highest-risk group

The cancer risk reducing effect of daily GYV consumption was also observed clearly even for those who smoke cigarettes daily, drink alcohol daily and eat meat daily.

People who smoke, drink and consume meat daily but do not consume GYV daily were identified as the highest-risk group for cancer. Those who do the opposite (Japanese with Seventh-Day Adventists like life styles) have the lowest risk for cancer. It was quite impressive that the daily consumption of GYV alone was shown to be effective in reducing the risks for cancer of most sites of the highest-risk group (Fig. 2.6).

2.4.1.6 Effect of change in GYV consumption on subsequent stomach cancer risk

A subsample of the cohort consisted of people who changed their eating habits during the observation period; 1,082 subjects who were non-daily eaters of GYV at the time of our first survey (1965) and had become daily consumers at the time of our second survey (1971) had a decreased relative risk for stomach cancer (0. 76) in the subsequent follow-up period (1971–1978), compared to 704 subjects



Green-yellow vegetables	Mantel-extension Chi	p value (two-tailed)
Daily	2.072	0.03827
Others	2.487	0.01288

Fig. 2.5—Lung cancer mortality ratio in nonsmoking wives by smoking habit of the husband: comparison between green-yellow vegetables daily and non-daily intakers

who remained infrequent eaters of GYV throughout the study period although the relative risk was higher than that for the 4,333 subjects who ate GYV daily at the time of both the first and second surveys (relative risk, 0.53) (Fig. 2.7). This observation supports the view of the practical value of nutritional intervention trials in cancer prevention even after reaching adulthood.

2.4.1.7 Discussion

Our study on 265,118 adults followed up for 17 years revealed reduced risk for all causes of death, heart disease, liver cirrhosis, cancers at all sites and cancers of the stomach, colon, lung, prostate (under age 75) and cervix (smokers) in frequent consumers of GYV.

The risk-lowering effect of daily GYV consumption on lung cancer in men persisted through different socioeconomic strata. Among ex-smokers, the extent of reduction in lung cancer risk with lapse of time after smoking cessation was greater among daily consumers of GYV than in others. A risk-lowering effect of daily GYV consumption on lung cancer was also observed in nonsmoking wives with smoking husbands, suggesting a beneficial effect of GYV consumption in

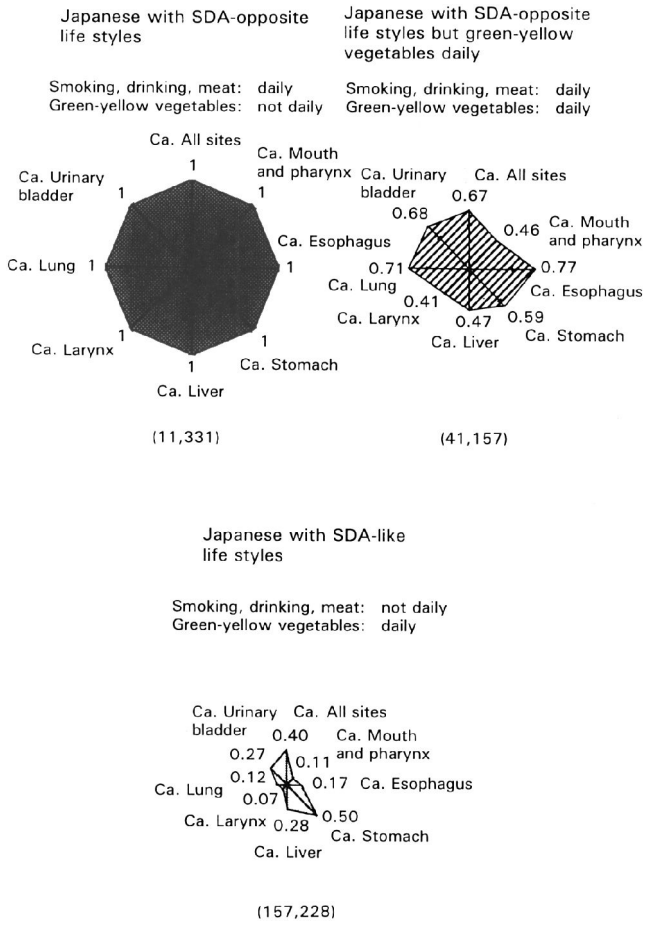


Fig. 2.6—Cancer risk in Japanese with different life styles (prospective study, 1966–81, Japan)

reducing lung cancer due not only to active smoking but also to passive smoking. The striking risk-reducing effect of daily GYV consumption particularly in heavier smokers strongly suggests an important role of oxygen radicals scavengers present in GYV, *eg* ß-carotene and vitamin C.

The risk-lowering effect of GYV on colon cancer is probably due mostly to the dietary fibre in GYV, in addition to ß-carotenes and vitamins, as the extent of risk reduction by daily consumption of GYV is much greater in daily meat consumers (relative risk, 0.21) than in non-daily meat consumers (0.94). A significant reduction in risk for stomach cancer was seen among people who increased their GYV consumption within five years after the start of the study: thus increased consumption of GYV even after reaching adulthood appears to be effective in reducing stomach cancer risk.

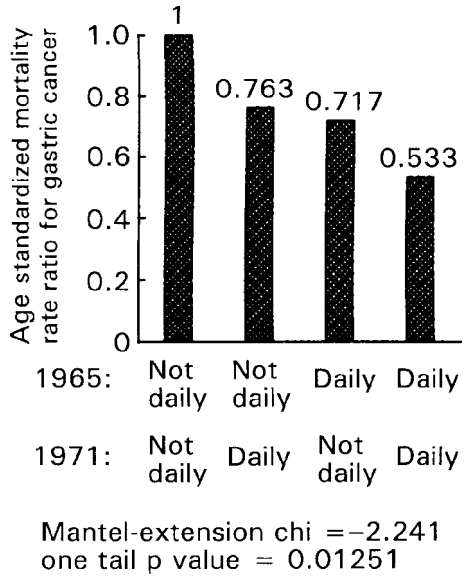


Fig. 2.7—Changes in frequency of green-yellow vegetable consumption and subsequent mortality rate ratio for gastric cancer (age standardized) (chort study, 1971–82, Japan) (Males)

Mortality from prostatic cancer was also lower in frequent consumers of GYV under the age of 74, but not in those aged 75 and over, suggesting a longer latent period or longer interval between latent carcinoma and invasive carcinoma with increased frequency of consumption of GYV. These observations are in line with those observed in a cohort study in Japanese in Hawaii (Kolonel *et al*, 1986).

The biological mechanisms of the risk-lowering effect of daily consumption of GYV observed in epidemiological studies for cancers, heart diseases and others must be due to the increased intake of oxygen radicals scavengers such as ß-carotene and vitamin C, in addition to the effects of minerals such as calcium and iron and dietary fibres, which are found in high quantities in these vegetables.

In addition to such benefits which will appear in later life our study also revealed a surprising immediate benefit of daily GYV consumption. The frequency of stress syndromes (insomnia at night, irritation in daytime) is much less in daily consumers of GYV than in non-daily consumers, the relative risk being 0.45 (0.27–0.74). Such an association was GYV specific and not observed for other diets. Therefore, daily consumption of GYV may also serve stress-prevention probably due to the known scavenger effect of ß-carotene on the continued action of active oxygen/lipid peroxide on nerve tissues. These latter are believed to be the causative agents of stress syndromes and fatigue.

As no adverse effects of GYV consumption are known at present, increased consumption of GYV should be strongly recommended to the public and

particularly to daily cigarette smokers and also to heavy drinkers of alcohol (together with instructions on smoking cessation and drinking moderation), as serum levels of ß-carotene are usually quite low in such people. The combined message of *stop smoking and eat more vegetables* or *carotene instead of nicotine* must contribute to reducing the risks for cancers at all sites and of the mouth/pharynx, oesophagus, stomach, colon, liver, larynx, lung, urinary bladder, cervix and prostate as well as for many other important causes of death, such as diseases of the heart. It may also serve to help prevent stress and fatigue which are of key importance in daily life.

2.4.2 Fish

Fish and shellfish are an important source of protein and fat in the Japanese diet; some also provide ß-carotene and vitamins A and E. More fish than meat is eaten in Japan, although the difference in consumption has diminished: *per caput* daily intake of fish and meat was 61.0 *vs* 8.4 g in 1950; 76.9 *vs* 18.7 g in 1960; 87.4 *vs* 42.5 g in 1970; 92.5 *vs* 67.9 g in 1980 and 90.2 *vs* 75.2 g in 1989. Fish contains unsaturated fatty acids (omega 3 fatty acids) like eicosapentaenoic acid (EPA), which had been shown by basic and clinical research to reduce the risk of both cardiovascular disease and cancer.

2.4.2.1 Effect of fish consumption on mortality from each cause of death

In this large scale cohort study, lower mortality from many causes of death was observed in daily fish consumers (Table 2.2). Compared to non-consumers, significant reductions in risk were observed in daily fish consumers for death from all causes, cerebrovascular disease, ischaemic heart disease, liver cirrhosis, and from cancer of all sites, the stomach, the liver and the cervix. The relative risks were, respectively, 0.77 (0.72–0.84); 0.90 (0.77–1.06); 0.74 (0.55–0.99); 0.53 (0.33–0.84); 0.74 (0.64–0.85); 0.69 (0.54–0.88); 0.43 (0.29–0.62) and 0.42 (0.26–0.69). The risks of stomach cancer for non-, rare, occasional and daily female fish consumers were 1.00, 0.82, 0.72 and 0.67 (P=0.014) and for cervical cancer were 1.00, 0.72, 0.54 and 0.42 (P=0.00004) respectively.

The reduction in risk for cancer of the uterine cervix with increasing frequency of fish consumption is quite noteworthy as it is commonly observed in any age group as shown in Fig. 2.8 and in both daily smokers and in nonsmokers as shown in Fig. 2.9. The risk in daily fish consumers was low also for cancer of the colon; in men of 50– 64 years of age the relative risk in daily vs non-daily consumers being 0.57 (0.36– 0.90). A similar tendency was also observed in this age group of men for rectum cancer, *rr* being 0.69 (0.47–1.01) and liver cancer, *rr* being 0.73 (0.59–0.89).

2.4.2.2 Discussion

The lower risks for cancers of the uterine cervix and other selected sites observed in daily consumers of fish and shellfish in our study may be due to the high vitamin A content of fish, especially since the Japanese often eat the whole fish, including the internal organs. Shellfish are also rich in carotene. The lowered risk of colon cancer in daily fish consumers in men (age 50–64) is in line with animal experiments reported

Table 2.2—Relative risks[a] (and 90 % confidence intervals) for major causes of death by frequency of fish consumption

Cause of death	Consumption of fish				chi^2 for trend
daily	occasional	rare	none		
Males					
Person-years	664,997	948,468	79,638	8,379	
All causes		1.05(1.03–1.07)	1.09(1.04–1.14)	1.35(1.20–1.52)	−5.400
Cerebrovascular disease		1.09(1.05–1.13)	1.09(1.05–1.13)	1.09(1.05–1.13)	−3.373
Subarachnoid haemorrhage		1.44(1.13–1.85)	1.71(1.05–2.80)	1.71(1.05–2.80)	−2.435
Ischaemic heart disease		0.96(0.89–1.04)	0.97(0.82–1.15)	1.20(0.76–1.90)	1.379
Other heart disease		1.21(1.12–1.30)	1.22(1.03–1.45)	1.02(0.60–1.75)	−3.695
Hypertensive heart disease		1.09(0.94–1.23)	1.15(0.82–1.59)	2.14(1.07–4.27)	−1.497
Ulcer of stomach		1.13(0.96–1.33)	1.23(0.86–1.77)	1.35(0.50–3.65)	−1.448
Liver cirrhosis		1.13(1.00–1.27)	1.06(0.80–1.41)	1.49(0.74–2.97)	1.503
Asthma		1.16(0.96–1.41)	2.04(1.46–2.86)	1.14(0.32–4.09)	−2.786
Aneurysm		1.41(0.93–2.15)	0.33(0.06–1.77)	–	−0.465
Peripheral vascular disease		0.26(0.14–0.49)	0.36(0.06–1.98)	–	3.106

Cause of death	Consumption of fish				chi^2 for trend
daily	occasional	rare	none		

Cause of death	Consumption of fish				chi^2 for trend
daily	occasional	rare	none		
Cancers at all sites		0.96(0.93–1.00)	0.94(0.86–1.02)	1.53(1.25–1.87)	0.726
Ca buccal/ pharynx		0.98(0.67–1.42)	1.67(0.84–3.33)	–	–0.583
Ca oesophagus		0.72(0.61–0.84)	0.68(0.44–1.03)	2.36(1.22–4.56)	2.476
Ca stomach		1.04(0.98–1.10)	0.95(0.83–1.10)	1.42(1.01–2.00)	–0.805
Ca intestine		1.00(0.81–1.24)	0.91(0.54–1.54)	0.64(0.10–3.96)	0.190
Ca rectum		1.10(0.90–1.33)	0.94(0.58–1.51)	0.67(0.13–3.50)	–0.281
Ca bile duct/ gall bladder		0.86(0.69–1.07)	0.83(0.48–1.43)	3.06(1.36–6.88)	0.347
Ca liver		1.03(0.91–1.16)	0.99(0.74–1.33)	3.19(2.01–5.05)	–1.360
Ca pancreas		1.02(0.86–1.21)	0.98(0.65–1.48)	0.92(0.27–3.17)	-0.086
Ca larynx		0.56(0.38–0.81)	1.14(0.55–2.38)	2.07(0.43–9.84)	1.239
Ca lung		0.91(0.83–1.00)	0.94(0.76–1.16)	0.95(0.51–1.77)	1.438
Ca prostate		0.87(0.67–1.11)	1.00(0.57–1.78)	1.84(0.54–6.27)	0.358
Ca kidney		0.92(0.59–1.43)	0.69(0.21–2.32)	–	0.537
Ca bladder		0.77(0.59–0.99)	0.59(0.29–1.21)	2.02(0.63–6.43)	1.590

Cause of death	Consumption of fish				chi^2 for trend
daily	occasional	rare	none		
Females					
Person-years	747,743	1,237,904	124,307	20,564	
All causes		1.10(1.07–1.12)	1.16(1.11–1.22)	1.25(1.13–1.39)	–7.611
Cerebrovascular disease		1.08(1.03–1.13)	1.12(1.03–1.23)	1.12(0.91–1.37)	–3.080
Subarachnoid haemorrhage		1.09(0.88–1.35)	0.93(0.58–1.48)	1.33(0.54–3.28)	–0.293

Cause of death	Consumption of fish				chi^2 for trend
daily	occasional	rare	none		
Ischaemic heart disease		1.04(0.95–1.15)	1.26(1.05–1.51)	1.49(1.02–2.19)	−2.155
Other heart disease		1.11(1.02–1.21)	1.15(0.98–1.35)	1.36(0.97–1.92)	−3.377
Hypertensive heart disease		1.00(0.86–1.15)	1.11(0.83–1.47)	0.52(0.20–1.31)	0.169
Ulcer of stomach		0.99(0.76–1.28)	1.56(1.00–2.44)	0.96(0.27–3.44)	−0.001
Liver cirrhosis		1.44(1.20–1.73)	1.94(1.42–2.65)	2.42(1.32–4.44)	4.312
Asthma		1.40(1.05–1.86)	1.33(0.76–2.34)	1.65(0.53–5.15	−1.631
Aneurysm		0.91(0.55–1.52)	–	2.52(0.56–11.34)	0.919
Peripheral vascular disease		0.43(0.15–1.27)	1.00(0.15–6.72)	–	0.579

Cause of death	Consumption of fish				chi^2 for trend
daily	occasional	rare	none		
Cancers at all sites		1.01(0.97–1.06)	1.11(1.01–1.22)	1.22(1.00–1.49)	−1.838
Ca buccal/ pharynx		1.24(0.70–2.17)	1.65(0.62–4.41))	–	−0.990
Ca oesophagus		0.78(0.59–1.03)	0.67(0.35–1.30)	0.96(0.26–3.56))	1.244
Ca stomach		1.06(0.98–1.16)	1.22(1.04–1.43)	1.49(1.06–2.07)	−2.476
Ca intestine		0.99(0.81–1.20)	1.01(0.67–1.52)	1.46(0.67–3.21)	−0.384
Ca rectum		1.15(0.91–1.44)	1.34(0.87–2.07)	0.33(0.05–2.11)	−0.913
Ca bile duct/ gall bladder		0.75(0.62–0.91)	0.54(0.33–0.89)	–	2.841
Ca liver		1.01(0.86–1.19)	1.47(1.10–1.97)	1.51(0.79–2.90)	−1.733
Ca pancreas		0.82(0.67–1.01)	0.67(0.41–1.09)	0.47(0.12–1.79)	2.070
Ca larynx		2.40(0.95–6.03)	–	–	−1.494

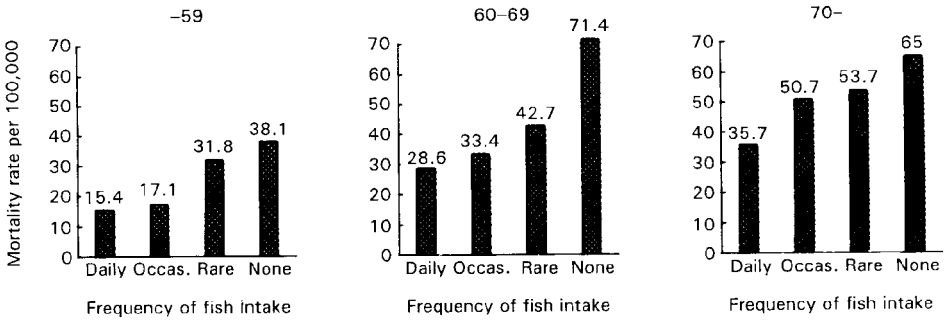


Fig. 2.8—Mortality rate for cancer of the uterine cervix by frequency of fish intake. Observation by age group (prospective study, 1966–81, Japan

Cause of death	Consumption of fish				*chi*[2] for trend
daily	occasional	rare	none		
Ca lung		0.95(0.81–1.12)	0.99(0.71–1.39)	1.21(0.60–2.46)	0.027
Ca breast		1.03(0.82–1.30)	0.87(0.52–1.45)	0.70(0.19–2.61)	0.160
Ca cervix		1.28(1.10–1.49)	1.71(1.31–2.23)	2.37(1.44–3.89)	–4.135
Ca ovary		1.04(0.74–1.47)	1.00(0.49–2.05)	0.87(0.15–5.14)	–0.039
Ca kidney		0.79(0.44–1.41)	0.37(0.06–2.11)	2.25(0.37–13.07)	0.397
Ca bladder		1.28(0.83–1.96)	1.28(0.55–2.96)	5.42(2.26–12.98)	–1.835

[2]Reference category is daily consumers.

in the literature.

The effect of fish intake was independent of cigarette smoking as observed with risk for cancer of the cervix (Fig. 2.9).

The significantly lower risk for cerebrovascular disease, ischaemic heart disease and other heart disease observed in daily fish consumers in this study (Table 2.2) is compatible with the hypothesis that fish contains fatty acids, *eg* EPA, that are beneficial in reducing the risk for these diseases.

2.4.3
Meat

Consumption of meat has been on the increase in Japan, as shown in the previous section, *per caput* daily consumption in 1950 and 1987 being 8.4 g and 69.1 g, respectively—an eight-fold increase. Of the total consumed in 1987, 23.2% was

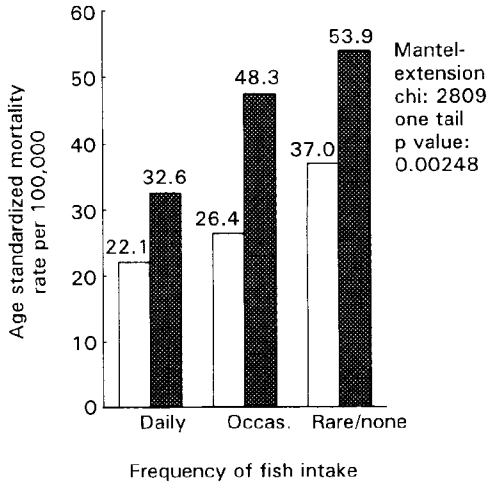


Fig. 2.9—Age standardized mortality rate per 100,000 for cancer of the cervix by frequency of fish intake in daily cigarette smokers (shaded bar) and in nonsmokers (blank bar) (prospective study, 1966–81, Japan)

beef, 38.6% was pork, 22.9% was chicken, 13.6% was ham and sausages and 1. 1% was other kinds of meat.

Meat is a major source of animal fats: 20.3% of all fat consumed by Japanese is from meat. Those who eat meat daily also consumed large quantities of other fat-rich foods, such as butter, lard and oil. The correlation coefficient between meat and those other foods was 0.31 (significant) in the national nutrition survey in 1987. A high-fat diet has been proposed as a risk factor for selected causes of death, such as heart disease and cancers of the breast, lung and colon. Whether or not daily meat consumption actually increases the risk for these diseases was examined in our study.

2.4.3.1
Effect of meat consumption on mortality from each cause of death

The standardized mortality rates for cancers at all sites, liver cancer and lung cancer in men and women and for lung cancer, breast cancer and ovarian cancer in women increased significantly with increased consumption of meat (Table 2.3).

An analysis stratified for smoking habits revealed that the observed apparent association between lung cancer and meat consumption in men was due mostly to confounding with smoking. When smoking habits were adjusted for, relative risks for lung cancer compared to non-consumers were 0.95 for rare consumption, 0.98 for occasional consumption and 1.3 for daily consumption.

The association between breast cancer and meat consumption, however, remained significant even after adjustment for smoking, women who had smoked 10,000–90,000 cigarettes, 100,000– 190,000 and 200,000 or more cigarettes and consumed meat daily had 0.9, 2.2 and 4.4 times higher risks for breast cancer, respectively, compared to nonsmokers consuming meat daily. This relationship was not observed in women who did not consume meat daily (Fig. 2.10). A similar risk elevation of breast cancer limited to daily consumers of meat was observed when effect of exposure to husband's smoking was examined by frequency of meat consumption (Fig. 2.11).

When the age-specific mortality rates for breast cancer in daily meat consumers and others were compared, the rates for daily meat consumers were similar to those in western countries and continued to rise after the menopause. For non-daily meat consumers, the curve was flat or slightly downward after the menopause, fitting the so-called Japanese-type breast cancer age curve (Fig. 2.12, Table 2.4). The effect of meat consumption on risk for breast cancer was independent of socioeconomic status, of marital status and of number of children (Fig. 2.13).

Table 2.3—Relative risks[a] (and 90% confidence intervals) for major causes of death by frequency of meat consumption

Cause of death	Meat consumption				chi^2 for trend
	daily	occasional	rare	none	
Males					
Person-years	150,576	1,204,448	306,118	35,060	
All causes		1.03(1.00–1.07)	1.09(1.05–1.13)	1.34(1.26–1.44)	−7.043
Cerebrovascular disease		1.17(1.09–1.25)	1.38(1.27–1.48)	1.78(1.58–2.01)	−9.679
Subarachnoid haemorrhage		0.66(0.46–0.93)	0.90(0.60–1.34)	0.55(0.21–1.42)	0.128
Ischaemic heart disease		0.85(0.76–0.96)	0.87(0.76–1.00)	0.92(0.71–1.20)	0.843
Other heart disease		1.04(0.91–1.18)	1.04(0.90–1.21)	0.90(0.67–1.21)	0.080
Hypertensive heart disease		1.15(0.87–1.51)	1.54(1.14–2.07)	2.24(1.45–3.45)	−3.920
Ulcer of stomach		1.01(0.76–1.34)	1.14(0.83–1.57)	1.67(1.01–2.75)	−1.665
Liver cirrhosis		0.90(0.74–1.09)	0.73(0.58–0.92)	1.31(0.90–1.90)	−0.877
Asthma		1.38(0.95–2.02)	1.78(1.18–2.67)	3.53(2.12–5.88)	−4.008

Cause of death	Meat consumption				chi^2 for trend
daily	occasional	rare	none		
Aneurysm		0.71(0.38–1.34)	0.85(0.40–1.77)	0.81(0.18–3.53)	0.405
Peripheral vascular disease		2.87(0.60–13.74)	2.01(0.35–11.62)	–	–0.102

Cause of death	Meat consumption				chi^2 for trend
daily	occasional	rare	none		
Cancers at all sites		0.96(0.90–1.02)	0.89(0.83–0.95)	1.02(0.90–1.17)	2.099
Ca buccal/ pharynx		0.90(0.51–1.61)	0.66(0.32–1.34)	–	0.891
Ca oesophagus		0.89(0.68–1.16)	0.83(0.60–1.13)	0.87(0.47–1.59)	0.790
Ca stomach		1.07(0.97–1.19)	0.91(0.80–1.02)	1.34(1.10–1.64)	0.777
Ca intestine		1.86(1.17–2.97)	1.52(0.90–2.57)	1.89(0.84–4.27)	–0.595
Ca rectum		1.50(1.01–2.22)	1.47(0.95–2.28)	1.54(0.74–3.20)	–0.987
Ca bile duct/ gall bladder		0.82(0.57–1.16)	0.83(0.55–1.26)	0.78(0.34–1.80)	0.398
Ca liver		0.76(0.63–0.91)	0.67(0.54–0.84)	0.50(0.30–0.85)	3.040
Ca pancreas		0.75(0.58–0.98)	0.82(0.60–1.12)	0.57(0.28–1.15)	0.940
Ca larynx		2.35(0.92–6.04)	3.25(1.24–8.50)	0.90(0.09–8.77)	–1.580
Ca lung		0.86(0.74–0.99)	0.81(0.68–0.96)	0.82(0.59–1.15	1.811
Ca prostate		0.93(0.61–1.42)	0.96(0.59–1.56)	0.69(0.24–1.99)	0.173
Ca kidney		0.61(0.33–1.14)	0.57(0.26–1.25)	–	1.114
Ca bladder		0.82(0.54–1.24)	0.85(0.52–1.38)	1.00(0.41–2.45)	0.215

Cause of death	Meat consumption				chi^2 for trend
daily	occasional	rare	none		
Females					

Cause of death	Meat consumption				chi^2 for trend
daily	occasional	rare	none		
Person-years	137,476	1,451,546	422,247	111,578	
All causes		1.07(1.02–1.12)	1.10(1.04–1.15)	1.18(1.11–1.26)	−4.375
Cerebrovascular disease		1.13(1.04–1.24)	1.25(1.14–1.38)	1.39(1.23–1.56)	−5.569
Subarachnoid haemorrhage		0.72(0.50–1.04)	0.94(0.53–1.39)	0.40(0.21–0.78)	0.542
Ischaemic heart disease		1.27(1.04–1.56)	1.32(1.06–1.64)	1.36(1.03–1.78)	−1.640
Other heart disease		0.95(0.81–1.10)	0.95(0.80–1.12)	0.97(0.78–1.21)	0.190
Hypertensive heart disease		1.09(0.81–1.45)	1.13(0.82–1.54)	1.41(0.96–2.06)	−1.468
Ulcer of stomach		1.41(0.80–2.51)	1.41(0.76–2.62)	1.43(0.67–3.05)	−0.511
Liver cirrhosis		1.25(0.91–1.72)	0.94(0.66–1.33)	1.00(0.64–1.58)	0.083
Asthma		0.85(0.54–1.34)	0.51(0.30–0.88)	0.54(0.25–1.17)	2.457
Aneurysm		2.55(0.60–10.88)	2.00(0.42–9.52)	2.22(0.37–13.34)	−0.110
Peripheral vascular disease		–	–	–	0.346

Cause of death	Meat consumption				chi^2 for trend
daily	occasional	rare	none		
Cancers at all sites		1.01(0.92–1.10)	0.95(0.86–1.04)	0.98(0.87–1.12)	1.295
Ca buccal/ pharynx		0.90(0.33–2.50)	1.05(0.35–3.17))	0.76(0.16–3.63)	0.012
Ca oesophagus		0.82(0.48–1.39)	0.74(0.41–1.36)	1.77(0.93–3.38))	−1.138
Ca stomach		1.04(0.89–1.23)	1.09(0.92–1.30)	1.11(0.89–1.39)	−1.065
Ca intestine		0.83(0.59–1.18)	0.74(0.50–1.10)	0.95(0.57–1.56)	0.616
Ca rectum		1.20(0.76–1.91)	1.08(0.65–1.79)	1.41(0.77–2.60)	−0.360

Cause of death	Meat consumption				chi^2 for trend
daily	occasional	rare	none		
Ca bile duct/ gall bladder		1.33(0.85–2. 08)	1.27(0.79–2. 06)	1.21(0.66–2. 23)	−0.034
Ca liver		1.12(0.80–1. 55)	1.07(0.75–1. 53)	0.99(0.62–1. 59)	0.255
Ca pancreas		1.73(1.04–2. 89)	1.51(0.87–2. 62)	1.44(0.73–2. 84)	0.677
Ca larynx		1.10(0.26–4. 77)	0.60(0.11–3. 38)	–	0.366
Ca lung		0.88(0.66–1. 18)	0.74(0.53–1. 03)	0.67(0.42–1. 06)	2.090
Ca breast		0.55(0.39–0. 78)	0.59(0.40–0. 87)	0.42(0.23–0. 78)	1.842
Ca cervix		1.41(1.02–1. 93)	1.18(0.83–1. 67)	1.53(1.01–2. 31)	−0.274
Ca ovary		1.16(0.60–2. 25)	0.67(0.31–1. 45)	0.53(0.17–1. 65)	1.887
Ca kidney		0.76(0.27–2. 12)	0.86(0.28–2. 67)	0.33(0.05–2. 45)	0.360
Ca bladder		3.31(0.86–12.69)	4.52(1.20–17.01)	6.02(1.55–23.29)	−2.514

[a]Reference category is daily consumers.

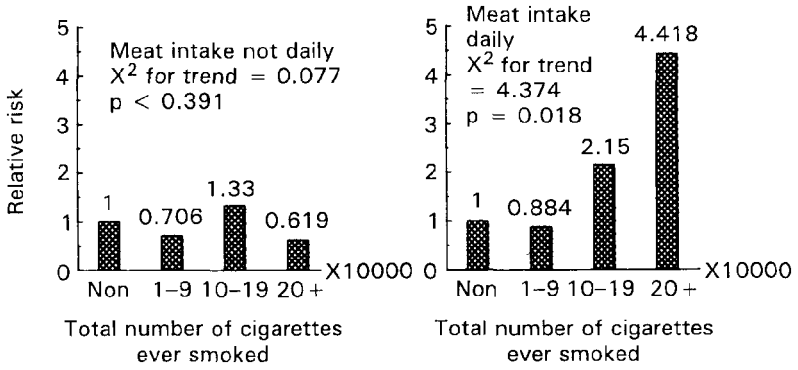


Fig. 2.10—Standardized mortality rate for breast cancer by total number of cigarettes ever smoked (prospective study, 1966–81, Japan).

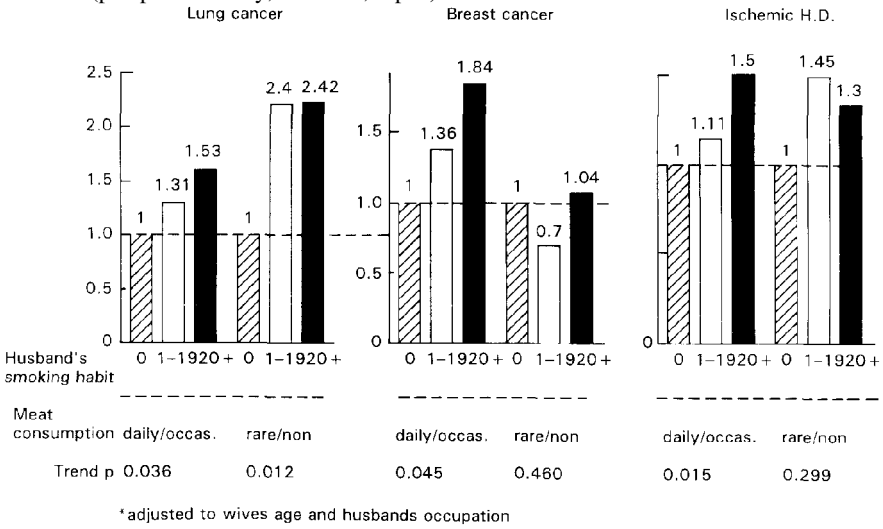


Fig. 2.11—Relative risk* for lung cancer, breast cancer and ischemic heart disease in never smoking wives (age 40–65) by husbands, smoking habit and by wives, habit of meat consumption (prospective study, 1966–81, Japan).

Table 2.4—Breast cancer mortality by age group and by frequency of meat consumption (prospective study, 1966–82, Japan)

	Frequency of meat consumption					
Age group	Daily		Occas/Rare		None	
Br Ca	P-y	Br Ca	P-y	Br Ca	P-y	
Total	25	137476	202	1873793	9	111578
40–44	0	5758	2	54112	1	1963
45–49	2	17170	15	174730	1	6693
50–54	4	25184	29	282758	1	11940
55–59	4	29359	49	365671	0	17479
60–64	6	23459	38	338551	1	19176
65–69	6	17128	26	290400	1	20528
70–74	3	10841	23	204310	2	17434
75–	0	7810	20	156343	2	15972

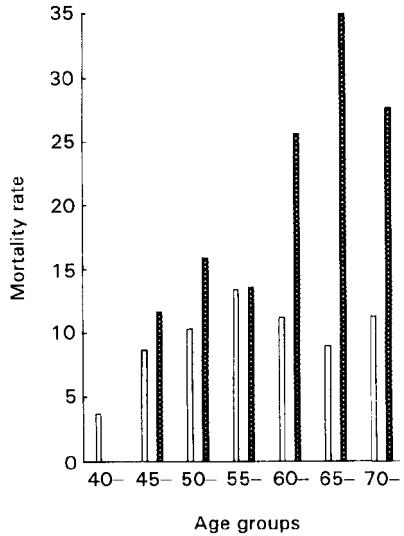
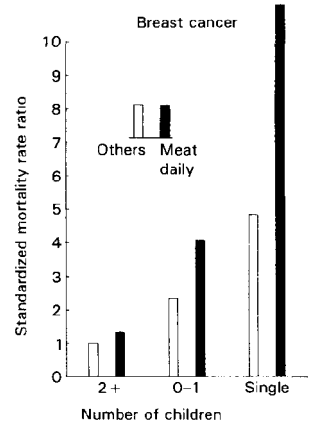


Fig. 2.12—Age specific mortality rate per 100,000 for breast cancer in daily meat intakers (shaded bar) and in non-daily meat intakers (blank bar) (prospective study, 1966–82, Japan).



Rate ratio:		1.0	1.3	2.3	4.0	4.8	11.3
90% conficence	upper		2.4	3.1	7.8	9.2	45.9
limits	lower		0.7	1.7	2.0	2.5	2.8

*adjusted also to prefecture of residence and place of birth

Fig. 2.13—Age standardized mortality rate ratio* for breast cancer by number of children and by frequency of meat consumption (prospective study, 1966–82, Japan)

All age group				
Mantel-extension chi		2.591	(*P*=0.00478)	
Standardized	2.442		1.357	1.000
Rate ratio				
40–59				
Mantel-extension chi		0.835	(*P*=0.20186)	
Standardized	1.686		1.405	1.000
Rate ratio				
60-				
Mantel-extension chi		2.739	(*P*=0.00308)	
Standardized	2.820		1.333	1.000

A much larger elevation of risk associated with daily meat consumption was found for cancers at most sites in non-daily consumers of GYV. When GYV were consumed daily, daily consumption of meat was observed to decrease the risk for cancers at many sites (Fig. 2.14). For instance, the risk for colon cancer is very low in daily meat consumers when GYV are also consumed daily, the age-standardized mortality rate per 100,000 being 3.87 as compared to 13.87 in non-daily meat consumers. When GYV were not eaten daily, the risk for colon cancer was higher in daily meat consumers than in non-daily meat consumers, the age-standardized mortality rates being 18.43 and 14.80, respectively. Thus, daily meat consumption is beneficial in reducing the risk for colon cancer and most other diseases when GYV are eaten daily; otherwise, daily meat consumption increases the risk for many diseases.

2.4.3.2 Discussion

Meat is an important source of protein, but, at the same time, increased consumption carries a risk of excess intake of animal fat. Therefore, it is

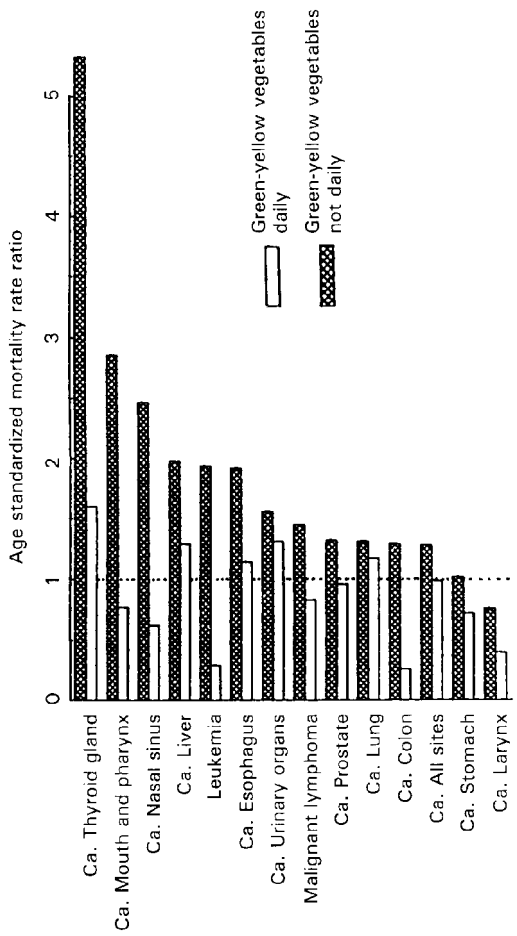


Fig. 2.14—Age-standardized mortality rate ratio for cancer of selected sites in daily meat consumers (risk in non-daily meat consumers=1.00). Observation by frequency of green-yellow vegetable consumption (cohort study, 1966–81, Japan).

understandable that daily consumption of meat increases the risks for several important diseases while reducing mortality from other major causes of death. It is important that lower risks for most disease are seen in daily meat consumers if they also eat GYV daily; otherwise, the risks in daily meat consumers were generally much higher than in non-consumers. Daily consumption of GYV is also strongly recommended for this reason. We should eat meat always with GYV, as our observations strongly suggest the importance of increased consumption of GYV which are rich in dietary fibre in addition to ß-carotene, vitamin C and calcium.

2.4.4
Cereals

The grains eaten most often by Japanese are rice and wheat. The amount and composition of cereals consumed in Japan has changed remarkably with time. The total amounts of cereals consumed (in grams *per caput* per day) were 476.8 in 1950; 452.6 in 1960; 374.1 in 1970; 319.1 in 1980 and 288.5 in 1989. The proportion of rice in these totals was 71.0% in 1950; 79.2% in 1960; 81.8% in 1970; 70.8% in 1980 and 68.8% in 1989.

Cereals are not only a source of energy but also one of the most important sources of dietary fibre, along with vegetables. There are large individual variations in the amount of cereals consumed; we examined the influence of this variation on mortality from cancers at all sites and at individual sites and from other major causes of death.

2.4.4.1
Effect of cereal consumption on mortality from selected causes of death

A significant negative association was seen with the amount of rice/wheat consumed for all causes of death, for diabetes, for cerebrovascular disease and for ischaemic heart disease, the risk decreasing with increasing consumption. Cancers of the oesophagus, colon and rectum showed similar negative association. No association was observed with stomach cancer (Fig. 2.15).

2.4.4.2
Discussion

The most likely explanation for these associations is the high fibre content of rice and wheat; however, the significant negative association with oesophageal cancer may need an additional explanation.

2.5
CHANGE IN CANCER MORTALITY BY DIET MODIFICATION

Promising trends in change of mortality in cancers of key sites are taking place in Japan in recent years mainly due to the changes in dietary behaviour of the public induced by a series of epidemiological indications provided by us.

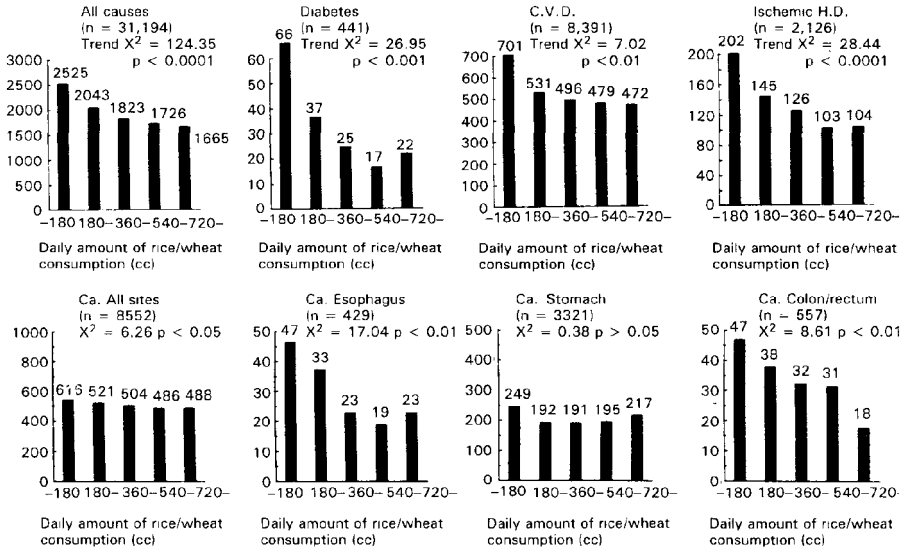


Fig. 2.15—Age-standardized mortality rate for selected causes of death by amount of daily rice/wheat intake (males)

2.5.1
Salted food and stomach cancer

Frequent consumption of highly salted food, widely used in Japan, was identified by us as the major reason for the extremely high incidence of stomach cancer in Japan (Hirayama, 1984a). Our correlation study showed that the higher the concentration of salt in soybean paste (mainly used for pickling) the higher the stomach cancer mortality (Fig. 2.16A). The case-control study of stomach cancer also conducted by us showed that the relative risk of stomach cancer increased in both men and women the more frequently salty foods were consumed (Fig. 2.16B). Such a risk enhancing association was confirmed by a series of laboratory studies (Takahashi *et al*, 1983). When the close association of salty food consumption and stomach cancer mortality was widely reported, a vigorous campaign to reduce salt consumption was spread country-wide by a team of oncologists, cardiologists and consumer groups. Aided by the introduction of electric refrigerators, the public in Japan responded by reducing *per capita* daily salt consumption by 16% in 17 years, from 14.5 g in 1971 to 12.2 g in 1988 (Fig. 2.16C), resulting in a drastic reduction of stomach cancer mortality, *ie* over 50% reduction in 30 years (Table 2.5). These sequential event can be considered a model for the plan shown in Fig. 2.17: *ie* epidemiological research for identification of risk factors and for establishment of a strategy for primary prevention; actions to modify public behaviour as indicated by this epidemiological research; and eventual reduction in mortality of the target cancer.

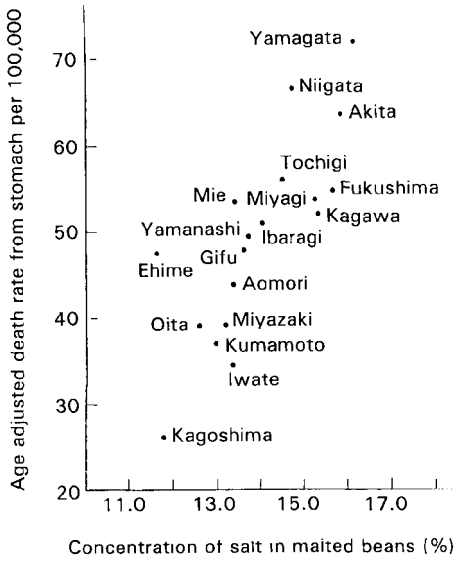


Fig. 2.16A—Age-adjusted death rate from stomach cancer according to the concentration of salt in malted beans (rural prefectures only).

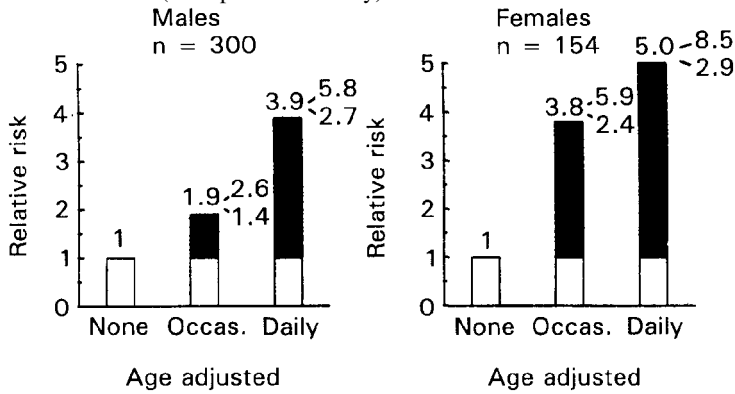


Fig. 2.16B—Relative risk of gastric cancer by frequency of salty food consumption (case-control study, 1960–61, Kanagawa, Japan).

Table 2.5—Trend of gastric cancer mortality in Japan (per 100,000 age-adjusted)

	1958	1968	1978	1988	Ratio 1988/1958
Male	48.7	44.9	32.9	23.2	0.47
Female	30.0	28.4	20.4	13.1	0.44

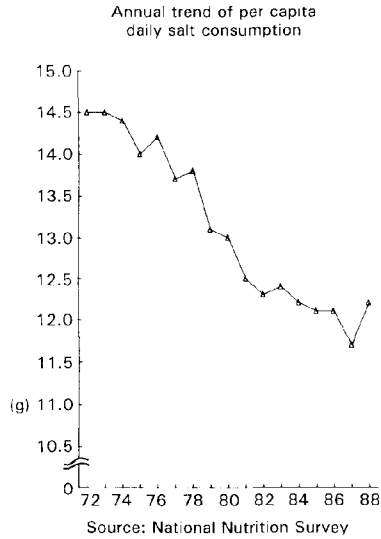


Fig. 2.16C—Annual trend of *per capita* daily salt consumption.

2.5.2
Fat and cancer

Meat consumption was positively associated with cancers of the breast, ovary and pancreas. Interaction with cigarette smoking appeared to affect these cancer (Fig. 2.18).

Evidence for a close association between breast cancer and high fat consumption was obtained from correlation studies by countries (Carroll *et al*, 1968), by ethnic groups in Hawaii (Kolonel *et al*, 1986), and by each district in Japan (Fig. 2.19A); from cross-sectional studies by *per capita* fat consumption in metropolitan areas, cities and counties in Japan (Fig. 2.19B); and from our cohort study (Fig. 2.19C). Daily meat consumption was noted as the leading risk factor of breast cancer among many life-style variables studied, relative risk being 1.83. The association was particularly apparent in post-menopausal women, showing a typical Western-type age curve in daily meat consumers and a typical Japanese-type age curve in non-daily meat consumers (Fig. 2.12) (Hirayama, 1990b).

In Japan, up to 1973, both *per capita* animal fat consumption and breast cancer mortality sharply increased, probably as the result of Westernisation of Japanese life styles. Therefore, the future trend could be predicted by fitting and extrapolating a log-quadratic curve to the trend from 1955 to 1973. It was estimated that both animal fat consumption and breast cancer mortality might approach the US level by 1988. Surprisingly, however, the increase in animal fat consumption virtually stopped after 1974 (Fig. 2.20). Incidentally, 1973 was the year of the first oil crisis. Again surprisingly, the increasing trend of both breast and colorectal cancer slowed significantly following that year. No such tendency

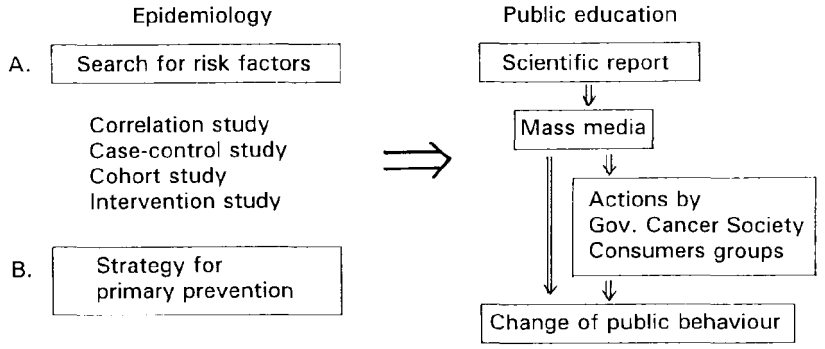


Fig. 2.17—Interaction of various strategies in cnacer prevention

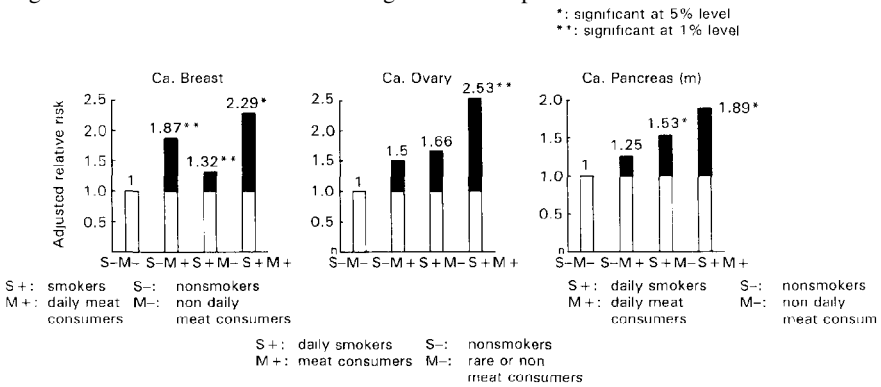


Fig. 2.18—Meat consumption and cancer with special reference to interaction with cigarette smoking (cohort study, 1966–82, Japan)

was observed for cancer of other sites (Fig. 2.20). The parallel reduction of the ratio of observed to expected or estimated value was impressive, suggesting a promising effect of animal fat consumption control on prevention of breast cancer (especially post-menopausal) and colorectal cancer. Although these values are relative to estimated trends, the parallel reductions of animal fat consumption and mortality from breast and colorectal cancers show the importance of planning strategies for control of these cancers.

2.5.3
Green-yellow vegetables and cancer

The lower the frequency of GYV consumption, the higher the risk of cancer of all sites and, specifically, stomach and colon cancers (Fig. 2.3A). For lung and cervical cancers, the effect was most striking in heavy smokers (Fig. 2.4).
Because GYV are defined by their high concentration of ß-carotene, and because ß-carotene is considered one of the potent scavengers of oxygen radicals, the

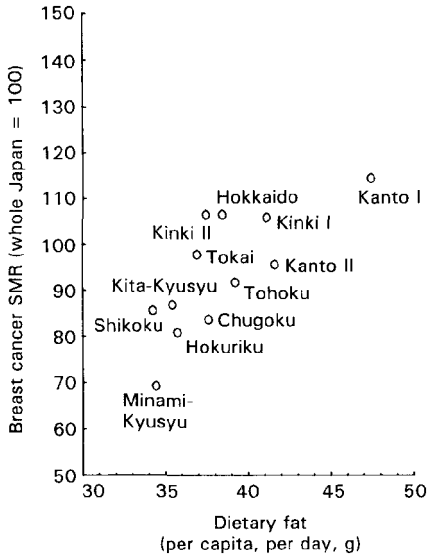


Fig. 2.19A—Dietary fat and breast cancer mortality (1966) (SMR, 1984–86) in 12 districts in Japan.

positive association between GYV and cancer is interpreted as resulting mainly from the beneficial action of the ß-carotene content. In addition, the vitamin C, minerals such as calcium and iron, and dietary fibre of GYV must also play a role in reducing cancer risk. For stomach cancer, the increase in GYV consumption, even after reaching adulthood, was shown to reduce the subsequent risk (Fig. 2.6).

Further merits of consuming GYV daily include its effects on passive smoking, *ie* decreasing the extent of risk of lung cancer in nonsmoking wives of smoking husbands (Fig. 2.5) (Hirayama T, 1984b) and acceleration of the effects of smoking cessation, *ie* faster approach to nonsmoker's level of lung cancer risk when GYV were consumed daily. Daily consumption of meat and GYV decreased the risk of cancers at many sites. In contrast, in non-daily consumers of GYV, daily meat consumption was associated with elevated risk of cancers at most sites (Fig. 2.14).

When the evidence that cancer risk is reduced by daily consumption of GYV was widely reported, the public responded immediately by raising *per capita* consumption of GYV (over 40% during a short period of 8 years) (Fig. 2.21). A nationwide opinion survey of 6,000 randomly selected individuals conducted by Mainichi Press in 1988 also revealed GYV consumption as *the primary daily practice for cancer prevention*, being listed by 74% of women and 53% of men. This is another example of successful implementation of strategies derived from epidemiological research.

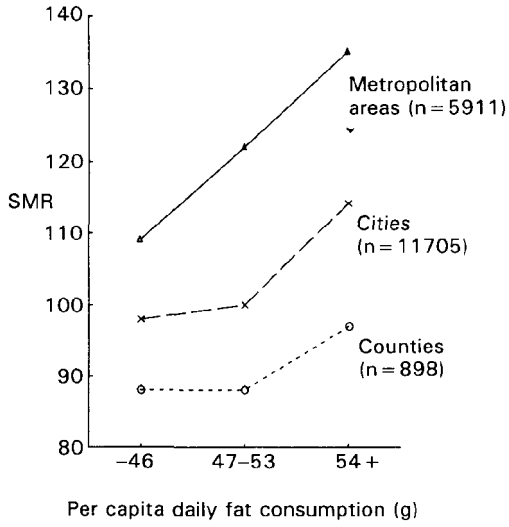


Fig. 2.19B—SMR for breast cancer (whole Japan=100, 1969–78) by amount of *per capita* daily fat consumption in countries, cities and metropolitan areas* (cross-sectional study).

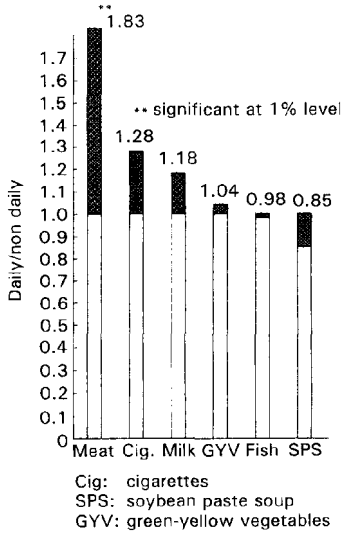


Fig. 2.19C—Age-standardized mortality rate ratio by selected life style variables (cohort study (1966–82, Japan).

2.6
DISCUSSION

Stomach cancer is the most prevalent cancer in Japan. Both correlation and case-control studies showed that the frequent consumption of the highly salted foods traditionally eaten in Japan must be the major risk factor for the disease. Active

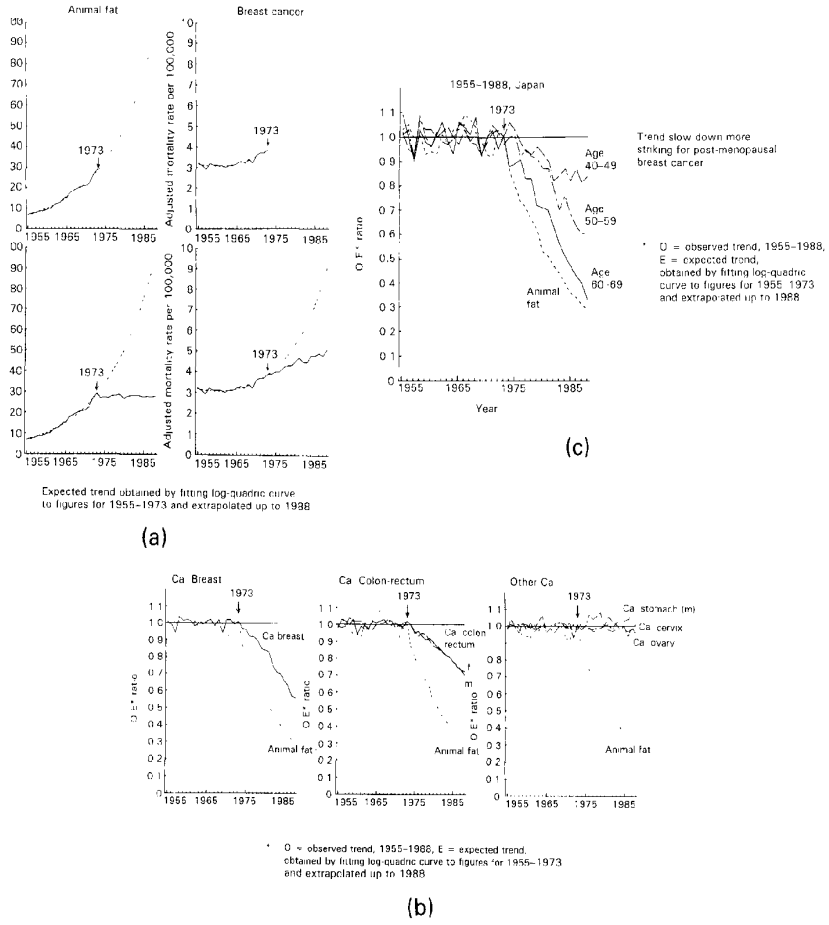
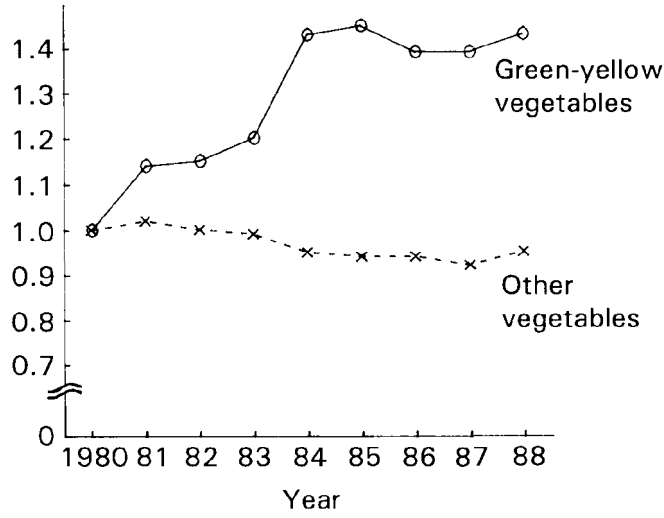


Fig. 2.20—Effect of stabilization of animal fat consumption on the trend of breast cancer (and colon-rectum cancer).

public education and campaigns advising people to reduce consumption of salty foods, together with the effect of the electric refrigerators introduced into the majority of households in the 1960s, prompted a drastic public behaviour change and eventually resulted in a dramatic reduction in gastric cancer mortality in Japan.

Frequent consumption of high-fat foods was closely associated with the risks of breast, ovarian and pancreatic cancers, particularly when combined with cigarette smoking. A high-fat diet seemed to be the common risk factor for these cancers and the risk became even greater when combined with known cancer promoters, *eg* cigarette smoking. The dramatic effect of the stabilization of animal fat intake on breast and colon cancer mortality observed in Japan after



Source: National Nutrition Survey, Japan

Fig. 2.21—Annual trend of *per capita* daily consumption of vegetables in Japan, 1980–88 (1980=1.00)

1974, immediately following the first oil crisis, is an example of an unintended nationwide dietary intervention against these cancers.

The daily consumption of GYV rich in ß-carotene, vitamin C, minerals and fibres was shown to generally lower risks of stomach, colon, lung, cervical and prostate cancers. The extent of risk reduction for lung and cervical cancers with the increase in frequency of consumption of GYV was most striking in heavy smokers. The antioxidant/antipromoter effect of ß-carotene and other constituents of GYV was particularly visible when exposed to large amounts of oxygen radicals/cancer promoters such as those originating from cigarette smoking. The drastic increase in the consumption of GYV in recent years in Japan strengthened our conviction that results of properly conducted epidemiological studies can modify public behaviour when they are widely reported to the public.

Finally, daily fish consumption was noted to lower the risk of cervical cancer, stomach cancer (in women) and colon cancer (in men age 50–64). The beneficial effects of fish consumption, therefore, should also be studied in depth, including the potential role of omega-3 fatty acids.

These examples obtained in Japan are important in that they show the validity of a scheme of dynamic flow from establishment of epidemiological evidence to public behaviour change and eventually to mortality reduction of target cancers (Table 2.6).

2.7 CONCLUSIONS

Diet is of essential importance in modulating risks of cancer of selected sites, as demonstrated by various epidemiological methods. Examples include demographic studies and correlation studies on selected diet and cancer risk. Much stronger evidence was obtained by a census-population-based large scale prospective study in Japan conducted by us in 1965–1982. Results included elevated risk from daily meat consumption for cancers of the pancreas, colon, lung and breast and reduced risk for cancers of the stomach, colon, lung, cervix and prostate from consumption of green-yellow vegetables. Increased consumption of GYV rich in ß-carotene, vitamin C and fibres was identified as the most promising factor in reducing risks for cancer, heart diseases, other diseases, premature aging and daily stress and fatigue.

Table 2.6—Promising changes in selected life styles in Japan

			1966	1988	% change
Adult smoking rate	→	m	83.7%	61.6%**	−27%
	→	f	18.0%	12.7%**	−29%
Salt	→		14.5 g*	12.2 g	−16%
Milk and milk products	→		54.4 g	122.2 g	+115%
Green-yellow vegetables	→		45.7 g	72.8 g	+59%

*=1971, **=1989, →=direction indicated by epidemiology

Reports of these results in scientific journals and intensive public education and guidance by governmental and nongovernmental organizations such as cancer societies, consumer groups and mass media resulted in notable changes in public behaviour, in particular dietary life styles in Japan in a desirable direction from the standpoint of cancer prevention such as *per capita* increase in GYV consumption, stabilization in animal fat consumption and reduction of salt consumption.

REFERENCES

Breslow NE, Day NE (1987). Statistical methods in cancer research, Vol II: The design and analysis of cohort studies (IARC Sci Publ No 82); International Agency for Research on Cancer, Lyon.

Carroll KK, Gammal EB, Plunkett ER (1968). Dietary fat and mammary cancer. *Can Med Assoc J* **98:** 590–4.

Hirayama T (1979). Diet and cancer. *Nutr Cancer* **1:** 67–81.

Hirayama T (1981). *Brit Med J* **282:** 183–5.

Hirayama T (1982). Does daily intake of green-yellow vegetables reduce the risk of cancer in man? An example of the application of epidemiological methods to the

identification of individuals at low risk. In *Host Factors in Human Carcinogenesis* (eds Bartsch, Armstrong); IARC Sci Publ No 39, International Agency for Research on Cancer, Lyon, pp. 531–40.

Hirayama T (1984a). Epidemiology of stomach cancer in Japan, with special reference to the strategy for the primary prevention. *Jpn J Clin Oncol* **14:** 159– 68.

Hirayama T (1984b). Cancer mortality in nonsmoking women with smoking husbands based on a large-scale cohort study in Japan. *Prev Med* **13:** 680–90.

Hirayama T (1986). A large scale cohort study on cancer risks by diet—with special reference to the risk reducing effects of green-yellow vegetable consumption. In *Diet Nutrition and Cancer* (eds Hayashi Y *et al*); Jpn SCI SOC Press, Tokyo? UNU SCI Press, Utrecht, pp. 41–53.

Hirayama T (1989). Association between alcohol consumption and cancer of the sigmoid colon: observations from a Japanese cohort study. *Lancet* **23:** 735–7.

Hirayama T (1990a). Life-style and mortality: a large-scale census-based cohort study in Japan. In *Contributions to Epidemiology and Biostatistics* (ed Wahrendorf J); Basel, Karger, pp. 6–17.

Hirayama T (1990b). Epidemiologia y factores de riesgo del cancer de mama. In *Cancer de Mama, Avances en Diagnostico y Tratamiento* (ed Dia-Faes J); ISBN, Leon, pp. 21–38.

Kolonel LN, Hankin JH, Nomura AMY (1986). Multiethnic studies of diet, nutrition and cancer in Hawaii. In *Diet Nutrition and Cancer* (eds Hayashi, Nagao, Sugimura, Takayama, Tomatis, Wattenberg, Wogan); Jpn SCI SOC Press, Tokyo, pp. 29–40.

Takahasni M, Kokubo T, Furukawa F *et al* (1983). Effect of high salt diet on rat gastric carcinogenesis induced by N-methyl-N'-nitro-N-nitrosoguanidine. *Gann* **74:** 28–34.

Appendix

Form 1. Initial Survey — Health Questionnaire

Name of prefecture health centre

District code | Household code | Individual code

Name | M | F

Date of birth | Year | Month | Day | 1. Single | 2. Married | 3. Divorced | 4. Widowed

Address

Place of birth | Prefecture | City | Occupation (in detail)

For women

Number of children | Length of breast feeding after last delivery month(s) | Age at first marriage

Anamnesis

Eating habits

Rice/Wheat | Amount/day | Frequency

Meat | 1. Daily | 2. Occas. | 3. Rare | 4. None | 5. Uncertain

Fish and shellfish | 1. Daily | 2. Occas. | 3. Rare | 4. None | 5. Uncertain

Milk and goat milk | 1. Daily (amount) | 2. Occas. | 3. Rare | 4. None | 5. Uncertain

Green-yellow vegetables | 1. Daily | 2. Occas. | 3. Rare | 4. None | 5. Uncertain

Pickles | 1. Every meal | 2. Daily | 3. Occas. | 4. Rare | 5. None | 6. Uncertain

Soybean paste soup | 1. Daily | 2. Occas. | 3. Rare | 4. None | 5. Uncertain

Favorites

Smoking | 1. Daily | (a) Cigarette | No./day | (b) Kizami | (c) Others | 2. Occas

3. Ex | No./day before cessation | Years after cessation | 4. None | 5. Uncertain | Age started

Alcohol | 1. Daily | 2. Occas. | 3. Rare | 4. None | 5. Uncertain

Type | (1) Sake | (2) Shochu | (3) Beer | (4) Whisky | (5) Others | (6) Uncertain

Green tea | 1. Very hot | 2. Moderate | 3. None | 4. Uncertain

Form 2. Second Survey — Health Questionnaire

Name of prefecture health centre

District code | Household code | Individual code

Name | M | F

Date of birth

Year | Month | Day | 1. Single | 2. Married | 3. Divorced | 4. Widowed

Address

Occupation (in detail)

Eating habits

Rice/Wheat

Amount/day | Frequency

Meat

1. Daily | 2. Occas. | 3. Rare | 4. None | 5. Uncertain

Kind usually eaten (beef, pork, chicken)

Fish and shellfish

1. Daily | 2. Occas. | 3. Rare | 4. None | 5. Uncertain

Milk and goat milk

1. Daily | 2. Occas. | 3. Rare | 4. None | 5. Uncertain

(amount)

Green-yellow vegetables

1. Daily | 2. Occas. | 3. Rare | 4. None | 5. Uncertain

Pickles

1. Every meal | 2. Daily | 3. Occas. | 4. Rare | 5. None | 6. Uncertain

Highly salty, average

Soybean paste soup

1. Daily | 2. Occas. | 3. Rare | 4. None | 5. Uncertain

Favorites

Smoking

1. Daily — (a) Cigarette with filter / without filter — No./day — (b) Kizami — (c) Pipe / Cigar — 2. Occas.

3. Ex — No./day before cessation — Years after cessation — 4. None — 5. Uncertain — Always inhale / Puff only — Age started

Alcohol

1. Daily | 2. Occas. | 3. Rare | 4. None | 5. Uncertain

Type

(1) Sake | (2) Shochu | (3) Beer | (4) Whisky | (5) Others | (6) Uncertain

Green tea

1. Very hot | 2. Moderate | 3. None | 4. Uncertain

Others

1. Tea | 2. Coffee | 3. Cola | 4. Cider

Current health status

Danger signals

1. Stomach trouble, indigestion, no appetite, change in food choice
2. Vaginal discharge, irregular bleeding
3. Lump in breast
4. Difficulty in swallowing
5. Blood or mucus in stool
6. Persistent cough, bloody sputum, hoarseness
7. Chronic ulcer in the mouth/skin
8. Difficulty in urination, blood in urine
9. Irritation/uneasiness
10. Difficulty in sleeping
11. Heart trouble

Currently

1. Healthy | 2. In bed by | from when

Major illness during past 5 years

1. | 2.

Name of illness, time, duration

Health check

1. None | 2. Yes (stomach X ray, chest X ray, blood pressure, others)

3
Diet and cancer
J D Potter

3.1
INTRODUCTION

The simplest objection to a link between chronic disease and diet comes from those who argue that humans have always had to eat, that diets have always contained the same nutrients—protein, fat, carbohydrates, vitamins, minerals, and that, therefore, the present pattern of diseases and changes in that pattern cannot be causally linked to dietary intake. This argument, despite its simplicity, raises some important issues for nutritional epidemiology. The contemporary epidemiologic endeavour that explores the relation between diet and specific diseases is based, obviously, on the premise that this argument is false. This chapter is an attempt to explore the evidence for a significant and causal association between eating patterns and cancer. Its second role is to show that, far from being an implausible link, much of the explanation for the relationship between dietary patterns and cancer comes from the dependence of humans on their food supply; this dependence is not merely the issue of providing the fuel for the organism but relates, rather, to long-standing adaptive patterns of food intake and aberrations in those patterns.

This chapter takes, as its starting point, a diet to which humans are adapted, noting, especially, intakes of substances for which we are dependent on the environment and intakes of substances to which we have low or infrequent exposure. It is a diet with seasonal variability in the availability of total food intake and of specific foods.

There are four broad ways in which aberrations in dietary patterns could produce disease and perhaps cancer. The first is an imbalance in energy intake and output. Secondly, there may be an alteration in the pattern of both macro- and micro-nutrients. Thirdly, there may be cases of specific deficiencies. Fourthly, there may be present, in the food supply, substances to which the organism is almost never exposed and therefore, for which there may not be the relevant metabolic responses.

3.2
IF THERE IS A DIET TO WHICH HUMANS ARE ADAPTED, WHAT MIGHT IT LOOK LIKE?

There is a long history of evoking a lost Golden Age to compare with current miseries or explain current misfortunes: from Eden (where fruit eating habits were a part of the problem) through Rousseau's noble savage to the recent discussion of the nature of paleolithic diets (Eaton and Konner, 1985). The fact is that we cannot know exactly to what kind of diets humans are well adapted biologically (although dentition, metabolic enzyme patterns, and the length and morphology of the GI tract provide some clues). Nonetheless, it is appropriate to ask if there is some probable picture we can draw of our early diet. If we can, we should also acknowledge the extensive variability in details that must have existed in the same way that we can describe extensive geographic variability in contemporary diets. Some of the common features of that early diet must have been: a high intake of a wide variety of foods—roots, leaves, nuts, seeds, fruit (grains become a staple only in the last 10 to 15 thousand years but were probably gathered regularly in season); sporadic intake of lean and/or saturated-fat meat (a more secure and regular supply of fish and seafood for coastal dwellers); intake would also have included insects, grubs (high in protein) and bone marrow and organ meats; very low intake of alcohol; little refining or fractionation of food into parts; low and irregular intake of eggs, milk and milk products; variability, by season, either of total amount of food available (and therefore body weight), of kinds of foods available, or both. Therefore, there would also have been variability in the availability of particular nutrients. Some of the variations in this overall intake pattern would have been the result of climate (as it varied over time and from place to place including the consumption of high-fat diets in extreme northern populations) but in general, until very recently, saturated fat and alcohol intake would have been low, vegetable food (but not grain) intake high, and the kinds of food eaten highly varied.

One of the significant arguments in favour of human adaptation to certain kinds of foods and eating habits, is that there are some substances for which we are dependent upon the environment. This well-established concept in nutrition has, as will be argued below, some important implications for cancer aetiology. The short-term and long-term consequences of a variety of nutrient deficiencies are a spectrum of well-described disorders. But deficiency disorders can arise only if the organism is incapable of synthesis. This argues that there has been no selection pressure to develop such a capacity in the population and, therefore, that the essential substances are widely available in the environment. Paradoxically, then, because essential nutrients are widely available in naturally-occurring human food, deficiencies are possible. Essential amino acids, essential fatty acids, micro-elements and vitamins are examples. The fact that what is essential varies among mammalian species underlines the importance of the adaptation process. To question whether we have defined all of the essential

nutrients and whether we have exhaustively characterized all the consequences of low/absent intake (whether that intake is in the *normal* range or not) is one function of this chapter.

In essence, the adaptation argument is as follows: the essential nutrients—both energy-bearing and micronutrients—are widely available in nature; they have important functions in growth, development and reproduction; the organism is adapted to their ubiquity; deficiencies impair growth, development and reproduction.

This argument regarding nutrients known to be important in growth, development and reproduction has a plausible analogy in relation to the presence of substances necessary for the maintenance of the organism including substances which reduce the risk of carcinogenesis. Here, the argument is that normal function of cells is dependent on the presence of a variety of widespread dietary constituents probably including, but not confined to, those necessary for growth and development. In their absence, cells malfunction. The malfunctioning state may make the cells more susceptible to exposure to carcinogens or may impair some specific protective mechanisms such as enzyme induction. It may even be characterized by an increase in cell replication rates as somatic cells seek to adapt to the new—deprived— conditions. It may be worth noting that maintenance is a continuous function from birth whereas growth, development and reproduction are time-limited.

A converse argument applies to those dietary constituents that are rare in nature. If substances are consumed only occasionally (or not at all), then high ingestion may have untoward consequences. This could apply both to very rare exposures which produce acute toxicity and to unaccustomed levels of intake that overwhelm the cellular and metabolic processes that normally handle the exposure. Bacterial, plant and fungal toxins are all potential members of the first class; a high fat/high calorie intake with consequences for cholesterol metabolism, insulin metabolism, adipose storage, and sex steroid hormone production is an example of the second. A high grain diet (such as that in predominantly agricultural communities) is often associated with a reduced intake of other plant foods: further, such diets contain large amounts of abrasive material that may increase cell replication rates particularly in the upper digestive tract. There may be differing degrees of adaptation in long-exposed *vs* unexposed populations.

One objection to an adaptation argument of any sort is that natural selection will be an influence only to the age of reproduction and that, as chronic diseases are largely diseases of post-reproductive years, dietary adaptation is an unnecessary postulate. There are four responses to this. The first is to argue that humans have a long period of infant and juvenile dependence and that survival of parents in a healthy state is likely to be selected for.

The second response requires consideration of the unit of selection. If the issue is the survival of tribes or bands, then those bands would have survived better that had sufficient elders who knew how to respond to infrequently met hazards—

food or water shortage, epidemic disease and natural hazards such as fire or extreme weather. The tribal wisdom maintained by the old would have meant survival of the tribe. Tribes without elders and without knowledge would be more likely to perish. Therefore, the tribes in which longevity was selected would, in turn, have survived other threats to pass on their wisdom, their adaptive eating habits, their adapted metabolisms, and their genes.

Thirdly, to argue that chronic diseases are a phenomenon of older age and therefore that resistance to them cannot have been selected for is to forget that these diseases are *not* a phenomenon of younger ages and that, therefore, some resistance (at least to the point of postponing them to older ages) has been selected for.

Finally, a diet that reduces risk of cancer may also improve reproductive success. There are a wide variety of substances that are both teratogenic and carcinogenic. So selection for improved reproductive success could directly select for reduced risk of cancer.

This chapter will explore the empirical evidence for the existence of unaccustomed exposures and protective dietary constituents, and for risks associated with nutrient and energy imbalance. Some evidence for likely biologic mechanisms and the implications for further research are considered.

3.3
DIETARY EXPOSURE AND CANCER RISK

The available empirical epidemiologic and biologic data on diet and cancer are not readily summarized in a single chapter. It is intended, therefore, to use, as a framework, the adaptation argument outlined above and show that some of the empirical relationships that have been established in the epidemiologic literature are explainable in relation to the four kinds of aberration from the dietary behaviour to which humans are adapted—energy imbalance, nutrient imbalance, specific deficiency, specific exposure. These four relationships will be illustrated in relation to certain cancers, particularly breast, colon and pancreas. Some plausible mechanisms will be outlined.

3.4
ENERGY IMBALANCE

3.4.1
Epidemiologic evidence

The nature of energy imbalance is a major topic; only one or two aspects of it will be considered here. Three measures relevant to energy balance (Pariza and Simopoulos, 1986) have been explored in epidemiologic studies of cancer—total intake (Potter and McMichael, 1986; Willett and Stampfer, 1986; Lyon *et al*,

1987), energy output (Garabrant *et al*, 1984) and a variety of measures of growth (Micozzi, 1985) and obesity (Paffenbarger, *et al*, 1980; Helmrich *et al*, 1983). There is no simple established relationship between any of these measures and all cancers, and even for some specific cancers, the empirical data are not clear. In addition, there are some paradoxes.

The present evidence suggests that higher physical activity is related to a lower risk of colon cancer (Garabrant *et al*, 1984; Vena *et al*, 1985; Gerhardsson *et al*, 1986; Paffenbarger *et al*, 1987; Wu *et al*, 1987; Slattery *et al*, 1988a) but that obesity is probably not a risk factor (Potter and McMichael, 1986; Sidney *et al*, 1986). For endometrial cancer (Elwood *et al*, 1977; La Vecchia *et al*, 1984; Folsom *et al*, 1989) and post-menopausal breast cancer (Lew and Garfinkel, 1979; Helmrich *et al*, 1983) obesity is a risk factor. However, for premenopausal breast cancer, obesity is associated with a reduced risk (Paffenbarger *et al*, 1980; Helmrich *et al*, 1983). Physical activity bears an uncertain but possibly negative relation to risk of breast cancer (Frisch *et al*, 1985). Total energy intake is an inconsistent risk factor for all three cancers—it is worth noting that dietary instruments vary extensively in their capacity to measure total energy. There are no established relationships with other specific cancers; there is a general association between obesity and overall cancer risk (Lew and Garfinkel, 1979). Fat distribution, known to be related to diabetes and CHD (Vague, 1956; Feldman *et al*, 1969; Larsson *et al*, 1984; Donahue *et al*, 1987; Selby *et al*, 1989) is currently under investigation as a cancer risk factor (Folsom *et al*, 1989, 1990; Sellers *et al*, 1992).

3.4.2
Plausible mechanisms

At least three mechanisms seem to present themselves as explanations—hormonal, mechanical and total cellular workload. Peripheral adipose tissue is the major source of oestrogens in postmenopausal women (Grodin *et al*, 1973) via conversion of adrenal androstenedione; this provides a plausible explanation for the association with endometrial and post-menopausal breast cancer, each of which is associated with higher (perhaps cumulative) lifetime oestrogen exposures. Why obesity should be associated with a lower risk of premenopausal breast cancer is unknown—it does not seem to be only a matter of failing to detect cancerous lesions in large breasts (Willett *et al*, 1985).

The role of physical activity in colon cancer is plausibly a mechanical effect—higher activity means shorter digestive tract transit time—but this is not an established negative risk factor for colon cancer. That obesity is not a risk factor for colon cancer (while high energy intake and low energy output are) suggests that there may be metabolic differences in those who get colon cancer compared with those who do not. It may also be that the total amount of food passing through the large bowel represents a measure of total cellular work load and therefore likely rates of cell replication (Potter, 1989, 1992).

It is probable that the complex relation between dietary intake, obesity and physical activity, on the one hand, and cancer risk on the other, will only be explicated when we have clarified some of the relevant intermediate metabolic steps including the effects on gut function, on cell turnover, and on hormone production. What remains, however, is the empirical observation that aspects of energy imbalance are related to cancer risk.

3.4.3 Adaptation

The human organism, it was argued above, is adapted to high variability in food intake and able to make rapid use of a sudden increase in food supply in order to survive better through the lean times. This is the original *thrifty gene* hypothesis proposed as an explanation for the survival advantage of the predisposition to diabetes (Neel, 1969). Clearly, a high intake of food as a regular, rather than sporadic, phenomenon is likely to *jam open* more than just insulin responses. In provoking obesity, it will also increase peripheral adipose production of oestrogen, a factor perhaps originally associated with reproductive success—sufficient body fat, plus hormonal support to carry a child to term. Is this related to the fact that obesity is actually protective against premenopausal breast cancer and only a liability later?

There are animal experimental data to show that on a low intake or in a fasting state, the structure of the gut epithelium is much simpler and cell replication rates much lower (Stragand and Hagemann, 1977). On refeeding, replication rates increase, as does the complexity of the epithelial surface and the total surface area. It seems probable that this is a highly adaptive response to variability in food availability—high cell turnover and large absorptive area during feast; low activity during fast to conserve energy. In the presence of a high-intake diet as a regular phenomenon, however, high cell turnover and maximal epithelial surface area provide a favourable environment for carcinogenesis. It is worth noting that our original observation on the association between increased frequency of food consumption and risk of colon (but not rectal) cancer (Potter and McMichael, 1986) has now been confirmed in several other studies (La Vecchia *et al*, 1988a; Young and Wolf, 1988). These data provide additional evidence for the idea that there is a cost for frequent food intake (one concommitment of a high food intake).

Thus, although obesity itself was probably uncommon in our ancestors, the capacity to assimilate food rapidly and store energy when it was available has probably been selected for. The inheritance of this kind of metabolism in a society where food is widely available appears to have consequences for cancer risk at a number of sites. It remains to be seen whether the tendency for different patterns of body fat distribution—now an established risk factor for several diseases—is a marker for the relevant metabolic differences.

3.5
IMBALANCE OF FOOD/NUTRITIONAL INTAKE

3.5.1
Epidemiologic evidence

Much of the current dietary epidemiology of cancer has focused on the role of intakes of specific macronutrients, particularly fat and alcohol. The evidence for a role of fat in the aetiology of breast cancer is rather poor and inconsistent but that for alcohol is surprisingly consistent. A number of ecologic studies of fat and breast cancer have been published. In a regional study in Great Britain, Stocks (1970) noted that dairy products were positively associated with risk but that other sources of fat were inversely associated. Hirayama (1978) noted that pork consumption (but not fat) correlated with risk across 12 regions of Japan. The study of ethnic groups within Hawaii found what many believe to be an implausibly strong relationship between fat and breast cancer given the data from other studies cited above and below: an approximately 35% difference in fat was associated with about a 200% difference in risk of breast cancer (Kolonel *et al*, 1981).

Studies have been made of sub-populations where the known intake of animal fat and animal protein is lower than that of the general community. Neither in vegetarian nuns (Kinlen, 1982) nor in Seventh-day Adventists (Phillips *et al*, 1980), the majority of whom are lacto-ovo-vegetarians, is the risk of breast cancer lower than in the general population. Although it may be argued that, in both these groups, the reproductive rate is lower than comparison populations, these two studies do not provide strong evidence for a role for fat in the genesis of breast cancer.

There have been at least nine case-control studies on the relation between meat or fat consumption and breast cancer (Table 3.1). The study of Lubin *et al* (1981)—the only study showing a significant increase in risk in association with consumption of fat—was based on frequency of consumption of just eight food items. Two of three studies reporting on dairy product consumption found positive associations with risk.

Of the four cohort studies (Table 3.2) only that of Hirayama (1978) found an association with daily consumption of meat and risk of breast cancer after age 54. This finding was based on just 14 cases in this category. Combining the risk associated with fat in all of the recent cohort studies results in a risk ratio between the highest and lowest quantiles of 1.01 (personal communication, W Willett and D Hunter).

These findings for breast cancer are in contrast to those for colorectal cancer (Table 3.3). Of 16 studies where saturated fat or total fat were studied, nine found a significantly increased risk. Similarly, meat has been shown to be a significant risk factor in 9 of the 14 studies in which it was examined. Protein was positively associated with risk in 4 of 5 studies.

Pancreas cancer shows an even more consistent relation with meat and fat. Each of the six reported studies shows an increased risk in association with higher consumption of meat, fat or fried foods (Table 3.4).

Alcohol consumption has been shown in ecologic studies to be related to rectal and colon cancer (Potter *et al*, 1982) and to cancers of the oesophagus and larynx. In analytic studies, there is a very consistent but not strong relation with breast cancer (Table 3.5) and somewhat less consistent association with cancers of colon and rectum (Table 3.6). Alcohol may interact with oestrogen replacement therapy to increase further the risk of breast cancer (Colditz *et al*, 1990; Gapstur *et al*, 1992). The evidence for a causal association with pancreas cancer is weak (Velema *et al*, 1986). However, alcohol is extensively implicated in cancers of the upper digestive and respiratory tracts; it is regarded by IARC as an established human carcinogen for this association in particular (IARC, 1988).

High grain consuming areas are at higher risk of oesophageal and stomach cancer. Van Rensberg (1981) has shown that there is a consistently higher risk for oesophageal cancer among populations with high corn and wheat consumption compared with those where sorghum, millet, cassava, yams or peanuts are staples. It is worth noting that a lower risk of colon cancer in high risk areas (*eg* US, Western Europe, Australia) is much more consistently found with high vegetable rather than high cereal intake (Table 3.3) although cereal eating communities are in general, at lower risk of cancer of the bowel.

Table 3.1—Case-control studies of consumption of fat, meat and dairy products in relation to breast cancer

Specific exposure	Relative Risk (95 % confidence limits) high *vs* low	Ref
Fat		
hard frying fat	2.0 (0.0–4.6)[b]	Phillips, 1975
total fat	1.8 (N/A)	Miller *et al*, 1978
saturated fat	1.2 (N/A)	
animal fat	0.9 (0.7–1. 2)[b]	Graham *et al*, 1982
total fat	1.3 (N/A)	Howe, 1985
saturated fat	1.5 (N/A)	
total fat	1.0 (0.6–17)	Hirohata *et al*, 1985
animal fat	1.3 (0.8–2.2)	
fat at age –50	1.6 (0.9–2.7)	Lubin *et al*, 1986
oils, fats	0.6 (0.2–1. 4)[b]	Katsouyanni *et al*, 1986
total fat (per 75.8 g/day)	1.7 (1.0–2.1)	Shun-Zhang *et al*, 1990
saturated fat (per 20.8 g/day)	0.9 (0.5–1.4)	
monounsaturated fat (per 54. 3 g/day)	1.9 (1.1–3.2)	
Meat		

Specific exposure	Relative Risk (95 % confidence limits) high *vs* low	Ref
beef	1.5 (1.1–2.1)	Lubin *et al*, 1981
pork	2.2 (1.6–2.9)	
meat	1.6 (1.2–2.6)	Talamini *et al*, 1984
meat, fish, eggs	1.2 (0.4–3.3)	Katsouyanni *et al*, 1986
Dairy products		
dairy products	3.4 (2.0–5.8)	Talamini *et al*, 1984
milk	1.8 (1.3–2.4)	Le *et al*, 1986
cheese	1.5 (1.0–2.3)	
butter	0.9 (0.7–1.1)	
yogurt	0.7 (0.3–1.6)	
dairy products	0.7 (0.3–1.6)	Katsouyanni *et al*, 1986
Fried foods		
fried foods	1.8 (0.9–3.5)[b]	Phillips, 1975
fried potatoes	2.4 (l.l–5.2)[b]	

[a]Reanalysis of Miller *et al*, 1978; [b]95% confidence limits from Rohan and Bain, 1987: N/A=not available.

Table 3.2—Cohort studies of fat and meat consumption in relation to breast cancer

Specific exposure	Relative Risk (95% confidence limits) high *vs* low	Ref
Fat		
fat	0.8 (0.6–1.02)	Willett *et al*, 1987a, 1992
saturated fat	0.9 (0.7–1.1)	
fat	1.15 (0.9–1.5)	Kushi *et al*, 1992
saturated fat	1.09 (0.8–1.4)	
Meat		
age 40–54	1.3 (0.6–2.2)[a]	Hirayama, 1978
aged 55	2.3 (1.5–3.0)[a]	
meat, poultry	1.2 (N/A)	Phillips and Snowdon, 1983

[a]95% confidence limits from Rohan and Bain, 1987; N/A=not available.

3.5.2 Plausible mechanisms

A variety of mechanisms have been proposed to account for an association between dietary fat, etc and cancer. Intriguingly, the explanations have been most prolific for the cancer—breast—for which the empirical evidence from analytic studies is weakest. Both direct and indirect mechanisms have been proposed. The proposed direct mechanisms are all via effects of (a) unsaturated

fatty acids on cell membrane structure and function (Welsch and Aylsworth, 1983), epithelial proliferation (Kidwell *et al*, 1982), immune responsiveness (Vitale and Broitman, 1981) and cell-to-cell communication (Welsch and Aylsworth, 1983) or (b) fatty acid and cholesterol metabolites (epoxides and peroxides) on promotion of transformed cells (Petrakis *et al*, 1980; Greunke *et al*, 1987).

The postulated indirect mechanisms are (a) via the effects of fat on hormone receptors (Welsch and Aylsworth, 1983) on prolactin production (Hill *et al*, 1980) or on bowel flora (Hill *et al*, 1971) which may (i) alter the bio-availability of oestrogens through effects on steroid deconjugation (Gorbach, 1984), or (ii) alter the bacterial production of specific anticarcinogenic agents (Adlercreutz *et al*, 1982; Adlercreutz, 1984, 1991); and (b) via the effects of higher food intake on age at menarche (Frisch and McArthur, 1974), age at menopause (De Waard *et al*, 1964) and the accumulation of adipose tissue, a site in the body where adrenal androstenedione is converted to oestrone (Grodin *et al*, 1973).

Conceptually attractive though many of these proposed mechanisms may be, the large number of them is itself a problem. Breast cancer, like all other cancers, is undoubtedly of multi-factorial origin, so that a list of potential aetiologic pathways is not an insurmountable problem. However, there is currently no clear understanding of human breast carcinogenesis, no unequivocal precursor lesion, and no known biochemical marker. Accordingly, it is probably inappropriate to search for a mechanism in the absence both of an understanding of the intermediate steps and of data establishing that a high fat diet is indeed a risk factor for mammary tumorigenesis.

Table 3.3—Case-control studies of dietary factors in relation to cancer of colon and rectum

Factor	Relationship to risk	No of studies showing relationship	No of studies done
Meat, fat, protein, energy			
meat	+	9	14
saturated fat/total fat	+	9	16
protein	+	5	6
energy	+	5	6
Vegetables			
vegetables	–	12	15
string beans	+	1	2
Fibre			
fibre	–	5	11
fibre	+	2	11
Cereals			

Factor	Relationship to risk	No of studies showing relationship	No of studies done
rice	–	1	4
rice	+	2	4
pasta/pasta and rice	+	3	3
cereals	+	2	7
Fruit			
fruit	–	2	9
fruit	+	1	9
vitamin C	–	3	4
vitamin A	–	1	4

Sources: Stocks, 1957; Pernu, 1960; Higginson, 1966; Wynder and Shigematsu, 1967; Wynder *et al*, 1969; Haenszel *et al*, 1973, 1980; Bjelke, 1973; Philips, 1975; Modan *et al*, 1975; Graham *et al*, 1978; Dales *et al*, 1979; Martinez *et al*, 1979; Jain *et al*, 1980; Miller *et al,* 1983; Manousos *et al*, 1983; Berta *et al*, 1985; Bristol *et al*, 1985; Macquart-Moulin *et al*, 1986; Potter and McMichael, 1986; Lyon *et al*, 1987; Graham *et al*, 1988; La Vecchia *et al*, 1988a; Young and Wolf, 1988; Tuyns *et al*, 1988; Heilbrun *et al*, 1989 (among *low* fat intake males only); Benito *et al*, 1990, 1991.

There are some data to suggest that a high intake of simple carbohydrate is associated with increased risk of colorectal cancer (Bristol *et al*, 1985; Tuyns *et al*, 1988).

For colon cancer, the dominant hypothesis has long been derived from the relation between dietary fat intake and bile acid metabolism. Fat intake, it is proposed, increases the amount or concentration of bile acids secreted into the small bowel; bacteria present in the large bowel metabolize the primary acids to secondary, and these, it is suggested, have greater toxicity, co-carcinogenic or promotional activity, and trophic effects. There is a considerable amount of corroborative human metabolic and animal experimental evidence; the body of evidence is, however, not totally coherent (McMichael and Potter, 1985, 1986). Other roles for fat have been proposed including direct toxic action on the bowel wall (Bruce, 1987). Arylamines, produced when meat is cooked, have been proposed as direct colon carcinogens (Sugimura and Sato, 1983) and there is a growing literature on the role of these compounds (Sugimura, 1985) and their metabolism, including especially, genetically variable acetylator (NAT2) status (Weber, 1987; Turesky *et al*, 1991; Kadlubar *et al*, 1992).

McMichael (1981) has argued that gastrointestinal (GIT) hormones have trophic and hyperplastic effects on the exocrine pancreas and could act as mediators of known or suspected dietary (and other) risk factors. Gastrin and cholecystokinin (CCK) are potent stimulators of pancreatic hyperplasia (Johnson, 1981). CCK has been shown, in animal models, to be a significant promoter of pancreatic neoplasia (Howatson and Carter, 1985). More recently,

Anderson *et al* (1992) have shown that the pancreas is capable of metabolizing arylamines (found in cooked meat *and* tobacco smoke—the major risk factors for pancreas cancer) thus suggesting another potential pathway from diet to cancer.

For the relation between alcohol and breast cancer, there have been no major advances in relation to biological mechanisms beyond that originally postulated by Williams (1976)—namely stimulation of prolactin secretion. It is also possible, as a number of workers have pointed out, that, because alcohol is a significant energy source, the mechanism could be related to those postulated for obesity or caloric intake in general. For colon and rectal cancer, the evidence suggests that the effect of alcohol on bile acid metabolism is rather like that of fat (McMichael and Potter, 1985, 1986). Several mechanisms have been postulated to account for causal association with cancers of larynx and oesophagus (IARC, 1988). These include acting as a chronic irritant and inducing excess cell replication, acting as a solvent for direct acting carcinogens, particularly those in cigarette smoke, being associated with specific nutrient deficiencies, and being a vehicle for other compounds present in alcoholic drinks.

Possible mechanisms for the association between grain consumption and higher risks of upper digestive tract cancer include traumatic effects of silicaceous fibres and resultant high epithelial cellular turnover and reduced intake of other plant foods which results in deficiencies either of micronutrients (Van Rensberg, 1981) or specific non-nutrient substances (see below).

Table 3.4—Studies of meat and fat in relation to pancreatic cancer

Study type	Comparison	Relative risk		Ref
Case-control	Fat per 10 gm/day	1.8		Durbec *et al*, 1983
		H	**P**	
Case-control	Butter ≥2 *vs*<2/wk	2.4	1.1	Gold *et al*, 1985
	Deep fried foods	<1.0		
	Beef	<1.0		
		D	**A**	
Case-control	Beef ≥5/wk *vs*<5/wk	2.1	1.2	Mack *et al*, 1986
	Eggs ≥5/wk *vs*<5/wk	0.7	0.8	
	Fried bacon/ham ≥5/wk *vs*<5/wk	1.4	0.9	
		H	**P**	
Case-control	Fried/grilled meat			
	<1/week	1.0	1.0	Norell *et al*, 1986
	Every week	1.5	1.7	
	Almost daily	4.6	13.4	
		M	**F**	
Case-control	Beef 6/month	1.0	1.0	Falk *et al*, 1988

Study type	Comparison		Relative risk		Ref
		6–15/month	1.2	0.8	
		≥16/month	1.1	0.7	
	Pork	<9/month	1.0	1.0	
		9–30/month	1.4	1.6	
		≥31/month	1.7	1.3	

Study type	Comparison		Relative risk		Ref
			M	**F**	
Case-control	Dairy	<34/month	1.0	1.0	
		34–67/ month	1.6	1.6	
		≥68/month	2.2	1.0	
	Seafood	<2/month	1.0	1.0	
		2–7/month	1.0	1.2	
		≥8/month	1.0	1.9	
Cohort	Current use of meat, poultry, fish				Mills *et al*, 1988
	<1/wk		1.0		
	1–2/wk		0.8		
	≥3/wk		2.2		
	Current use of eggs				
	<1/wk		1.0		
	1–2/wk		1.5		
	≥3/wk		2.5		
	Butter		~1.0		
	Milk		~1.0		

H=Hospital controls; P=Populations controls; D=Directly interviewed; A= All: M=Male: F=Female

Table 3.5—Studies on alcohol and breast cancer

Comparison	Relative risk (95% confidence levels)	Ref
Cohort studies		
≥3 drinks/day *vs* never	1.4 (N/A)	Hiatt and Bawol, 1984
≥5 g/day *vs* none	2.0(1.1–3.7)	Schatzkin *et al*, 1987
≥15 g/day *vs* none	1.6(1.3–2.0)	Willett *et al*, 1987b
≥5 g/day *vs* none	0.8(0.5–1.2)	Schatzkin *et al*, 1989

Comparison	Relative risk (95% confidence levels)	Ref
Case-control studies		
>50 ounce-years *vs* never	1.6 (N/A)	Williams and Horm, 1977
ever vs never	1.9(1.5–2.4)	Rosenberg *et al*, 1982
–26 drinks/month *vs* never	1.1 (N/A)	Byers and Punch, 1982
–1 drink/day *vs* never	1.4(0.9–2.0)	Begg *et al*, 1983
–2 drinks/day *vs* never	1.0 (N/A)	Paganini-Hill and Ross, 1983
ever *vs* never	1.0(0.8–1.2)	Webster *et al*, 1983
–300 g/wk *vs* never	1.1 (0.6–1.8)	
ever *vs* never	2.5(1.7–3.7)	Talamini *et al*, 1984
–0.5 litres wine *vs* no wine	16.7(3.1–89.7)	
alcohol with meals *vs* not	1.5 (1.3–1.7)	Le *et al*, 1984
–240 g/wk *vs* never	1.2(0.7–2.0)	
–4 drinks/day *vs* never	2.1 (1.1–4.0)	La Vecchia *et al*, 1985
–1 drink/wk *vs*<1/wk	1.5(0.99–2.1)	O'Connell *et al*, 1987
>2 drinks/day *vs* never	1.7(1.2–2.4)	Harvey *et al*, 1987
>9.3 g/day *vs* never	1.6 (0.99–2.5)	Rohan and McMichael, 1988
ever *vs* never	0.9 (N/A)	Harris and Wynder, 1988
10 *vs* 0 drinks/wk		Young, 1989
early age drinking	2.1 (1.3–3.5)	
later age drinking	1.9(1.3–3.0)	

N/A=not available

3.5.3 Adaptation

An argument for adaptation in relation to these exposures is more than a general affirmation of a human incapacity to handle a high fat or a high alcohol intake but remains rather speculative and possible circular. The primary premise is that high fat, high alcohol, or high grain intakes were not part of the *regular* dietary patterns of early humans. An intermittent high intake (a feast/fast economy) produced rapid adaptive responses—increased gut epithelial cell proliferation, increased secretion of appropriate hormones—both trophic and secretory-control hormones—and bile acids etc. These, as an energy conserving mechanism, then subsided when food became scarce; high metabolic and cellular activity is a cost to the organism which is not a good investment in the presence of reduced food availability. This capacity for rapid response (an extension of the thrifty gene hypothesis) becomes non-adaptive in the presence of consistent high intake leading not only to alcoholism and obesity but also to chronic high gut hormone

levels and elevated epithelial proliferation rates. High intakes of abrasive fibres will result in elevated upper digestive tract proliferation rates and heightened risk of carcinogenesis.

Table 3.6—Studies of alcohol and colorectal cancer

Study type	No of studies done	No showing increased risk
Case-control	8	5
Cohort	4	4
Cohort (brewery workers)	2	1[a]

[a]The other study (Jensen, 1979) shows a higher risk than would be expected for rectal cancer in this blue-collar workforce.

Sources: Stocks, 1957; Pernu, 1960; Higginson, 1966; Wynder and Shigematsu, 1967; Wynder *et al*, 1969; Bjelke, 1973, 1974; Graham *et al*, 1978; Potter and McMichael, 1986; Sundby, 1967; Wu *et al*, 1987; Klatsky *et al*, 1988; Dean *et al*, 1979; Jensen *et al*, 1979.

There is an additional aspect to the adaptation argument which is particularly related to the internal ecology of the large gut. The large bowel can be regarded as a complex ecosystem in which the colonic contents can be regarded as a culture medium for bacterial and colonic cells (McMichael and Potter, 1986; Potter, 1989, 1992). The culture medium in turn is influenced extensively by both host conditions, including a variety of hormones, and ingested foods and alcohol. This complex ecosystem may be one of the most flexible part of the human-environment adaptation. It is argued, however, that there are limits to its flexibility with consequences for carcinogenesis (McMichael and Potter, 1986; Potter, 1989, 1992).

3.6
SPECIFIC DEFICIENCIES—NUTRIENTS AND NON-NUTRIENTS

3.6.1
Epidemiologic evidence

The most obvious specific deficiencies are those of micronutrients. It is important to note that, in relation to ß-carotene, retinol and ascorbate, higher risks of particular cancers have been reported in individuals with lower intakes or blood levels but these have largely been within the normal range (Wald *et al*, 1980; Kark *et al*, 1981; Peto *et al*, 1981). There are several cancers that have a probable relation with micronutrient deficiencies—notably lung cancer and cervix cancer (Peto *et al*, 1981; Ziegler, 1989) with reduced intakes or lower levels of vitamin A. Other squamous epithelial cancers (*eg* skin) may be related to lower ß-carotene or retinol levels. Lower dietary ascorbate levels have been associated

with a higher risk of rectal cancer (Bjelke, 1973; Potter and McMichael, 1986). Minerals, such as calcium, and trace elements, such as selenium, have also been examined for their possible role in cancer aetiology (Bruce, 1987; Willett *et al*, 1983; Slattery *et al*, 1988b).

Of most interest, and, until recently, not clearly identified as the most consistent rinding in the dietary aetiology of cancer, is the more general relation between a higher intake of vegetables and a lower risk of cancer at a wide variety of sites including mouth and pharynx, lung, stomach, pancreas, colon and rectum (see Potter, 1990; Steinmetz and Potter 1991a, 1991b for a comprehensive review of data and mechanisms).

Of the 15 studies of colorectal cancer which have looked at the role of vegetables, 12 have reported a lower risk in association with higher consumption (Table 3.3). Of the five studies of pancreas cancer, all have reported a lower risk in association with a higher intake of vegetables, or fruit or both (Table 3.7). Recent studies of prostate (Oishi *et al*, 1988), mouth and pharynx (McLaughlin *et al*, 1988), lung (Byers *et al*, 1987; Koo, 1988) cervix (Brock *et al*, 1988; La Vecchia *et al*, 1988b) and stomach (La Vecchia *et al*, 1987; You *et al*, 1988) show similar findings for vegetables or fruit or both.

The obvious question is whether these data, particularly given the consistency of the ß-carotene/lung cancer story (Peto *et al*, 1981; Ziegler, 1989) are merely providing less specific support for the association between high intakes of defined micronutrients such as ß-carotene and ascorbate and lower risk of cancers or whether additional factors are at work. Some animal and *in vitro* studies suggest that this is a broader and more interesting phenomenon related to more than specific vitamins (but, importantly, not excluding them).

Vegetables contain a wide variety of substances which have been shown to have anti-carcinogenic properties—phenols, isothiocyanates, flavonoids, indoles, lignans etc (Wattenberg, 1985; Steinmetz and Potter, 1991b) as well as (possibly important for colon cancer at least) fermentable fibre with its effect on pH, bile acid metabolizing enzymes, and VFA production, and of course vitamins and trace elements. A recent nested case-control study found serum lycopene levels to be markedly different between cases of pancreas cancer and controls (*RR* low *vs* high fertile=5.40). Lycopene is a carotenoid without retinoid activity (Burney *et al*, 1989).

Table 3.7—Studies of vegetables and fruit in relation to pancreatic cancer

Study type	Dietary variable	Relative risk		Ref
Case-control	Raw fruits and vegetables	**H**	**P**	Gold *et al*, 1985
	Ever *vs* never	0.5	0.2	
	–2 *vs*<2/week	0.5	0.7	
	–5 *vs*<5/weeks	0.6	0.6	

Study type	Dietary variable	Relative risk		Ref
Case-control	Fresh fruits and vegetables	**D**	**A**	Mack *et al*, 1986
	≥5 *vs*<5/week	0.8	0.7	
		H	**P**	
Case-control	Vegetables<l/wk	1.0	1.0	Norell *et al*, 1986
	Every week	1.0	1.0	
	Almost daily	0.5	0.8	
	Raw vegetables<l/wk	1.0	1.0	
	Every week	0.5	0.7	
	Almost daily	0.5	0.6	
	Citrus fruits<l/wk	1.0	1.0	
	Every week	0.6	1.0	
	Almost daily	0.3	0.5	
	Fruit juices<l/wk	1.0	1.0	
	Every week	0.9	0.6	
	Almost daily	0.6	0.6	
Case-control	Fruits and juices	**M**	**F**	Falk *et al*, 1988
	<25/month	1.0	1.0	
	25–63/month	0.6	0.6	
	≥64/month	0.4	0.5	
	Vitamin C			
	<2000 mg/month	1.0	1.0	
	2000–4455 mg/month	0.5	0.8	
	≥4456 mg/month	0.4	0.6	
Cohort	Beans, lentils, peas			Mills *et al*, 1988
	<l/wk	1.0		
	1–2/wk	0.5		
	≥3/wk	0.4		
	Dried fruits			
	<l/wk	1.0		
	1–2/wk	0.5		
	≥3/wk	0.4		
	Green salad	>1.0(NS)		
	Cooked green vegetables	>1.0(NS)		

H=Hospital controls; P=Populations controls; D=Directly interviewed; A= All: M=Male: F=Female

At present, we are not able to provide a summary estimate of the intakes of most of the *non-nutrient* substances—food tables do not provide the data, most of the relevant food analyses have not been done, and it is probable that whole classes of these constituents, and certainly individual constituents, remain to be identified.

3.6.2
Plausible mechanisms

Several roles have been identified (Wattenberg, 1985) for the known substances including:

(a) Inhibiting formation of direct-acting carcinogens. Ascorbate is effective in blocking the formation of N-nitrosamines *in vivo* from precursor nitrates and amines (Mirvish, 1981; Bartsch *et al*, 1988).
(b) Acting to prevent agents reacting with target tissues. There are a variety of ways in which this may occur (Wattenberg, 1985). Agents include non-nutrient compounds, such as phenols, found in plant foods (Wood *et al*, 1982) that can react with active carcinogens.
(c) Inducing enzymes that detoxify or conjugate carcinogenic compounds. A variety of plant-related substances have been shown to be effective (Wattenberg, 1977, 1983).
(d) Acting to inhibit carcinogenesis even when delivered after known carcinogen exposure in animals. Carotenoids and selenium are included in this category but the mechanisms are unclear (Wattenberg, 1985).
(e) Specific deficiencies of micronutrients have been shown to be associated with hyperplasia in a variety of epithelial tissues.

More generally, the steps from pro-carcinogen exposure to cell transformation can be considered as follows. Pro-carcinogen is activated to ultimate carcinogen (each of these may be solubilized and excreted); carcinogen passes through membranes; carcinogen interacts with DNA—perhaps forming adducts and/or producing mutations; DNA synthesis and replication (or DNA repair) occur; repair may have varying degrees of fidelity; cell replication with abnormal DNA and subsequent abnormal protein synthesis result (or cell differentiation occurs). At almost everyone of these steps, specific known phytochemicals can alter the likelihood of carcinogenesis, occasionally in a way that enhances risk, but usually in a favourable direction. For example, such substances as glucosinolates and indoles, isothiocyanates and thiocyanates, phenols, and coumarins can induce a multiplicity of solubilizing and (usually) inactivating enzymes; ascorbate and phenols block the formation of carcinogens such as nitrosamines; flavonoids and carotenoids can act as antioxidants; lipid-soluble compounds such as carotenoids and sterols may alter membrane integrity; some sulphur-containing compounds can suppress DNA and protein synthesis; carotenoids

suppress DNA synthesis and enhance differentiation (Steinmetz and Potter, 1991b; Wattenberg, 1992).

3.6.3
Adaptation

It is here that the adaptation argument has its most interesting implications (and perhaps significant testability). There are known to be substances, including vitamins and trace elements, without which the organism cannot grow, be maintained, or reproduce optimally. The consequences of low levels (dietary or tissue) of these substances may include carcinogenesis. It is argued here that we are equally dependent on the environment to provide other substances which have specific anticarcinogenic properties. In the absence of these substances, humans (perhaps all vertebrates) are at higher risk of cancers at a number of sites particularly those where epithelial surfaces are more exposed to the environment —lung, digestive tract and cervix. It is argued that these dietarily supplied compounds act to induce detoxifying enzymes to block activation, etc and that the organism is reliant on them to do so.

As is clear from the whole chapter, the adaptation hypothesis can be related to each of the four dietary phenomena associated with increased cancer risk. However, there are more problems in testing the notion that humans are exposed to *unaccustomed levels* of total energy or specific nutrients than in testing whether specific deficiencies or specific exposures are carcinogenic. There is no way to modify unaccustomed levels in a controlled trial that does not also modify others: *eg* any attempt to decrease fat will result in decreased calories or increased levels of other nutrients; similarly weight modification changes nutrient intakes, energy intake, energy expenditure, or all three. On the other hand, addition of either specific compounds to the diet or modification of vegetable intake provides both tests of the protective hypothesis (and perhaps of their *essential nutrient* status) and of possible public health strategies. There are also ways to test the adaptation argument with *in vitro* studies.

3.7
SPECIFIC EXPOSURES

3.7.1
Epidemiologic evidence

The mostly widely accepted theory of carcinogenesis implicates specific damage (either physical or chemical) to cellular DNA and now, more specifically, to protooncogenes and tumour-suppressor genes. The diet contains a number of naturally-occurring substances which have been shown to be carcinogenic—*eg* aflatoxins, N-nitroso compounds—but there are very few human cancers

(primary hepatocellular cancer where aflatoxins are strongly implicated is the major exception (IARC, 1976; Peers *et al*, 1987) for which a specific dietary carcinogen has been identified unequivocally. While DNA-interacting carcinogens are a major focus of animal experiments, most human studies to date have implicated the effect of promoters or cocarcinogens, such as alcohol, or host phenomena, such as obesity, as discussed above. There is also, however, evidence for the importance of arylamines in colon cancer and N-nitroso compounds in the upper alimentary tract and it may still be the case that specific dietary carcinogens will be identified for many of the epithelial cancers where dietary practices are implicated.

3.7.2
Plausible mechanisms

The mechanisms of action of DNA-damaging carcinogens in general (Pilot, 1986) and aflatoxins (IARC, 1976), N-nitroso compounds (Bartsch *et al*, 1982) and arylamines (Sugimura, 1985) in particular have been well reviewed elsewhere.

3.7.3
Adaptation

The adaptation argument in relation to specific exposures has three facets. The first is that we appear not to have developed specific mechanisms to detoxify certain carcinogens. (It is equally clear that there are mechanisms to detoxify some (Chasseaud, 1979) and to activate others.) The second is that the mechanisms may become overloaded at high exposures. The third is that the specific enzymes may not be lacking but the exposure to the agents themselves is relatively uncommon and that the induction of the detoxifying enzyme(s) is normally achieved by other ubiquitous substances. It seems likely that this is the nature of the relationship that we have with a wide variety of so-called non-nutrient substances. There are areas of the world where cancer has been attributed both to reduced intakes of specific nutrients and to exposure to specific dietary carcinogens (*eg* China where oesophageal cancer is associated with N-nitroso compounds (Yang, 1980) and low intakes and blood levels of a variety of vitamins and trace elements (Thumham *et al*, 1985)). To this point, supplementation with the missing nutrients has been disappointingly ineffective in reducing risk (Muñoz *et al*, 1985; Wahrendorf *et al*, 1988). This may suggest that what are missing are not the obvious micronutrients (these may be just markers for the real deficiencies) but specific compounds that keep the detoxifying enzymes *tuned*. The experiment that follows from this hypothesis is obvious—either add a variety of fruits and vegetables or add some specific non-nutrient enzyme-inducers, blocking agents etc to the diet. The advantage of this strategy is that there is an identified precursor lesion. This allows more rapid

tests of a variety of strategies on relatively small populations over short time periods than do studies of the cancers themselves. Similar arguments apply to testing the role of vegetables in the prevention of recurrence of adenomatous polyps in addition to existing studies of single likely preventive agents (Bertram *et al*, 1987). Such studies are now being undertaken in a number of settings.

3.8
SUMMARY

There are a variety of ways in which diet may influence the development of human cancers. Reviews of this topic have often been descriptive and mechanistic: exposure to substance X is associated with increases in cancer A; increased intake of substance Y appears to reduce the risk of cancer B. What is proposed here is a theoretical framework and an argument, which has the following features:

(a) There is a dietary pattern to which humans are well-adapted—the *original diet*.
(b) This original dietary pattern had specific features which included regular exposure to a variety of substances on which human metabolism is dependent but which have not, till now, been explicitly labelled as *essential nutrients*. I would argue that this is now worthy of serious consideration.
(c) The original dietary pattern was low in highly abrasive cereal products (consumption of large amounts of grains is a relatively recent phenomenon) with less resultant damage and frequent cell repair particularly to the upper gastrointestinal tract.
(d) The original dietary pattern involved variability in intake that ensured variability in cell replication rates particularly in the gastrointestinal tract, and little risk of obesity.
(e) The original dietary pattern involved almost no intake of alcohol and therefore little capacity for its solvent and chronic cell damage capacities.
(f) Abandonment of each of these aspects of dietary adaptation has consequences for carcinogenesis. Most notable is the reduction of intake of vegetables and fruit with subsequent loss of appropriate enzyme *tuning* etc and a generally increased susceptibility to cancer at a number of sites. A high intake of fat, of grains and of alcohol, and increased obesity are each associated with recognizable patterns of cancers.
(g) There are a variety of testable consequences to this argument. For instance, increasing vegetables and fruit should reduce the risk of colon cancer and perhaps of colonic adenomatous polyps even in the presence of a high fat intake, and of oesophageal cancer even with exposure to specific carcinogenic compounds including those from cigarette smoke. Testing of the relevant compounds *in vitro* and *in vivo* will provide more definitive answers regarding the specific compounds and their sites and modes of

action. In the meanwhile, the empirical data encourage us, above all, to eat more vegetables.

ACKNOWLEDGEMENT

This work was supported in part by NIH/NCI grants CA-46618, CA-46013, CA-39742 and CA-50305.

REFERENCES

Adlercreutz H (1984). Does fiber-rich food containing animal lignan precursors protect against both colon and breast cancer? An extension of the "fiber hypothesis". *Gastroenterology* **86:** 761–6.

Adlercreutz H (1991). Diet and sex hormone metabolism. In *Nutrition, Toxicity and Cancer* (ed Rowland IR); CRC Press Boca Raton, pp. 137–95.

Adlercreutz H, Fotsis T, Heikkinen R *et al* (1982). Excretion of the lignans enterolactone and enterodiol and of equol in omnivorous and vegetarian postmenopausal women and in women with breast cancer. *Lancet* **2:** 1295–9.

Anderson KE, Potter JD, Hammons GJ *et al* (1992). metabolic activation of aromatic amines by human pancreas. *Proc AACR* **33:**153.

Bartsch H, Castegnaro M, O'Neill IK, Okada M (1982). N-nitroso compounds: occurrence and biologic effects. IARC Sci Publications No 41; IARC, Lyon.

Bartsch H, Oshima H, Pignatelli B (1988). Inhibitors of endogenous nitrosation. Mechanisms and implications in human cancer prevention. *Mutat Res* **202:** 307– 24.

Begg CB, Walker AM, Wessen B *et al* (1983). Alcohol consumption and breast cancer (letter). *Lancet* **1:** 293–4.

Benito E, Obrador A, Stiggelbout A *et al* (1990). A population-based case-control study of colorectal cancer in Majorca. I. Dietary factors. *Int J Cancer* **45:** 69–76.

Benito E, Stiggelbout A, Bosch FX *et al* (1991). Nutritional factors in colorectal cancer risk: a case-control study in Majorca. *Int J Cancer* **49:** 161–7.

Berta J-L, Coste T, Rautureau J, Guilloud-Bataille M, Pequinot G (1985). Alimentation et cancers rectocoliques. Resultats d'une etude "cas-temoin". *Gastroenterol Clin Biol* **9:** 348–53.

Bertram JS, Kolonel LN, Meyskens FL (1987). Rationale and strategies for chemoprevention of cancer in humans. *Cancer Res* **47:** 3012–31.

Bjelke E (1973). Epidemiological studies of cancer of the stomach, colon and rectum, Vol III, case-control study of gastrointestinal cancer in Norway, Vol IV, case-control study of the digestive tract cancers in Minnesota. *Ann Arbor Univ Microfilms.*

Bjelke E (1974). Epidemiologic studies of cancer of the stomach, colon and rectum; with special emphasis on the role of diet. *Scand J Gastroenterol* **9:** 124–229.

Bristol JB, Emmett PM, Heaton KW, Williamson RCN (1985). Sugar, fat and the risk of colorectal cancer. *Br Med J* **291:** 1467–70.

Brock KE, Berry G, Mock PA *et al* (1988). Nutrients in diet and plasma and risk of *in situ* cervical cancer. *J Natl Cancer Inst* **80:** 580–5.

Bruce WR (1987). Recent hypotheses for the origin of colon cancer. *Cancer Res* **97:** 4237–42.

Burney PGJ, Comstock GW, Morris JS (1989). Serologic precursors of cancer: serum micronutrients and the subsequent risk of pancreatic cancer. *Am J Clin Nutr* **49:** 895–900.

Byers T, Punch DP (1982). Alcohol and breast cancer (letter). *Lancet* **1:** 799–800.

Byers TE, Graham S, Haughey BP *et al* (1987). Diet and lung cancer risk: findings from the western New York diet study. *Am J Epidemiol* **125:** 351–63.

Chasseaud LF (1979). The role of glutathione and glutathione S-transferases in the metabolism of chemical carcinogens and other electrophilic agents. *Adv Cancer Res* **29:** 175–274.

Colditz GA, Stampfer MJ, Willett WC *et al* (1990). Prospective study of estrogen replacement therapy and risk of breast cancer in postmenopausal women. *JAMA* **264:** 2648–53.

Dales LG, Friedman GD, Ury HK, Grossman S, Williams SR (1979). A case-control study of the relationships of diets and other traits to colorectal cancer in American Blacks. *Am J Epidemiol* **109:** 132–44.

Dean G, MacLennan R, McLoughlin H, Shelley E (1979). Causes of death of blue-collar workers at a Dublin brewery, 1954–73. *Br J Cancer* **40:** 581–9.

De Waard F, Baanders-van Halewijn EA, Huizinga J (1964). The bimodal age distribution of patients with mammary carcinoma: evidence for the existence of 2 types of human breast cancer. *Cancer* **17:** 141–51.

Donahue RB, Abbott RD, Bloom F *et al* (1987). Central obesity and coronary heart disease in men. *Lancet* **1:** 821–4.

Durbec JP, Chevillotte G, Bidart JM, Berthezene P, Sarles H (1983). Diet, alcohol, tobacco and risk of cancer of the pancreas: a case-control study . *Br J Cancer* **47:** 463–70.

Eaton BS, Konner M (1985). Paleolithic nutrition. *N Eng J Med* **312:** 283–9.

Elwood JM, Cole P, Rothman KJ, Kaplan SD (1977). Epidemiology of endometrial cancer. *J Nat Cancer Inst* **59:** 1055–60.

Falk RT, Pickle LW, Fontham ET, Correa P, Fraumeni JF (1988). Life-style risk factors for pancreatic cancer in Louisiana: a case-control study. *Am J Epidemiol* **128:** 324–36.

Feldman R, Sender AJ, Siegelaub AB (1969). Difference in diabetic and non-diabetic fat distribution patterns by skinfold measurements. *Diabetes* **18:** 478–86.

Folsom AR, Kaye SA, Potter JD, Prineas RJ (1989). Association of incident carcinoma of the endometrium with body weight and fat distribution in older women. Early findings of the Iowa Women's Study. *Cancer Res* **49:** 6828–31.

Folsom AR, Kaye SA, Prineas RJ, Potter JD, Gapstur SM, Wallace RB (1990). Increased incidence of carcinoma of the breast associated with abdominal adiposity in post-menopausal women. *Am J Epidemiol* **131:** 794–803.

Frisch RE, McArthur JW (1974). Menstrual cycles: fatness as a determinant of the minimum weight for height necessary for their maintenance or onset. *Science* **185:** 949–51.

Frisch RE, Wyshak G, Albright NL *et al* (1985). Lower prevalence of breast cancer and cancers of the reproductive system among former college atheletes compared to non-atheletes. *Br J Cancer* **52:** 885–91.

Gapstur SM, Potter JD, Sellers TA (1992). Increased risk of breast cancer with alcohol consumption in postmenopausal women. *Am J Epidemiol* **136:** in press.

Garabrant DH, Peters JM, Mack TM, Bernstein L (1984). Job activity and colon cancer risk. *Am J Epidemiol* **119:** 1005–14.

Gerhardsson M, Norell SE, Kiviranta H, Pedersen NL, Ahlbom A (1986). Sedentary jobs and colon cancer. *Am J Epidemiol* **123:** 775–80.

Gold EB, Gordis L, Diener MD *et al* (1985). Diet and other risk factors for cancer of the pancreas. *Cancer* **55:** 469–7.

Gorbach SL (1984). Estrogens, breast cancer and intestinal flora. *Rev Infect Dis* **6 (Suppl):** 85–90.

Graham S, Dayal H, Swanson M, Mittelman A, Wilkinson G (1978). Diet in the epidemiology of cancer of the colon and rectum. *J Natl Cancer Inst* **61:** 709–14.

Graham S, Marshall J, Haughey B *et al* (1988). Dietary epidemiology of cancer of the colon in Western New York. *Am J Epidemiol* **128:** 490–503.

Graham S, Marshall J, Mettlin C *et al* (1982). Diet in the epidemiology of breast cancer. *Am J Epidemiol* **116:** 68–75.

Greunke LD, Wrensch MR, Petrakis NH *et al* (1987). Breast fluid cholesterol and cholesterol epoxides: relationship to breast cancer risk factors and other charcteristics. *Cancer Res* **47:** 5483–7.

Grodin JM, Siiteri PK, MacDonald PC (1973). Source of estrogen production in postmenopausal women. *J Clin Endocrinol Metab* **36:** 207–14.

Haenszel W, Berg JW, Segi M, Kurihara M, Locke FB (1973). Large bowel cancer in Hawaiian Japanese. *J Natl Cancer Inst* **51:** 1765–99.

Haenszel W, Locke FB, Segi M (1980). A case-control study of large bowel cancer in Japan. *J Natl Cancer Inst* **64:** 17–22.

Harris RE, Wynder EL (1988). Breast cancer and alcohol consumption: a study in weak associations. *JAMA* **259:** 2867–71.

Harvey EB, Schairer C, Brinton LA *et al* (1987). Alcohol consumption and breast cancer. *JNCI* **78:** 657–61.

Heilbrun L, Nomura A, Hankin J, Stemmermann G (1989). Diet and colorectal cancer with special reference to fiber intake. *Int J Cancer* **44:** 1–6.

Helmrich SP, Shapiro S, Rosenberg L *et al* (1983). Risk factors for breast cancer. *Am J Epidemiol* **117:** 35–54.

Henderson BE, Casagrande JT, Pike MC, Mack T, Rosario I, Duke A (1983). The epidemiology of endometrial cancer in young women. *Br J Cancer* **47:** 749–56.

Hiatt RA, Bawol RD (1984). Alcoholic beverage consumption and breast cancer incidence. *Am J Epidemiol* **120:** 676–83.

Higginson J (1966). Etiological factors in gastrointestinal cancer in man. *J Natl Cancer Inst* **37:** 527–45.

Hill P, Garbaczewski L, Helman P *et al* (1980). Diet, lifestyle and menstrual activity . *Am J Clin Nutr* **33:** 1192–8.

Hill MJ, Goddard P, Williams REO (1971). Gut bacteria and aetiology of cancer of the breast. *Lancet* **2:** 472–3.

Hirayama T (1978). Epidemiology of breast cancer with special reference to the role of diet. *Prev Med* **7:** 173–95.

Hirohata T, Shigematsu T, Nomura AMY *et al* (1985). Occurrence of breast cancer in relation to diet and reproductive history: a case-control study in Fukuoka, Japan. *Natl Cancer Inst Monogr* **67:** 187–90.

Howatson AG, Carter DC (1985). pancreatic carcinogenesis—enhancement by cholecystokinin in the hamster-nitrosamine model. *Br J Cancer* **51:** 107–14.

Howe GR (1985). The use of polytomous dual response data to increase power in case-control studies: an applicaiton to the association between dietary fat and breast cancer. *J Chronic Dis* **38:** 663–670.

IARC (International Agency for Research on Cancer) (1988). Alcohol drinking. IARC Monographs, Vol 44; IARC, Lyon.

IARC (International Agency for Research on Cancer) (1976). Some naturally occurring substances. IARC Monographs Vol 10; IARC, Lyon.

Jain M, Cook GM, Davis FG, Grace MG, Howe GR, Miller AB (1980). A case-control study of diet and colorectal cancer. *Int J Cancer* **26:** 757–68.

Jensen OM (1979). Cancer morbidity and causes of death among Danish brewery workers. *Int J Cancer* **23:** 454–63.

Johnson LR (1981). Effects of gastrointestinal hormones on pancreatic growth. *Cancer* **47:** 1640–5.

Kadlubar FF, Butler MA, Kaderlik KR, Chou HC, Lang NP (1992). Plymorphisms for aromatic amine metabolism in humans: relevance for human carcinogenesis. *Environ Health Persp* **98:** in press.

Kark JD, Smith AH, Switzer BR, Hames CG (1981). Serum vitamin A (retinol) and cancer incidence in Evans County, Georgia. *J Natl Cancer Inst* **66:** 7–16.

Katsouyanni K, Trichopoulos D, Boyle P *et al* (1986). Diet and breast cnacer: a case-control study in Greece. *Int J Cancer* **38:** 815–20.

Kidwell WR, Knazek RA, Vonderhaar BK *et al* (1982). Effects of unsaturated fatty acids on the development and proliferation of normal and neoplastic breast epithelium. In *Molecular Interrelations of Nutrition and Cancer* (eds Arndt MS, van Eys J, Wang YM); Raven Press, New York, pp. 219.

Kinlen LJ (1982). Meat and fat consumption and cancer mortality: a study of strict religious orders in Britain. *Lancet* **1:** 946–9.

Klatsky AL, Armstrong MA, Friedman GD, Hiatt RA (1988). The relations of alcoholic beverage use to colon and rectal cancer. *Am J Epidemiol* **128:** 1007– 525.

Kolonel LN, Hankin JH, Nomura AM, Chu SY (1981). Dietary fat intake and cancer incidence among five ethnic groups in Hawaii. *Cancer Res* **41:** 327–8.

Koo LC (1988). Dietary habits and lung cancer risk among Chinese females in Hong Kong who never smoked . *Nutr Cancer* **11:** 155–72.

Kushi LH, Sellers TA, Potter JD *et al* (1992). Dietary fat and postmenopausal breast cancer. *JNCI* **84:** 1092–9.

Larsson B, Svarsudd K, Welin L *et al* (1984). Abdominal adipose tissue distribution, obesity and risk of cardiovascular disease and death: 13 year follow-up of participates in the study of men born in 1913. *Br Med J* **288:** 1401–4.

La Vecchia C, Franceschi S, Decarli A, Callus G, Tognoni G (1984). Risk factors for endometrial cancer at differnet ages. *J Nat Cancer Inst* **73:** 667–71.

La Vecchia C, Decarli A, Franceschi S *et al* (1985). Alcohol consumption and the risk of breast cancer in women. *JNCI* **75:** 61–5.

La Vecchia C, Negri E, Decarli A *et al* (1987). A case-control study of diet and gastric cancer in Northern Italy. *Int J Cancer* **40:** 484–9.

La Vecchia C, Negri E, Decarli A *et al* (1988a). A case-control study of diet and colorectal cancer in Northern Italy. *Int J Cancer* **41:** 492–8.

La Vecchia C, Decarli A, Fasoli M *et al* (1988b). Dietary vitamin A and the risk of intraepithelial and invasive cervical neoplasia. *Gynecol Oncol* **30:** 187–95.

Le MG, Hill C, Kramar A *et al* (1984). Alcoholic beverage consumption and breast cancer in a French case-control study. *Am J Epidemiol* **120:** 350–7.

Le MG, Moulton LH, Hill C *et al* (1986). Consumption of dairy produce and alcohol in a case-control study of breast cancer. *J Natl Cancer Inst* **77:** 633–6.

Lew EA, Garfinkel L (1979). Variations in mortality by weight among 750,000 men and women. *J Chron Dis* **32:** 563–76.

Lubin F, Wax Y, Modan B (1986). Role of fat, animal protein and dietary fiber in breast cancer etiology: a case-control study. *J Natl Cancer Inst* **77:** 605–12.

Lubin JH, Burns PE, Blot WJ *et al* (1981). Dietary factors and breast cancer risk. *Int J Cancer* **28:** 685–9.

Lyon JL, Mahoney AW, West DW *et al* (1987). Energy intake: its relationship to colon cancer risk. *J Natl Cancer Inst* **78:** 853–61.

Mack TM, Paganini-Hill A (1981). Epidemiology of pancreas cancer in Los Angeles. *Cancer* **47:** 1474–83.

Mack TM, Yu MC, Hanisch R, Henderson BE (1986). Pancreas cancer and smoking, beverage consumption and past medical history. *JNCI* **76:** 49–60.

Macquart-Moulin G, Riboli E, Cornee J, Charnay B, Berthezene P, Day N (1986). Case-control study on colorectal cancer and diet in Marseilles. *Int J Cancer* **38:** 183–91.

Manousos O, Day NE, Trichopoulos D, Gerovassilis F, Tzonou A, Polychronopoulou A (1983). Diet and colorectal cancer: a case-control study in Greece. *Int J Cancer* **32:** 1–5.

Martinez I, Torres R, Frias Z, Colon JR, Fernandez N (1979). Factors associated with adenocarcinomas of the large bowel in Puerto Rico. *Adv Med Oncol Res Ed* **3:** 45–52.

McLaughlin JK, Gridley G, Block G *et al* (1988). Dietary factors in oral and pharyngeal cancer. *J Natl Cancer Inst* **15:** 1237–43.

McMichael AJ, Potter JD (1985). Diet and colon cancer: integration of the descriptive, analytic and metabolic epidemiology. *NCI Monogr* **69:** 223–8.

McMichael AJ, Potter JD (1986). Dietary influences upon colon carcinogenesis. In *Diet, Nutrition and Cancer* (eds Hayshi Y *et al*); Japan Sci Soc Press, Tokyo, pp. 275–90.

McMichael AJ (1981). Coffee, soya and pancreatic cancer. *Lancet* **2:** 689–90.

Micozzi MS (1985). Nutrition, body size and breast cancer. *Year Book Phys Anthropol* **28:** 175–206.

Miller AB, Howe GR, Jain M, Craib KJP, Harison L (1983). Food items and food groups as risk factors in a case-control study of diet and colorectal cancer. *Int J Cancer* **32:** 155–61.

Miller AB, Kelly A, Choi NW *et al* (1978). A study of diet and breast cancer. *Am J Epidemiol* **107:** 499–509.

Mills PK, Beeson L, Abbey DE, Fraser GE, Phillips RL (1988). Dietary habits and past medical history as related to fatal pancreas cancer risk among Adventists. *Cancer* **61:** 2578–85.

Mirvish SS (1981). Ascrobic acid inhibition of N-nitroso compound fomation in chemical, food and biological systems. In *Inhibition of Tumor Induction and Development* (eds Zedeck MS, Lipkin M); Plenum Publishing Corp, New York, pp. 101–26.

Modan B, Barell V, Lubin F, Modan M, Greenberg RA, Graham S (1975). Low-fiber intake as an etiologic factor in cancer of the colon. *J Natl Cancer Inst* **55:** 15–18.

Muñoz N, Wahrendorf J, Lu J-B *et al* (1985). No effect of riboflavine, retinol and zinc on prevalence of pre-cancerous lesions of oesophagus. Randomized double-blind intervention study in high-risk population of China. *Lancet* **2:** 111–14.

Neel JV (1969). Current concepts of the genetic basis of diabetes mellitus and the biological significance of the diabetic predisposition. In *Diabetes* (eds Ostman J, Milner RDG); Excerpta Medica, Amsterdam, pp. 68–78.

Norell SE, Ahlbom A, Erwald R *et al* (1986). Diet and pancreatic cancer: a case-control study. *Am J Epidemiol* **124:** 894–902.

O'Connell DL, Hulka BS, Chambless LE *et al* (1987). Cigarette smoking, alcohol consumption and breast cancer risk. *J Natl Cancer Inst* **78:** 229–34.

Oishi K, Okada K, Yoshida O *et al* (1988). A case-control study of prostatic cancer with reference to dietary habits. *Prostate* **12:** 179–90.

Paffenbarger RS, Hyde RT, Wing AL (1987). Physical activity and incidence of cancer in diverse populations: a preliminary report. *Am J clin Nutr* **45:** 311–7.

Paffenbarger RS, Kampert JB, Chang H-G (1980). Characteristics that predict risk of breast cancer before and after the menopause. *Am J Epidemiol* **112:** 258–68.

Paganini-Hill A, Ross RK (1983). Breast cancer and alcohol consumption (letter). *Lancet* **2:** 626–7.

Pariza MW, Simopoulos AP (1986). Calories and energy expenditure in carcinogenesis. *Am J Clin Nutr* **45 (Suppl):** 149–272.

Peers F, Bosch X, Kaldor J *et al* (1987). Aflatoxin exposure, hepatitis B virus infeciton and liver cancer in Swaziland. *Int J Cancer* **39:** 545–53.

Pernu J (1960). An epidemiological study on cancer of the digestive organs and respiratory systems. A study based on 7078 cases. *Ann Med Intern Fenn* **49(Suppl 3):** 1–117.

Peto R, Doll R, Buckley JD, Sporn MB (1981). Can dietary beta-carotene materially reduce human cancer rates? *Nature* **290:** 201–8.

Petrakis NL, Maack CA, Lee RE *et al* (1980). Mutagenic activity in nipple aspirtes of human breast fluid. *Cancer Res* **40:** 188–9.

Phillips RL (1975). Role of life-style and dietary habits in risk of cancer among Seventh-day Adventists. *Cancer Res* **35:** 3513–22.

Phillips RL, Garfinkel L, Kuzma JW *et al* (1980). Mortality among California Seventh-day Adventists for selected cancer sites. *J Natl Cancer Inst* **65:** 1097– 1107.

Phillips RL, Snowdon DA (1983). Association of meat and coffee use with cancers of the large bowel, breast and prostate among Seventh-day Adventists: preliminary resutls. *Cancer Res* **43 (Suppl):** 2403–8.

Pitot HC (1986). *Fundamentals of Oncology*. 3rd Ed. Marcel Dekker Inc, New York.

Potter JD (1989). The epidemiology of fiber and colorectal cancer: Why don't the analytic epidemiology data make better sense? In *Dietary Fiber: Chemistry, Physiology and Health Effects* (eds Kritchevsky D *et al*); Plenum Press.

Potter JD (1990). The epidemiology and prevention of pancreas cancer. In *The Prevention of Cancer: Vital Statistics to Intervnetion* (eds Zatonski W *et al*); PA Interpress, Warsaw.

Potter JD (1992). Colon cancer—reconciling the epidemiology, physiology and molecular biology. *JAMA* **268:** 1573–7.

Potter JD, McMichael AJ (1986). Diet and cancer of the colon and rectum. A case-control study. *J Natl Cancer Inst* **76:** 557–69.

Potter JD, McMichael AJ, Hartshorne JM (1982). Alcohol and beer consumption in relation to cancer of bowel and lung: an extended correlation analysis. *J Chronic Dis* **35:** 823–4.

Rohan TE, Bain CJ (1987). Diet in the etiology of breast cancer. *Epidemiol Rev* **9:** 120–45.

Rohan TE, McMichael AJ (1988). Alcohol consumption and risk of breast cancer. *Int J Cancer* **41:** 695–9.

Rosenberg L, Slone D, Shapiro S *et al* (1982). Breast cancer and alcoholic-beverage consumption. *Lancet* **1:** 267–71.

Schatzkin A, Carter CL, Green SB *et al* (1989). Is alcohol consumption related to breast cancer? Results from the Framingham Heart Study. *J Natl Cancer Inst* **81:** 31–5.

Schatzkin A, Jones Y, Hoover RN *et al* (1987). Alcohol consumption and breast cancer in the epidemiologic follow-up study of the first Naitonal Health and Nutrition Examination Survey. *N Engl J Med* **316:** 1169–73.

Selby JV, Friedman GD, Quesenberry CP (1989). Precursors of essential hypertension. The role of body fat distribution pattern. *Am J Epidemiol* **129:** 43– 53.

Sellers TA, Kushi LH, Potter JD *et al* (1992). Effect of family history, body fat distribution and reproductive factors on risk of postmenopausal breast cancer. *N Eng J Med* **326:** 1323–9.

Shun-Zhang Y, Rui-Fang L, Da-Dao X, Howe GR (1990). A case-control study of dietary and non-dietary factors for breast cancer in Shanghai. *Cancer Res* **50:** 5017–121.

Sidney S, Friedman GD, Hiatt RA (1986). Serum cholesterol and large bowel cancer: a case-control study. *Am J Epidemiol* **124:** 33–8.

Slattery ML, Schumacher MC, Smith KR, West DW, Abd-Elghany N (1988a). Physical activity, diet and risk of colon cancer in Utah. *Am J Epidemiol* **128:** 989– 99.

Slattery ML, Sorenson AW, Ford MH (1988b). Dietary calcium intake as a mitigating factor in colon cancer. *Am J Epidemiol* **128:** 504–14.

Steinmetz K, Potter JD (1991a). A review of vegetables, fruit and cancer. I. Epidemiology. *Cancer Causes and Conrol* **2:** 325–57.

Steinmetz K, Potter JD (1991b). A review of vegetables, fruit and cancer. II. Mechanisms. *Cancer Causes and Control* **2:** 427–42.

Stocks P (1970). Breast cancer anomalies. *Br J Cancer* **24:** 633–43.

Stocks P (1957). Cancer incidence in North Wales and Liverpool region in relation to habits and environment. *Brit Emp Cancer Campaign 35th Annual Report* **Suppl to Part 2:** pp. 1–127, London.

Stragand JJ, Hagemann RF (1977). Effect of lumenal contents on colonic cell replacement. *Am J Physiol* **233:** E208–11.

Sugimura T, Sato S (1983). Mutagens-carcinogens in foods. *Cancer Res* **43:** 2415s– 21s.

Sugimura T (1985). Carcinogenicity of mutagenic heterocyclic amines formed during the cooking process. *Mutat Res* **150:** 33–41.

Sundby P (1967). *Alcoholism and Mortality*. Universitetsforlaget, Oslo.

Talamini R, La Vecchia C, Decarli A *et al* (1984). Social factors, diet and breast cancer in a northern Italian population. *Br J Cancer* **49:** 723–9.

Thurnham DI, Zheng S-F, Muñoz N *et al* (1985). Comparison of riboflavin, vitamin A and zinc status of Chinese populations at high and low risk for esophageal cancer . *Nutr Cancer* **7:** 131–43.

Turesky RJ, Lang N, Butler MA *et al* (1991). Metabolic activation of carcinogenic heterocyclic aromatic amines by human liver and colon. *Carcinogenesis* **12:** 1417–22.

Tuyns AJ, Kaaks R, Haelterman M (1988). Colorectal cancr and the consumption of foods: a case-control study in Belgium. **11:** 189–204.

Vague J (1956). The degree of masculine differentiation of obesities: a factor determining predisposition to diabetes, atherosclerosis, gout and uric calculous disease. *Am J Clin Nutr* **4:** 20–34.

van Rensburg SJ (1981). Epidemiolgoic and dietary evidence for a specific nutritional predisposition to esophageal cancer. *J Natl Cancer Inst* **67:** 243–51.

Velema JP, Walker AM, Gold EB (1986). Alcohol and pancreatic cancer: insufficient epidemiological evidence for a causal relaitonship. *Epidemiol Rev* **8:** 28–41.

Vena JE, Graham S, Zielezny M, Swanson MK, Barnes RE, Nolan J (1985). Lifetime occupational exercise and colon cancer. *Am J Epidemiol* **122:** 357–65.

Vitale JJ, Broitman SA (1981). Lipids and immune function. *Cancer Res* **41:** 3706– 10.

Wahrendorf J, Muñoz N, Lu J-B *et al* (1988). Blood retinol, zinc, riboflavin status in relation to pre-cancerous lesions of the eosphagus: findings for a vitamin intervention trial in the People's Republic of China. *Cancer Res* **48:** 2280–3.

Wald N, Idle M, Boreham J, Bailey A (1980). Low serum-vitamin A and subsequent risk of cancer. Preliminary results of a prospective study. *Lancet* **2:** 813–5.

Wattenberg LW (1985). Chemoprevention of cancer. *Cancer Res* **45:** 1–8.

Wattenberg LW (1977). Inhibition of carcinogenic effects of polycyclic hydrocarbons by benzyl isothiocyanate and related compounds. *J Natl Cancer Inst* **58:** 395–8.

Wattenberg LW (1983). Inhibition of neoplasia by minor dietary constituents. *Cancer Res* **43 (Suppl):** 2448s–53s.

Wattenberg LW (1992). Inhibition of carcinogenesis by minor dietary constituetns. *Cancer Res* **52 (Suppl):** 2085s–91s.

Weber WW (1987). *The Acetylator Genes and Drug Response*. Oxford University Press, Oxford.

Webster LA, Layde PM, Wingo PA *et al* (1983). Alcohol consumption and risk of breast cancer. *Lancet* **2:** 724–6.

Welsch CW, Aylsworth CF (1983). Enhancement of murine mammary tumorigenesis by feeding high levels of dietary fat: a hormonal mechanism. *J Natl Cancer Inst* **70:** 215–21.

Willett WC, Polk BF, Morris JS *et al* (1983). Prediagnostic serum selenium and risk of cancer. *Lancet* **2:** 130–4.

Willett WC, Browne ML, Bain C *et al* (1985). Relative weight and risk of breast cancer among premenopausal women. *Am J Epidemiol* **122:** 731–40.

Willett WC, Stampfer MJ (1986). Total energy intake: implications for epidemiologic analyses. *Am J Epidemiol* **124:** 17–27.

Willett WC, Hunter DJ, Stampfer MJ *et al* (1992). Dietary fat and fiber in relation to risk of breast cancer. *JAMA* **268:** 2037–44.

Willett WC, Stampfer MJ, Colditz GA *et al* (1987a). Dietary fat and risk of breast cancer. *N Engl J Med* **316:** 22–8.

Willet WC, Stampfer MJ, Colditz GA *et al* (1987b). Moderate alcohol consumption and the risk of breast cancer. *N Engl J Med* **316:** 1174–80.

Williams RR (1976). Breast and thyroid cancer and malignant melanoma promoted by alcohol-induced pituitary secretion of prolactin, TSH and MSH. L*ancet* **1:** 996–9.

Williams RR, Horm JW (1977). Association of cancer sites with tobacco and alcohol consumption and socioeconomic status of patients: interview study from the Third National Cancer Survey. *J Natl Cancer Inst* **58:** 525–47.

Wood AW, Huang MT, Chang RL *et al* (1982). Inhibition of the mutagenicity of bay-region diol epoxides of polycyclic hydrocarbons by naturally occurring plant phenols: exceptional activity of ellagic acid. *Proc Nat Acad Sci* **79:** 5513–7.

Wu AH, Paganini-Hill A, Ross RK, Henderson BE (1987). Alcohol, physical activity and other risk factors for colorectal cancer: a prospective study. *Br J Cancer* **55:** 687–94.

Wynder EL, Kajitani T, Ishikana S, Dodo H, Tako A (1969). Environmental factors of cancer of the colon and rectum. II. Japanese epidemiological data. *Cancer* **23:** 1210–20.

Wynder EL, Shigematsu T (1967). Environmental factors of cancer of the colon and rectum. *Cancer* **20:** 1520–61.

Yang CS (1980). Research on esophageal cancer in China: a review. *Cancer Res* **40:** 2633–44.

You W-C, Blot WJ, Chang Y-S *et al* (1988). Diet and high-risk of stomach cancer in Shandong, China. *Cancer Res* **48:** 3518–23.

Young TB (1989). A case-control study of breast cancer and alcohol consumption habits. *Cancer* **64:** 552–8.

Young TB, Wolf DA (1988). Case-control study of proximal and distal colon cancer and diet in Wisconsin. *Int J Cancer* **42:** 167–75.

Ziegler RG (1989). A review of epidemiologic evidence that carotenoids reduce the risk of cancer. *J Nutr* **119:** 116–22.

4
Epidemiology of cancer in Europe: the national level
M J Hill, C P J Caygill

4.1
INTRODUCTION

It is well recognized that there is a wide range in the incidence and mortality of all cancers within Europe. All countries in Europe have reliable mortality statistics and these have been collated in, for example, the compilations published by Segi (*eg* Segi (1980) which gives the mortality data for 1975). In 1953 the campaign began to make cancer a notifiable disease in all countries, and these data were collected and tabulated by cancer registries. In some countries (*eg* the Scandinavian countries, UK, Ireland) the whole population is covered by either a single registry (*eg* Denmark) or a series of registries (*eg* Scotland which is divided into 5 registration areas). In most European countries there is incomplete coverage and incidence data are only available for defined regions (*eg* in Spain there are registries in Tarragona, Zaragosa and Navarra; in Hungary there are registries in Szabolcs county and in Vas; in Romania registration is only available for the Cluj region). In order to determine incidence data for whole countries, Doll (1969) used reliable incidence data where available and calculated the incidence from mortality data for the other countries (using a formula which took account of the survival rates for the different cancer sites). The same basic procedure was used by Jensen *et al* (1990) when he calculated the incidence of cancer at various sites for all EC countries.

The data have been available for sufficiently long in most countries to permit time-trends in incidence to be determined. Many registries also relate incidence to such variables as population density and socioeconomic status as well as giving the sex ratio.

In this chapter a broad overview of the pattern of cancer in Europe will be given. More detailed information on the pattern in individual countries will be given in the chapters that follow.

4.2
VARIATIONS BETWEEN COUNTRIES

The best data permitting comparison of incidence and mortality from cancer in Europe come from the tables of Levi *et al* (1989) and Jensen *et al* (1990) for the period around 1980, and from Doll (1969) for the 1960 period. In addition the tables of mortality data compiled by Segi provide useful information concerning intermediate years. Detailed information for specific regions can be obtained from individual registries and these are particularly useful in determining time trends. Registries vary in their level of completeness of registration; the series of publications *Cancer in Five Continents* list data only from those registries that satisfy the IARC criteria on completeness and reliability of data and so provide useful guidelines in this respect.

Table 4.1 lists incidence data for 22 countries for the period 1958–62 arranged into 4 broad regions of Europe, namely northern, western, southern and central/eastern. The data are age adjusted (age 35–64) to the world population. Clearly such an arrangement is fraught with difficulties; is Finland best grouped with the Scandinavian countries or with the central/eastern group? Is Yugoslavia in southern or eastern Europe? Is Switzerland in western or in central Europe? The difficulty is partly due to the fact that the terms *eastern* and *western* Europe have a political/socioeconomic meaning as well as a geographical one; since socioeconomic factors are associated with cancer risk factors, the fact that Germany is strongly associated culturally with western Europe cannot be ignored, even though geographically it could be regarded as being in central Europe. Table 4.2 arranges the same countries into the same groups but gives data on cancer incidence for the period 1978–82. Table 4.3 gives mortality data for the period 1978–82. Figs. 4.1 to 4.8 portray the data in pictorial form for the geographical variation in cancer incidence for cancers of the oesophagus, stomach, colon, liver, prostate and bladder for males, and for breast and cervix uteri for females. Fig. 4.9 reminds the reader of the map of Europe.

The range in incidence in site specific cancers within Europe was wide; in 1960 the range was as high as 11 fold (rectum), 10 fold (oesophagus) and 9 fold (lung); for some cancers the range was much less (*eg* 2 fold for leukemia and pancreas). When examined by site, the data show that in 1960 cancer of the oesophagus was very high in France, Switzerland and Portugal and lowest in Greece, Bulgaria and the Netherlands. Gastric cancer was most common in the central/east European group of countries plus Finland and Romania whilst the lowest incidence rates were seen in Scandinavia, France, The Netherlands and England and Wales. For breast cancer, in contrast, the highest incidence rates were in the British Isles, The Netherlands and Scandinavia and the lowest rates in southern and eastern Europe.

Comparison of Table 4.1 and Table 4.2 illustrates the temporal changes in cancer patterns. The most dramatic changes in incidence have occurred with

gastric cancer which decreased to less than 50% of their 1960 values by 1982 in most countries and

Table 4.1—Incidence of cancer at various sites in 22 European countries in 1960 (data from Doll, 1969)

	146	150	151	153	154	157	162	174	180	185	188	204
North												
Norway	3.1	3.9	38.6	12.7	7.5	8.1	27.4	86.3	38.1	12.5	7.0+	7.5
Sweden	1.3	3.4	32.5	16.0	12.8	9.4	29.4	96.4	43.7	15.9*	12.1	11.3
Denmark	–	3.9	37.4	17.1	20.8	8.6	50.6	91.5	68.6	10.5	18.5*	9.0
Finland	0.5	8.6	72.0	8.3	7.5	12.8*	119.7	58.7	39.6	10.3	7.8	8.1
West												
Belgium	–	6.2	42.1	20.9	19.6	8.0	89.3	91.5	–	12.6	–	9.8
France	–	25.5*	33.0	20.2	16.8	–	50.6	67.6	–	13.7	–	9.4
FRG	–	4.8	51.3	14.2	16.6	8.7	76.9	72.5	93.2*	11.1	–	9.2
Ireland	–	8.0	38.8	25.2	13.9	9.2	66.1	94.9	–	10.7	–	9.7
Netherlands	0.6	2.5+	26.4	12.8	9.5	6.0+	81.3	95.6	51.0	7.5	10.2	5.4
England/Wales	0.9	5.1	30.7	17.4	16.2	9.2	128.4	103.4	26.6+	7.4	16.9	6.8
Scotland	–	6.2	43.0	28.2*	23.3	10.7	154.3*	111.0*	–	11.1	–	7.2
South												
Bulgaria	–	2.5	56.4	7.8	13.2	–	60.6	44.4	–	12.4	–	8.7
Greece	–	2.5	25.1+	10.0	2.1+	–	54.1	33.2+	–	5.0	–	9.0

146=Nasopharynx; 150=oesophagus; 151=stomach; 153=colon; 154=rectum; 157=pancreas; 162.3=lung and bronchus; 174=breast; 180=cervix; 185=prostate; 188=bladder; 204=leukemia; *=highest in Europe; +=lowest in Europe.

	146	150	151	153	154	157	162	174	180	185	188	204
Portugal	–	11.5	56.9	15.0	9.6	–	18.5+	53.1	–	12.2	–	6.7
Yugoslavia	–	4.0	38.6	6.2+	13.9	–	40.3	38.2	–	5.9	–	6.6
Italy	–	6.5	52.9	16.0	11.6	6.1	57.4	68.7	–	10.5	–	9.0
Romania	–	5.2	64.2	8.9	7.9	–	53.8	39.8	–	9.6	–	6.5
Central/East												
Austria	–	4.9	59.0	18.0	17.5	11.6	96.4	71.0	–	12.9	–	9.4
Czechoslovakia	–	3.3	67.3	12.9	23.3*	–	103.3	61.9	–	10.7	–	8.8
Hungary	–	4.3	68.2	14.2	15.2	–	61.6	59.7	–	12.9	–	11.2
Poland	–	8.2	74.8*	8.2	7.5	–	45.4	37.3	–	4.8+	–	11.4*
Switzerland	–	15.1	34.4	20.9	16.4	8.7	69.2	92.2	–	12.4	–	8.8

146=Nasopharynx; 150=oesophagus; 151=stomach; 153=colon; 154=rectum; 157=pancreas; 162.3=lung and bronchus; 174=breast; 180=cervix; 185=prostate; 188=bladder; 204=leukemia; *=highest in Europe; +=lowest in Europe.

Table 4.2—Incidence of cancer at various sites in 24 European countries in 1982 (Data from Levi *et al* 1989 and Jensen, 1989)

	140–149	150	151	153	154	157	162	174	180	185	188	204	155
North													
Norway	7.7	2.7	18.1	17.4	14.8	8.5	30.9	51.8	15.6	42.0	17.0	7.7	1.8
Sweden	7.4	3.0	15.0	16.8	11.6	8.7	25.3	60.7	9.9	45.9	15.5	8.4	4.7
Denmark	8.9	2.9	14.8	18.9	17.4	3.9	56.5	63.1	19.5	27.7	24.7	8.8	3.6
Finland	8.8	3.7	24.6	10.0	10.1	10.0	74.2	44.7	5.5	34.2	12.7	8.2	4.0
West													

	140–149	150	151	153	154	157	162	174	180	185	188	204	155
Belgium		4.2	20.1	22.3	11.7	7.4	87.5	70.9	9.7	37.9	22.8		4.8
France		11.2	16.4	20.8	10.3	7.4	50.3	50.6	9.2	40.8	17.9		20.1
FRG	6.1	4.0	27.2	24.6	12.6	8.4	57.1	55.6	10.2	43.0	17.8	7.9	8.0
Ireland	16.9	6.5	20.1	23.2	14.0	8.4	50.3	75.7	10.1	27.3	12.6	8.0	2.2
Netherlands	6.4	3.4	20.7	20.6	10.6	9.4	85.4	71.6	7.6	36.3	18.4	8.2	2.0
England/Wales		5.4	22.2	21.6	13.3	8.2	76.3	75.8	12.4	33.3	18.5		2.6
Scotland	7.5	8.7	21.7	20.4	13.3	8.0	100.4	58.7	13.5	21.5	20.1	7.5	2.7

140–149 Mouth and pharynx; 155=liver. For others see key to Fig. 4.1.

	140–149	150	151	153	154	157	162	174	180	185	188	204	155
South													
Bulgaria													
Greece		2.0	15.4	7.5	2.0	5.3	52.5	43.6	9.2	16.1	17.3		34.7
Portugal		5.4	39.4	12.0	10.1	4.5	22.4	44.5	14.3	27.2	12.9		0.5
Spain		4.8	26.7	9.1	7.8	4.3	39.7	38.3	8.7	30.6	18.6		21.9
Yugoslavia	19.9	7.1	34.9	8.7	14.4	6.8	57.6	37.7	8.4	18.7	9.3	6.0	12.0
Italy		4.2	31.7	15.8	9.8	6.9	67.2	51.4	9.2	28.5	22.7		27.3
Romania	13.6	1.2	34.2	4.1	8.5	6.4	34.7	30.4	19.4	9.8	9.5	6.3	18.0
Central/East													
Austria													
Czechos	17.6	4.1	31.7	11.8	15.2	8.3	70.0	31.2	15.0	15.8	11.9	8.4	5.1

	140–149	150	151	153	154	157	162	174	180	185	188	204	155
lovakia													
Hungary	15.6	2.5	32.4	7.8	10.9	5.4	53.2	22.9	9.5	12.6	7.6	3.0	5.5
Poland	7.9	4.5	23.2	10.5	9.1	7.8	55.8	32.4	14.7	11.5	10.4	5.4	6.6
Switzerland	24.3	9.0	13.5	24.3	12.8	8.4	72.9	72.2	8.1	39.6	19.8	7.8	10.2
GDR	6.0	3.0	25.2	11.6	13.9	7.1	58.9	41.4	24.6	19.9	11.6	6.6	3.6

140–149 Mouth and pharynx; 155=liver. For others see key to Fig. 4.1.

Table 4.3—Mortality from cancer at various sites in 24 European countries in 1982 (Data from Levi *et al*, 1989)

	140–149	150	151	153	154	155	157	162	174	180	185	188	204
North													
Norway	2.5	2.6	14.6	18.1		1.6	8.1	26.4	18.3	8.1	19.9	5.7	6.1
Sweden	2.7	2.9	12.8	16.5		3.7	9.2	24.6	18.5	6.8	19.5	4.4	6.4
Denmark	3.1	3.5	12.2	24.3		2.4	9.2	53.4	25.4	11.6	15.9	9.1	7.0
Finland	2.5	3.6	20.2	12.1		3.7	9.5	64.4	15.2	5.4	16.3	4.8	6.5
West													
Belgium	3.5	4.3	16.4	22.6		3.1	7.9	77.8	25.8	7.8	17.5	8.6	6.5
France	15.6	13.3	12.5	22.9		2.8	7.0	42.1	18.6	7.8	15.3	6.7	6.9
FRG	3.9	4.0	21.2	18.0		1.6	7.8	49.0	21.1	8.4	15.9	7.3	6.3
Ireland	3.9	6.1	16.2	24.2		0.9	8.7	46.8	26.6	6.3	14.0	4.4	5.7
Netherlands	2.0	3.4	17.5	20.0		1.2	9.3	77.6	26.2	6.4	16.0	7.4	6.3
England/	2.8	5.8	16.8	21.1		1.1	8.1	69.9	28.2	8.2	12.5	7.8	5.6

	140–149	150	151	153	154	155	157	162	174	180	185	188	204
Wales													
Scotland	3.2	8.1	17.4	23.1		1.5	8.2	83.5	27.9	7.6	12.1	8.0	5.1

	140–149	150	151	153	154	155	157	162	174	180	185	188	204–
South													
Bulgaria	2.1	1.3	24.7	12.1		8.7	4.9	36.0	13.3	7.7	6.3	4.0	4.5
Greece	1.7	1.9	12.1	7.7		1.7	4.8	45.1	14.6	5.3	7.3	6.2	6.6
Portugal	5.0	5.8	29.7	16.9		0.9	4.6	20.1	15.0	9.0	13.8	4.7	5.4
Spain	4.0	5.3	19.8	11.8		9.1	4.3	33.9	13.5	7.1	12.8	7.2	4.8
Yugoslavia	4.5	3.6	21.1	11.8		6.4	4.9	39.3	12.7	9.8	10.4	4.1	3.4
Italy	6.2	4.8	22.7	18.2		4.7	6.3	52.9	19.2	8.7	10.8	8.2	6.8
Romania	3.1	1.2	29.7	8.1		1.9	5.5	26.1	9.9	12.1	6.2	3.3	3.7
Central/East													
Austria	4.6	3.9	25.5	23.8		3.4	8.7	49.1	19.8	11.3	15.3	6.7	6.0
Czechoslovakia	5.3	3.1	25.7	27.3		1.2	8.8	69.3	19.1	11.2	11.8	7.0	7.1
Hungary	7.9	4.1	31.6	24.3		8.0	9.1	58.8	20.6	14.5	15.8	6.9	6.6
Poland	4.8	4.2	30.4	11.7		7.7	6.9	54.8	14.6	12.6	8.4	6.7	5.8
Switzerland	6.5	6.6	14.3	18.8		3.9	7.6	48.8	24.1	8.3	19.8	6.6	5.9
GDR	3.2	3.1	21.7	23.7		1.9	6.7	50.9	16.5	11.8	9.8	6.9	5.7

to less than a third in some countries (*eg* Poland, Finland, Ireland). In some countries the decreases were very much less (*eg* less than 20% in The Netherlands and Yugoslavia). The incidence of colon cancer appears to be

Fig. 4.1—Geographical variation of oesophgeal cancer incidence in Europe (males)

increasing in northern Europe and in parts of western Europe (Fig. 4.10), but decreasing in much of southern and eastern Europe. This contrasts with the changes in lung cancer incidence, where it is the northern and western countries (*eg* Finland, England and Wales, Germany) that have experienced dramatic falls in incidence whilst southern countries (*eg* Italy, Yugoslavia, Portugal) and some

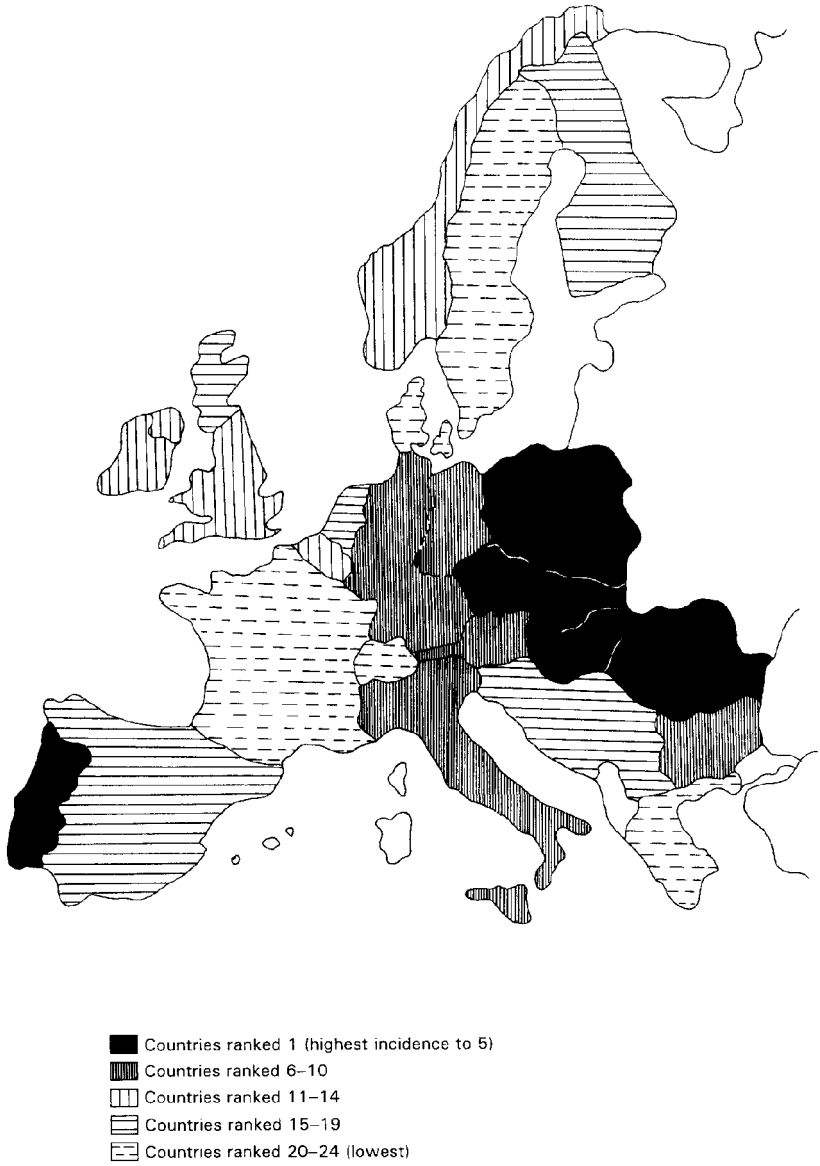


Fig. 4.2—Geographical variation of gastric cancer incidence in Europe (males)

central and eastern countries (*eg* Poland, Switzerland) have seen increases in lung cancer incidence rates.

Table 4.2 includes data for Spain and for hepatic cancer which were not included in the tables of Doll, 1969. The incidence of hepatic cancer is low in northern and western Europe but is high in Switzerland and the southern

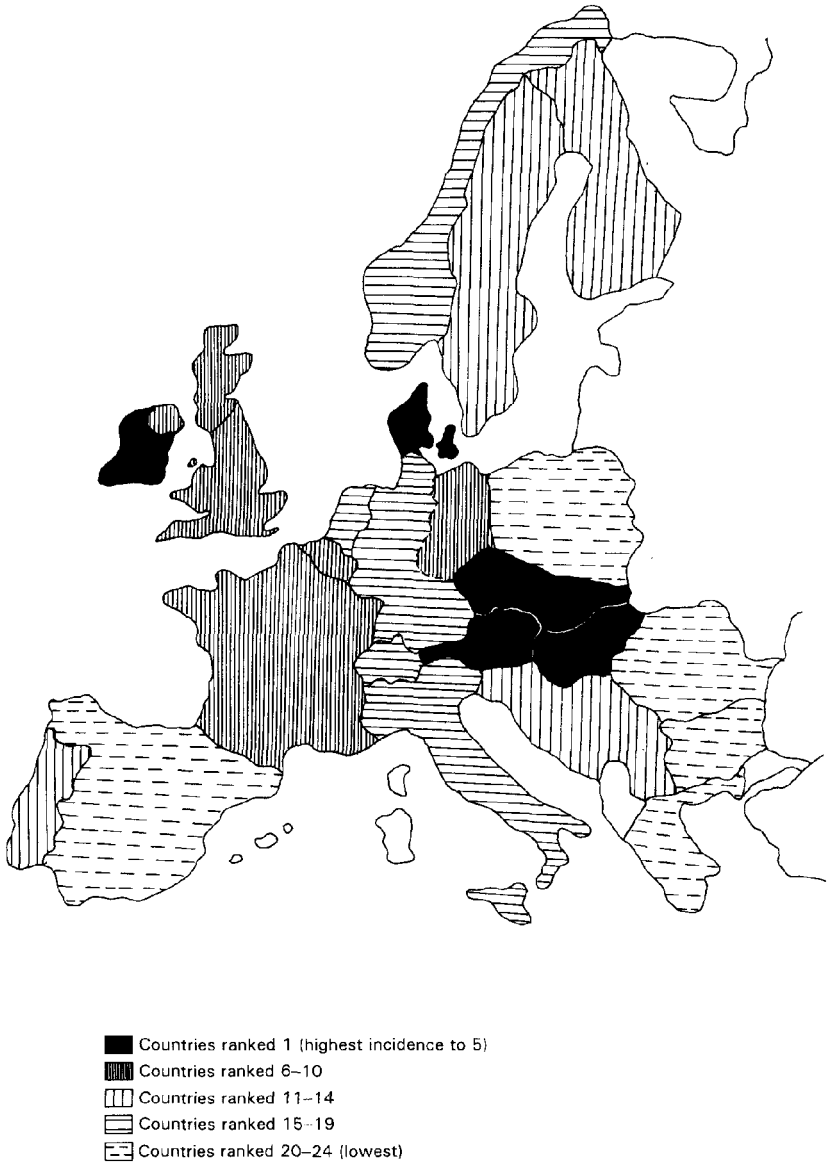


Fig. 4.3—Geographical variation of colon cancer incidence in Europe (males)

European countries (Romania, Italy, Spain). Thus southern Europe tend to have high incidences of the alcohol related cancers (oropharynx, oesophagus and liver), eastern Europe tends to have high incidences of the cancers associated with poor nutrition (upper gastrointestinal tract) and western Europe tends to have

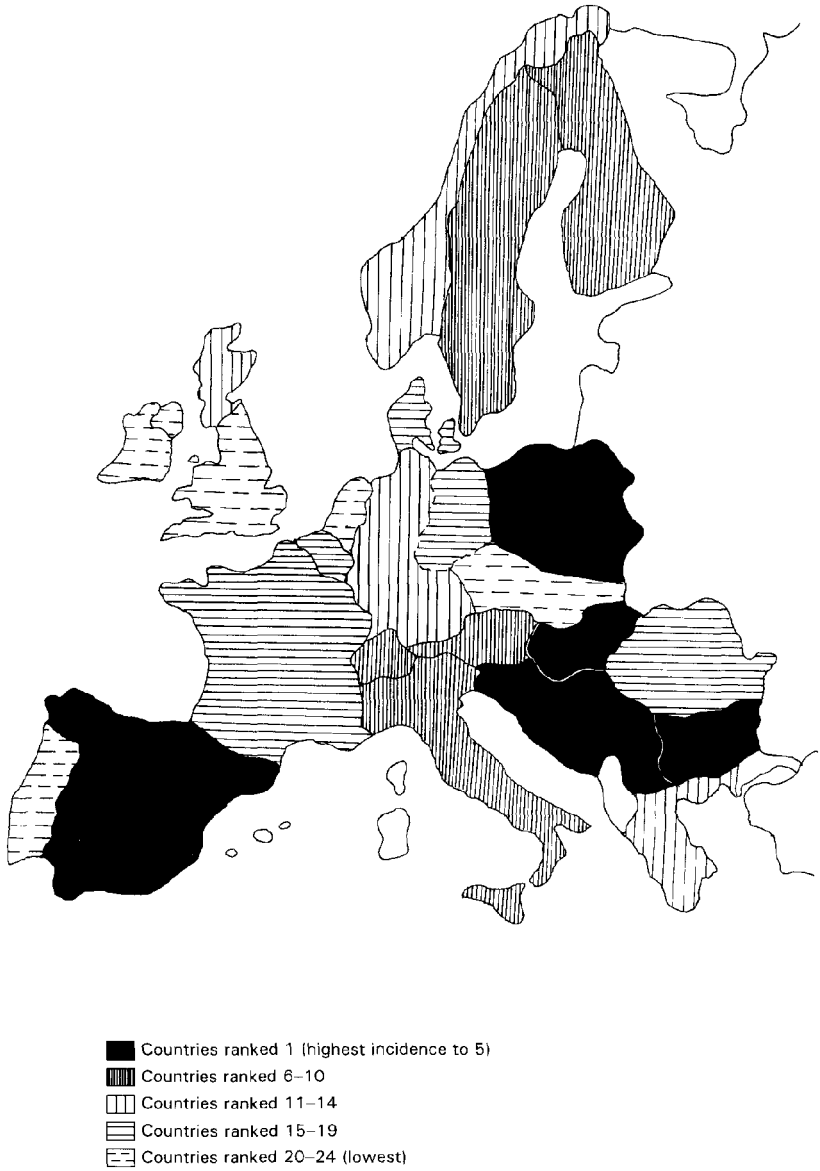


Fig. 4.4—Geographical variation of liver cancer incidence in Europe (males)

high incidences of the cancers related to a high fat/low fibre diet (large bowel, breast).

Table 4.3, which contains mortality data for the same countries and cancer sites as are covered in Tables 4.1 and 4.2, carries the same general message but with some differences. The mortality data indicate strongly that central and

Fig. 4.5—Geographical variation of prostate cancer incidence in Europe (males)

eastern Europe have the highest incidences of both gastric and colorectal cancer, thus if the countries are ranked in order of mortality rate (1 is highest and 24 is lowest), then central/eastern European Austria, Czechoslovakia, Poland and Hungary occupy 4 of the top 6 places for gastric cancer mortality and 3 of the top 5 rankings for colorectal cancer. Similarly the southern countries occupy 4 of the

Fig. 4.6—Geographical variation of bladder cancer incidence in Europe (males)

6 top rankings for primary hepatic cancer but the lowest 3 rankings for colorectal and oesophageal cancer; (indeed they occupy 5 of the lowest 7 rankings for colorectal cancer and all 7 are ranked in the lower half of the list). Western European countries occupied the top 5 rankings in breast cancer mortality and southern countries occupied the bottom 5 rankings. Northern countries occupied

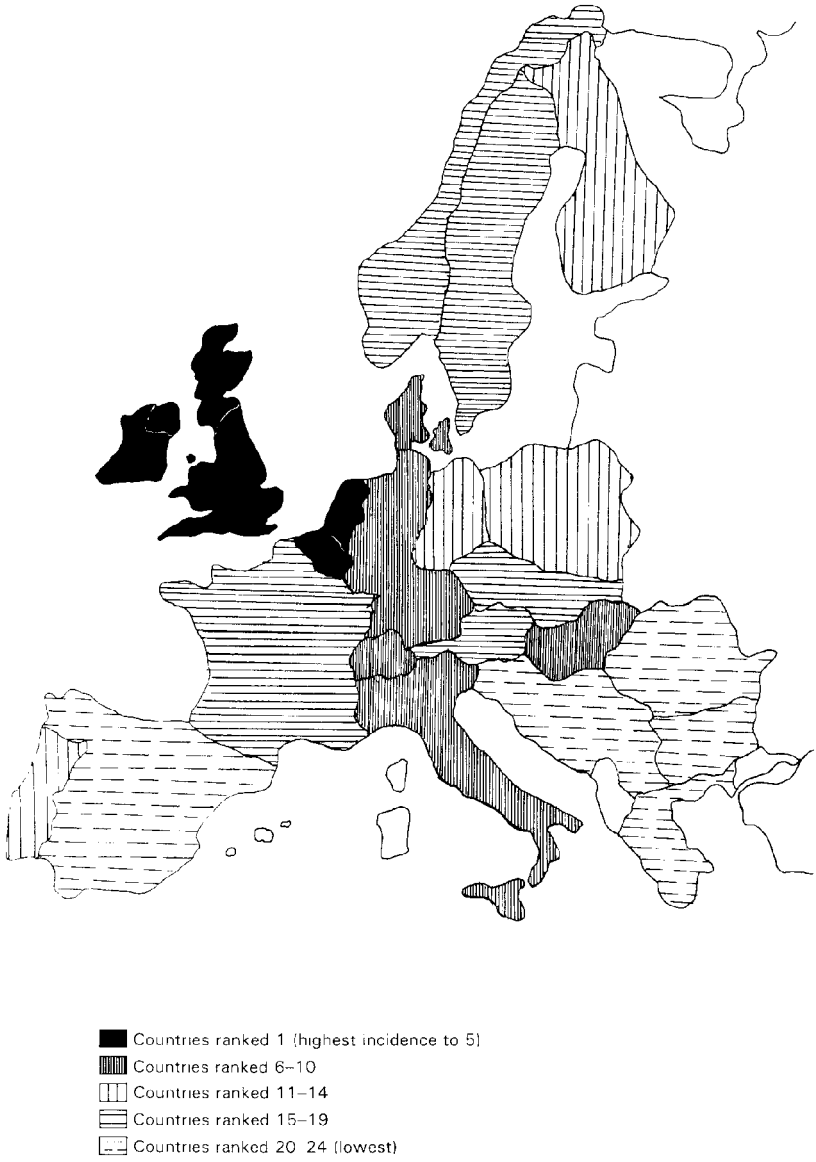


Fig. 4.7—Geographical variation of breast cancer incidence in Europe (females)

4 of the top 7 rankings for prostatic cancer but low rankings for oesophageal and gastric cancer and for cervical cancer. These rankings are summarized in Table 4.4.

The data in Table 4.3 also illustrate the inverse relation between risk of gastric and of colorectal cancer. Of the 10 registries with the highest gastric cancer

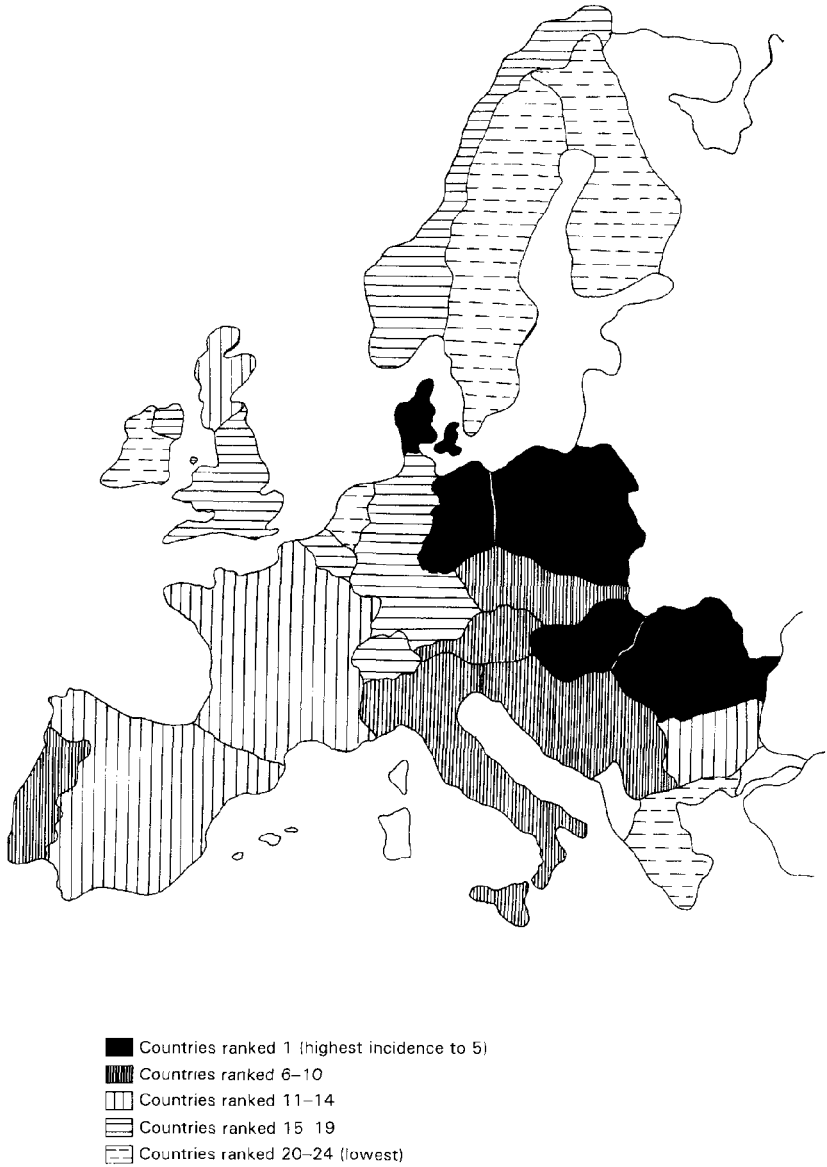


Fig. 4.8—Geographical variation of cervix uteri cancer incidence in Europe (females)

incidences 8 are in the 10 lowest rates of large bowel cancer; conversely of the registries with the 10 highest rates of colorectal cancer 6 are in those with the lowest rates for gastric cancer.

Fig. 4.9—Map of Europe as used in Figs. 4.1 to 4.8.

4.3
REGIONAL VARIATIONS WITHIN COUNTRIES

Regional and temporal variations can be illustrated further by data from individual registries or by data from reviews of national data. For example, Cayolla La Motta and Marinho Falcao (1987) analysed the mortality by subsite and by district in Portugal for the years 1980–82 and reported north-south differences in cancer patterns. Mortality from cancer of the oesophagus and stomach was highest in the north; cancers of the female breast, bladder, lung, liver and colon were more common in the south while mortality from cancer of the rectum and of the prostate was highest in the middle part of the country. The range in standardized mortality rates between the 18 districts of Portugal are

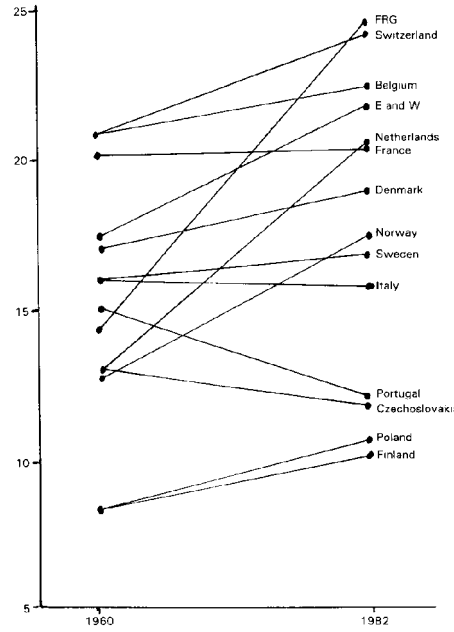


Fig. 4.10—Change in colon cancer incidence in European countries between 1960 and 1982

listed in Table 4.5 and ranged from 6 fold for oesophagus to 2 fold for the stomach. The Swedish cancer registry regularly publishes standardized incidence rates for the 24 counties of Sweden. Gastric cancer was much more common in the northern counties whilst cancers of the colon, rectum, lung, breast, uterus and ovary were more common in the southern counties. Malignant myeloma was relatively evenly spread amongst the Swedish counties. The high incidence of gastric cancer in northern counties adjacent to Finland could be related to the very high gastric cancer incidence in that country; similarly the high incidence of colon and rectal cancer in counties adjacent to Denmark may be related to the high incidence of those cancers in Denmark. The north-south distributions illustrated well the inverse relation between gastric and colorectal cancer rates. Djordjevic (1989), as an introduction to a report on cancer incidence in Serbia, reported overall standardized cancer mortality rates for the component countries of former Yugoslavia for the period 1969–74. It ranged from 174 for Slovenia through 156 (Novi Sad), 154 (Croatia), 100 (Serbia), 63 (Bosnia and Herzegovina, Montenegro) and 71 (Macedonia), and finally 30 (Pristina). He also published standardized mortality rates by sex; the ratios were as low as M/F=1.21 (Serbia) and as high as 1.67 (Pristina) with ratios being intermediate at 1.33 (Slovenia), 1.38 (Croatia), 1.22 (Novi Sad), 1.41 (Bosnia), 1.48 (Montenegro) and 1.49 (Macedonia). The Finnish Cancer Registry (1989) gave data on cancer incidence rates for 1981–85 in 5 Finnish regions and overall national rates

allowing SIRs to be calculated. Because of the small number of regions the ranges in SIR were small but were 43 % for colon cancer and 32% for breast cancer, but only 16% for lung cancer (Table 4.5).

Table 4.4—The top and bottom 5 in the rank-order amongst 24 European countries for mortality in various cancer sites

	Top 5					Bottom 5				
	1	2	3	4	5	20	21	22	23	24
140–149 Mouth/ pharynx	Fran	Hun	Switz	Ital	Port	Nor	Fin	Bulg	Neth	Gre
150 Oesophagus	Fran	Scot	Switz	Ire	Eng	Swe	Nor	Gre	Bulg	Rom
151 Stomach	Hung	Pol	Port	Rom	Czech	Switz	Swe	Fran	Den	Gre
153–4 Colorectum	Czech	Hung	Den	Ire	Aus	Spain	Pol	Bulg	Rom	Gre
155 Liver	Spain	Bulg	Hung	Pol	Yugo	Neth	Czech	Eng	Port	Ire
157 Pancreas	Fin	Neth	Swed	Den	Hung	Bulg	Yugo	Gre	Port	Spain
162 Lung	Scot	Belg	Neth	Eng	Fin	Spain	Nor	Rom	Swe	Gre
174 Breast	Eng	Scot	Ire	Neth	Belg	Gre	Spain	Bulg	Yugo	Rom
180 Cervix	Hung	Pol	Rom	DDR	Den	Swed	Neth	Ire	Fin	Gre
185 Prostate	Nor	Swiss	Swe	Belg	Fin	DDR	Pol	Gre	Bulg	Rom
188 Bladder	Den	Belg	Ital	Scot	Eng	Ire	Swed	Yugo	Bulg	Rom
204–9	Czech	Den	Fran	Ital	Hun	Scot	Spain	Bulg	Rom	Yugo

	Top 5					Bottom 5				
	1	2	3	4	5	20	21	22	23	24
Leukemias										

4.4
TIME TRENDS IN CANCER INCIDENCE/MORTALITY

Time trends have been published for Italy, Finland, Switzerland, UK. The data for the UK and Italy are discussed in more detail in later chapters. Hill *et al* (1991) reviewed the time trends in cancer mortality for France, 1950 to 1985. The most rapid increases (Table 4.6) have been in mortality from malignant melanoma (increasing at a rate of 8.4% per year for males and 7.7% per year for females) and primary hepatic cancer (males: 8.1% per year; females: 4.0% per year). The most

Table 4.5—Examples of regional variations in cancer incidence

	Oesoph	Stom	Colon	Rect	Liver	Lung	Breast	Year
	M	M	M	M	M	M	F	
18 Portuguese provinces								1980–82
+Islands—high SMR	235	129	158	146	228	172	141	
—low SMR	40	162	42	50	*	39	45	
24 Swedish counties								1969
highest SIR	–	136	129	145	–	184	120	
lowest SIR	–	85	<84	<84	–	69		
5 Finnish regions								1981–5
highest SIR		100	115	113	·	110	115	
lowest SIR		90	72	86	·	94	83	

rapid decreases have been in gastric cancer (2.8% per annum for males, 3.6% per annum for females) and cancer of the uterus (1.8% per year). Levi *et al* (1991) published data from Switzerland on time trends (in 5 year increments) for the period 1950–85. During that period of time there has been a steady decrease in mortality from cancers of the oesophagus, stomach and colorectum; this has been accompanied by a steady increase in cancers of the pancreas, lung, prostate and bladder and little change in the mortality from cancer of the mouth, breast and ovary. The Finnish Cancer Registry (1989) published a similar analysis of statistics for the period 1954 to 1985, followed by projections to the year 2008. They observed a steady decrease in incidence of gastric cancer from 600 to 224 per million per year and of cervical cancer from approximately 150 per million per year to 45 per million per year. In contrast there have been steady increases

between 1954 and 1985 of cancers of the colon (120%), rectum (106%), prostate (about 130%) and breast (100%). In the case of lung cancer there was a steady increase in rates in women from 40 to 80 per million per year; in males there was an increase until 1970 and then a steady decrease so that rates in 1985 were similar to those in 1954 (at a little over 500 per million per annum). The pattern of change in cancer rates in the three countries—France from western Europe, Switzerland from central Europe and Finland from the north—was similar in many respects. The rate of decrease in gastric cancer was similar in the three countries as was the rate of increase in bladder cancer. Finland, which had relatively low rates of breast and colon cancer, showed the fastest rate of increase in each. Lung cancer rates increased relatively rapidly in all three countries but this masked marked differences in the success of anti-smoking campaigns in the three countries so that currently lung cancer rates are decreasing steadily in males in Finland—a process that had yet to get underway in France or Switzerland in 1985 or in Finnish women.

Table 4.6—Rate of change in cancer mortality in France and Switzerland and in incidence in Finland

	France 1950–1985		Switzerland 1950–1985		Finland 1954–1985	
	Males	Females	Males	Females	Males	Females
Oesophagus	0.6%	−0.4%	−2.8%	–	–	–
Stomach	−2.8%	−3.6%	−4.3%	−5.6%	−3.5%	–
Large bowel	0.6%	−0.6%	−0.7%	−0.7%	+2.7%	2.7%
Liver	8.7%	4.0%	–	–	–	–
Pancreas	2.4%	1.5%	1.6%	1.2%	2.2%	2.5%
Lung and bronchus	4.2%	1.2%	2.4%	2.7%	1.1%	2.4%
Malignant melanoma	8.4%	8.1%	–	–	–	–
Breast	–	1.2%	–	0.3%	–	2.4%
Prostate	1.8%	–	0.7%	–	4.3%	–
Bladder	2.9%	0.8%	1.6%	–	2.5%	2.4%

4.5
SEX RATIO

Study of the ratio of incidence or mortality in males compared to females can give clues to the role of environmental factors, and such ratios are tabulated in Table 4.7. The hormone related cancers obviously show a very high sex ratio (*eg* breast) or are denied to one sex. Alcohol related cancers (*eg* cancers of the mouth, oesophagus and liver) show a very wide range in sex ratio; for example those countries where cancer of the oesophagus has a high incidence in males also have a high sex ratio (*eg* France, Switzerland) and the same countries have a

relatively high sex ratio for primary liver cancer and for oropharyngeal cancer. Similarly, lung cancer shows a very wide range in sex ratio (from 12.8 to 3.0) reflecting differences in social attitudes towards smoking between countries. The sex ratio for bladder cancer is much higher in countries with weak controls on industrial pollutants (*eg* eastern European countries) compared with those with strong controls (such as the nordic countries and the UK) or with little heavy industry (*eg* Ireland, Romania). This is consistent with the hypothesized importance in bladder cancer of industrial exposures which obviously will affect males much more than females. In contrast to the cancers related to alcohol or tobacco consumption or to industrial exposure, those related to dietary intakes show only small ranges in sex ratio (*eg* 1.9 to 2.6 for gastric cancer; 1.2 to 1.6 for colorectal cancer).

Table 4.7—Ratio of mortality (males: females) for various sites of cancer in the 24 European countries

	140–9	150	151	153/4	155	157	162	188
North								
Norway	2.9	4.2	2.0	1.2	1.8	1.6	4.6	3.1
Sweden	2.9	3.7	1.9	1.3	1.7	1.4	3.4	3.2
Denmark	2.2	3.0	2.0	1.3	1.4	1.3	3.6	3.7
Finland	2.1	1.9	1.9	1.3	1.6	1.5	11.4	5.1
West								
Belgium	4.3	4.0						
Belgium	4.3	4.0	2.1	1.3	1.7	1.7	12.5	4.5
France	12.9	12.7	2.3	1.6	4.5	2.1	11.0	5.2
FRG	5.1	5.4	1.9	1.3	2.3	1.6	8.5	4.3
Ireland	2.9	1.9	1.9	1.3	1.9	1.5	3.0	3.3
Netherlands	2.6	2.9	2.4	1.3	2.2	1.7	12.8	4.7
England & Wales	2.2	2.1	2.3	1.3	2.4	1.6	4.0	3.5
Scotland	2.1	2.0	2.1	1.3	2.4	1.4	3.6	2.7
South								
Bulgaria	3.2	3.3	1.7	1.3	1.6	1.7	6.3	4.8
Greece	2.7	3.1	1.8	1.1	2.1	1.8	7.0	5.8
Portugal	5.8	3.5	2.0	1.3	2.1	1.7	5.5	4.3
Spain	6.8	6.3	2.0	1.3	1.4	1.8	8.7	6.3
Yugoslavia	5.7	5.0	2.1	1.4	1.7	1.7	6.1	4.1
Italy	6.9	5.7	2.1	1.4	2.1	1.8	8.9	5.9
Romania	4.0	3.4	2.4	1.1	2.2	1.9	5.4	3.9
Central/East								
Austria	7.3	7.4	2.1	1.5	2.7	1.6	6.7	3.7
Czechoslovakia	5.7	7.3	2.1	1.6	1.8	1.7	10.3	6.1

	140–9	150	151	153/4	155	157	162	188
Hungary	6.7	7.4	2.3	1.3	2.0	1.6	5.9	5.3
Poland	4.7	4.9	2.6	1.3	1.1	1.6	8.0	7.3
Switzerland	5.9	7.3	2.1	1.5	3.5	1.6	9.3	4.1
GDR	4.4	5.2	2.1	1.2	2.1	1.7	9.9	4.9

An interesting observation is the very low sex ratios for oesophageal cancer in the British Isles, due to the relatively high rates in females; this has prompted considerably current research activity.

4.6
URBAN-RURAL DIFFERENCES

Since the general environment in urban and rural areas differ, it would be expected that cancers related to the environment would also differ. The nature of the environmental differences varies between countries, however. In all countries industrial exposures will be greater in urban populations. Therefore, whilst in affluent countries the standard of living, quality of the diet etc will be higher in urban areas, in times or places of severe economic depression life can often be better in the rural areas.

Table 4.8 gives urban-rural differences in cancer incidence for a number of European registries; the figures are based on age-standardized incidence rates for the period 1978–1982. Whereas in Norway and England/Wales the incidences are higher in the urban areas for all cancer sites and for both sexes, in the Calvados region of France the incidence of the alcohol related cancers (oropharynx, oesophagus and liver) are more common in the rural areas for both sexes except for female hepatic cancer. When analysed by cancer site, the urban/rural ratio is greater than one for all countries and for both sexes, but was close to one in England and Wales, Norway and Germany and much higher in Romania and Czechoslovakia. Similarly lung cancer

Table 4.8—Urban-rural differences in incidence of cancer at various sites in 8 European countries

		Urban/rural cancer incidence						
		150	151	153/4	155	162	174	180
Czechoslovakia	M	1.02	0.93	1.46	1.65	0.97	·	·
	F	(3.0)	1.10	1.47	1.00	1.45	1.54	1.65
Germany (Saarland)	M	1.09	1.14	1.11	1.75	1.23	·	·
	F	1.25	1.04	1.23	0.94	1.29	1.24	1.16
France (Calvados)	M	0.73	0.90	1.32	0.71	1.16	·	·
	F	0.85	0.92	1.28	5.00	1.17	1.00	0.81

		Urban/rural cancer incidence						
		150	151	153/4	155	162	174	180
Hungary	M	0.23	1.00	1.38	2.04	1.21	·	·
	F	–	1.35	1.26	0.83	1.66	1.66	1.67
Norway	M	1.67	1.04	1.22	1.93	1.61	·	·
	F	1.33	1.02	1.18	1.33	1.85	1.21	1.35
Romania	M	0.85	0.91	1.72	1.49	1.00	·	·
	F	–	0.86	1.90	1.60	1.42	1.44	0.93
England/Wales	M	1.05	1.24	1.07	1.23	1.32	·	·
	F	1.11	1.25	1.04	1.14	1.30	1.01	1.21

was more common in urban than in rural areas in all populations listed except Czechoslovakian males. As with colorectal cancer, breast cancer was generally more common in urban than in rural populations, especially so in Hungary, Romania and Czechoslovakia.

4.7
CONCLUSIONS

A wide range of putative cancer causes has been identified including smoking and air pollution (lung and respiratory tract), industrial pollutants (respiratory tract, bladder), diet (digestive tract, hormone-related cancers), use of exogenous hormones in birth control or in hormone-replacement therapy (hormone-related cancers), alcohol (oesophagus, liver, oropharynx), sunlight (melanoma) etc. All of these factors vary greatly geographically within Europe and so it would be expected that within Europe the patterns of cancer incidence would show wide variation. Further, since in some countries industrialization has taken place in a relatively uncontrolled manner whilst in others all industrial processes, exposures and effluents are closely controlled; diet is rapidly changing everywhere; cigarette consumption is increasing in southern Europe and decreasing in the north etc; the temporal changes in cancer would be expected to vary greatly within Europe.

As expected, wide variations are readily demonstrated. Europe represents an ideal laboratory in which to carry out epidemiological and aetiological studies of human cancer causation and prevention.

REFERENCES

Cayolla La Motta L, Falcao JM (1987). Atlas do Cancro em Portugal 1980–2. Ministerio da Saude, Lisboa.

Djordjevic M (1989). Descriptive and analytical epidemiological data on malignant diseases in Serbia-Yugoslavia. *Inst Oncol Radiol* Belgrade.

Doll R (1969). The geographical distribution of cancer. *Br J Cancer* **23:** 1–9.

Doll R, Muir C, Waterhouse J (1970). Cancer in Five Continents, Vol II. Springer-Verlag, Berlin.

Finnish Cancer Registry (1989). Cancer in Finland in 1954–2008. Finnish Foundation for Cancer Research, Helsinki.

Hill C, Benhamou E, Doyon F (1991). Trends in cancer mortality, France 1950–85. *Br J Cancer* **63:** 587–90.

Jensen OM (1989). Dietary fibre, carbohydrate and cancer: epidemiologic evidence. In *Diet and the Aetiology of Cancer* (ed Miller AB); Springer-Verlag, Berlin, pp. 21–30.

Jensen OM, Esteve J, Moller H, Renard H (1990). Cancer in the European community and its member states. *Eur J Cancer* **26:** 1167–1256.

Levi F, La Vecchia C, Negri E *et al* (1991). Le cancer en l'an 2000. Ligue Suisse Contrele Cancer, Lausanne.

Levi F, Maisonneuve P, Filiberti R *et al* (1989). Cancer incidence and mortality in Europe. *Med Soc Prev* **34(Suppl 2)**.

Muir C, Waterhouse J, Mack T, Whelan S 91987). Cancer Incidence in Five Continents, Vol V. IARC, Lyon.

Segi M (1980). Age adjusted death rates for cancer for selected sites (a classification) in 51 countries in 1975. (note: these volumes have been produced annually since 1975.)

Swedish Cancer Registry (1971). Cancer incidence in Sweden 1959–65. NBHW, Stockholm.

Waterhouse J, Muir C, Correa P, Powell J (1976). Cancer Incidence in Five Continents, Vol III. IARC, Lyon.

Waterhouse J, Muir C, Shanmuguratnam K, Powell J (1982). Cancer Incidence in Five Continents, Vol IV. IARC, Lyon.

5
Epidemiology of cancer within the United Kingdom

M J Hill, C P J Caygill

5.1
INTRODUCTION

For a variety of reasons, very good cancer statistics have been available for England and Wales, and for Scotland for most of the twentieth century. Before 1900 the mortality from infectious disease was so high that the cancer risk was only a relatively minor hazard and was not listed separately. As infectious disease was brought under control and life expectancy increased so the diseases of old age became relatively more important causes of death, and mortality rates for the major cancer sites are available in the Registrar General's Reports back to 1910.

Cancer registration was introduced in 1953 and incidence data have been reliable since 1960. For the last 30 years incidence data have been available by hospital region (or registry area) and data are available on regional variations (and its variation with time), time trends, and in relation to age, socioeconomic status, sex and population density for the major cancer sites.

Table 5.1 place the UK countries in their European context; Levi *et al* (1989) ranked the European countries in terms of their mortality from cancer at various sites. By European standards the UK countries have high mortalities of cancer of the lung, oesophagus and breast and relatively low male mortality of cancer of the liver, prostate, larynx and leukemias. An interesting feature is the relatively high mortality amongst women of a wide range of cancers which have a relatively moderate or low mortality amongst men (*eg* oropharyngeal, laryngeal).

The cancers most often related to diet are those of the digestive tract and the hormone-related cancers. Of these, UK males have, by European standards, relatively low mortalities of prostatic (males), hepatic (males and females), oropharyngeal (males), stomach (males and females) and uterus (females), whilst mortalities tend to be relatively high for cancer of the breast and ovary (females), oesophagus (males and females) and colorectum (particularly females). Table 5.2 gives the mortality rates for the diet-related cancers. Amongst males the most important are colorectal, gastric and prostatic cancer whilst amongst females, breast and colorectal cancer predominate.

Table 5.1—Rank of mortality in various sites in the countries of the United Kingdom (data from Levi *et al*, 1989)

	England/ Wales		Scotland		N Ireland	
	M	F	M	F	M	F
Oropharynx	19	5	15	1	23	2
Oesophagus	6	3	2	1	9	4
Stomach	17	19	16	17	14	13
Colorectum	12	12	8	7	11	3
Liver	23	24	20	19	24	20
Pancreas	12	12	10	5	11	7
Larynx	24	5	22	4	23	3
Bronchus/lung	4	2	1	1	9	5
Skin	15	13	13	11	20	9
Breast	–	1	–	2	–	5
Ovary	–	3	–	11	–	16
Uterus	–	14	–	19	–	22
Prostate	17	–	18	–	15	–
Bladder	5	3	4	1	17	7
Leukemias	20	20	22	24	13	17

5.2
VARIATION WITH AGE

Figs. 5.1 and 5.2 show the variation with age in incidence of the diet-related cancers for males and females respectively. Amongst males, the incidence increases sharply with age at each of the sites, with gastric and prostatic cancers being even more markedly diseases of old age than colorectal cancer. Cancer is more common at ages below 50 years in women than in men. Note that although ovarian cancer is in the second rank of mortality (Table 5.2) it is the commonest cause of cancer incidence and death in premenopausal women in the UK. The pattern of breast cancer incidence, as expected, is that of a high incidence population, and increases post-menopausally. The relation between incidence or mortality and age is similar in all UK countries and does not vary between the regions.

Table 5.2—Mortality of diet-related cancers in the UK countries (data from Levi *et al*, 1989)

	England/ Wales		Scotland		N Ireland	
	M	F	M	F	M	F
Oropharynx	2.8	1.3	3.2	1.5	2.4	1.4
Oesophagus	5.9	2.8	8.1	4.0	5.2	2.4

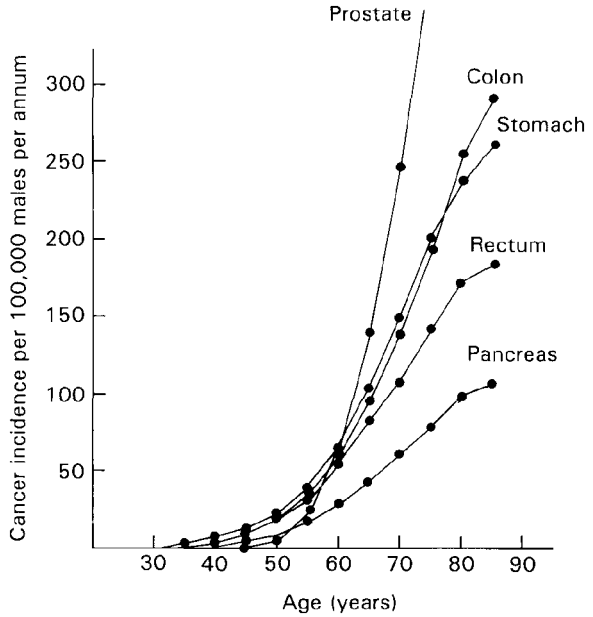


Fig. 5.1—Variation in incidence of various diet-related cancers in men (data for England and Wales)

	England/ Wales		Scotland		N Ireland	
	M	F	M	F	M	F
Stomach	16.8	7.4	17.4	8.2	17.5	9.0
Colorectum	21.1	15.6	23.1	17.8	21.5	18.6
Liver	1.1	0.5	1.5	0.6	0.9	0.6
Pancreas	8.1	4.9	8.2	5.9	8.2	5.6
Breast	–	28.2	–	27.9	–	25.9
Ovary	–	8.7	–	8.0	–	6.4
Uterus	–	8.2	–	7.6	–	6.7
Prostate	12.5	–	12.1	–	12.9	–

5.3
TEMPORAL VARIATIONS IN INCIDENCE

Figs. 5.3–5.9 show the temporal variations in incidence per 100,000 persons per annum in England and Wales of cancer of the endometrium, ovary, breast, pancreas, stomach, colon and rectum respectively for the period 1962–1985. There was no change with time seen for cancer of the endometrium (Fig. 5.3) in any of the age bands 45–54, 55–64 or 65–74; similarly, there was no change in

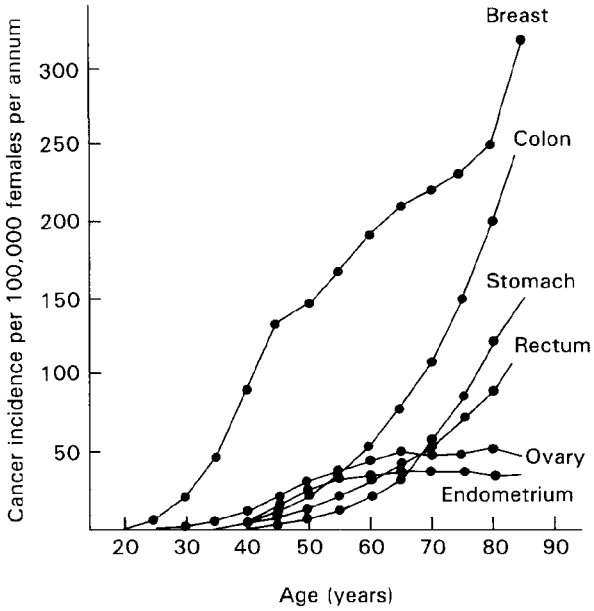


Fig. 5.2—Variation in incidence of various diet-related cancers in women (data for England and Wales)

the incidence of rectal cancer (Fig. 5.9) in either sex or in any age band (only ages 55–64 and 65–74 are shown). In ovarian cancer (Fig. 5.4) there was no change in incidence with time in age bands below 55 (and indeed there may have been a small decrease since 1977) but there was a steady increase in incidence over the time period studied for women aged 55–64 and 65–74.

For cancers of the breast (Fig. 5.5), colon (Fig. 5.8) and pancreas (Fig. 5.6) there was a steady increase in incidence at all ages from 1962–1974, after which the incidence reached a plateau for all three cancers at all ages.

In contrast, the incidence of gastric cancer (Fig. 5.7) decreased steadily throughout the study period at all ages.

The period 1962 onwards was chosen for the presentation of these data because by that time registration of cancer incidence had been established for almost a decade and so was reliable. Mortality could have been studied over a longer time period but the data are distorted by the effect of improvements in treatment. This has not been the case with gastric cancer, where treatment is still largely unsuccessful (despite more optimistic reports in the recent literature; *eg* Sue Ling, 1993); here the mortality has been decreasing steadily since the early 1940s (at which time gastric cancer was by far the commonest cause of cancer mortality in UK males). In colorectal cancer mortality data are available since 1910 (Hill, 1975); the mortality increased steadily to reach its maximum value in the 1940s, then decreased subsequently before its recent plateau. Put into this longer

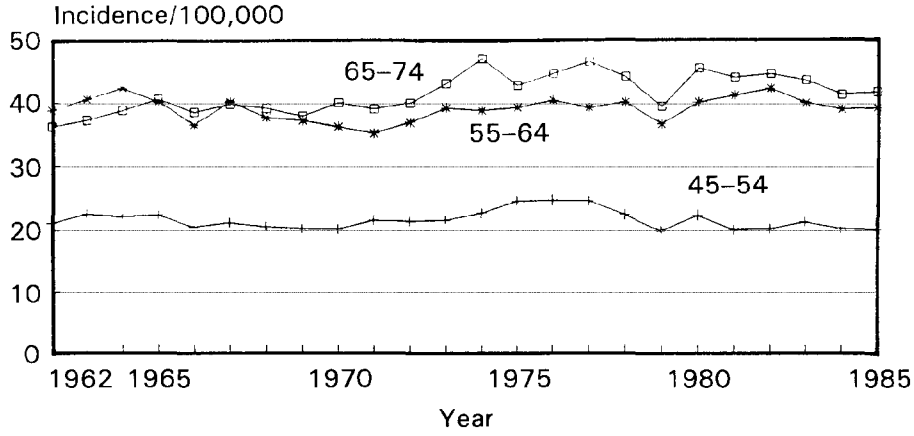


Fig. 5.3—Endometrial cancer incidence in different age bands, 1962–1985

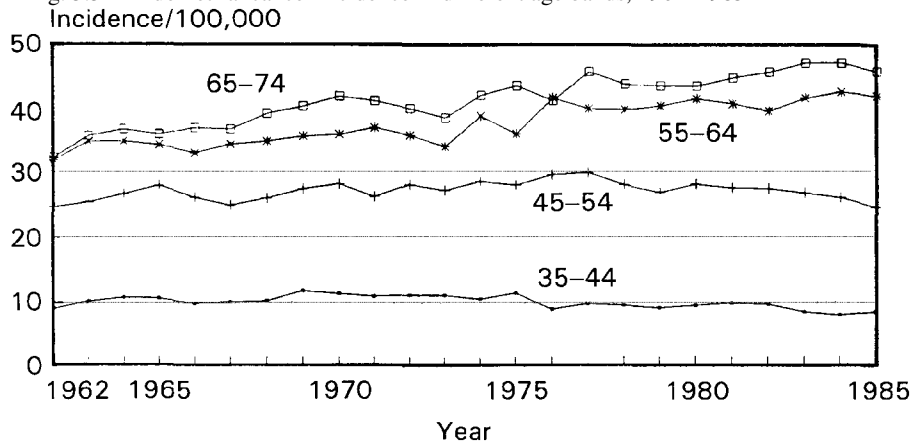


Fig. 5.4—Ovarian cancer incidence in different age bands, 1962–1985

context the increase in mortality during the period 1962– 1974 was small and against a background of greater (earlier) decreases.

None of the diet-related cancers shows the wide variations that can be seen in, for example, male lung cancer incidence which has seen huge increases in incidence at all ages until the 1970s, followed by large decreases in mortality and incidence in the younger age groups (which amounted to 50% in the under 55 year group between 1970 and 1988) following the impact of anti-smoking campaigns.

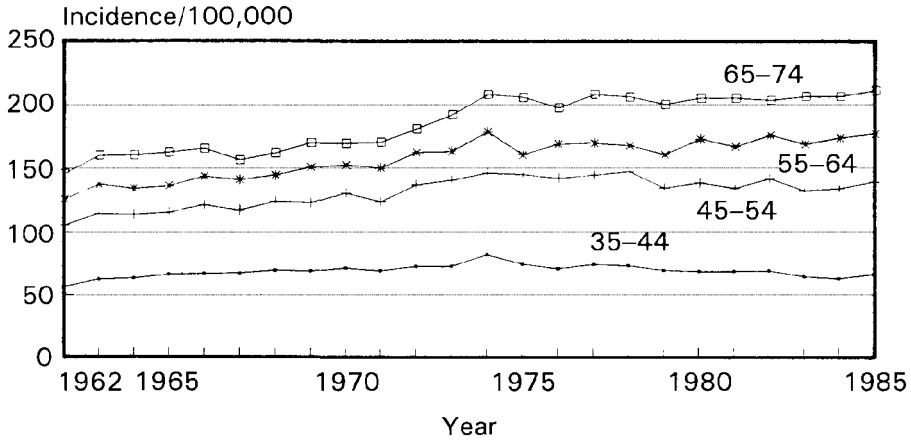


Fig. 5.5—Breast cancer incidence in different age bands, 1962–1985

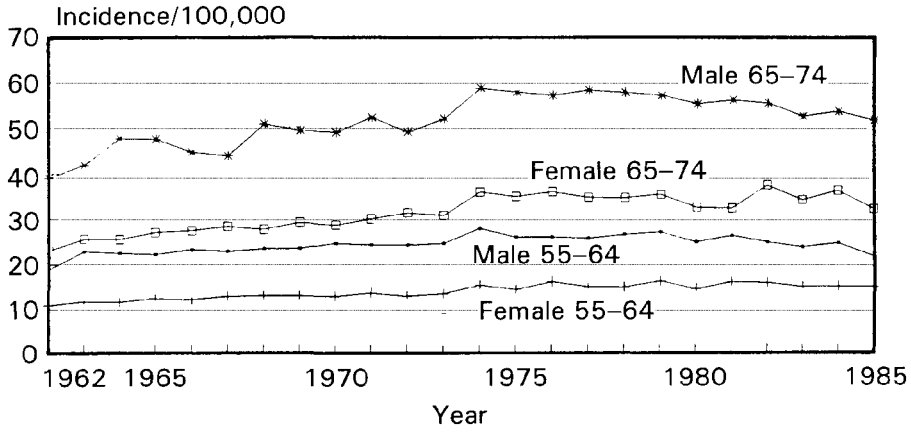


Fig. 5.6—Pancreatic cancer incidence in different age bands, 1962–1985

5.4
RELATION TO SOCIAL CLASS

Because diet is known to be related to socioeconomic status (as discussed in detail for the UK in Chapter 9) it would be expected that the risk of the diet-related cancers might also be related to income and to social status. This is certainly true, but interestingly, the relationship has been changing temporally for certain cases (though not for others).

In the UK statistics, socioeconomic status is determined largely by occupation and is subdivided into five groups namely group I—managers and employers; group II— professional persons; group III—skilled workers (divided into IIIN—non-manual and IIIM—manual skilled workers); group IV are semiskilled

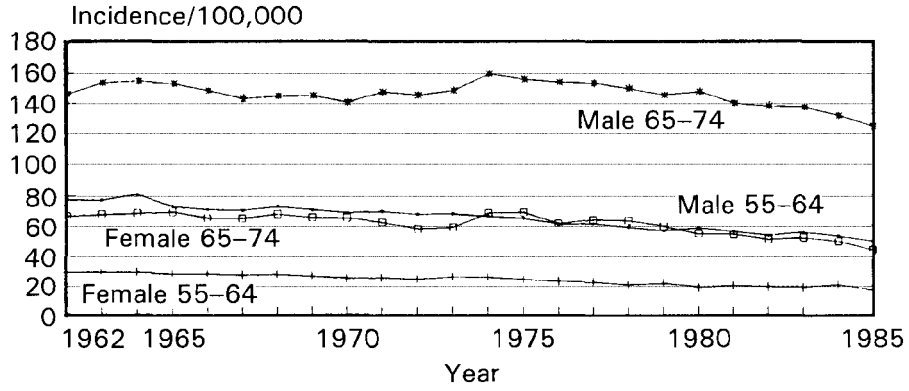


Fig. 5.7—Stomach cancer incidence in different age bands, 1962–1985

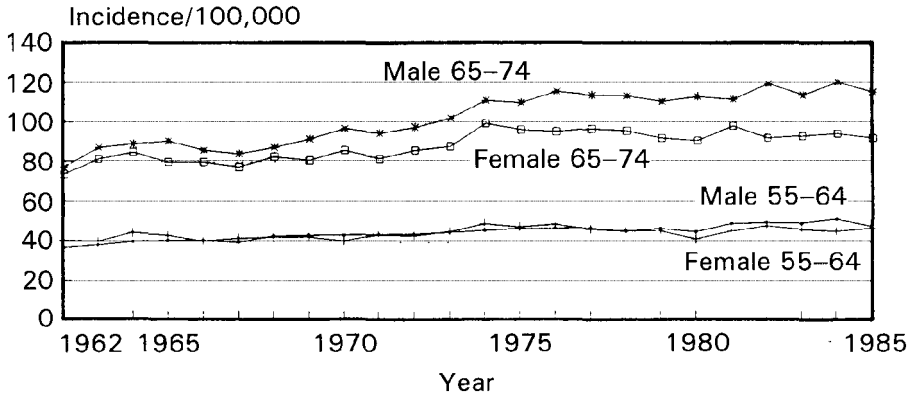


Fig. 5.8—Colon cancer incidence in different age bands, 1962–1985

workers and group V are unskilled workers. The socioeconomic classification of married women is based on the occupation of the husband.

5.4.1
Oesophageal cancer

The standardized mortality rate (SMR) for oesophageal cancer (England and Wales= 100) is inversely related to social class (Table 5.3) for men, marred women and unmarried women. The gradient was greatest for single women and increased between 1931 and 1971 for married women but not for men. The cumulative mortality rate (Table 5.4) decreased sharply between 1931 and 1971 for all classes of married women and men but not significantly for single women. The decrease presumably represents the result of improvements in the UK diet during this century.

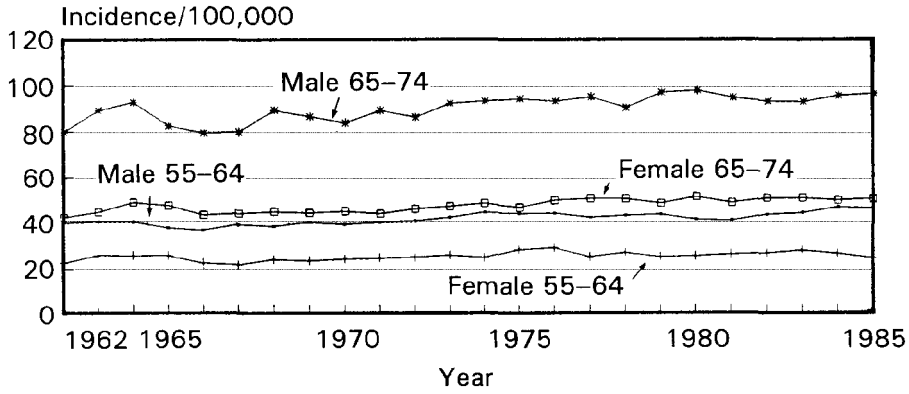


Fig. 5.9—Rectal cancer incidence in different age bands, 1962–1985

5.4.2
Gastric cancer

As with oesophageal cancer the SMR for gastric cancer was inversely related to socioeconomic status for men, married women and single women; the gradient increased sharply for men between 1911 and 1971, but less so for married women and not at all for single women. These changes were against a background of decreasing CMRs which were greatest in social class I and II (from 1–31 in 1921 to 0–58 in 1971—a 2.3 fold decrease in men) compared to class III (1.6 fold) or class IV and V (1.5 fold); similar differences between social classes with time were seen for married women and, less clearly, for single women.

5.4.3
Large intestine

In contrast to the oesophagus and stomach there was little relation between the risk of large intestine (mainly colon) cancer and social class, the standard mortality rate being only a little higher in social class I and II than in groups IV and V. As with the other cancers there has been a steady decrease in CMR in all socioeconomic groups which was relatively small than that for the upper digestive tract.

5.4.4
Rectum

In contrast to the large intestine but as with the oesophagus and stomach, there was an inverse relation between SMR and social class for both men and married women at all time periods studied (Table 5.3). This was against a steadily decreasing

trend in cumulative mortality rate which was steeper than that for the large intestine. In consequence, whereas the CMR for colon and rectal cancer in men was similar in 1921 and 1931 for all social class groups by 1971 the ratio of colonic to rectal CMR was 1.4 to 1.6 (Table 5.4).

Table 5.3—Standard mortality rates (UK=100) for various diet-related cancers at various times (1911 to 1971)

		Social class									
		I		II		III		IV		V	
		M	F	M	F	M	F	M	F	M	F
Oesophagus	1931	74	95	87	84	98	101	94	95	130	116
	1971	81	76	86	72	103	116	113	119	139	142
Stomach	1911	75	–	96	–	102	–	91	–	129	–
	1931	55	49	83	77	98	105	112	106	122	121
	1971	50	60	66	84	109	112	125	123	147	145
Large intestine	1911	127	–	101	–	97	–	85	–	98	–
	1931	110	119	104	99	102	102	99	89	94	102
	1951	109	102	103	108	102	99	92	101	99	95
	1971	104	118	100	93	106	112	100	112	111	110
Rectum	1911	99	–	95	–	107	–	98	–	100	–
	1931	–	100	–	97	–	105	–	86	–	106
	1961	79	69	89	81	106	107	98	106	120	132
	1971	84	99	90	98	111	111	106	105	108	135
Pancreas	1911	124	–	97	–	95		95	–	95	–
	1931	118	52	99	98	101	98	95	94	104	118
	1951	120	–	101	–	101	–	93	–	103	–
	1971	103	106	97	93	109	113	101	105	104	134
Breast	1931	–	138	–	116	–	103	–	84	–	82
	1951	–	137	–	110	–	104	–	84	–	85
	1971	–	117	–	112	–	109	–	103	–	92
Endometrium	1951	–	103	–	93	–	106	–	92	–	99
	1961	–	100	–	94	–	103	–	99	–	122
	1971	–	75	–	97	–	113	–	120	–	102
Ovary	1931	–	143	–	116	–	102	–	77	–	83
	1957	–	157	–	106	–	106	–	80	–	82
	1971	–	118	–	104	–	111	–	108	–	93
Prostate	1911	144	–	102	–	98	–	90	–	75	–
	1931	111	–	98	–	106	–	88	–	106	–
	1971	91	–	89	–	111	–	106	–	115	–

Table 5.4—Cumulative mortality rates (age 25–64) by social class and year

	Social class														
	I and II					III					IV and V				
	1921	1931	1951	1961	1971	1921	1931	1951	1961	1971	1921	1931	1951	1961	1971
Oesophagus															
Men	0.50	0.39	0.19	0.15	0.20	0.59	0.45	0.18	0.17	0.23	0.57	0.52	0.22	0.20	0.28
Married women	–	0.12	0.09	0.07	0.07	–	0.14	0.08	0.08	0.11	–	0.15	0.09	0.11	0.12
Stomach															
Men	1.31	1.32	1.01	0.73	0.58	1.62	1.63	1.50	1.19	1.00	1.88	1.95	1.77	1.52	1.21
Married women	–	0.72	0.51	0.34	0.28	–	1.02	0.67	0.49	0.39	–	1.10	0.75	0.59	0.45
Large Intestine															
Men	0.80	0.74	0.61	0.48	0.52	0.74	0.70	0.60	0.49.	0.55	0.69	0.66	0.55	0.46	0.53
Married women	–	0.66	0.66	0.47	0.48	–	0.67	0.60	0.53	0.55	–	0.64	0.59	0.52	0.55
Rectum															
Men	0.72	0.68	0.42	0.32	0.31	0.71	0.71	0.53	0.39	0.39	0.69	0.67	0.48	0.38	0.38
Married women	–	0.37	0.29	0.18	0.22	–	0.40	0.32	0.25	0.25	–	0.37	0.30	0.26	0.25
Pancreas															
Men	0.20	0.22	0.31	0.31	0.37	0.18	0.22	0.29	0.32	0.41	0.18	0.21	0.29	0.34	0.39

	Social class														
	I and II					III					IV and V				
	1921	1931	1951	1961	1971	1921	1931	1951	1961	1971	1921	1931	1951	1961	1971
Married women	–	0.15	0.17	0.17	0.19	–	0.15	0.17	0.19	0.23	–	0.16	0.17	0.19	0.23
Breast															
Married women	–	1.90	1.69	1.58	2.05	–	1.62	1.52	1.56	1.97	–	1.31	1.24	1.48	1.79
Endometrium															
Married women	–	–	0.23	0.19	0.15	–	–	0.25	0.20	0.19	–	–	0.23	0.21	0.19
Ovary															
Married women	–	0.42	0.60	0.56	0.66	–	0.35	0.56	0.55	0.68	–	0.28	0.42	0.54	0.64
Prostate															
Men	0.20	0.21	0.21	0.18	0.16	0.19	0.22	0.17	0.17	0.19	0.14	0.20	0.19	0.17	0.19

5.4.5
Pancreas

In contrast to all of the sites considered so far, cancer of the pancreas showed an increasing CMR between 1921 and 1971; this was accompanied by a change in the relation to social class in males from a positive correlation in 1921 to no relation in 1971 and in females from an inverse correlation in 1931 to no relation in 1971. Any thesis concerning the causation of pancreatic cancer needs to be able to explain these changes.

5.4.6
Breast

The CMRs of breast cancer were very much higher in social class I and II than in class IV and V but the differences were much smaller in 1971 than in 1931. Indeed, whereas there was little change in the CMR in class I and II during that period (Table 5.4) there was a 37% increase in the CMR of classes IV and V and an intermediate 22% increase in class III. Consistent with this the very high gradient of SMR from social class I (138) to class V (82) seen in 1931 moderated to 117 versus 92 in 1971. Thus, a component of the aetiology of breast cancer which was strongly associated with socioeconomic status in 1931 was less so by 1971.

5.4.7
Endometrium

Although there was no relation between social class and SMR in 1957 and 1961, then SMR in highest social classes were well below average in 1971, with the maximum SMR seen amongst the wives of skilled workers. The CMR decreased steadily in all 3 social class bands from 1957 to 1971. This fall in social class gradient was against a background of increasing CMR; this was, of course, most dramatic in social class IV and V where the CMR increased by 129% between 1931 and 1971 (compared with 57% for social classes I and II).

5.4.8
Prostate

The social class gradient for prostate cancer changed from being strongly positive in 1911, to no relation in 1931, to modestly inverse by 1971, against a background of no change in CMR in social class I and II and a 35% increase in CMR of social class IV and V. However, although these observations are the most interesting in terms of the changes in social class pattern with time they are also the least reliable. Prostate cancer is notoriously under-diagnosed, because it is a disease of old age. In 1911 the medical services for social class I and II would have been very much better than those for the lower socioeconomic groups and this could be the explanation for the very strong correlation between the disease and socioeconomic status seen at that time. The CMR data are extremely misleading for this cancer because they only cover ages up to 64; the vast majority of cases would occur at higher ages (*eg* 75+).

5.5
REGIONAL VARIATIONS

Tables 5.5 to 5.7 illustrate the regional variations in risk of a number of diet-related cancers. In Table 5.5 the SMR are shown for 1966 for some hospital regions representing various parts of England and Wales. Cancers of the upper digestive tract (oropharynx, oesophagus and stomach) have a much higher SMR in the north and west (Wales, North, North-West, Mersey) than in the southern part of England (W Midlands, South-West and NE Thames). In the oropharynx the range in SMR is very wide (138 to 68 for women, 128 to 66 for men) in the selected regions but Table 5.8, which shows the range in SMR when all regions are considered. For cancers of the oesophagus the South-West behaves more like Wales than south-east England (represented by NE Thames). In the case of gastric cancer Table 5.5 gives a false impression of the range since NE Thames has a SMR which, while well below than of Northern England and Wales, is much higher than that in NW Thames (SMR=79 for men). The regional variation in SMR for colorectal cancer is much lower than for the upper digestive tract, although the pattern is qualitatively similar. Similarly the range for breast cancer is low (Table 5.8) with the highest SMRs seen in South-East England and the Midlands; the SMRs for the northern regions shown in Table 5.5 are all below 100, in contrast to those for the digestive tract. The regional distribution of SMR for cancer of the endometrium and prostate is much less clear perhaps because the mortality from endometrial cancer is, in any case, relatively low and the diagnosis rate for prostatic cancer is dependent on the enthusiasm of the post-mortem pathologist.

Table 5.5—Regional variation in standardized mortality rates by sex and site (England and Wales=100) 1966

		Wales	North	NW	Mersey	W Mid	NE Thames	SW
Oropharynx	M	107	123	128	116	111	66	110
	F	138	110	119	110	88	66	91
Oesophagus	M	101	116	102	145	98	98	108
	F	135	118	109	91	102	85	122
Stomach	M	132	115	117	118	101	102	97
Colorectum	M	103	112	104	102	110	89	97
	F	97	104	107	108	107	93	100
Breast	F	93	94	97	86	108	104	98
Endometrium	F	105	88	108	83	114	87	125
Prostate	M	104	88	98	98	94	98	110

The regional distribution for 1977 was very similar to that for 1966 except that the ranges had widened and the benefits of living in the South-East were even more apparent. Note that for the diet-related cancers the SIR for NE Thames

were almost always well below 100. In contrast the SIRs for Wales were very high and were well above 130 for males for all sites considered, whilst the SIRs for the regions in the north of England were more than 100 in all except one or two cases per region. In Table 5.8 the lowest SIR for 1966 for all cancer sites was for a region in the south of England; in 1977 this was also true except for two sites—female oropharynx (Yorkshire region) and male pancreas (Mersey region). In 1977 the region with the highest SIR was Wales for each of the diet-related cancers.

Table 5.6—Regional variations in standardized incidence rate of diet related cancers in England and Wales in 1977 (England and Wales=100)

		Hospital Region						
		Wales	North	NW	Mersey	W Mid	NE Thames	SW
Oropharynx	M	183	85	106	133	77	100	89
	F	119	101	81	122	71	64	85
Oesophagus	M	141	110	110	120	104	78	105
	F	167	105	111	136	103	72	114
Stomach	M	148	107	119	117	101	80	92
Colon	M	135	102	101	104	92	84	103
	F	129	101	100	105	99	69	107
Rectum	M	146	106	100	109	102	78	112
Breast	F							
Ovary	F							
Endometrium	F							
Prostate	M							
Pancreas	M	143	108	108	84	90	87	93
	F	130	89	106	104	92	74	98

Standardized incidence rates (England and Wales=100) of diet-related cancers by region for 1977.

The regional distribution for the same cancers for 1986 is shown in Table 5.7. Whilst the range in SIRs (249 to 32) had further increased for cancer of the oropharynx it had narrowed somewhat for all of the other digestive tract cancers and remained remarkably steady for all 3 time periods for the hormone-related cancers. However, the qualitative pattern remained consistent; in all cases the lowest SIR was for a region in southern England whilst the highest SIR in the digestive tract cancers was in Wales or northern England. Again, the SIRs for NE Thames were all below 100; similarly those for the South-West were below 100

for digestive tract cancers (but not for the hormone-related cancers). Only in the West Midlands were the SIRs above 100 for all cancers, and those for the northern regions showed a tendency to move closer to 100 between 1977 and 1986.

Table 5.7—Regional variaitons in standardized incidence rates of diet-related cancers in England and Wales in 1986 (England and Wales=100)

		Wales	North	NW	Mersey	W Mid	NE Thames	SW
Oropharynx	M	114	100	249	193	111	89	90
	F	169	80	161	124	110	54	43
Oesophagus	M	118	126	130	100	103	82	92
	F	96	129	129	129	111	72	88
Stomach	M	109	118	119	120	126	91	70
Colon	M	91	112	107	120	111	73	90
	F	88	104	105	98	110	83	92
Rectum	M	131	120	107	121	132	71	84
Breast	F	103	90	102	102	110	94	103
Ovary	F	100	100	113	97	119	86	90
Endometrium	F	92	89	79	83	118	86	103
Prostate	M	93	89	98	96	107	86	106
Pancreas	M	110	102	115	106	105	93	90
	F	87	111	114	109	103	98	91

5.6
RELATION TO POPULATION DENSITY

Table 5.9 shows the relation between population density and SMR for cancers at various sites for 1966. The strong correlation between population density and SMR for cancer at all sites for males is largely due to the very strong correlations for cancer of the lung and the bladder, both of which are related to smoking and to industrial exposures. In contrast, there is very little relation for cancer of the large bowel, prostate, breast or male oesophagus. There is, if anything, an inverse correlation for the female oesophagus. For gastric cancer, although the SMR for conurbations were only modestly elevated, there was a correlation with population density for non-conurbation urban and rural areas for both males and females. Similarly for males oropharyngeal cancer SMR was correlated with population density in non-conurbation areas.

Data for 1978–1982 are available on very broad urban-rural differences (Table 5.10). As for the 1966 data the urban-rural differences were very strong for cancer of the lung and bladder for both males and females, and were very weak for colorectal, breast and oropharyngeal cancer. The only diet-related

cancers which show a strong urban-rural difference in incidence are the oesophagus and the liver (both alcohol-related).

Table 5.8—The highest and lowest SIR amongst the hospital regions of England and Wales

		1966		1986		1977	
		H	L	H	L	H	L
Oropharynx	M	N West	NE Met	N West	Wessex	Wales	Wessex
		128	66	249	32	183	70
	F	Wales	Oxford	Wales	S West	Wessex	Yorks
		138	54	169	43	218	41
Oesophagus	M	Mersey	Oxford	N West	Oxford	Wales	Oxford
		145	70	130	49	141	76
	F	Wales	E Anglia	N West	NE Met	Wales	NE Met
		135	75	129	72	167	72
Stomach	M	Wales	NW Met	W Mid	S West	Wales	Wessex
		132	79	126	70	148	77
	F	N West	NW Met	N West	SW Met	Wales	Wessex
		129	78	128	72	169	62
Colon	M	Wessex	NW Met	Mersey	NE Met	Wales	NE Met
		113	87	120	73	135	78
	F	SE Met	Oxford	E Anglia	NE Met	Wales	NE Met
		114	74	117	83	129	69
Breast	F	SW Met	Oxford	Wessex	SE Met		
		116	83	113	86		
Uterus	F	S West	SW Met	E Anglia	NW Met		
		125	86	127	83		
Prostate	M	SE Met	NW Met	E Anglia	NE Met		
		126	87	122	86		
Pancreas	M			N West	S West	Wales	Mersey
				115	90	143	84
	F			N West	SE Met	Wales	NE Met
				114	79	130	74

Table 5.9—The relation between population density and SMRs for cancers at various sites, for 1966

			Urban			
		Conurbations	>100,000	50–100,000	<50,000	Rural
All sites	M	109	108	102	97	84
	F	102	105	99	99	94

			Urban			
		Conurbations	>100,000	50–100,000	<50,000	Rural
Oropharynx	M	94	125	109	100	91
	F	100	94	96	109	97
Oesophagus	M	105	105	93	101	92
	F	96	105	85	101	111
Stomach	M	102	117	100	100	88
	F	105	113	97	96	89
Colorectum	M	100	102	113	103	90
	F	102	105	104	99	93
Breast	F	100	108	96	102	96
Endometrium	F	93	94	88	115	105
Prostate	M	97	95	105	104	100
Lung/bronchus	M	118	109	102	91	76
	F	119	100	97	83	87
Bladder	M	111	112	104	102	74
	F	115	100	106	97	75

Table 5.10—Urban-rural differences in incidence of cancer at various sites (age-standardized rates for 1978–82, taken from Cancer in Five Continents Vol 5)

	Males			Females		
	Urban	Rural	U/R	Urban	Rural	U/R
Oropharynx	5.8	5.5	1.05	3.1	2.8	1.11
Oesophagus	18.9	15.0	1.24	8.0	6.4	1.25
Colorectum	30.1	28.0	1.07	22.7	21.8	1.04
Liver	1.6	1.3	1.23	0.8	0.7	1.14
Cervix				12.0	9.9	1.212
Breast				53.8	53.2	1.01
Bladder	17.2	14.0	1.23	4.7	3.8	1.24
Lung	74.8	56.2	1.32	19.7	15.1	1.30

Note that the urban-rural differences are weaker in the UK than in Europe in general for cancers of the colorectum, liver and breast; in contrast, it is abnormally high for gastric cancer.

5.7
CONCLUSIONS

Within the United Kingdom there are wide regional variations in incidence of a range of cancers; however, with time the variations have moderated so that the range in incidence was less in the 1980s than it had been two decades earlier.

The UK shows an atypical sex ratio for oesophageal cancer, thought to be due to an incidence in women that is higher than expected on the basis of alcohol and tobacco consumption. This high rate is seen in all regions of the British Isles and is the subject of much current investigation.

Urban-rural differences are smaller in the UK than elsewhere in industrial Europe. The Clean Air Act that greatly reduced the amount of air pollution by banning domestic burning of coal in urban areas from the early 1960s, may be responsible for much of the decreased urban-rural difference. However, a further explanation may be that the overall population density has meant that the proportion of people living in rural areas that are distant from an urban centre is small. This lack of isolation probably results in smaller urban-rural differences in, for example, diet or social attitudes to birth control etc.

In contrast, the temporal changes in cancer patterns in the UK have been marked, as the *island mentality* was dissipated in response to improved communications. Surely the familiarity with European recipes as a result of holidays abroad has had a marked effect on the UK diet, reinforced by the relative ease of purchase of imported fresh foods in comparison with the 1960s.

REFERENCES

Cancer in Five Continents Vol 2 (1970). Doll R, Muir CS, Waterhouse J (eds). IARC, Lyon.

Cancer in Five Continents Vol 3 (1976). Waterhouse J, Muir C, Correa P, Powell J (eds). IARC, Lyon.

Cancer in Five Continents Vol 4 (1982). Waterhouse J, Muir C, Shanmuguratnam K, Powell J (eds). IARC, Lyon.

Cancer in Five Continents Vol 5 (1987). Muir C, Waterhouse J, Mack T, Powell J, Whelan S (eds). IARC, Lyon.

Hill MJ (1975). The etiology of colon cancer. *Crit Rev Toxicol* **4:** 31–82.

Levi F, Maisonneuve P, Filiberti R *et al* (1989). Cancer incidence and mortality in Europe. *Soz Praev Med* **34(Suppl 2)**.

OPCS (1962 to 1988). Cancer statistics: registrations for England and Wales, HMSO, London (published annually).

Sue-Ling H, Johnston D (1993). Gastric cancer is curable in the west. *Eur J Cancer Prev* **2:** 13–16.

6
Cancer epidemiology in Italy
R Filiberti, A Giacosa, P Visconti, L Borsa

6.1
INTRODUCTION

Cancers account for about 22% of all deaths in European countries. Cancer occurrence differs greatly between and within countries (Levi *et al*, 1989) and this is not simply an artefact due to the differences in the registration of data, but may be explained by variations in the levels of various aetiologic factors such as environmental exposure or specific life style habits such as smoking and diet (Armstrong *et al*, 1975; Doll and Peto, 1981). Generally, mortality rates for all cancers show a tendency to be lower in southern Europe than central Europe and Scotland.

Estimated incidence rates, based on mortality figures, for selected sites in the Europe Community have been calculated by Jensen *et al* (1990) for the period 1978– 82. Data for oesophagus, stomach, colon, lung, breast and ovary have already been presented in Chapter 4 (see Figs. 4.1 and Fig. 4.2 for example). In these figures Italy ranks respectively second and third for stomach and bladder cancer (estimated rates standardized to world population *x* 100,000 for males SR: 33.0 *vs* 40.3, Portugal and 22.8 *vs* 24.8, Denmark). It ranks fifth for lung (70. 0 *vs* 91.8, Belgium) and seventh for oesophageal and prostatic cancers (4.3 *vs* 11. 5, France and 28.8 *vs* 43.4, Germany). Conversely, it has been estimated that Italy has one of the lower incidence rates in Europe for cancer of the colon (16.0 *vs* 24.9, Germany), breast (52.6 *vs* 75.6, UK) and ovary (8.3 *vs* 15.5, UK) (Jensen *et al*, 1990).

Cancer rates for a whole country are average values that do not take account of marked differences existing within each country. Italy, in particular, has a very wide range of variation in site specific cancer incidence in different areas (North, Centre and South); this is illustrated in Fig. 6.1. These regions differ also in geodemographic factors, showing, for example, an increase for both sexes, from North to South, in the number of unemployed, illiterate persons and number of individuals living in the same house (crowding index) (Table 6.1).

Incidence data in Italy are available from nine cancer registries which *cover* about 10% of the whole population and are located mainly in the Northern

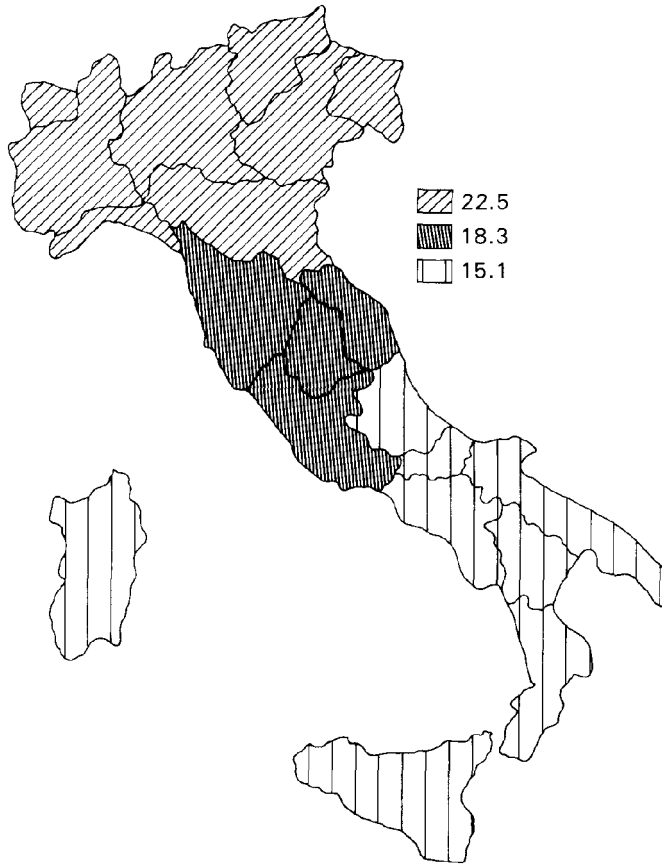


Fig. 6.1—Cancer mortality rates* by geographical areas (males, 1988).

regions (Fig. 6.2). Incidence and mortality data for some site specific cancers in the Italian registries for the period 1983–87, together with mortality in the three geographical areas for 1985, are shown in Figs. 6.3 to 6.23. Trends in mortality/ increase of these neoplasms in Italy (1964–88) and in the various areas (North, Centre, South) (1970– 85) are presented in Figs. 6.24 to 6.39) (La Vecchia *et al*, 1986, 1990; Capocaccia *et al*, 1991; Decarli *et al*, 1991, 1992; Zanetti and Crosignani, 1992).

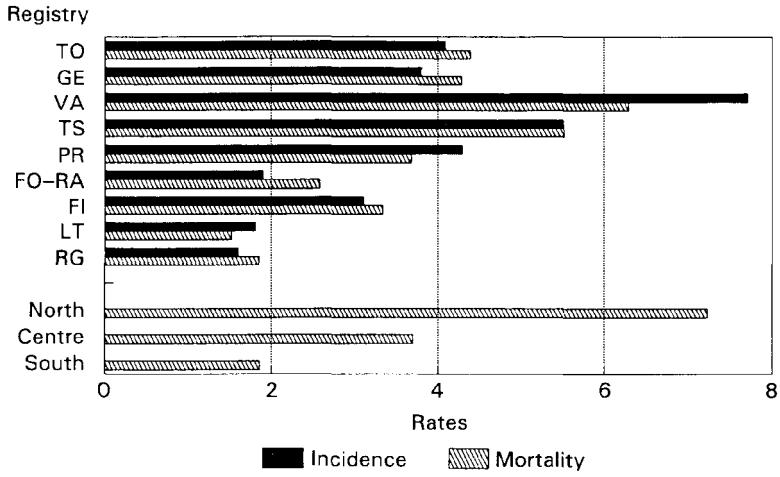
*Age-standardized rates to Italian populatin 1971×10,000.

Fig. 6.2—Geographical distribution of Italian cancer registries.

Table 6.1—Geodemographic and environmental Italian parameters

Parameters	Geographical areas		
North	Centre	South	
Territory (sq km)	99451	52057	111519
Forest (%)	33	31	54
Inhabitant/hospital bed (1988)	106	130	155
Unemployed:			
males (%) (1990)	2.94	6.22	13.55
females (%) (1990)	8.59	15.68	31.88
Crowding index of the main house:			
>1.60 (%) (1988)	1.33	2.64	6.72
Education of the head of the family:			
illiterate (%) (1988)	7.85	10.40	20.81
secondary school (%) (1988)	26.54	25.81	23.83
degree (%) (1988)	4.51	5.99	5.01

For all cancers there is an evident decrease in rates from North to South (*ie* to the truly Mediterranean areas of the country). Total cancer mortality rates are around



Age standardized rates (world population) x 100,000
Source: Zanetti et al., 1992

Fig. 6.3—Oesophagus cancer incidence and mortality in Italy. Males.

35% higher for males and 25% for females in Northern areas in comparison to Southern regions (Table 6.2 and Fig. 6.1).

6.2
GASTROINTESTINAL CANCERS

Oesophageal cancer is one of the non-sexual-related site specific neoplasms with a high sex ratio. Incidence approximates to the mortality rates and is very high in Northern areas (Figs. 6.3 and 6.4) which compares with the highest values in European countries. Indeed, northern areas have repeatedly been found to have higher mortality values which correlate to intake of tobacco and alcohol (Zanetti and Crosignani, 1990) (SR for males: 7.3 in the North *vs* 1.9 in the South). These data are confirmed by the highest male incidence rate in Varese (7.7 *vs* 1.6 in Ragusa) (Fig. 6.3). The mean incidence value is 3.8 for males (Fig. 6.3) and 0.7 for females (Fig. 6.4). Mortality rates have shown a slight increase with time in males in Northern regions (from 6.2 in 1970 to 7.2 in 1985; Fig. 6.26) but not in females (Fig. 6.27).

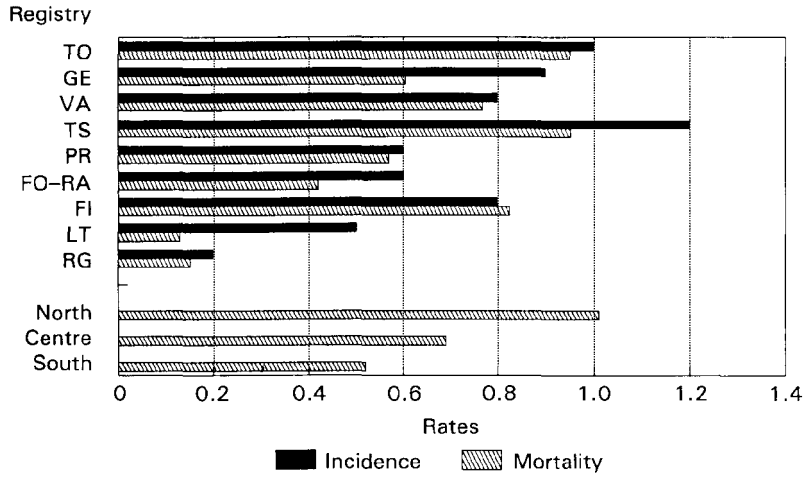
Table 6.2—Cancer mortality rates* in Italian regions (1988). All sites

	Males	Females
North West Italy		
Piemonte	20.4	11.8

	Males	Females
Val d'Aosta	21.4	12.7
Lombardia	25.1	12.6
Liguria	20.3	11.6
North East Italy		
Trentino AA	20.2	11.9
Veneto	23.5	11.3
Friuli VG	24.5	12.9
Emilia R	19.9	12.2
Total Northern Italy	22.5	12.1
Central Italy	18.3	11.0
Toscana	19.2	11.4
Umbria	16.7	10.5
Marche	16.4	9.4
Lazio	18.6	11.4
Southern Italy	15.1	9.7
Abruzzi	14.2	9.2
Molise	13.7	8.3
Campania	17.1	10.3
Puglia	15.8	10.0
Basilicata	13.6	9.5
Calabria	12.9	8.4
Sicilia	13.6	9.5
Sardegna	16.8	9.8
Total Italy	19.3	11.1

*Age-standardized rates to Italian population 1971x10,000.

Stomach cancer frequency is higher in Central and Northern regions (Fig. 6.5 and 6.6), the ratio between highest and lowest registries being around 2.5 (Firenze 40.1 and Ragusa 16.1 for males) (Fig. 6.5). Distribution by subsite reveals a higher frequency of cancers of the antrum, together with a high percentage of *nonspecified sites* due to inaccuracies in cancer notification (Fig. 6.7). The mean incidence rate is 27.0 for males and 13.0 for females. Stomach cancer mortality has been decreasing throughout the country, from 29.6 to 18.9 for males and from 15.1 to 8.9 for females (Figs. 6.28 and 6.29) but this disease is still one of the most common neoplasms (Figs. 6.24 and 6.25). A more marked diminution is evident, nevertheless, in Northern and Central areas (around —50%) than in the South (Fig. 6.28 and 6.29). Even if the aetiology of stomach cancer remains largely unknown, it is evident that changes occurred in high risk areas which represent the results of changes in dietary habits (including lower consumption of preserved foods). Analytical studies support the hypothesis of a



Age standardized rates (world population) x 100,000
Source: Zanetti et al., 1992

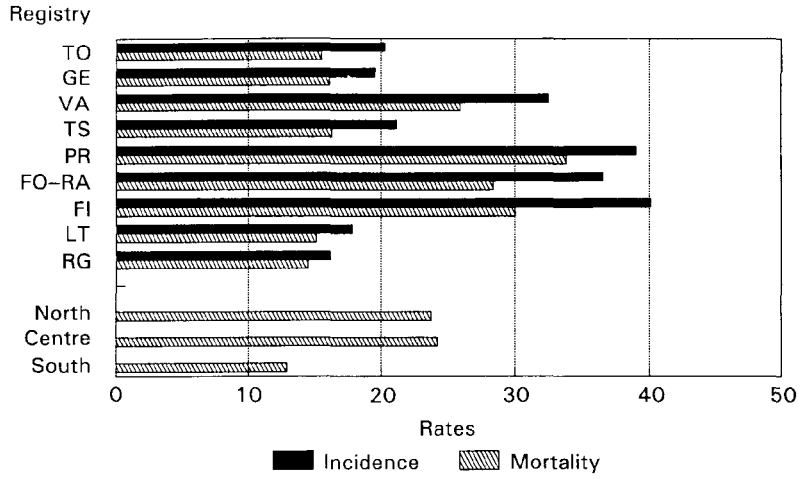
Fig. 6.4—Oesophagus cancer incidence and mortality in Italy. Females.

protective effect of fresh fruits and vegetables (see also Chapter 17) and, between micronutrients, such as →tocopherol which is present at high levels in olive oil (see Chapter 13), which is used in large amounts in the rural areas and particularly in the more Mediterranean areas (Buiatti *et al*, 1990).

The range of mortality for colon cancer is about 2-fold from Northern to Southern areas (respectively SR around 11 and 6 for males) and mortality figures are approximately half the incidence (Figs. 6.8 and 6.9). The number of new cancer cases, occurring mostly in the sigmoid region (Fig. 6.10), is higher in Northern registries (Trieste 30.9, Parma 23.4 and Varese 24.0; males). Mean incidence rates are 20.7 for males and 15.5 for females (Figs. 6.8 and 6.9). The different rates observed among the areas could be partially attributed to different dietary intakes and in particular to a higher animal fat consumption (Zanetti and Crosignani, 1992).

When considering the statistics for cancer of the liver (Fig. 6.11) it should be kept in mind that there are difficulties concerning the distinction between primary and secondary tumours at this site. This problem is more relevant to the mortality statistics of this neoplasm which is suspected to be associated, at least in part, to a viral aetiology. Mean incidence values in Italy are 8.9 for males and 3.1 for females. The highest values are observed for males in Trieste (14.9), Varese (10.6) and Torino (10.4) (Fig. 6.11) and for females in Latina (4.7) and Ragusa (3.6), affecting younger age groups in these areas than in the other regions.

Pancreatic cancer mortality rates have shown increasing values in all areas, but this trend could be attributable, at least in part, to the improvements in diagnostic techniques which occurred in the last ten years. Trieste has the highest



Age standardized rates (world population) x 100,000
Source: Zanetti et al., 1992

Fig. 6.5—Stomach cancer incidence and mortality in Italy. Males.

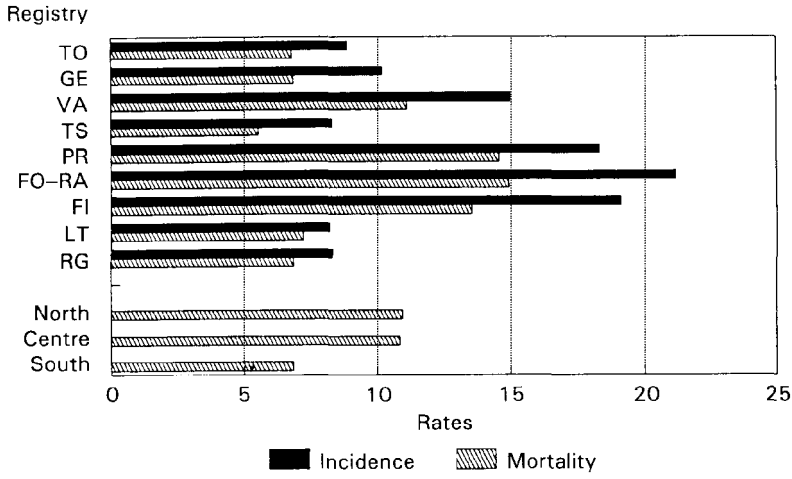
incidence rate in females (SR: 6.6) and has high rates in males also (9.8 compared to 10.2 in Parma, the highest SR) (Figs. 6.12 and 6.13).

6.3
LUNG CANCER

Lung cancer is the site with the highest incidence and mortality in the male population. Geographically, a decreasing mortality gradient from North (SR: 68. 3) to Centre (55.5) and South (44.3) is observed (Figs. 6.14 and 6.15). Incidence, too, is twofold higher in Northern areas, particularly Trieste (88.1) and Varese (83.6), with a mean value of 65.4 for males and 8.1 for females (Figs. 6.14 and 6.15). This neoplasm has dramatically increased in incidence in Italy during the last 20 years (Figs. 6.32 and 6.33) for both sexes (higher than 60% for females and 100% for males), with a more marked increment of mortality rate in the South (from 42.1 to 68.3 in the North and from 25.9 to 44.3 in the South; males).

6.4
FEMALE CANCERS

Sex-related cancers in females, *ie* breast and ovary, show similar patterns, with the highest mortality rate in the North (22.8, 5.8 in the North and 16.7, 3.4 in the South respectively) (Figs. 6.16 and 6.17). This gradient is confirmed by estimated incidence rates for breast cancer in 20 Italian regions (Fig. 6.18) (Micheli *et al*, 1992). For both sites, incidence values are elevated in the areas of



Age standardized rates (world population) x 100,000
Source: Zanetti et al., 1992

Fig. 6.6—Stomach cancer incidence and mortality in Italy. Females.

Forli-Ravenna (64.8, 11.9 respectively), Varese (66.4, 10.7) and Genova (65.9 and 9.4). Mean national incidence rates are around 59.0 for breast and 9.2 for ovary. Breast cancer represents about 25% of all female cancers in Italian registries; within Europe, Italy occupies a medium-high position, similar to that of other industrialized countries (Zanetti and Crosignani, 1992). From 1970 to 1985 an increasing trend is observed for both cancers throughout the country (around 12% breast and 20% ovary in North and 18% and 32% in the South respectively) (Figs. 6.34 and 6.35). Ovarian cancer shares some risk factors with neoplasms of the breast, namely, hormonal correlations and, it has been suggested, dietary factors in terms of high consumption of calories and/or fats: this may explain the geographical variation in the incidence of these diseases (Boyle, 1988).

Mortality statistics for cancers of the uterus are not able to distinguish between cervical and corpus uteri which have two distinct pathologies from the aetiological point of view (a viral aetiology for the cervix and hormonal factors and obesity for corpus uteri). Mortality from cancer of the uterus (site not specified) is around 40% higher in Southern regions (SR: 6.8 *vs* 4.7, North) but has halved in the last 15 years (Fig. 6.36). Incidence data (Fig. 6.20) show that rates for cervical cancer are higher in the South (Ragusa 11.5 *vs* 7.2 Varese), but differences between the areas are less marked than was previously thought on the basis of mortality data (Zanetti and Crosignani, 1992). Corpus uteri incidence is higher in Varese (14.1) Firenze (13.1) and Ragusa (13.1), but nevertheless quite uniform rates are observed throughout the country (Figs. 6.19 and 6.20).

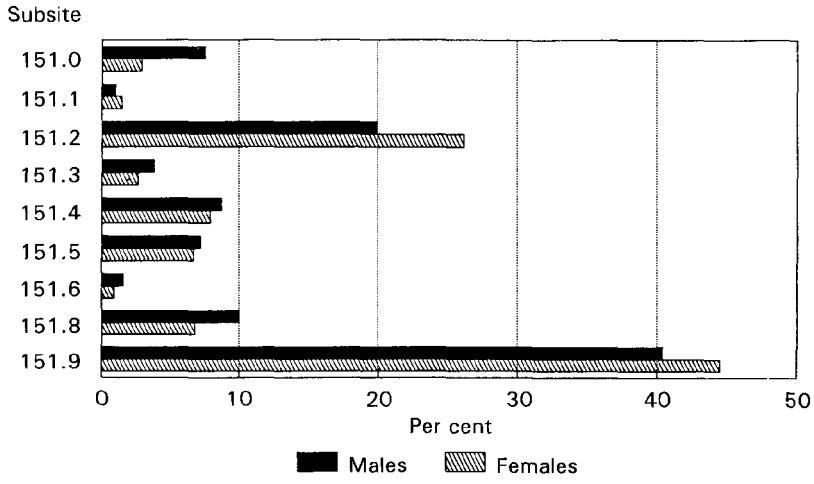


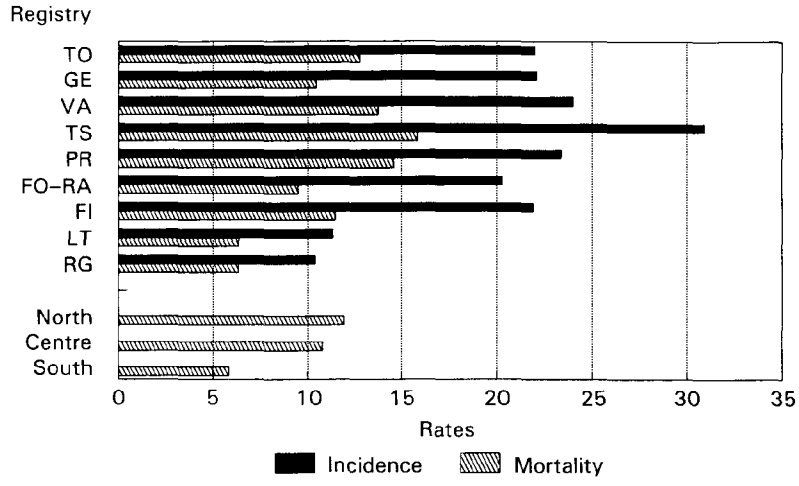
Fig. 6.7—Stomach cancer incidence in Italy (1983–87). Distribution by subsite.

6.5
OTHER CANCERS

Diet, particularly consumption of animal fats, is supposed to be an aetiological factor in cancer of the prostate (Snowdon *et al*, 1984). This tumour is more frequent in Northern areas (Fig. 6.21) and shows slowly increasing mortality trends with time (from 11.4 to 12.9 in the North and from 7.4 to 9.4 in the South) (Fig. 6.37). The highest incidence rate is observed in Trieste (Fig. 6.21; SR=34.5): it is important, nevertheless, to remember that statistics on prostatic cancer occurrence may be influenced by casual findings (*ie* with autopsies).

The last cancer site we considered was the bladder, the incidence of which cancer is about fourfold higher in males. Environmental factors such as smoking and some occupation exposures are strongly suspected in the aetiology of this disease, together with a high consumption of animal fats and a low intake of vitamins (Riboli *et al*, 1991). Analysing the frequency of this tumour one must consider registration problems regarding multifocality and malignancy of the disease. Mortality rates present a narrow range in different areas (SR: 9.2 North, 8.9 Centre and 8.8 South for males) (Figs. 6.22 and 6.38) and the highest incidence values, with rates higher than 30 per 100,000 are observed in Firenze (36.1) and Trieste (33.8) (Figs. 6.22 and 6.23).

Differences in overall cancer risk in the different areas in Italy are supported by the analysis of incidence rates by sex and age group which show a trend towards low risk in the most Southern registries and high risks in Northern and Central areas (Zanetti and Crosignani, 1992). The cumulative risk of having a



Age standardized rates (world population) x 100,000
Source: Zanetti et al., 1992

Fig. 6.8—Colon cancer incidence and mortality in Italy. Males.

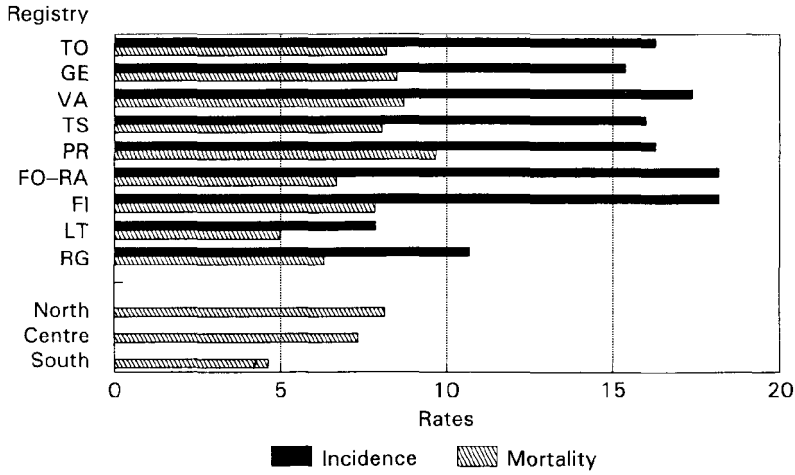
tumour by the age of 75 years is higher in Varese (37 % in males and 23 % in females) and is lower in Latina (23% in males and 16% in females). In the country overall, the incidence rates increase in males with age to the power of five. In females incidence increases quickly until the age of 50–55 years and then slowly. This postmenopausal trend is attributable mostly to breast and gynaecological cancers (Zanetti and Crosignani, 1992).

6.6
CONCLUSION

In Italy nationwide statistics for cancer are available only for mortality, while incidence data are provided only by local registries that account for only a small part of the country and mostly in the Northern area. The mortality statistics derive from a relatively uniform source; nevertheless the range of variation in Italian regions is considerable, reflecting different socioeconomic and environmental situations (Decarli and La Vecchia, 1986).

Comparisons of cancer data show a North/South gradient for all sites considered, showing a similar distribution between males and females, with a higher frequency in northern areas (except for the uterus). This confirms the previously described lower cancer incidence in the Mediterranean areas, which in Italy corresponds to the southern part of the country.

Analysis of data shows that in general the trends with time for different cancer sites are similar in the different geographical areas. Generally, increasing rates



Age standardized rates (world population) x 100,000
Source: Zanetti et al., 1992

Fig. 6.9—Colon cancer incidence and mortality in Italy. Males.

are observed in both sexes for cancers of the pancreas, lung and bladder. Similar trends are present for cancers of the prostate in males and the breast and ovary in females. Neoplasms of the stomach and uterus show a decreasing trend, while a quite stable value is observed for tumours of the oesophagus and colon in males.

Geographical and temporal trends of some neoplasms may possibly be explained by the observed time variations of *environmental* factors such as smoking, reproductive habits and diet which could act as interactive or independent factors to influence the risk of these diseases.

REFERENCES

Armstrong B, Doll R (1975). Environmental factors and cancer incidence and mortality in different countries, with special reference to dietary practices. *Int J Cancer* **15:** 617–31.

Boyle P (1988). Epidemiology of breast cancer. *Bailliere's Clin Oncol* **2:** 1–57.

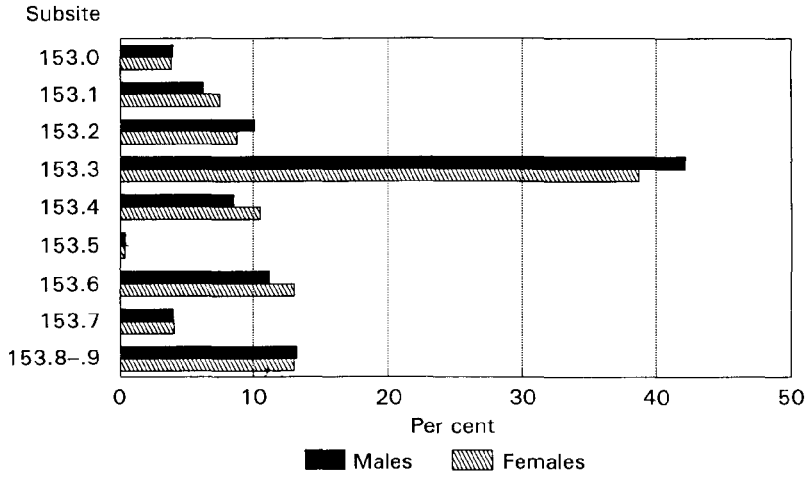
Buiatti E, Palli D, Decarli A *et al* (1990). A case-control study of gastric cancer and diet in Italy. II. Association with nutrients. *Int J Cancer* **45:** 896–901.

Capocaccia R, Farchi G, Prati S *et al* (1991). La mortalità in Italia nell'anno 1988. Rapporti dell'Istituto Superiore di Sanità, ISTISAN 91/37.

Decarli A, La Vecchia C (1986). Environmental factors and cancer mortality in Italy: correlation exercise. *Oncology* **43:** 116–26.

Decarli A, La Vecchia (1991). Cancer mortality in Italy, 1985–1987. *Tumori* **7:** 1–6.

Decarli A, La Vecchia C (1992). Cancer mortality in Italy, 1988. *Tumori* **78:** 69–74.



Legend:.0:flessura epatica,.1:trasverso
.2:discen.,.3:sigmoid,.4:cleco,.5:app
.6:ascend.,.7:fless. splen.,.8–.9:nass

Fig. 6.10—Colon cancer incidence in Italy (1983–87). Distribution by subsite.

Doll R, Peto R (1981). The causes of cancer: quantitative estimates of avoidable risks of cancer in United States today. *J Nat Cancer Inst* **66:** 1191–1308.

Jensen OM, Esteve J, Moller H, Renard H (1990). Cancer in the European Community and its member states. Eur J Cancer **26:** 1167–256.

La Vecchia C, Decarli A (1986). Cancer mortality in Italy. Temporal trends and geographical distribution. *Eur J Cancer Oncology* **22:** 1425–9.

La Vecchia C, Negri E, Decarli A, Fasoli M, Cislaghi C (1990). Cancer mortality in Italy: an overview of age specific and age-standardised trends from 1955 to 1984. *Tumori* **76:** 87–166.

Levi F, Maisonneuve P, Filiberti R, La Vecchia C, Boyle P (1989). Cancer incidence and mortality in Europe. *Sozial und Präventivmedizin* **34.**

Micheli A, Verdecchia A, Capocaccia R *et al* (1992). Estimated incidence and prevalence of females breast cancer in Italian regions. *Tumori* **78:** 13–21.

Moller Jensen O, Estève J, Moller H, Renard H (1990). *Eur J Cancer*, Vol 26, **11/12:** 1167–1256.

Riboli E, González CA, López-Abente G *et al* (1991). Diet and bladder cancer in Spain: a multi-centre case-control study. *Int J Cancer* **49:** 214–19.

Snowdon DA, Phillips RL, Choi W (1984). Diet, obesity and risk of fatal prostate cancer. *Am J Epidem* **120:** 244–50.

Zanetti R, Crosignani P (1992). Cancer in Italy. Incidence data from cancer registries 1983–87. Lega Italiana per la Lotta contro i Tumori. Associazione Italiana di Epidemiologia.

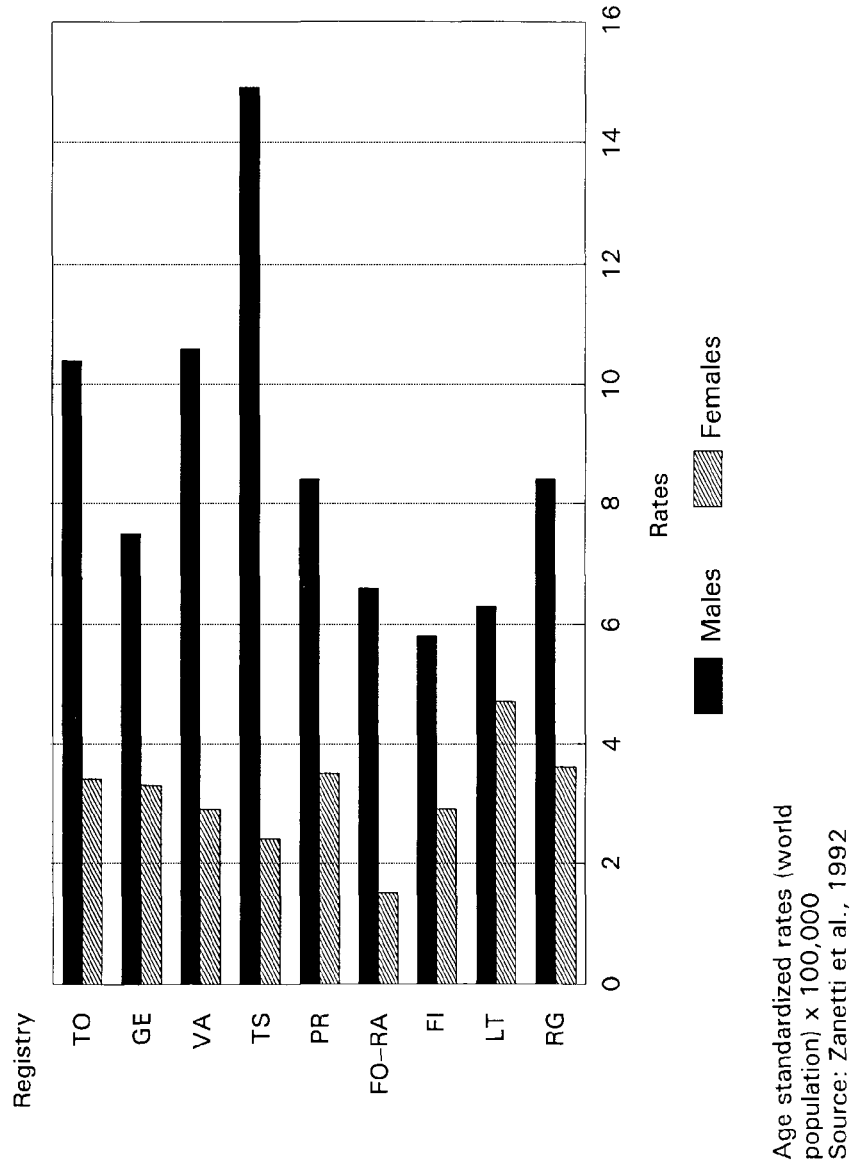
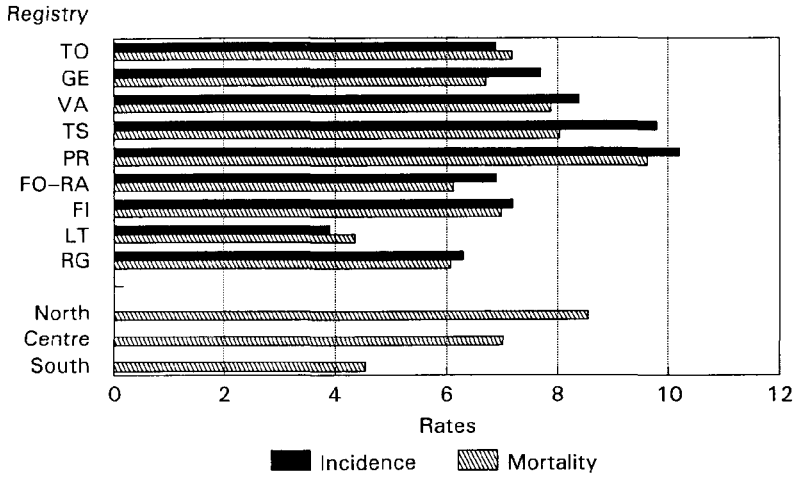
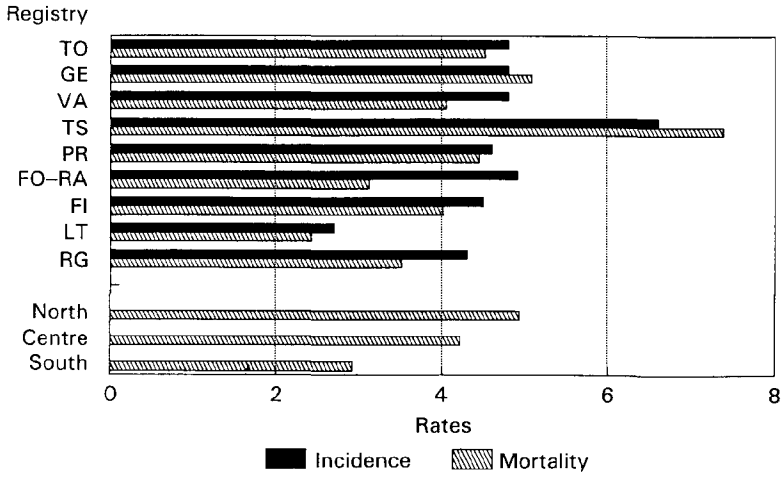


Fig. 6.11—Liver cancer incidence in Italy



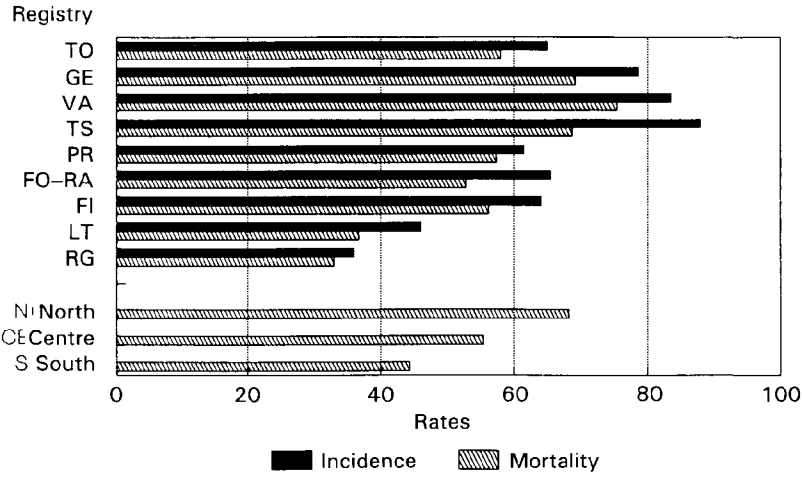
Age standardized rates (world population) x 100,000
Source: Zanetti et al., 1992

Fig. 6.12—Pancreas cancer incidence and mortality in Italy. Males.



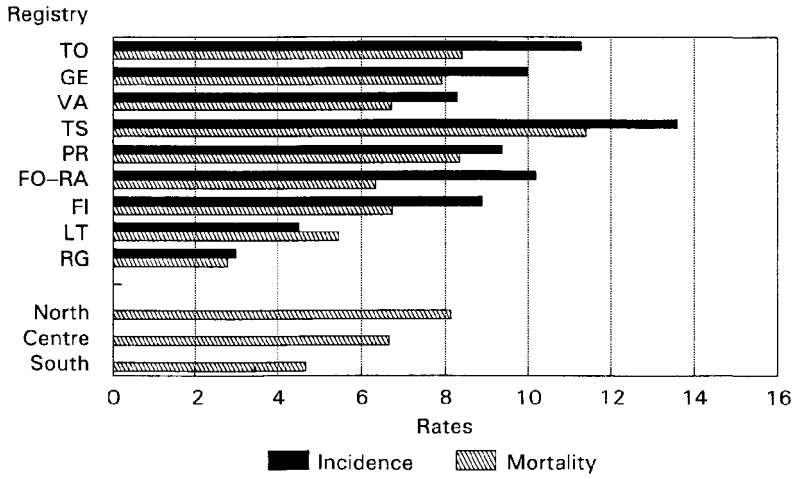
Age standardized rates (world population) x 100,000
Source: Zanetti et al., 1992

Fig. 6.13—Pancreas cancer incidence and mortality in Italy. Females.



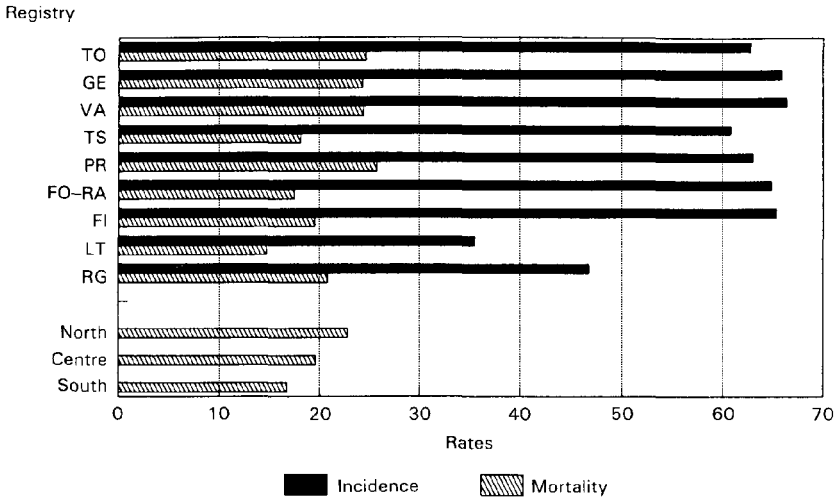
Age standardized rates (world population) x 100,000
Source: Zanetti et al., 1992

Fig. 6.14—Lung cancer incidence and mortality in Italy. Males.



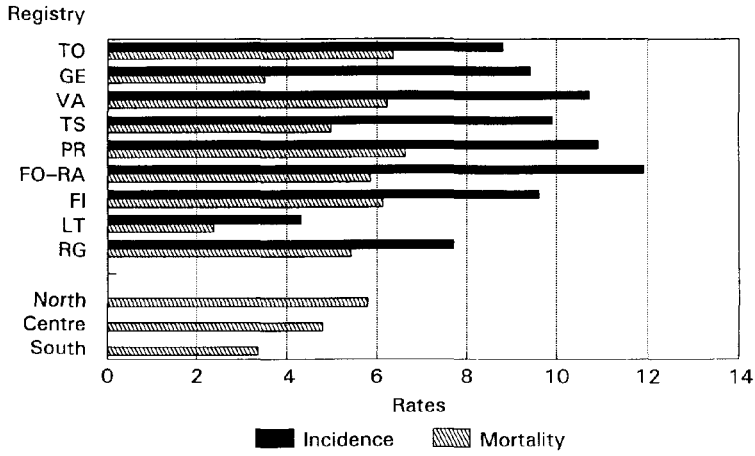
Age standardized rates (world population) x 100,000
Source: Zanetti et al., 1992

Fig. 6.15—Lung cancer incidence and mortality in Italy. Females.



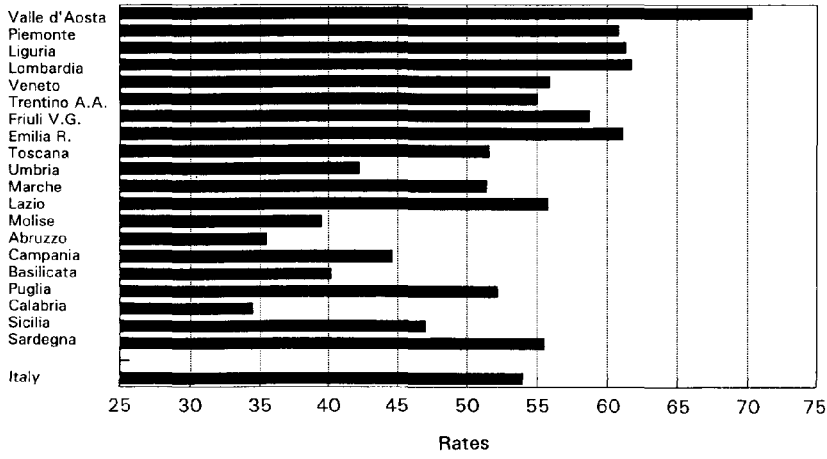
Age standardized rates to (world population) x 100,000
Source: Zanetti et al. 1992

Fig. 6.16—Breast cancer incidence and mortality in Italy.



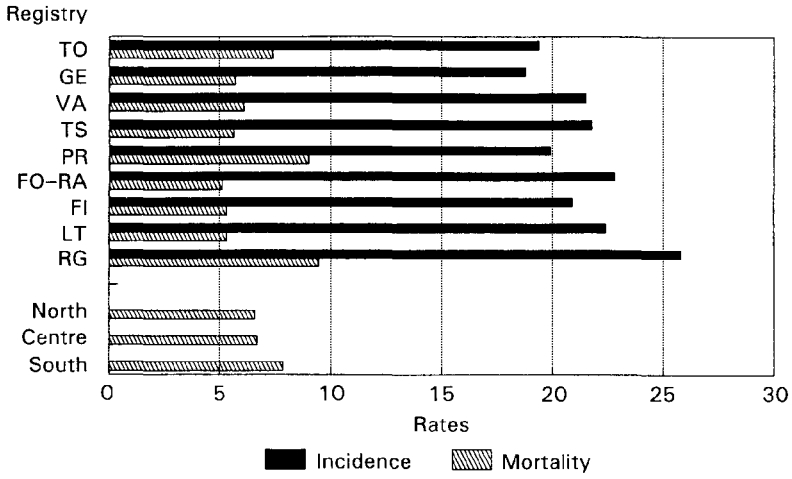
Age standardized rates (world population) x 100,000
Source: Zanetti et al., 1992

Fig. 6.17—Ovary cancer incidence and mortality in Italy.



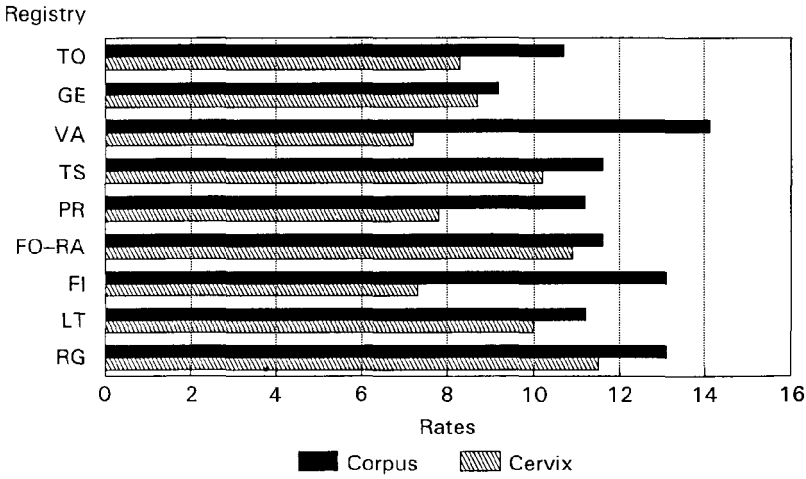
Age standardized rates to (world population) x 100,000
Source: Micheli et al., 1992

Fig. 6.18—Breast cancer estimated incidence in Italian regions (1987).



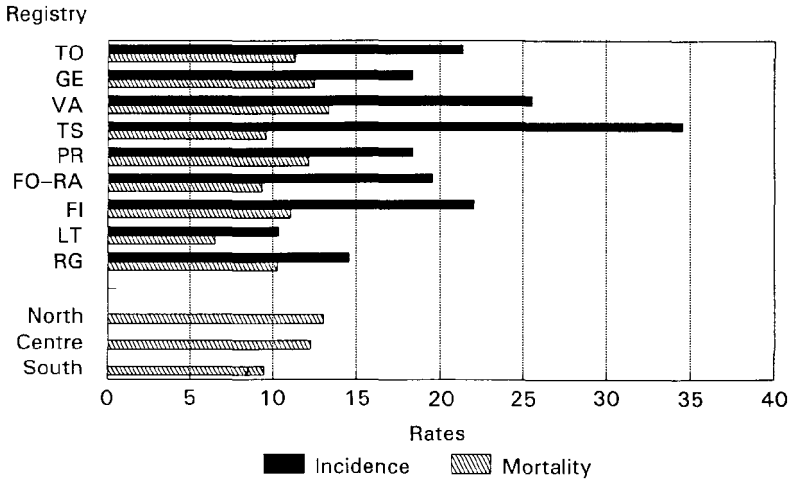
Age standardized rates (world population) x 100,000
Source: Zanetti et al., 1992

Fig. 6.19—Uterus cancer incidence and mortality in Italy.



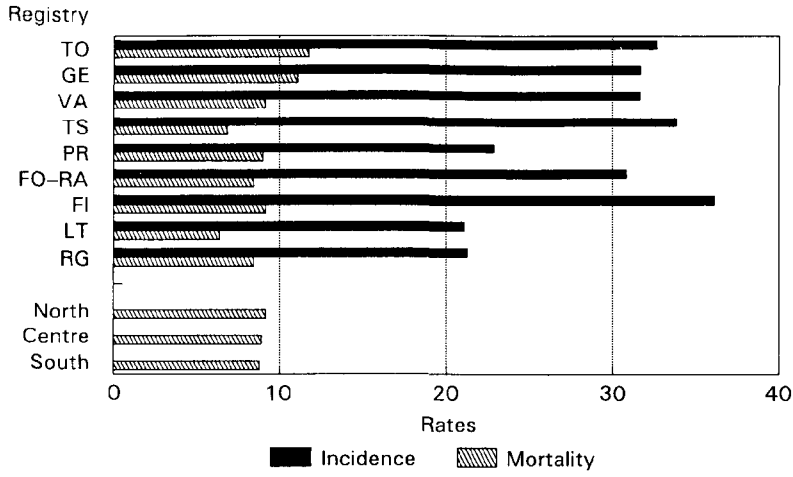
Age standardized rates (world population) x 100,000
Source: Zanetti et al., 1992

Fig. 6.20—Uterus cancer incidence in Italy (1983–87). Distribution by subsite.



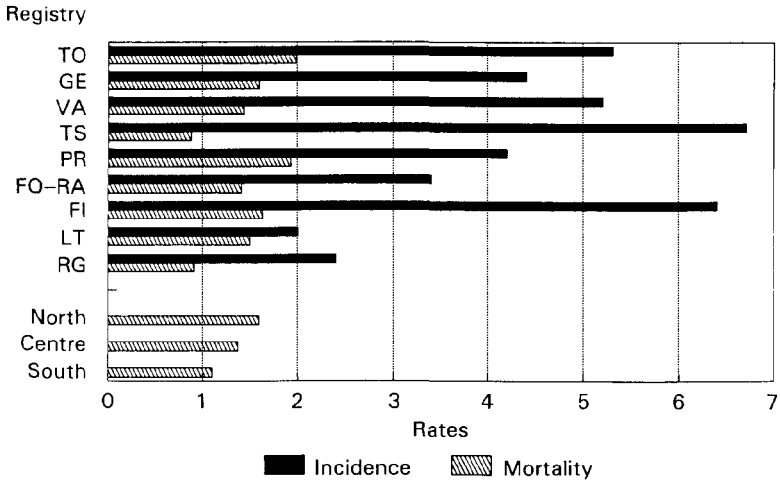
Age standardized rates (world population) x 100,000
Source: Zanetti et al., 1992

Fig. 6.21—Prostate cancer incidence and mortality in Italy.



Age standardized rates (world population) x 100,000
Source: Zanetti et al., 1992

Fig. 6.22—Bladder cancer incidence and mortality in Italy. Males.



Age standardized rates (world population) x 100,000
Source: Zanetti et al., 1992

Fig. 6.23—Bladder cancer incidence and mortality in Italy. Females.

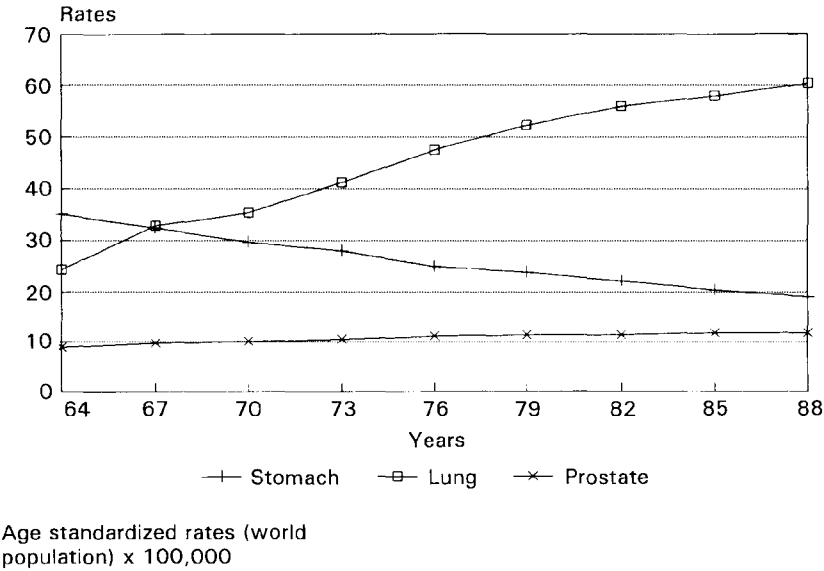


Fig. 6.24—Cancer mortality in Italy 1964–88. Males.

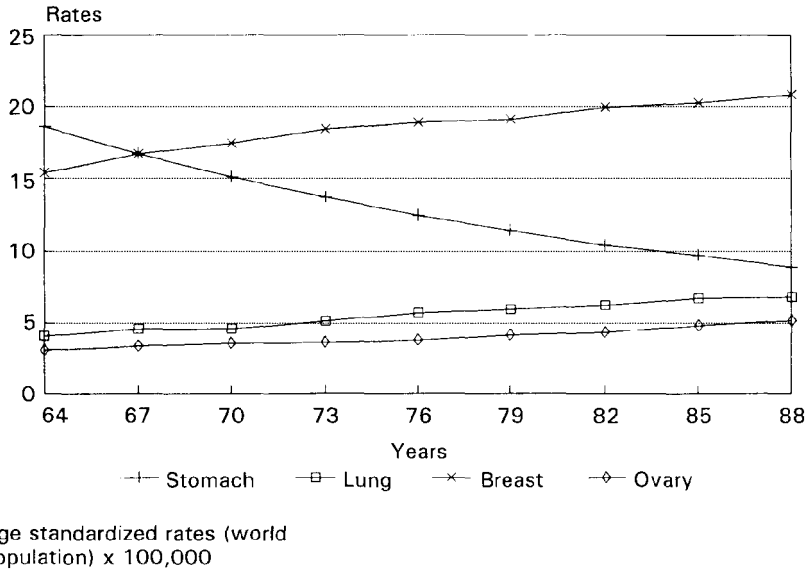


Fig. 6.25—Cancer mortality in Italy, 1964–88. Females.

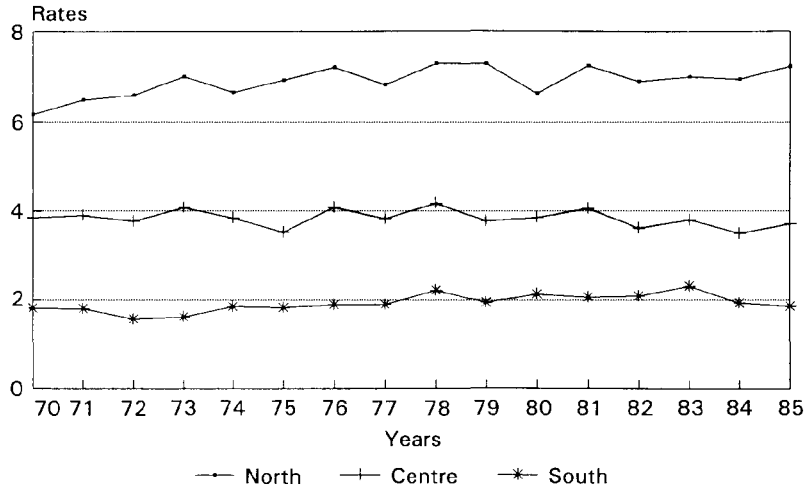


Fig. 6.26—Oesophagus cancer mortality in Italian areas, 1970–85. Males.

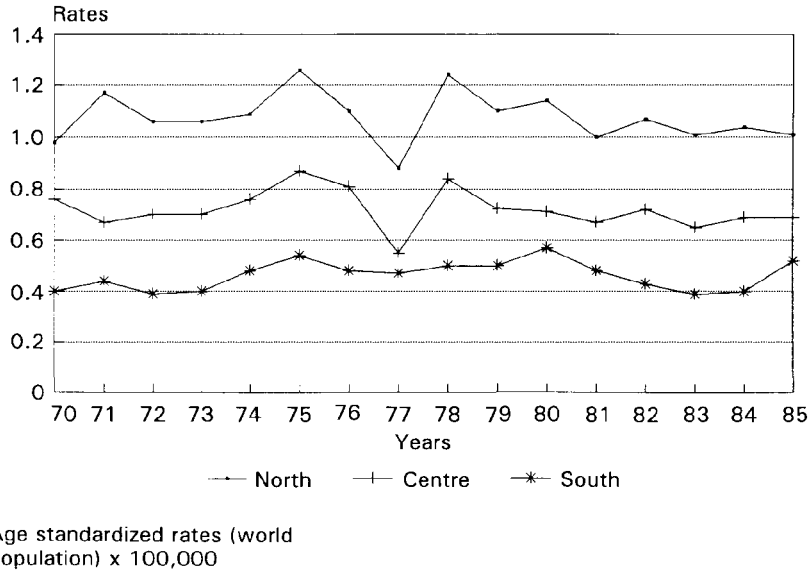


Fig. 6.27—Oesophagus cancer mortality in Italian areas, 1970–85. Females.

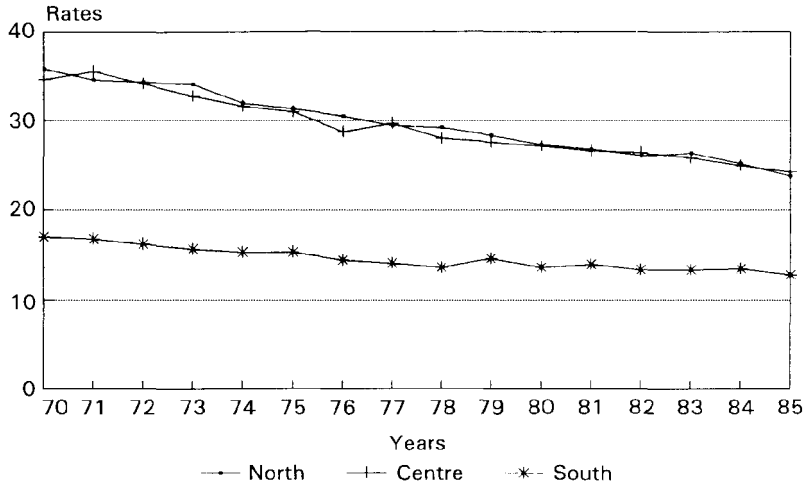
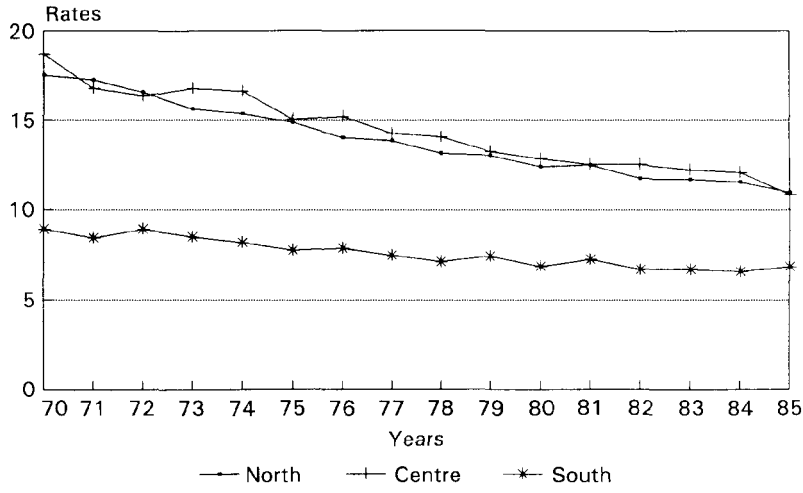


Fig. 6.28—Stomach cancer mortality in Italian areas, 1970–85. Males.



Age standardized rates (world population) x 100,000

Fig. 6.29—Stomach cancer mortality in Italian areas, 1970–85. Females.

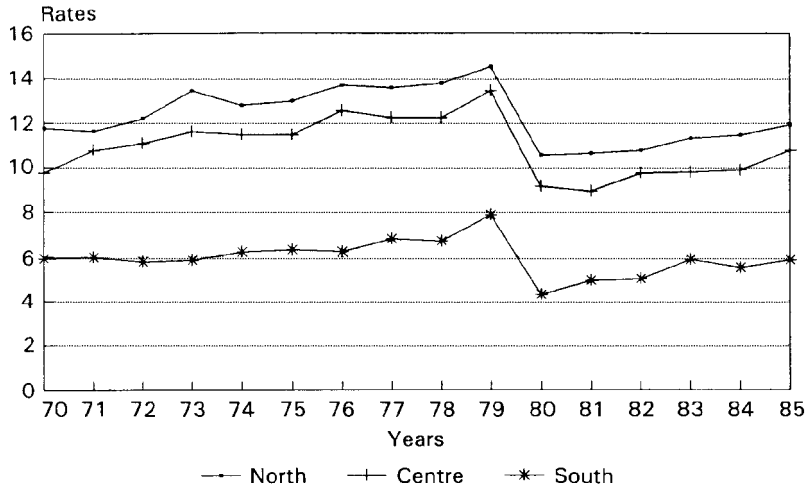


Fig. 6.30—Colon cancer mortality in Italian areas, 1970–85. Males.

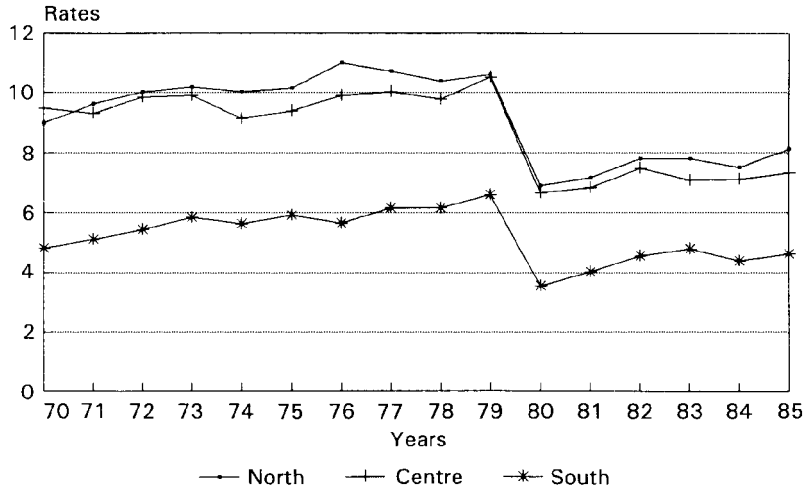


Fig. 6.31—Colon cancer mortality in Italian areas, 1970–85. Females.

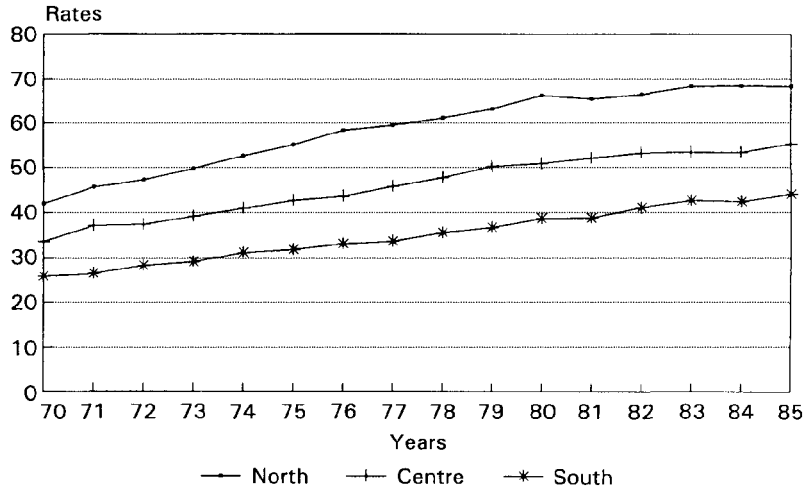


Fig. 6.32—Lung cancer mortality in Italian areas, 1970–85. Males.

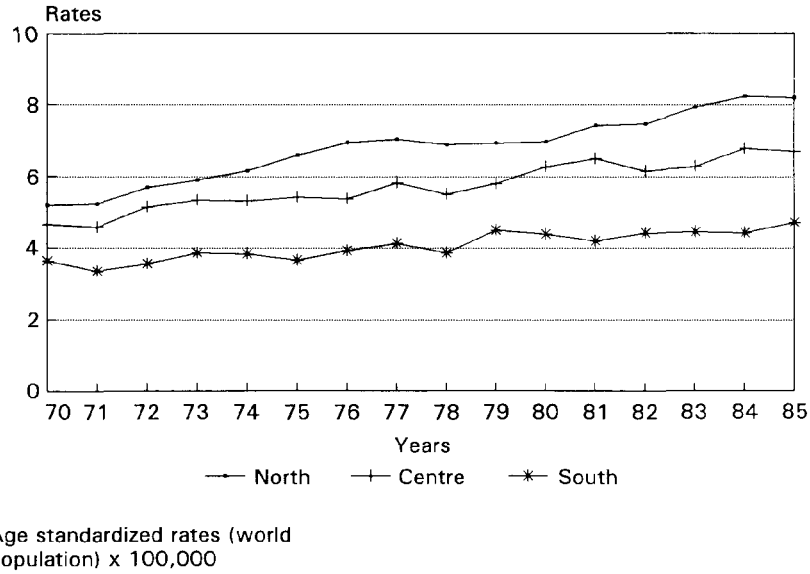


Fig. 6.33—Lung cancer mortality in Italian areas, 1970–85. Females.

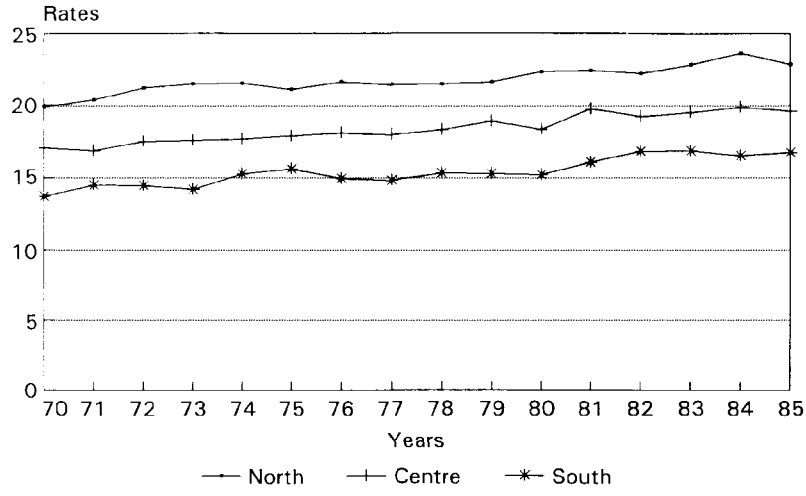


Fig. 6.34—Breast cancer mortality in Italian areas, 1970–85.

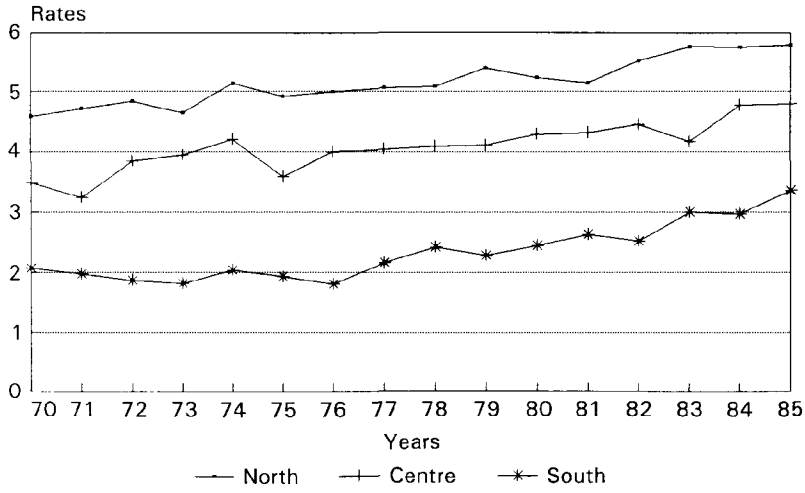


Fig. 6.35—Ovary cancer mortality in Italian areas, 1970–85.

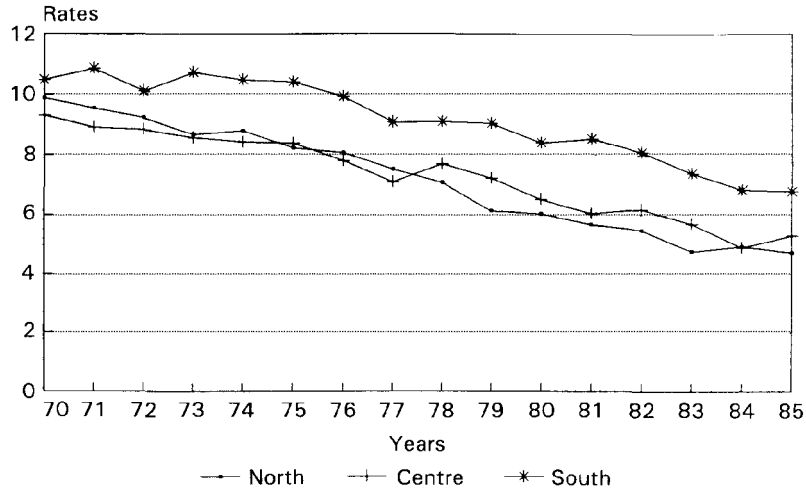


Fig. 6.36—Uterus cancer mortality in Italian areas, 1970–85.

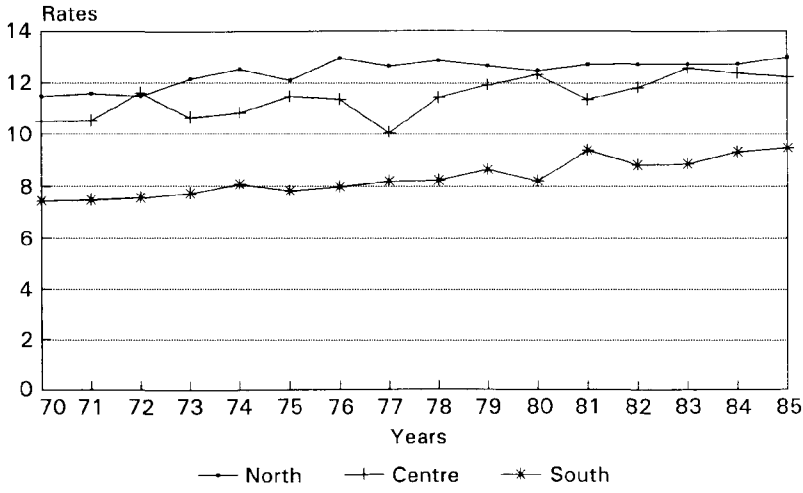


Fig. 6.37—Prostate cancer mortality in Italian areas, 1970–85.

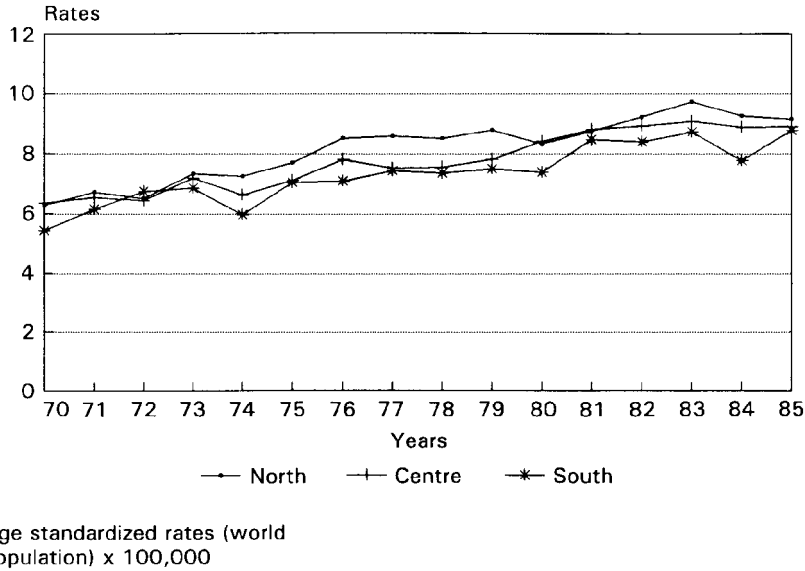


Fig. 6.38—Bladder cancer mortality in Italian areas, 1970–85. Males.

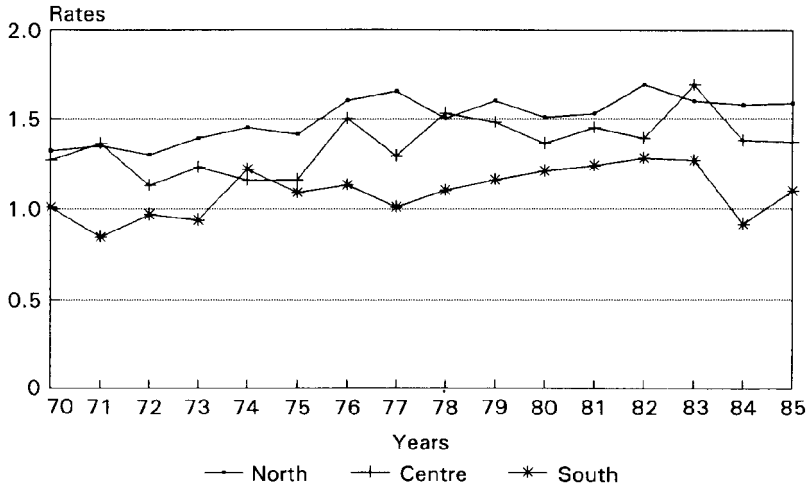


Fig. 6.39—Bladder cancer mortality in Italian areas, 1970–85. Females.

7
Patterns and trends in mortality from selected cancers in Mediterranean countries

C La Vecchia, F Lucchini, E Negri, F Levi

7.1
INTRODUCTION

A beneficial effect of the Mediterranean diet on disease was first suggested by the low mortality from cardiovascular diseases in these countries (Uemura and Pisa, 1988). Mortality from several important cancer sites, including intestines, pancreas, breast and prostate is also low in the Mediterranean countries as compared to central and northern Europe (Levi *et al*, 1989) and these favourable rates have been attributed, at least in part, to a beneficial impact of dietary habits in this area on the risk of these neoplasms.

To obtain further documentation on this issue, we have therefore considered in this chapter the recent mortality data from a few selected cancer sites in Mediterranean countries, as compared to other European areas. Further, since inspection of trends in cancer mortality over the last few decades offers interesting clues for revealing and understanding the implications of changes in dietary habits on national cancer rates, we have presented selected trends in mortality in southern European countries.

7.2
MATERIAL AND METHODS

Official death certification numbers for 28 European countries (excluding the Soviet Union and a few small countries like Andorra, Liechtenstein, etc) were derived from the World Health Organization (WHO) database (La Vecchia *et al*, 1992a, 1992b, 1992c, 1992d, 1992e). During the calendar period considered (1955–89) four different revisions of the International Classification of Diseases (ICD) were used. Classification of cancer death was thus re-coded, for all calendar periods and countries, according to the Ninth Revision of the International Classification of Diseases (ICD-9).

Estimates of the resident population, generally based on official censuses, were obtained from the same WHO databank. From the matrices of certified death and resident populations, age-specific rates for each five-year age group

and calendar period were computed. Age-standardized rates, at all ages and truncated 35–64 years, were based on the world standard population.

In a few countries, data were missing for part of one or more calendar periods. When a single year was missing within a quinquennium, numerators and denominators were interpolated linearly for the previous and subsequent calendar year. No extrapolation was made for missing data at the beginning or the end of the calendar period considered, or when data on one or more quinquennia were not available.

7.3 RESULTS

7.3.1 Intestines, chiefly colon and rectum

Although the causes of neoplasms of the rectum, colon and of various subsites within the colon are, at least in part, different, we had to group all intestinal subsites since it is difficult, on the basis of death certification, even to distinguish reliably neoplasms from the colon and the rectum (Doll, 1980). In the 1950s a substantial heterogeneity was present in colorectal cancer mortality, since Britain and central European countries had elevated rates, while southern and eastern Europe had considerably lower mortality.

A systematic tendency towards levelling of various rates over more recent calendar periods around higher values (*ie* between 18 and 25/100,000 males, and between 13 and 20/100,000 females, world standard) was observed (Fig. 7.1). In particular, appreciable rises in intestinal cancer mortality were observed in Italy, Spain and Yugoslavia (Fig. 7.2). Rates were, however, still somewhat lower in Greece, Spain and Yugoslavia, though the persisting upward trends in these countries suggest that they may reach levels comparable to those of other European areas in the near future.

Inspection of age-specific rates shows that rates were often more favourable at younger ages, particularly in women. Taken together, however, trends in colorectal cancer mortality in various European countries are consistent with a systematic levelling of rates towards high values. Since diet plays an important role in the aetiology of the disease (Doll, 1980; Willett, 1989), this pattern of trends probably reflects the tendency towards more uniform dietary habits throughout Europe.

7.3.2 Pancreas

In both sexes, the lowest mortality rates in Europe were observed in Greece, Portugal and Spain, but also Yugoslavia, France and Italy tended to have

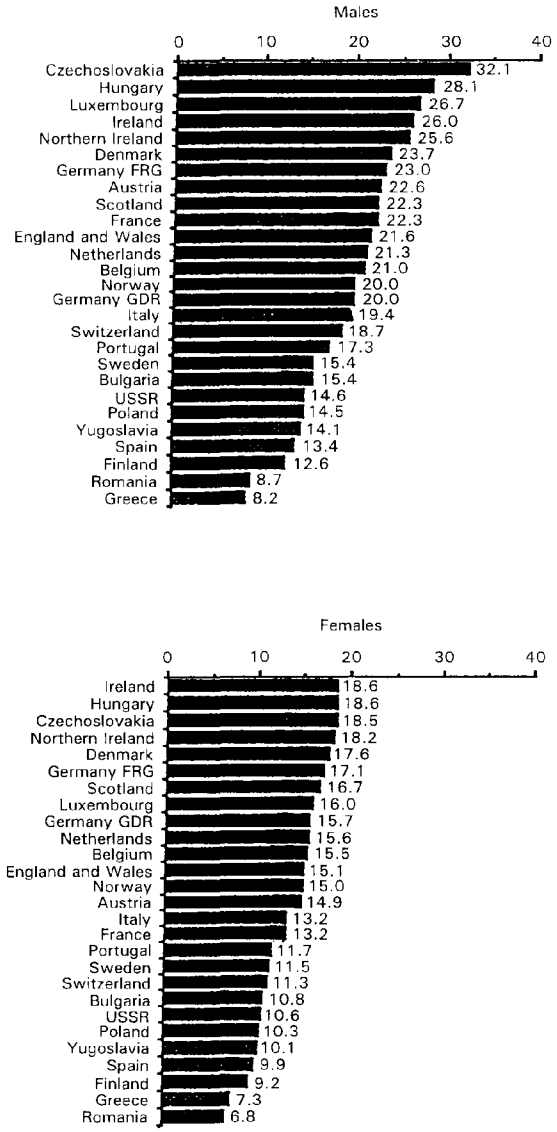


Fig. 7.1—Geographical variation in overall age-standarized (on the world standard population) death certification rates from intestinal cancer in various European countries, 1955–89.

mortality in the lower part of the distribution. Rates were two to three times higher in northern and central Europe (Fig. 7.3). Certified mortality from pancreatic cancer over the last four decades has been systematically upwards in all European countries. Only in Britain has some favourable trend been observed since the late 1970s particularly in middle aged men. Since this is a tobacco-

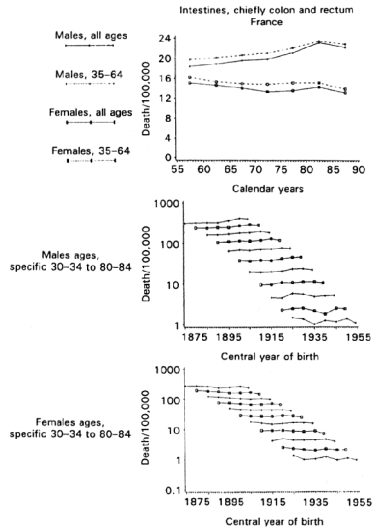


Fig. 7.2a

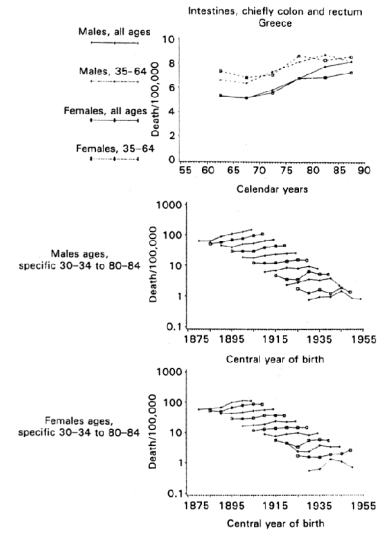


Fig. 7.2b

Fig. 7.2—Trends in age-standardized and age-specific death certification rates for intestinal cancer in various Mediterranean countries, 1955–89.

related site (US Office on Smoking and Health, 1982; Boyle *et al*, 1989), some of these generalized upward trends are probably real and related to increased tobacco consumption over the past decades. Dietary factors are also likely to

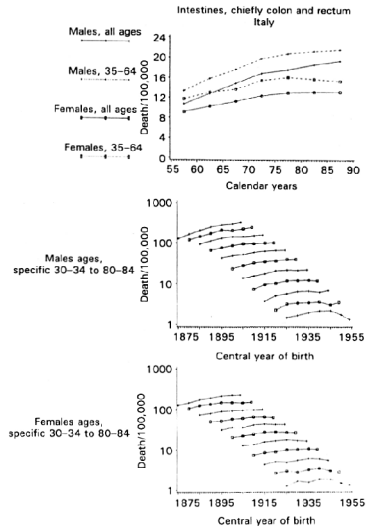


Fig. 7.2c

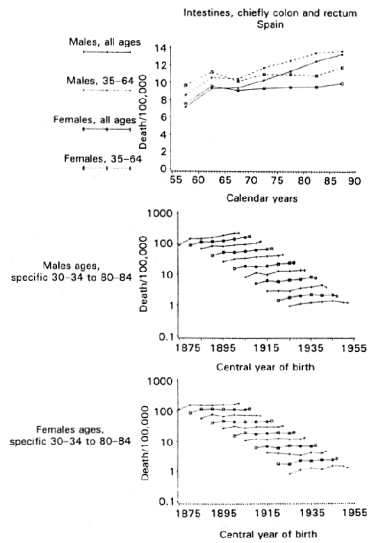


Fig. 7.2d

Fig. 7.2—Trends in age-standardized and age-specific death certification rates for intestinal cancer in various Mediterranean countries, 1955–89.

have a role in pancreatic carcinogenesis, and positive associations have been suggested with total energy intake, fats and cholesterol (Boyle *et al*, 1988).

Fig. 7.4 gives trends in mortality from pancreatic cancer in various Mediterranean countries over the period 1955–89: all the trends are appreciably

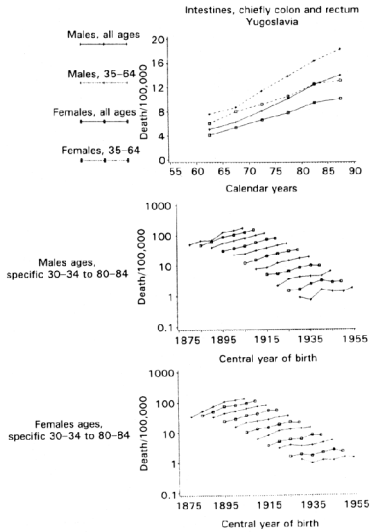


Fig. 7.2e

Fig. 7.2—Trends in age-standardized and age-specific death certification rates for intestinal cancer in various Mediterranean countries, 1955–89.

upwards. These trends should, however, be considered with due caution, since the diagnosis of pancreatic cancer is difficult and hence the reliability of death certification relatively poor. Thus, at least part of the upward trends registered are probably attributable to improved diagnosis and certification (Boyle, 1988). Not surprisingly, therefore, the upward trends were more moderate in middle age and even smaller in the younger age groups, when death certification is more accurate and reliable.

Despite these cautions European mortality data for pancreatic cancer indicate a substantial advantage for Mediterranean countries with appreciably lower rates in all these areas.

7.3.3
Female breast

For this neoplasm, too, the highest mortality rates were recently observed in various regions of the UK, followed by The Netherlands, Belgium and Denmark, and the lowest ones in Yugoslavia, Spain and Greece, together with a few eastern European countries (Fig. 7.5). Some of the differences may be due to reproductive factors since, particularly in the past, mean parity was lower and age at first birth older in northern Europe as compared to Mediterranean countries, while differences in reproductive patterns have tended to decline over the more recent calendar period. Diet, however, is also likely to play a role in breast carcinogenesis, since it has been suggested that the amount and the

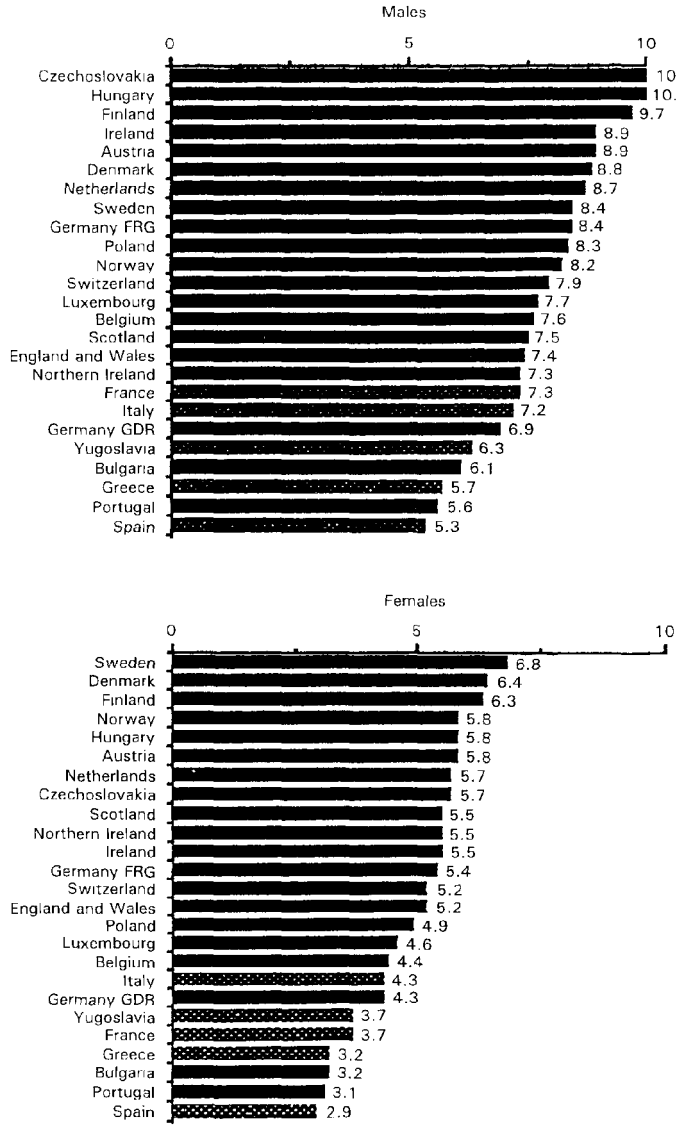


Fig. 7.3—Geographical variation in overall age-standardized (on the world standard population) death certification rates from pancreatic cancer in various European countries, 1955–89.

composition of fats may be associated with risks while certain vegetables appear protective (Willett, 1989; Boyle, 1988) although epidemiological evidence is still open to debate.

In the 1950s the variation in breast cancer mortality in Europe was even greater, since rates in Britain were already over 23/100,000, while those of Spain

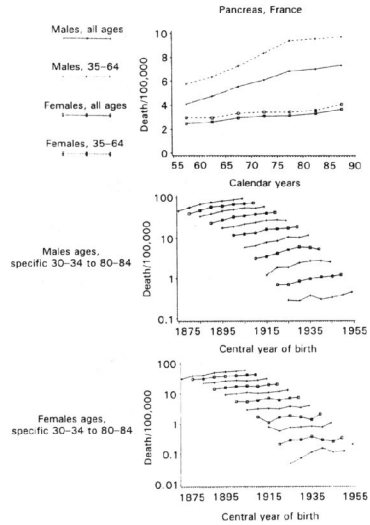


Fig. 7.4a

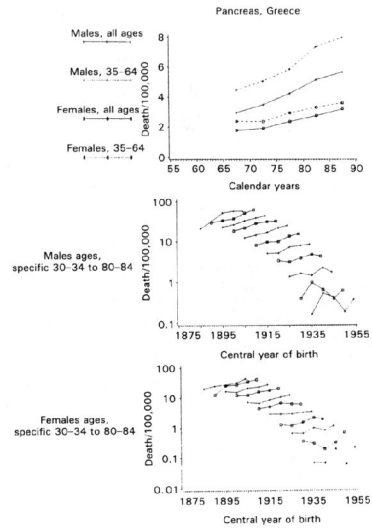


Fig. 7.4b

Fig. 7.4—Trends in age-standardized and age-specific death certification rates for pancreatic cancer in various Mediterranean countries, 1955–89.

or Greece were well below 10/100,000. This variation has subsequently become smaller, since rates have increased to a much greater extent in countries starting from low values. Fig. 7.6 gives trends in mortality from breast cancer in Mediterranean countries. Substantial rises were observed in Spain and

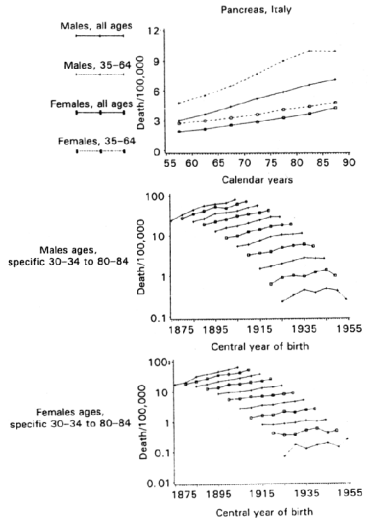


Fig. 7.4c

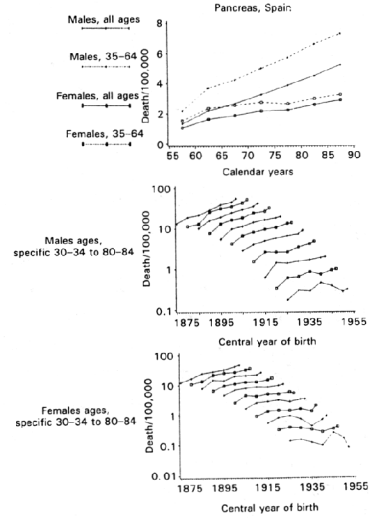


Fig. 7.4d

Fig. 7.4—Trends in age-standardized and age-specific death certification rates for pancreatic cancer in various Mediterranean countries, 1955–89.

Yugoslavia, but trends were also somewhat upwards in France, Greece and Italy. Thus, overall age-standardized rates for most European countries in the late 1980s were between 20 and 30/100,000. Breast cancer mortality was lower in Scandinavian countries (whose rates remained constantly below 20/100,000) and

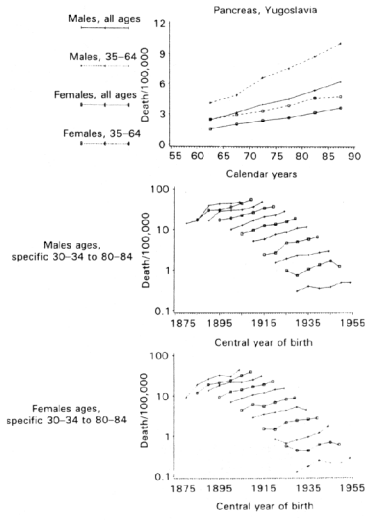


Fig. 7.4e

Fig. 7.4—Trends in age-standardized and age-specific death certification rates for pancreatic cancer in various Mediterranean countries, 1955–89.

in a few southern and eastern European countries, whose mortality has, however, substantially increased over recent periods. The pattern of trends was generally similar in middle age (35–64 years), although accurate inspection of age-specific rates may suggest that recent trends in some countries were somewhat more favourable in younger women.

As in the case of intestinal cancer, the levelling of rates around high values in most European countries may reflect a systematic tendency towards more uniform reproductive, dietary and general life style habits in various areas of the continent over recent decades.

7.3.4 Prostate

Again, a three-fold variation was present in prostatic cancer mortality across various European countries and there was a systematic tendency for most Mediterranean countries (except France) to be in the lower part of the distribution (Fig. 7.7).

The causes of prostatic cancer are to a large extent undefined (Zaridze and Boyle, 1987) although this is one of the most common sites of cancer in males. Still, it is possible that for this neoplasm also, diet has a relevant role and the pattern of rates observed would suggest that Mediterranean diet may exert some beneficial influence.

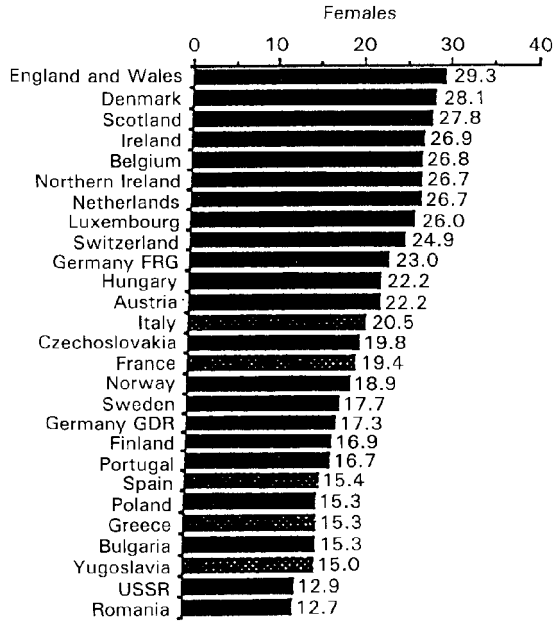


Fig. 7.5—Geographical variation in overall age-standardized (on the world standard population) death certification rates from breast cancer in various European countries, 1955–89.

Generalized upward trends were observed at older ages in most European countries which, however, can be influenced by recent improvement in diagnostic accuracy, since neoplastic foci in the prostate are found in a large proportion of elderly men. Little reliable inference, therefore, can be based on the pattern of overall age-standardized trends (Doll and Peto, 1981; Breslow *et al*, 1977). Trends in rates tend to be more favourable in middle age. This pattern of age-specific trends is evident also from accurate inspection of prostatic cancer mortality between 1955 and 1989 in various Mediterranean countries (Fig. 7.8).

7.4
DISCUSSION

We have chosen to present only a few examples of the pattern and trends of cancer mortality in Europe, in order to offer documentation on the favourable mortality rates for a number of important cancer sites in Mediterranean countries. Almost certainly, diet is only one factor in this favourable pattern, and its role is, for each specific cancer site, difficult to understand and to quantify (Doll and Peto, 1981; Byers, 1988). Even more difficult is to identify any specific dietary factor which may be responsible for the low rates observed for several important cancer sites in this area of Europe.

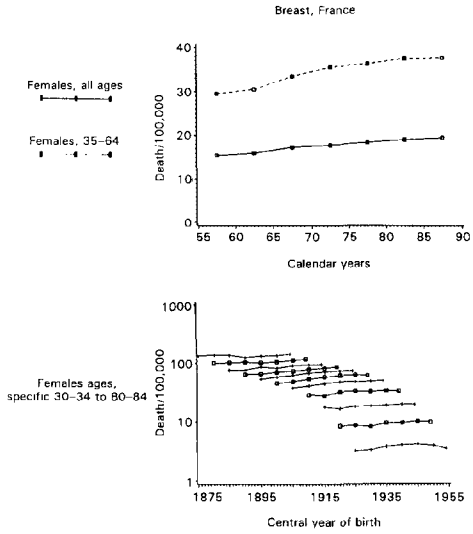


Fig. 7.6a

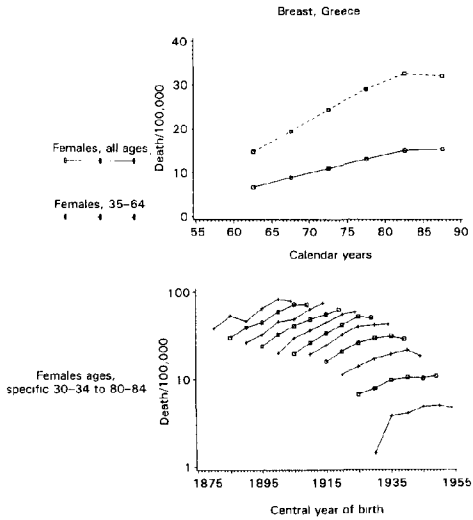


Fig. 7.6b

Fig. 7.6—Trends in age-standardized and age-specific death certification rates for breast cancer in various Mediterranean countries, 1955–89.

Characteristics of the Mediterranean diet have been described elsewhere in this volume, and it is useful here only to mention briefly the possible role of types and composition of fats (La Vecchia, 1992)—and in particular the potential favourable impact of olive oil and other mono- and polyunsaturated fats in fish—

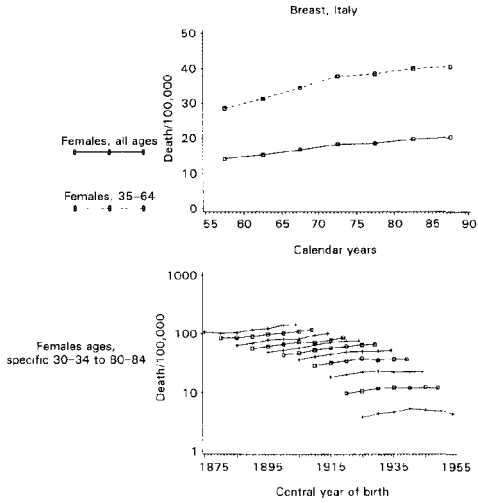


Fig. 7.6c

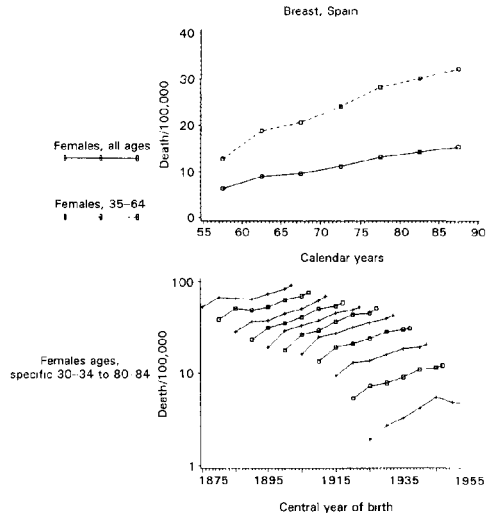


Fig. 7.6d

Fig. 7.6—Trends in age-standardized and age-specific death certification rates for breast cancer in various Mediterranean countries, 1955–89.

and of fruits and vegetables (Negri *et al*, 1991; Steinmetz and Potter, 1991), in reducing the risk of several common epithelial cancers.

For most countries and cancer sites considered, recent trends in Mediterranean countries have been, however, unfavourable over the last few decades. This has

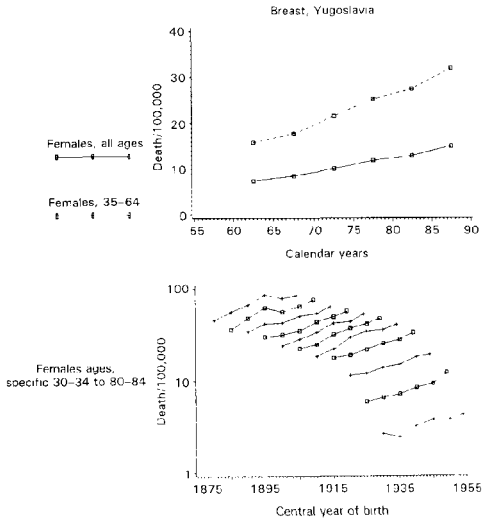


Fig. 7.6e

Fig. 7.6—Trends in age-standardized and age-specific death certification rates for breast cancer in various Mediterranean countries, 1955–89.

relevant implications for analytical epidemiology, since substantial heterogeneities in standard of life and several risk factor exposures across Europe were present in the first half of the current century, which have systematically tended to flatten off over more recent decades, at least in western Europe. Thus, inspection of trends in various countries between the mid 1950s and the late 1980s offers interesting clues for understanding and assessing the implications of these changes on national cancer rates to an extent that, probably, will be difficult to reproduce in the future (La Vecchia *et al*, 1992a). It is important, nonetheless, to focus epidemiological research towards understanding and quantifying the role of each specific component of the Mediterranean diet on cancer risk, in order to open perspectives for intervention for the food industry and for information and education on a public health scale.

ACKNOWLEDGEMENTS

This work was made possibly by a grant by the Swiss League against Cancer, Berne. The contributions of the Italian Association for Cancer Research and the Italian League against Tumours, Milan, Italy are gratefully acknowledged. This study was conducted within the framework of the CNR (Italian National Research Council) Applied Project *Clinical Applications of Oncological Research*. We wish to thank Mrs Hanne-Christine Janin for editorial assistance.

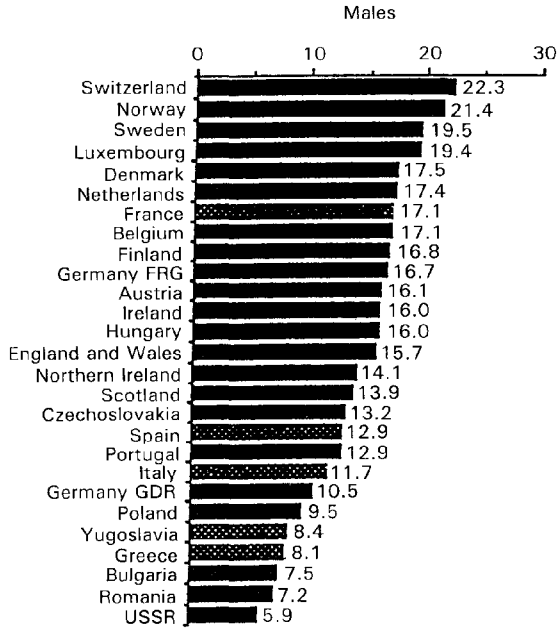


Fig. 7.7—Geographical variation in overall age-standardized (on the world standard population) death certification rates from prostate cancer in various European countries, 1955–89.

REFERENCES

Boyle P (1988). Epidemiology of breast cancer. *Bailiéres Clin Oncol* **1:** 1–57.

Boyle P, Hsieh CC, Maisonneuve P *et al* (1989). Epidemiology of pancreas cancer. *Int J Pancreatol* **5:** 327–46.

Breslow N, Chan CW, Dhom G *et al* (1977). Latent carcinoma of prostate at autopsy in seven areas. *Int J Cancer* **20:** 680–88.

Byers T (1988). Diet and cancer. Any progress in the interim? *Cancer* **62:** 1713–24.

Doll R (1980). General epidemiolgoic considerations in etiology of colorectal cancer. In *Colorectal Cancer: Prevention, Epidemiology and Screening* (eds Winawer S, Schottenfeld D, Sherlock P); Progress in cancer reseach and therapy, Vol. 3, Raven Press, New York, pp. 3–12.

Doll R, Peto R (1981). The causes of cancer: quantitative estimates of avoidable risks of cancer in the United States today. *J Natl Cancer Inst* **66:** 1191–1308.

La Vecchia C (1992). Cancers associated with high fat content diets. *J Natl Cancer Inst* in press.

La Vecchia C, Lucchini F, Negri E, Maisonneuve P, Boyle P, Levi F (1992a). Trends of cancer mortality in Europe, 1955–89. I—Digestive sites. *Eur J Cancer* in press.

La Vecchia C, Lucchini F, Negri E, Maisonneuve P, Boyle P, Levi F (1992b). Trends of cancer mortality in Europe, 1955–89. II—Respiratory tract, bone, connective and soft tissue sarcomas and skin. *Eur J Cancer* in press.

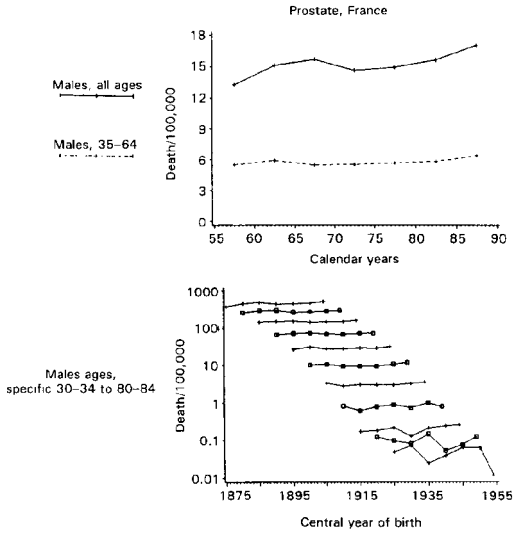


Fig. 7.8a

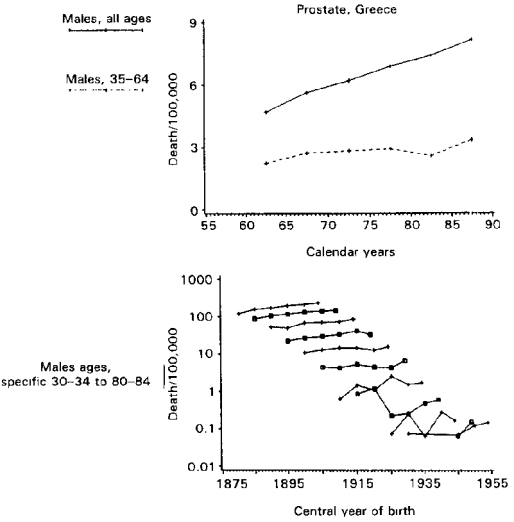


Fig. 7.8b

Fig. 7.8—Trends in age-standardized and age-specific death certification rates for prostate cancer in various Mediterranean countries, 1955–89.

La Vecchia C, Lucchini F, Negri E, Maisonneuve P, Boyle P, Levi F (1992c). Trends of cancer mortality in Europe, 1955–89. III—Breast and genital sites. *Eur J Cancer* in press.

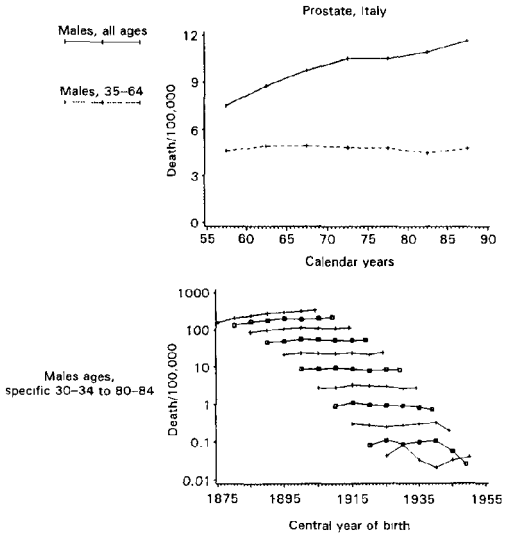


Fig. 7.8c

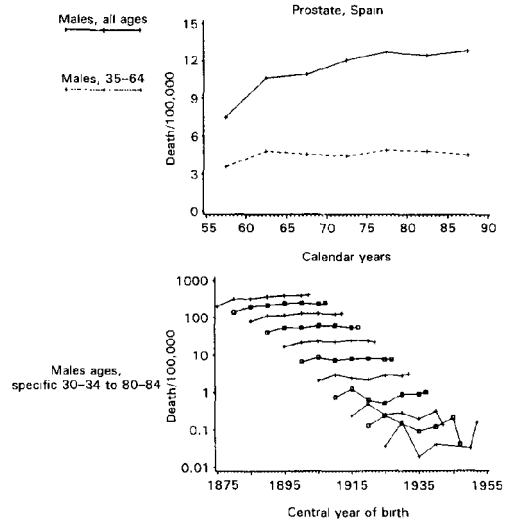


Fig. 7.8d

Fig. 7.8—Trends in age-standardized and age-specific death certification rates for prostate cancer in various Mediterranean countries, 1955–89.

La Vecchia C, Lucchini F, Negri E, Maisonneuve P, Boyle P, Levi F (1992d). Trends of cancer mortality in Europe, 1955–89. IV—Urinary tract, eye, brain and nerves and thyroid. *Eur J Cancer* in press.

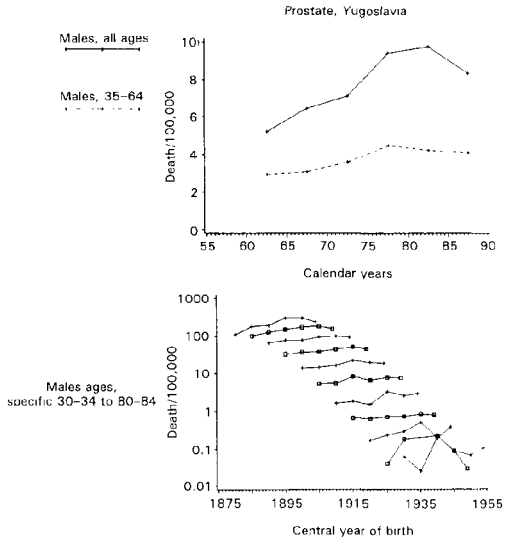


Fig. 7.8e

Fig. 7.8—Trends in age-standardized and age-specific death certification rates for prostate cancer in various Mediterranean countries, 1955–89.

La Vecchia C, Lucchini F, Negri E, Maisonneuve P, Boyle P, Levi F (1992e). Trends of cancer mortality in Europe, 1955–89. V—Lymphohaemopoietic neoplasms and all cancers. *Eur J Cancer* in press.

La Vecchia C, Negri E, Boyle P (1989). Reproductive factors and breast cancer: an overview. *Soz Praventivmed* **34:** 101–07.

Levi F, Maisonneuve P, Filiberti RR, La Vecchia C, Boyle P (1989). Cancer incidence and mortality in Europe. *Soz Praventivmed* **Suppl 2:** 8–82.

Negri E, La Vecchia C, Franceschi S, D'Avanzo B, Parazzini F (1991). Vegetable and fruit consumption and cancer risk. *Int J Cancer* **48:** 350–54.

Steinmetz KA, Potter JD (1991). Vegetables, fruit and cancer. I. Epidemiology. *Cancer Causes and Control* **2:** 325–57.

Uemura K, Pisa Z (1988). Trends in cardiovascular disease mortality in industrialized countries since 1950. *WHO Stat Q* **41:** 155–78.

US Office on Smoking and Health: the health consequences of smoking: cancer (1982). A report of the Surgeon General of the Public Health Service. Washington DC, USGPO.

Willett WC (1989). The search for the causes of breast and colon cancer. *Nature* **338:** 389–94.

Zaridze DG, Boyle P (1987). Cancer of the prostate: epidemiology and aetiology. *Br J Urol* **59:** 493–502.

8
Diet in Europe—the general picture
M J Hill, C P J Caygill

8.1
INTRODUCTION

The primary function of diet is to supply the essential nutrients and the necessary energy required for a healthy and active life. Preferably these requirements should be satisfied in ways that are economical but which are also palatable and attractive. The pressures which determine the composition of the diet include factors in both the physical and the cultural environment.

The physical environment is that which is determined by geography and is shared, of necessity, by all of those living in a particular locality. It includes climate (*eg* temperature, total rainfall, rain patterns, severity of winters etc), latitude, altitude, seasonality—all factors which help to determine which foods are most readily available. For example, the range of fruits available in the Mediterranean countries is very much greater than in the Scandinavian countries. Fish are obviously more traditionally eaten and available in coastal areas; the type of fish (and their fat content) depends on the latitude of the fishing grounds. Historically the rearing of cattle depended on a ready availability of lush pastures, which depends in turn on rainfall.

The cultural environment can be determined largely by the individual although it is, of course, subject to peer pressure. It includes religious, racial, familial and other factors and determines which of the dietary items that are readily available are actually consumed. Pigs will thrive in all European countries but are not used as food by certain religious groups such as Jews, Muslims, Hindus. Vegetarian groups exist in all European countries. Horses are used as a food source in some European countries (*eg* France) and not in others (*eg* UK) for non-religious cultural reasons.

It is clear, therefore, that wide dietary differences are certain to occur within Europe and that the main problem is to identify and to describe and define these differences. These differences occur both between European regions and countries, and within the countries. Superimposed on these differences there have been changes in diet with time, due to improved and more widespread cultural contacts (increasing awareness of non-traditional and exotic foods and recipes),

improvements in animal husbandry and in plant strains (increasing the range of foods that can be produced in an individual country or region) and improvements in food storage and transport (increasing the availability and cheapness of imported foods and virtually abolishing their seasonality).

In attempting to describe the dietary variations within Europe the first step is to describe the differences between countries. This requires comparative data, and the most comprehensive source of such information is from the tables published by the Food and Agriculture Organization (FAO). In addition, many European countries carry out regular surveys of food consumption within their countries and these can be used to further define the inter-country differences in diet.

8.2
ANALYSIS OF FAO DATA

The FAO publishes annually tables of mean food consumption calculated from sales of food in shops. It therefore takes no account of food grown in gardens or from the wild, and it also takes no account of food wastage which will vary between countries and between cultures. Nevertheless the data can be used to detect gross differences in dietary patterns between countries and to demonstrate temporal changes.

8.2.1
Regional variations within Europe

Table 8.1 compares the food consumption of four countries from the four regions of Europe, namely Sweden (for Scandinavia) the United Kingdom (for western Europe), Italy (for southern Europe) and Poland (for eastern Europe). Data are presented for the periods 1961–3, 1972–4 and 1986–8 to indicate temporal trends in consumption.

In 1961–3 there was a wide range in intake of cereals (3.2 fold between Poland and Sweden), starchy roots (3 fold between Poland and Italy), sugar (2 fold between UK and Italy), vegetables (3.5 fold between Italy and Sweden), fruit (6 fold between Italy and Poland), meat (2 fold between UK and Italy), alcohol (3.5 fold between Italy and Poland), animal fat (3 fold between UK and Italy) and vegetable fat (3 fold between Italy and Poland). Although the range in total fat intake was only 1.6 fold, the ratio of vegetable to animal fat was more than 5 fold (1.29 in Italy and 0.22 in Poland). As would be expected there was little range in total protein intake. It is notable that Italy was at one extreme of intake in all of the ranges described above with only one exception (cereals) which suggests that in 1961–3 the Mediterranean diet really differed markedly from that of the rest of Europe.

Table 8.1 also demonstrates that, although many of these differences were still clearly detectable in 1986–8 they were much smaller than in 1961–3. For

example, between 1961–3 and 1986–8 the range in consumption decreased for all foods (*eg* cereals from 3.2 to 2.1; sugar from 2.2 to 1.7; meat from 2.1 to 1.4; animal fat from 3.1 to 1.4). Further, the identity of the countries at the extremes changed; consumption of meat in Italy was the lowest of the four countries in 1961–3 but had increased rapidly to reach the highest by 1986–8 (since consumption in the UK and Sweden had changed little).

Table 8.1—Variations in intakes of food and food groups between countries representing north (Sweden), west (UK), south (Italy) and east (Poland) Europe for the periods 1961–63, 1972–74 and 1986–88 Data are in kg/person/year

	1961–63				1972–74				1986–88			
	UK	S	P	I	UK	S	P	I	UK	S	P	I
Cereals	108	81	260	180	93	79	186	185	86	82	175	163
Starchy roots	98	99	166	52	99	85	136	40	111	72	107	41
Sugar	55	45	34	25	53	48	46	34	49	46	48	30
Vegetables	63	35	91	126	77	42	97	149	90	58	116	162
Fruit	59	68	19	108	63	84	29	129	72	88	30	132
Meat	74	53	47	36	74	55	67	64	76	62	73	84
Eggs	15	11	8	9	15	12	11	11	12	13	11	12
Fish	20	26	7	12	18	28	16	12	19	28	18	18
Milk	232	277	214	157	225	308	269	207	228	364	241	278
Stimulants	7	13	1	3	8	15	2	4	7	14	2	6
Alcohol	92	39	33	117	119	73	52	133	123	60	47	95
Calories/day	3312	2850	3227	2988	3254	2883	3472	3522	3218	3030	3434	3571
Fat:												
Vegetable	29	32	17	48	33	38	22	65	49	43	25	72
Animal	112	90	75	37	108	78	94	53	92	88	99	72
Protein:												
Vegetable	38	30	52	53	36	30	48	54	35	31	46	50

	1961–63				1972–74				1986–88			
	UK	S	P	I	UK	S	P	I	UK	S	P	I
Animal	56	56	43	31	55	58	59	46	54	66	57	61

Conclusions regarding the existence of a distinct *Mediterranean diet* can only be sustained from Table 8.1 if the four countries chosen were truly representative of their region and if the differences are therefore regional rather than specific to the four countries compared. Since the existence of a healthy Mediterranean diet was first proposed in the 1950s and 1960s, comparisons will be made for the 1961–3 period; 1986–8 will be used to check continuity of such distinctions.

8.2.2
Variations within European regions

Tables 8.2 to 8.5 compare countries within the 4 broad geographical regions of Europe—Scandinavia, western Europe, the Mediterranean region and the eastern countries.

Table 8.2—Variations in intakes of foods and food gorups in four countries of norther Europe (Sweden, Norway, Denmark and Finland) for the periods 1961–63, 1972–74 and 1986–88 Data are in kg/person/year

	1961–63				1972–74				1986–88			
	S	N	D	F	S	N	D	F	S	N	D	F*
Cereals	81	104	100	130	79	93	84	98	82	119	98	97
Starchy roots	99	100	116	116	85	84	84	93	72	88	72	86
Sugar	45	46	52	45	48	40	53	51	46	40	42	40
Vegetables	35	38	42	18	42	40	45	22	58	50	81	33
Fruit	68	66	57	43	84	79	64	63	88	100	81	87
Meat	53	42	61	39	55	49	64	55	62	57	100	62
Eggs	11	9	12	8	12	10	11	10	13	12	15	11
Fish	26	40	18	20	28	45	25	24	28	36	29	28
Milk	277	253	264	345	308	269	238	329	364	291	217	330
Stimulants	13	10	12	9	15	12	15	13	14	13	13	14

	1961–63				1972–74				1986–88			
	S	N	D	F	S	N	D	F	S	N	D	F*
Alcohol	39	29	82	27	73	48	137	66	60	60	146	67
Calories/day	2850	3062	3423	3213	2883	3115	3371	3178	3030	3266	3605	3088
Fat:												
Vegetable	32	34	41	16	38	51	37	26	43	51	30	26
Animal	90	97	118	106	78	93	124	105	88	86	146	105
Protein:												
Vegetable	30	35	34	40	30	33	30	33	31	38	35	33
Animal	56	53	53	54	58	57	53	58	66	66	66	61

*Data for 1979–81, since 1986–88 not available.

In Table 8.2 the countries compared are Sweden, Norway and Denmark together with Finland (which could be classed together with the Scandinavian or the eastern countries). In 1961–3 there was considerable homogeneity in intakes of all foods and food groups within Sweden, Norway and Denmark, with the mean and range usually being mean±20% or less. Exceptions were fish (range=2.2 fold) and alcohol (range almost 3 fold); in the case of alcohol the Danes consumed the highest and the Norwegians the lowest amount while in the case of fish the reverse was true. The Finns had a diet broadly similar to that of the Scandinavians but consumed more cereals and milk and less pulses, fruit and vegetables. The diet of the Finns was more similar to that of Scandinavia than to that of the other European regions.

Table 8.3 compares countries usually classed as western European, namely UK, France, Belgium (for BeNeLux) and western Germany). Again the range in 1961–3 rarely exceeded±20%; the exceptions were alcohol (2 fold), fish (1.76 fold) fruit (1.7 fold) and vegetables (2.6 fold). As with Scandinavia the western European countries are more similar to each other in diet than to the other regions.

Table 8.3—Variations in intakes of foods and food groups in four Western European countries (UK, Belgium, France and Germany) for the periods 1961–63, 1972–74 and 1986–88 Data are in kg/persons/year

	1961–63				1972–74				1986–88			
	UK	B	F	G	UK	B	F	G	UK	B	F	G
Cereals	108	115	130	84	93	99	101	87	86	98	98	98
Starchy roots	98	132	113	129	99	109	94	96	111	104	78	79
Sugar	55	38	33	35	53	36	41	42	49	42	41	49
Vegetables	63	90	136	53	77	100	109	64	90	111	120	85
Fruit	59	61	79	102	63	80	82	117	72	108	72	122
Meat	74	68	80	74	74	89	94	86	76	101	105	108
Eggs	15	14	11	13	15	13	13	17	12	12	16	16
Fish	20	17	20	12	18	17	21	10	19	18	27	12
Milk	232	197	219	193	225	177	230	193	228	198	280	224
Stimulants	7	8	5	6	8	9	7	7	7	12	8	11
Alcohol	92	126	183	119	119	157	168	174	123	150	128	176
Calories/day	3312	3352	3184	2968	3254	3508	3124	3210	3218	3802	3312	3528
Fat:												
Vegetable	29	40	32	38	33	44	34	44	49	48	47	45
Animal	112	105	70	87	108	126	77	93	92	152	95	108
Protein:												
Vegetable	38	42	45	33	36	38	38	33	35	39	36	37
Animal	56	52	57	50	55	59	64	56	54	66	76	67

Table 8.4 compares 4 countries usually regarded as nutritionally *Mediterranean*, namely Italy, Spain and Greece together with Yugoslavia (which might be thought of as Mediterranean or eastern European). The range in intakes within these four countries in 1961–3 were very much greater than for the two regions considered so far. When Yugoslavia is considered separately there remain wide

differences in intake of starchy roots (4 fold between Spain and Greece), sugar (1.7 fold between Greece and Italy), pulses (1.7 fold between Greece and Italy), fruit (2 fold between Greece and Spain), fish (2.3 fold between Spain and Italy), milk (1.7 fold between Spain and Italy) and alcohol (3 fold between Greece and Italy). When Yugoslavia is included there are additional wide ranges in intake of cereals (1.6 fold, Yugoslavia and Spain), vegetables (2.4 fold, Yugoslavia and Spain), eggs (3 fold, Yugoslavia and Spain), fish (2.6 fold, Yugoslavia and Spain), vegetable oil (3.7 fold, Yugoslavia and Greece) animal oil (6 fold, Yugoslavia and Spain), alcohol (3 fold, Yugoslavia and Italy) and vegetable fat (2.7 fold, Yugoslavia and Greece).

Table 8.4—Variations in intakes of foods and food groups in four Southern European countries (Italy, Spain, Greece and Yugoslavia) for the periods 1961–63, 1972–74 and 1986–88 Data are in kg/person/year

	1961–63				1972–74				1986–88			
	I	S	G	Y	I	S	G	Y	I	S	G	Y
Cereals	180	153	174	244	185	118	160	223	163	116	142	210
Starchy roots	52	31	121	66	40	118	59	64	41	104	72	49
Sugar	25	21	15	20	34	30	28	32	30	30	35	40
Vegetables	126	138	97	58	149	142	204	82	162	142	201	76
Fruit	108	79	129	60	129	121	169	66	132	130	186	63
Meat	36	27	28	35	64	55	58	49	84	85	78	70
Eggs	9	9	6	3	11	13	11	7	12	17	10	9
Fish	12	29	20	1	12	38	14	3	18	34	18	5
Milk	151	87	128	113	207	128	182	133	278	160	224	160
Stimulants	3	2	1	1	4	3	2	3	6	5	3	3
Alcohol	117	77	39	38	133	94	39	70	95	114	60	77
Calories/day	2988	2767	2877	3120	3522	3061	3401	3370	3571	3494	3701	3569
Fat:												
Vegetable	48	45	60	22	65	56	73	34	72	69	82	45
Animal	37	32	33	44	53	53	53	55	72	82	72	68

	1961–63				1972–74				1986–88			
	I	S	G	Y	I	S	G	Y	I	S	G	Y
Protein:												
Vegetable	53	52	56	69	54	45	58	65	50	44	54	41
Animal	31	29	32	22	46	44	48	30	61	57	59	49

Table 8.5 compares 4 countries from eastern Europe namely Poland, Czechoslovakia, Hungary and Romania; the latter could also be considered a southern country. The range of intakes seen in this group for the period 1961–3 was relatively small for Poland, Hungary and Czechoslovakia, the most notable differences being consumption of fruit (3.7 fold, Hungary and Poland), fish (3.2 fold, Czechoslovakia and Hungary) milk (1.8 fold, Poland and Hungary), vegetable oils (6 fold, Czechoslovakia and Hungary) and alcohol (3.6 fold, Czechoslovakia and Poland). Romania fell within the range of the other 3 countries except for intake of pulses and fish (high) and vegetables, eggs, oils and fats (lower than the other countries); it was clearly more similar to the eastern than to the Mediterranean countries.

Table 8.5—Variations in intakes of foods and food groups in four Eastern European countries (Poland, Czechoslovakia, Hungary and Romania) for the periods 1961–63, 1972–74 and 1986–88 Data are in kg/person/year

	1961–63				1972–74				1986–88			
	P	C	H	R	P	C	H	R	P	C*	H	R
Cereals	260	176	186	217	186	145	168	192	175	140	151	168
Starchy roots	166	107	94	132	136	107	67	122	107	76	47	103
Sugar	34	45	31	33	46	45	40	44	48	45	43	50
Vegetables	91	79	86	67	97	74	92	84	116	113	85	98
Fruit	19	41	67	26	29	46	75	38	30	52	74	50
Meat	47	68	71	45	67	86	94	58	73	99	110	70
Eggs	8	10	9	7	11	15	11	11	19	20	15	
Fish	7	7	2	16	16	7	4	27	18	5	4	28
Milk	214	160	120	163	269	189	139	180	241	202	161	171
Stimulants	1	2	1	1	2	3	4	1	2	3	7	2

	1961–63				1972–74				1986–88			
	P	C	H	R	P	C	H	R	P	C*	H	R
Alcohol	33	120	71	30	52	163	105	47	47	158	131	36
Calories/day	3227	3370	3105	3147	3474	3408	3375	3319	3434	3418	3635	3382
Fat:												
Vegetable	17	32	14	23	22	33	21	29	25	35	35	35
Animal	75	76	83	50	94	85	98	62	99	91	115	69
Protein:												
Vegetable	52	49	53	59	48	44	51	54	46	42	48	51
Animal	43	43	36	38	59	56	46	49	57	61	55	55

*Data for 1981–83, since 1986–88 not available.

It is clear from Tables 8.1 to 8.5 that, despite the crudity of the FAO data, the pattern of food consumption in the Mediterranean countries can be clearly distinguished from that in the other European regions. Further, the food consumption patterns in the other regions show distinctive features. It would be unwise to read more into these data, because they lack precision. However, it is possible to use the FAO data for two further purposes, namely to study time trends and to put the ranges in food patterns in Europe into a world perspective.

8.2.3
Time trends in the food consumption patterns in Europe

In Tables 8.2 to 8.5 the food consumption patterns of 1961–3, 1972–4 and 1986–8 can be compared. The time trends in the four regions show some similarities but many differences and these are illustrated in Table 8.6. Thus in Scandinavia there has been a trend towards lower consumption of root vegetables and sugar, and higher consumption of fruit, vegetables, meat and dairy and products. Intake of cereals, oils

Table 8.6—Change in consumption in various foods and food groups between 1961–3 and 1986–8 (Data from FAO tables)

	UK	F	B	G	S	N	D	I	S	G	Y
Cereals	↓	↓↓	↓	↑	·	↑	·	·	↓↓	↓	↓
Starchy roots	↑	↓↓	↓↓	↓↓↓	↓↓	↓	↓↓	↓↓	↓	↑↑	↓↓
Sugar	↓	↑	↑	↑↑	·	·	↓	↑	↑↑↑	↑↑↑	↑↑↑
Pulses	↑	↑	↑↑	↑	·	↑	↑↑	·	·	·	↓↓
Vegetables	↑↑↑	↓	↑↑	↑↑↑	↑↑↑	↑↑	↑↑↑	↑↑	↑↑	·	↑↑↑
Fruit	↑↑	·	↑↑↑	↑↑	↑↑	↑↑	↑↑	↑	↑↑	↑	·
Meat	·	↑↑	↑↑↑	↑↑↑	↑	↑↑	↑↑↑	↑↑↑	↑↑↑	↑↑↑	↑↑↑
Eggs	↓↓	↑↑↑	·	↑↑	↑↑	↑↑	↑↑	↑↑	↑↑↑	↑↑↑	↑↑↑
Fish	·	↑↑	·	·	·	·	↑	↑↑↑↑		·	↑↑↑
Milk	·	↑↑	·	↑	↑↑	↑	·	↑↑↑	↑↑↑	↑↑↑	↑↑↑
Oils											
veg	↑↑	↑↑↑	↑	↑	↑	↑↑	↑	↑↑↑	↑↑↑	↑↑	↑↑↑
animal	↓	↑↑↑	↑↑	↑	·	↓↓	↓	↑↑↑	↑↑	·	↑↑
Fat											
veg	↑↑↑	↑↑	↑↑	↑↑	↑↑	↑↑	↓↓	↑↑↑	↑↑↑	↑↑↑	↑↑↑
animal	↓↓	↑↑	↑↑	↑	·	↓	↑	↑↑↑	↑↑↑	↑↑↑	↑↑↑
total	·	↑↑	↑↑	↑	·	·	↓	↑↑↑	↑↑↑	↑↑↑	↑↑↑
Protein											
veg	·	·	·	·	·	·	↑	·	↓↓	↓↓	↓↓
animal	·	↑↑	↑	↑↑	↑	↑	↑	↑↑↑	↑↑↑	↑↑↑	↑↑↑
total	·	↑	·	↑	·	↑	↑	↑↑	↑↑	↑↑	·
Alcohol	↑↑	↓↓	↑	↑↑	↑↑↑	↑↑↑	↑↑↑	↓	↑↑↑	↑↑↑	↑↑↑

· = 0 to 10% change; ↑ or ↓ = inc or dec by 10-20%;
↑↑ or ↓↓ = inc or dec by 20-40%; ↑↑↑ or ↓↓↓ = change by >40%

and fish were unchanged. There were modest increases, in consequence, of intake of fat and protein. In western Europe there was also a decreased intake of starchy root vegetables and increases in fruit, vegetables and meat, whilst fish intake was unchanged. However, the intake of cereals tended to decrease and of sugar and cooking oils to increase. Thus, although as in Scandinavia there was little change in protein intake there was a tendency towards increased intake of fat. In the Mediterranean countries the increases in intake of fruit and vegetables (already high) were relatively modest but were accompanied by large increases in intake of sugar, meat, eggs, fish, milk, cooking oils (both vegetables and animal), all forms of fat and total protein. In all regions the alcohol intake rose

with the biggest increases being in the (abstemious) Scandinavians and the smallest in western Europe. The overall result of these changes has been a tendency towards *harmonization* of the European diet and a decrease in the regional differences. However, despite this, large difference remain.

8.2.4
Food intake in Europe in a world context

Table 8.7 compares the food consumption patterns in our four representative European countries together with the United States (representing affluent North America and Australasia), India (as being typical of Asia) and Nigeria (as an African country).

1961–3. When compared to India and Nigeria it is clear that all European regions consume a diet rich in milk and dairy products, meat, fish, eggs, oils/fats, protein and alcohol. In Nigeria the consumption of starchy roots and pulses is much higher than in Europe whilst in India only consumption of pulses is higher than in Europe although cereal consumption exceeds that of northern and western Europe.

In addition to having a relatively low intake of total fat, the African and Asian countries get most of their fat from vegetable sources; the percentage from animal sources (20% for India and 8% for Nigeria) is very much lower even than Italy (42%). This is due to the low intake of meat and dairy products in the non-European countries.

In comparison with the European countries the consumption in the United States is relatively low for cereals, starchy roots and fish and relatively high for sugar, meat, eggs, milk, total fat and protein. Intakes of pulses, vegetables, fruit and oils/fats were well within the European range.

1986–8. By 1986–8 the diet in neither India nor Nigeria had improved in any respect to make it more comparable to the European diet; in fact in most respects the differences became even greater.

In contrast, the diets in the US and in Europe merged somewhat so that, although the US retained relatively high intakes of sugar, meat and total fat their intakes of milk and of total protein were overtaken by European countries and the consumption of eggs decreased to a level similar to that of all four European countries.

Table 8.7—The pattern of food consumption in European regions compared to the patterns in the rest of the world (1961–3 and 1986–8)

	1961–3							1986–8						
	S	UK	I	P	US	Ind	Nig	S	UK	I	P	US	Ind	Nig
Cereals	81	109	17 9.9	26 1	89. 1	17 7.9	11 2.7	82	86	16 2.9	17 5	10 0.1	17 5.9	11 8.2

	1961–3							1986–8						
	S	UK	I	P	US	Ind	Nig	S	UK	I	P	US	Ind	Nig
Starchy roots	99	98	51.7	166	54.6	9.7	252.6	72	111	41.2	107	58.7	18.5	226
Sugar	45	55	24.9	36	54.8	18.6	1.8	46	49	29.5	48	62.1	20.4	5.8
Pulses	5.8	6.4	11.9	2.1	10.6	28.1	18.2	6.4	7.5	13.2	2	11.5	18.7	14.7
Vegetables	35	63	125.8	91	87.1	44.1	34.3	58	90	162	116	105	54	33
Fruit	68	59	108	19	89	26	30	88	72	132	30	125	28	28
Meat	53	74	36	47	101	1.5	11.1	62	76	84	73	119	1.8	9.5
Eggs	11	15	9	8	18	0.3	1.5	13	12	12	11	14	1	2.2
Fish	26	20	12	7	14	2	4	28	19	18	18	18	3	5
Milk	277	232	151	214	263	38	4	364	228	278	241	247	51	4
Oils/fats:														
Total	31	27.1	18.5	25	23.6	5.3	9.6	34	27	33	33	28	7.6	8.8
Vegetable	9	8.6	14.1	4	12.5	4.3	9.2	13	11	23	7	23	6.5	8.5
Animal	22	18.5	4.4	21	11.1	1	0.4	21	16	10	26	5	1.1	0.3
Spices:														
Stimulants	12.5	7.4		0.7				13.6			2.4			
Alcohol	39	92	117	33	70	0.6	45	60	123	95	47	116	2	10
Cals/day														
Fat:														
Total	122	141	84	92	140	31	49	131	141	144	123	164	37	42
Vegetable	32	29	48	17	42	24	45	43	49	72	25	71	28	39

	1961–3							1986–8						
	S	UK	I	P	US	Ind	Nig	S	UK	I	P	US	Ind	Nig
Animal	90	112	36	75	99	7	4	88	92	72	98	92	10	4
Protein:														
Total	86	93	83	95	100	51	51	96	89	110	102	109	51	48
Vegetable	30	37	53	52	33	46	45	31	35	50	46	37	44	42
Animal	56	56	30	43	67	5	6	66	54	60	56	72	7	6

8.3
CONCLUSIONS

The analysis presented in this chapter has been based entirely on FAO data. These data are crude and based on sales of food in shops, not on actual consumption patterns. They take no account of home-produced food etc or of food wastage. In consequence there is a grave danger of over-interpretation of the data. Nevertheless, the ranges in intakes shown in Tables 8.1 to 8.5 permit a number of conclusions to be drawn with confidence. These are:

(a) There are clear differences in food consumption patterns between geographical regions within Europe, particularly between Scandinavia, the Mediterranean, western and eastern/central Europe.
(b) These differences have been eroded slowly since 1960 but are still clearly present currently. Some differences are likely to remain as a result of the response of diet patterns to climate; however, previously important factors such as ease of local production are decreasing in impact with improvements in food transport and distribution.
(c) The variations between countries within regions are very much smaller than those between regions.

A more detailed study of dietary patterns in Europe using more reliable data than those provided by WHO would be unlikely to provide much more information than that summarized above. The data from UK and Scandinavia, for example, are internally comparable, but because methodological differences it would be difficult to carry out an accurate comparison with the diet patterns of, for example, Greece or Romania. For many countries the FAO data provide the best available information on diet patterns.

In proceeding further, the best way forward is the more detailed study of diet in specific countries, and this is dealt with in the next 3 chapters.

REFERENCES

Food and Agriculture Organization of the United Nations (1969). *Production Year Book, Vol 23.* FAO, Rome.

Food and Agriculture Organization of the United Nations (1980). *Food Balance Sheets 1972–4 Average.* FAO, Rome.

Food and Agriculture Organization of the United Nations (1991). *Food Balance Sheets 1986–8 Average.* FAO, Rome.

9
Dietary patterns within the United Kingdom

C P J Caygill, M J Hill

9.1
INTRODUCTION

Detailed data on food consumption patterns have been available in the United Kingdom since 1940 when the National Food Survey began. At that time more than 30% of total expenditure was on food; that figure had fallen to 24% by 1970 and to 18% by 1988. The survey records differences between regions of the United Kingdom, between different income groups, between families of different size and between urban and rural areas.

During the period to the early 1950s a wide range of foods were subject to rationing and so there was a pre-ordained uniform simplicity to the UK diet. After the end of rationing there was a period of reaction to rationing with food choice being determined in part by response to the years of deprivation. With time there was a general improvement in food distribution which increased the availability of a wide range of imported foods; memories of war-time food restrictions began to soften and the increasing trend towards holidays abroad increased awareness of alternative food patterns. Similarly the increased travel within the United Kingdom led to a gradual erosion of regional differences in food patterns.

This brief review of dietary patterns within the United Kingdom will begin in 1962, when strong regional differences in food consumption still existed. It will consider time trends during the last 30 years in national and in regional consumption of food and in the differences between urban and rural areas. In particular an attempt will be made to interpret the food consumption patterns in terms of their likely effect on cancer risk in the light of current knowledge on diet and cancer.

9.2
TEMPORAL CHANGES IN THE UK DIET

Figs. 9.1–9.5 show temporal changes in food intake in the UK between 1962 and 1988. during that period there was a general decrease in food energy intake,

corresponding to changes in life style and employment towards lower levels of energy usage. To take account of this all nutrients have been expressed as per 1000 kJ. For ease of presentation, the data are expressed as percentages of the 1962 values.

Fig. 9.1 shows data for a group of foods thought to be protective against cancer — fruit and vegetables. Disappointingly, there has been little change in intake of either total or fresh green vegetables and for total fruit and citrus fruit and berries. This is despite 20 years of health education promoting these items and despite the more ready availability of fresh fruits and fresh vegetables. Fig. 9.2 is more encouraging and shows the rapid and massive increase in consumption of fruit juice; the 1500% increase since 1970 is due largely to its adoption as an important part of breakfast. Despite the huge percentage increase, fruit juice still accounts for only a small fraction of the total intake of vitamin C; nevertheless, there has been a large increase in total vitamin C intake since 1970 (Fig. 9.5).

Fig. 9.3 illustrates changes in intake of meat. There has been a steady but slow decrease in intake of carcase meat (often referred to as "red meat") and this has been offset by a more than 3-fold increase in the consumption of chicken and poultry. Fish consumption has remained steady during the 26 year period, as has the intake of total meat.

Fig. 9.3 also shows the changes in consumption of beverages, with a general decrease in tea consumption, matched by a general increase in coffee intake. Despite these changes, the relative consumptions were tea:72% and coffee:28% even as late as 1988.

Fig. 9.4 shows changes in consumption of minor food items. There has been a decrease of more than 50% in egg consumption, despite a major decrease cost (following the introduction of intensive farming techniques). This decrease predates the very bad publicity that eggs received following the demonstration that a proportion carried highly virulent strains of salmonella—a problem that has still to be overcome at the time of writing. There was an even greater decrease in intake of sugar and preserves, and an equal decrease in salt intake; both of these have been strongly urged by those making dietary recommendations. There has been an interesting increase in consumption of pickles and sauces, probably reflecting the changes in food patterns to include more Indian and Chinese recipes.

Within the dairy products there has been a decrease in intake of milk and cream and an increased intake of cheese. However, the type of milk has changed and Fig. 9.4 shows the above changes together with the changing proportion of reduced fat products within the total milk intake.

Variations in cereal and cereal product consumption are illustrated in Table 9.1. Although bread intake has decreased by more than 20% since 1970 there has been a major increase in the intake of wholemeal bread. Despite this major increase wholemeal bread still accounts for only a relatively minor proportion of the total (at 27%) and sliced white bread still dominates the bread market as it has in the UK since the 1950s.

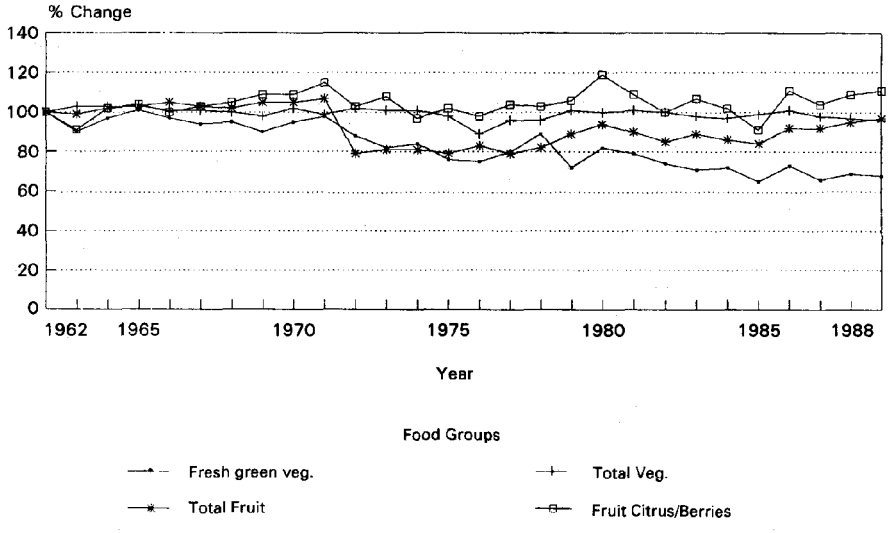


Fig. 9.1—% Change in fresh fruit and vegetables consumption, 1962–89

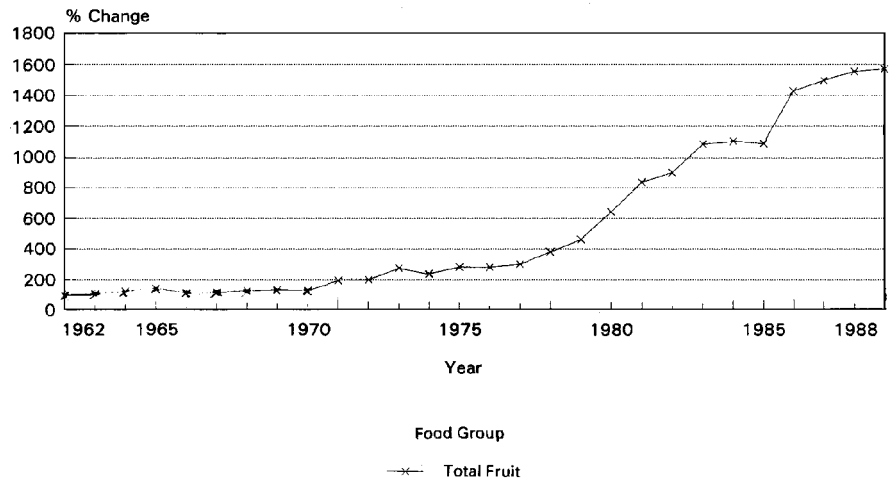


Fig. 9.2—% Change in fruit juice consumption, 1962–89

Table 9.1—Change in consumption of certain key foods between 1980 and 1988

	Average consumption (ounces per person per week)			% Change 1970–88
	1970	1980	1988	
Milk and cream	5.08	4.58	4.01	−21.1
Cheese	3.59	3.89	4.13	+15.0
Fats	12.00	11.20	9.80	−18.0

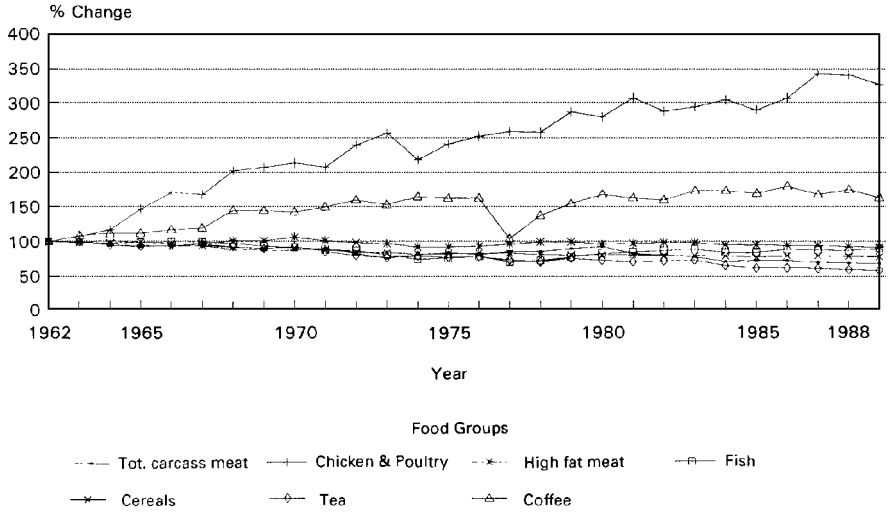


Fig. 9.3—% Change in meat and beverage consumption, 1962–89

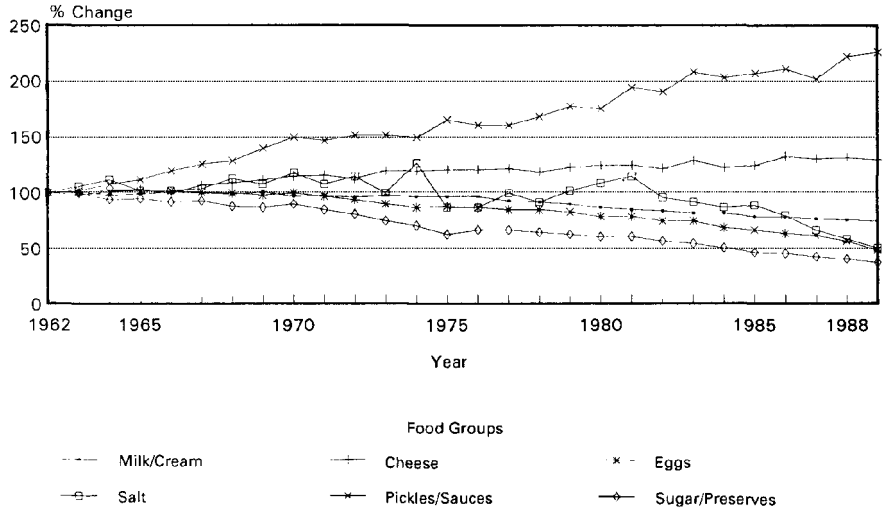


Fig. 9.4—% Change in minor food consumption, 1962–89

	Average consumption (ounces per person per week)			% Change 1970–88
	1970	1980	1988	
butter	5.00	4.10	2.00	–66.6
margarine	2.90	3.80	3.80	+32.9
low fat spreads	0	0	1.4	–
Meats	39.50	40.20	36.60	–7.4

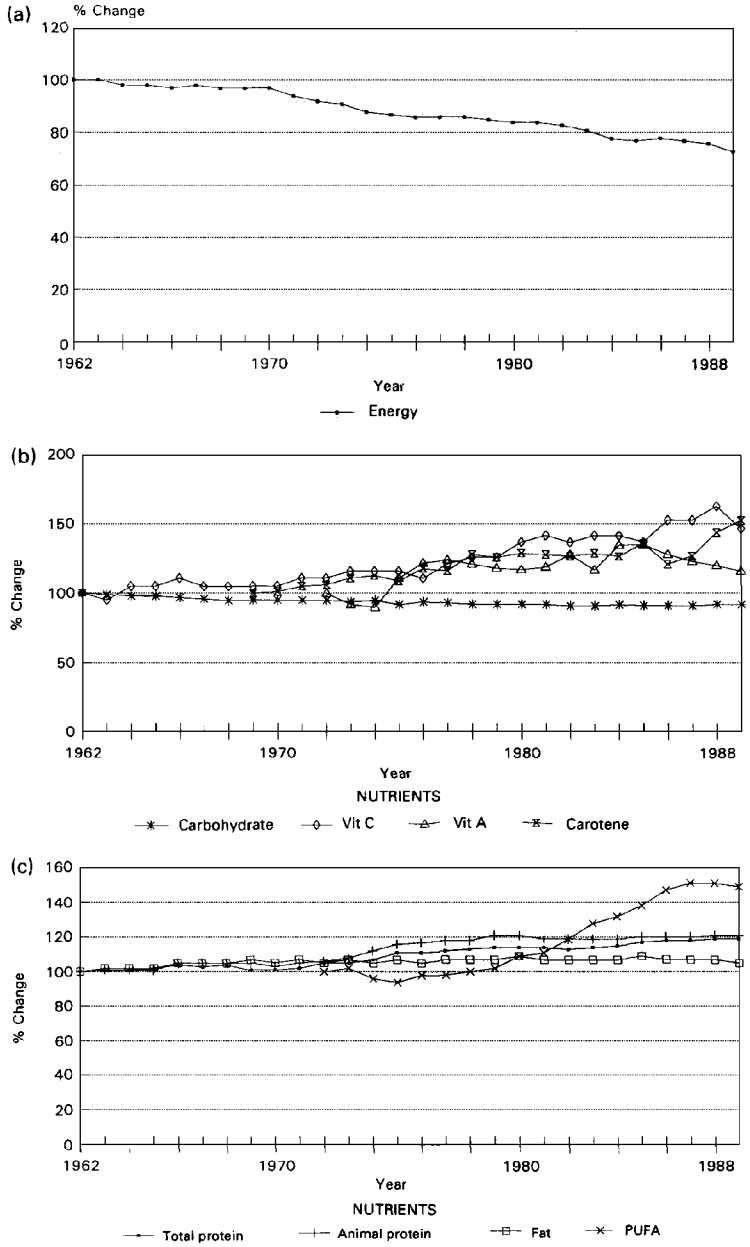


Fig. 9.5—% Change in energy intake 1962–89.

	Average consumption (ounces per person per week)			% Change 1970–88
	1970	1980	1988	
beef and veal	7.80	8.10	6.30	–19.2

	Average consumption (ounces per person per week)			% Change 1970–88
	1970	1980	1988	
poultry	4.80	6.70	8.10	+67.4
Fish	5.40	4.80	5.10	–4.7
Fresh green vegetables	14.50	12.40	10.40	–28.0
Fresh fruits	23.10	20.80	21.00	–9.2
citrus	5.00	5.20	5.10	+1.8
fruit juices	0.60	3.08	7.43	1140%
Sugar and preserves	19.50	13.20	8.80	–54.9
Bread	38.10	31.10	30.30	–20.5
brown/ wholemeal	2.90	5.60	8.20	+180.8

Table 9.1 also summarizes the changes in consumption of a number of other foods between 1970 and 1988. Fat consumption has decreased by 18% (mostly since 1980); within this there has been a major switch away from butter (animal fat) and towards margarine (vegetable fat). There has been a small decrease in consumption of meat, but within this there has been a nearly 20% decrease in consumption of beef and veal and a 67% increase in poultry consumption. There has been a massive decrease in intake of sugar and preserves. The 20% decrease in bread consumption masks a 180% increase in consumption of brown and wholemeal bread (although this still accounts for less than 30% of the total). All of these changes are consistent with dietary advice for healthy eating (although they are likely to be more due to economic factors than to the effect of public education).

In contrast there has been a tendency for consumption of fresh fruit and fresh green vegetables to decrease, even though increases in their consumption has been a major feature of public education programmes. Intake of fresh green vegetables has decreased by 28%; the intake of fresh fruit decreased by 9% but within this there was a small increase in consumption of citrus fruits.

9.3
REGIONAL VARIATIONS

Despite the small size of England, traditionally there has been little mobility between the regions, and even less between the countries that make up the United Kingdom. This led to the development of relatively distinct food consumption patterns and even meal patterns, with, for example, the main cooked meal being taken in the middle of the day more commonly in the north of

England and Scotland than in southeast England. More recently, with the improvements in communications and ease of travel, there has been more internal migration and a moderation in the regional differences in food consumption patterns.

The National Food Survey publishes analyses of regional differences in food consumption patterns for the year 1969. The data are expressed as actual amounts (ounces per week) and as percentage differences from the mean value. Table 9.2 shows the regional differences in food consumption for 7 regions of England plus Scotland and Wales for 1969, expressed as percentage differences from mean values. There was little variation in the consumption of staple foods such as bread (range from +16 to −11), potatoes (+15 to −10) or milk (+6 to −14). In contrast, there were large ranges in intake of non-staple foods, particularly fresh green vegetables (−55 to +45), cooking fat (+34 to −35), fish (+29 to −14) and cheese (+13 to −25). Within spreading fats there were great ranges in preference between butter and margarine (*eg* Wales: butter +32/ margarine −17; Yorkshire: butter −15/margarine 32)

Similarly there is a range in beverage preference. In the UK *in toto* tea consumption exceeds that of coffee by 3 fold; in Wales the consumption of tea is 24% above average and coffee is 33% below the national average, whilst in London coffee consumption is 12% above average and tea consumption is normal. In Scotland consumption of both tea and coffee is below average.

Meat preferences also show great variations between regions. Consumption of beef is highest in Scotland (+19%) and lowest in Wales (−20%); pork consumption is highest in the West Midlands (+55%) and lowest in Scotland (−59%); poultry consumption is highest in south-east England (+21%) and lowest in Yorkshire (− 26%).

Certain foods have featured in dietary advice as being deemed *healthy* or *unhealthy*. Thus fresh fruit and fresh green vegetables are associated with decreased cancer risk whilst beef is associated with an increased risk of colon cancer. Within meat sources, poultry has much less fat than carcase meat—particularly lamb and beef—and so is thought to be relatively healthy. Within fat spreads butter (animal fat) is thought to be less healthy than margarine (vegetable fat). Table 9.3 selects out some *healthy* and some *unhealthy* foods. In general, south-east England tends to have above average intakes of *healthy* foods and below average intakes of *unhealthy* foods. In contrast, Scotland tends to have low intakes of *healthy* and high intakes of *unhealthy* foods. Many foods, particularly fresh green vegetables and fresh fruit, preserves and cakes and biscuits, show a consistent north-south gradient.

Table 9.2—Regional variations in consumption of various foods. Data are expressed as percentage difference from the mean national intake

			England regions			
	Wales	Scotland	North	E Mid	S West	SE
Meats						
Beef/veal	−20	+19	/	−9	−8	/
Poultry	+12	−20	−23	−13	+8	+21
Pork	−20	−59	−24	/	+35	+22
Fats						
Butter	+32	/	−15	/	+12	/
Margarine	−17	+10	+22	/	−11	−19
Pufa	−27	−8	+33	−10	/	+27
Vegetables						
Fresh green	/	−55	−39	+26	+45	+31
Potatoes	+15	/	/	/	/	−10
Fresh fruit	−11	−14	−16	/	+19	+21
Other fruit	−9	−6	−7	+8	/	+10
Dairy products						
Milk	−9	/	−14	+6	/	/
Cheese	−6	−7	−25	/	+13	+11

/=less than 5% different from the national mean value.

Table 9.4 shows a similar analysis of regional variations in food consumption for 1988. Note that the wide ranges seen in 1969 have virtually disappeared. South-east England still has a low intake of eggs, sugar/preserves, and of meat and meat products and a high intake of fruit. Further, Scotland still has an above average intake of sugar/preserves (+19%) and eggs (+36%) and a low intake of fruit (−14%) and brown/wholemeal bread (−30%). As in 1969, Wales had the highest tea and the lowest coffee intake, but the percentage differences from the average were relatively small (+11% for tea; −12 % for coffee) compared with those seen in 1969.

If diet is important for health, then the risks of the diet-related cancers should become much more even than have been seen in the past.

Table 9.3—Variations in consumption of *healthy* and of *unhealthy* foods between regions in 1969

	Scotland	Yorks	Wales	East Mid	South East
Healthy foods					
Fresh green veg	−55	−7	-	+12	+31
Fresh fruit	−14	−6	−11	Ave	+21
Poultry	−20	−26	+12	−13	+21

	Scotland	Yorks	Wales	East Mid	South East
Margarine	+10	+32	−17	Ave	−19
Unhealthy foods					
Sugar	Ave	Ave	+19	+7	−6
Preseves	+25	+6	+12	Ave	Ave
Cakes/biscuits	+13	+7	Ave	−13	−7
Beef/veal	+19	+8	−20	−9	Ave
Eggs	+10	Ave	Ave	Ave	Ave
Butter	Ave	−15	+32	Ave	Ave

Table 9.4—Variation in consumption of various foods and food gorups between the UK regions

	Ave	N	Y/H	NW	EM	SW	SE/EA	E	S	W
Milk/cream	4.01	−5	·	·	+5	+7	·	·	·	−9
Cheese	4.13	−13	−10	·	·	+16	·	·	·	−16
Meat/meat products	36.6	·	·	·	−7	+6	−5	·	·	·
Fish	5.06	+10	+20	−8	−11	·	·	·	−6	−12
Eggs	2.7	+24	+12	·	·	·	−15	·	+36	−10
Fats	9.86	·	·	·	·	+7	−8	·	·	+6
Sugar/preserves	8.8	·	·	·	·	+21	−12	·	+19	−7
Fruit	31.9	−13	−15	−10	−12	+10	+18	·	−14	−10
Veg	83.1	+10	·	·	+6	+10	−8	·	·	·
Cereals	54.1	+9	·	·	+6	·	−8	·	·	+10
Brown/wholemeal	8.5	·	−12	·	+11	·	·	·	−30	·

·•=Within 5% of the average value; N=North; Y/H=Yorkshire and Humberside; NW=northwest; EM=East Midlands; SW=southwest; SE/EA=southeast and East Anglia; E=England; S=Scotland; W=Wales.

Table 9.5 shows the urban-rural differences in food consumption patterns in 1969. Total fat intake was much lower in London than in rural areas as was the

consumption of bread and flour, sugar/preserves and of milk/cheese/eggs. In contrast the London population consumed much more fresh fruit, most types of meat and fish, and more vegetables. In all, the diet in London is closer to that recommended in public education programmes than is the diet of medium towns or rural areas.

Table 9.5—Urban-rural differences in consumption of foods in 1969 and 1975 (expressed in ounces/person/week)

	London		Large towns		Rural	
	1969	1975	1969	1975	1969	1975
Milk & cream	5.42	5.00	5.25	5.14	6.18	5.40
Cheese	3.80	4.03	3.46	3.70	3.98	4.01
Meat	42.90	41.88	37.67	34.64	38.25	36.39
Fish	5.91	4.93	5.50	4.36	4.28	3.98
Eggs	4.63	4.18	4.56	4.01	5.29	4.20
Sugar & preserves	16.99	12.14	19.26	14.01	20.15	14.09
Fats	11.07	10.49	12.03	11.13	12.98	11.30
Veg	82.43	89.40	83.71	83.77	78.83	81.46
Fruit	29.54	28.64	21.62	23.46	23.34	24.04
Bread (total)	32.84	32.35	38.11	33.76	37.68	32.86
Cereals (total)	55.43	53.34	63.35	57.54	64.14	56.42

9.4
RELATION TO SOCIOECONOMIC STATUS

Consumption of food in England and Wales varies with socioeconomic status, although the relationship has become weaker in recent years. This is illustrated in Table 9.6 for the years 1969 and 1989. When income group A (high) was compared with income group D (low) in 1969 they consumed more milk and cream, cheese, meat and fruit, and less fish, vegetables, sugar and preserves, cereals and bread. There was little difference in consumption of eggs or of fats. Although group A ate 25% less breast than group D, within those totals group A ate 6 times as much wholemeal breast (although this still only represented 3% of the total).

By 1989 there had been some big changes in eating patterns and these were not uniformly spread through the socioeconomic groups. Cheese consumption increased in the higher income groups but not in the lower, so that the gap between the groups widened. Similarly, group A increased its fruit intake whilst the low consumption of

Table 9.6—Variation in food consumption pattern between income groups A (high) to D (low)

	A		B		C		D	
	1969	1989	1969	1989	1969	1989	1969	1989
Milk and cream	5.81	3.82	5.26	3.85	5.03	3.72	5.00	3.75
Cheese	3.85	4.49	3.46	4.40	3.30	3.87	3.22	3.27
Meat	40.21	32.91	38.05	34.46	37.41	36.69	37.53	36.73
Fish	5.34	4.81	5.14	4.74	5.49	4.81	6.03	4.57
Vegetables	74.75	73.06	85.49	77.19	88.32	83.48	92.91	90.04
Fruit	40.17	45.56	30.37	34.30	25.94	26.13	22.69	20.79
Eggs	4.84	1.84	4.44	2.00	4.61	2.25	4.56	2.76
Sugar and preserves	16.83	5.43	18.48	6.49	19.37	7.45	20.01	9.65
Fats	11.44	8.00	11.57	8.51	12.13	9.23	11.21	10.22
Cereals (total)	54.99	46.74	62.24	51.83	66.79	52.73	63.78	57.47
Bread - total	31.24	23.69	37.73	28.04	41.38	30.11	41.00	34.21
- wholemeal	0.96	4.07	0.47	4.19	0.36	3.29	0.16	3.10

Data are in ounces consumed per person per week.

fruit by group D in 1969 had fallen even lower by 1989. In contrast, meat consumption decreased by 18% in income group A but only by 2% in group D so that by 1989 there was an *inverse* relation between income and meat consumption (in contrast to the 1969 situation).

Total bread intake decreased in all groups but the proportion of wholemeal bread increased to 17% in group A and 9% in group D. Some of the changes in food patterns can be accounted for in terms of price changes. Thus, between 1969 and 1989 the price of poultry fell sharply relative to that of other meats and fish. At the same time strong messages about healthy eating were being transmitted. The decrease in consumption of meat, eggs, white bread and fats and the increased intake of fruit and of wholemeal bread by group A could have been partly in response to these health messages. In group D the long term health message carries much less weight in comparison with other more immediate problems and so the decrease in egg and fat consumption was much less, the increase in wholemeal bread intake much less than in group A.

9.5
CONCLUSIONS

The diet in the United Kingdom has shown major temporal and regional variations during the last 20 years. In general, in 1969 the diet was closer to that recommended in public education programmes in the south of England than in Scotland, with the English Midlands and North intermediate; these regional variations have decreased with time but were still apparent in 1988. Since 1969

the diet has improved greatly, in that it is closer to that recommended in public education programmes. However, many of the changes have been due to economic factors (*eg* the switch from beef to chicken) or to health scares (*eg* the switch away from eggs) rather than to public education.

The diet in the UK is clearly moving closer to that consumed in the Mediterranean countries, and it will be interesting to see whether this is followed by a decreased incidence of heart disease and the diet-related cancers.

REFERENCES

National Food Survey: Household food consumption and expenditure. HMSO, London for the years 1962–1989.

10
Diet in Italy: trends and geographical distribution

F Merlo, R Filiberti, G Reggiardo, P Visconti, A Giacosa

10.1 INTRODUCTION

Diet may play a role in carcinogenesis directly because of the presence of carcinogens or certain protective factors or through indirect effects such as under or over nutrition. Although there is good agreement that diet is directly involved in the process of carcinogenesis, quantification of the causal relationship between diet and cancer risk remains unclear (Miller, 1980; Henderson *et al*, 1991). In particular, questions are still open whether cancer risk is due to specific food items, to nutritional components (lipids, vitamins, etc) or, more generally, to a complex of dietary habits, with a higher intake of calories and an increase of body weight.

There are indications that a diet rich in vegetables and fruit provides protection against some epithelial cancers of the upper digestive and respiratory tracts, breast, ovary and prostate (Miller, 1980; Negri *et al*, 1991). On the other hand, a diet rich in proteins, fats (particularly meat and animal fats) and calories is associated with hormone-related malignancies and colon cancer (Willett *et al*, 1990; WHO, 1990). A protective role of fibre in the occurrence of colorectal cancer has been hypothesized; cereal fibre increases the rate of colonic transit, affects carcinogen concentration through stool bulking, and carcinogen production through caecal acidification (Hill, 1991). In addition, fibre appears to provide →protection in breast carcinogenesis, acting as an antioestrogenic factor (Adlercreutz, 1990). Results from correlational or ecological studies, which compare countries differing in cancer mortality rates, life style and consumption of different food items, support the hypothesis of a role of diet in cancer development (La Vecchia *et al*, 1988).

Europe shows relevant differences in cancer mortality with generally higher rates in Northern countries and lower rates in the Mediterranean areas. This north/south gradient is also found within Southern countries, suggesting possible within-country life style differences, particularly dietary habits (La Vecchia and Decarli, 1986; Levi *et al*, 1989). Italy, especially, shows large differences in cancer mortality both between and within regions according to latitudes, together

with different dietary and smoking habits (La Vecchia and Decarli, 1986; Ferro-Luzzi and Sette, 1989; Spiller, 1991; Testa *et al*, 1992) (Table 10.1, Fig. 10.1). Consumption of cereals and fish is 33% and 45% lower in northern than in southern regions (Figs. 10.2, 10.3; ISTAT, 1990). In addition, north western areas have generally a lower intake of vegetables as compared to the other regions (Table 10.2). Conversely, foods derived from animal sources are more frequently eaten in northern and central regions where consumption of beef and cheese is respectively 14% and 10% higher than in the south (Fig. 10.3– 10.6). Evaluation of calorie intake from specific foods shows also a higher intake of energy from butter in the north as compared to the south (+60%), in contrast with a lower intake of olive oil (−22%) in northern Italy (Fig. 10.7). Examination of dietary habits by socioeconomic status (assuming that a distinction between white-collar workers and blue-collar workers is an indicator of this parameter) shows a higher consumption of cereals in the lower classes, while white-collar workers eat more fruit and second courses (Fig. 10.8). Cereals are eaten more by persons working in agriculture, while people involved in industry consume more fish and fruit (Fig. 10.9). Specific differences are also observed when comparing the consumption of selected food items in urban and rural areas (Fig. 10.10).

Table 10.1—Cancer mortality in different areas in Italy, 1988

		Site				
		All cancers	Stomach	Colon	Lung	Breast
North	M	22.5	1.91	1.37	7.68	–
F	12.1	0.93	1.03	1.03	2.75	
Centre	M	18.3	1.83	1.23	5.98	–
F	11.0	0.93	0.95	0.97	2.31	
South	M	15.1	1.20	0.78	5.03	–
F	9.7	0.63	0.73	0.38	2.08	

Age-standardized rates to Italian population 1971×10,000

A statistical exercise of correlation between Italian regional death rates for some cancer sites in the period 1985–1987 and consumption of specific food items and of cigarette sales was performed. Correlational studies may provide opportunities for generating hypotheses on linkage between occurrence of some diseases and the influence of specific environmental factors such as dietary habits.

Table 10.2—Consumption of fruits and vegetables in different Italian geographical areas (g/per-capita/die) (Turrini *et al*, 1991)

	North West	North East	Centre	South
Fruits				
Apples	72.5	93.8	85.9	54.6
Citrus fruits	51.5	55.3	66.4	42.8

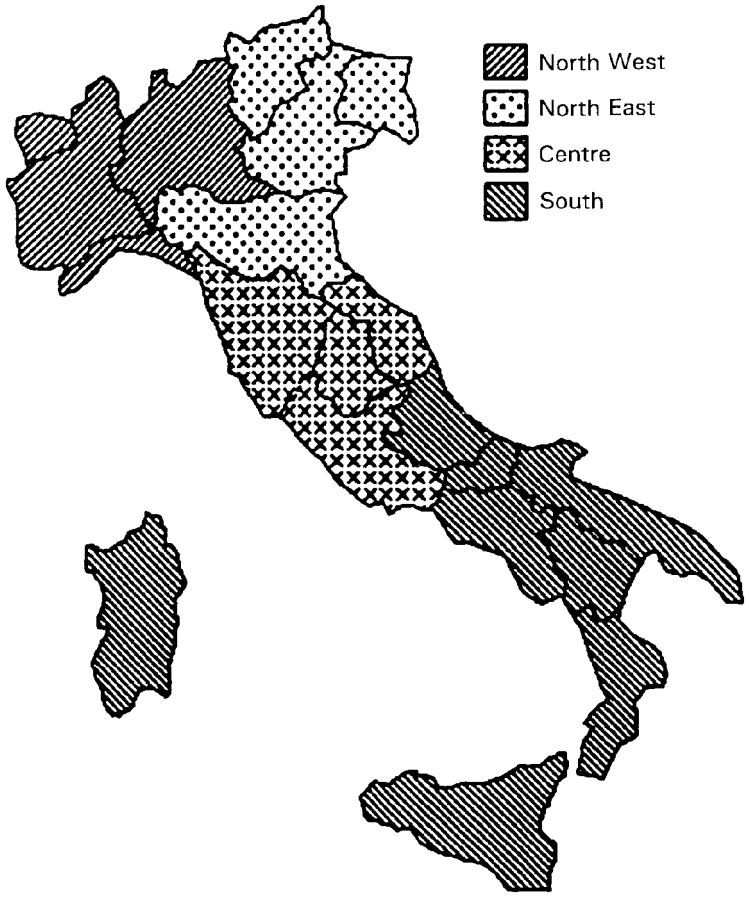


Fig. 10.1—Italian sub-regions as defined by the central Institute of Statistics (ISTAT)

	North West	North East	Centre	South
Figs, plums	4.1	0.9	4.7	5.3
Grapes	9.5	10.6	20.7	15.7
Peaches, apricots	31.3	8.0	18.0	32.5
Pears	21.7	16.0	23.0	23.4
Persimmons	4.0	4.3	5.1	3.5
Sour cherry, cherry, strawberries, loquats	9.8	5.2	7.1	11.3
Tropical fruits	15.2	14.9	13.6	9.6
Watermelon, melon	12.1	3.3	5.2	5.9
Vegetables				
Artichokes	2.6	4.6	7.1	5.1
Cabbages, cauliflowers, broccoli	5.5	10.0	13.2	9.7

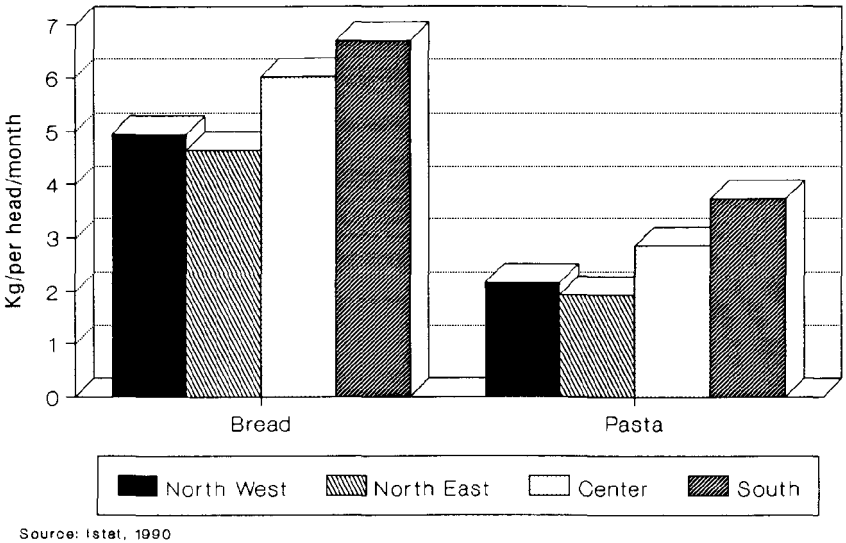


Fig. 10.2—Consumption of bread and pasta by geographical areas in Italy, 1988

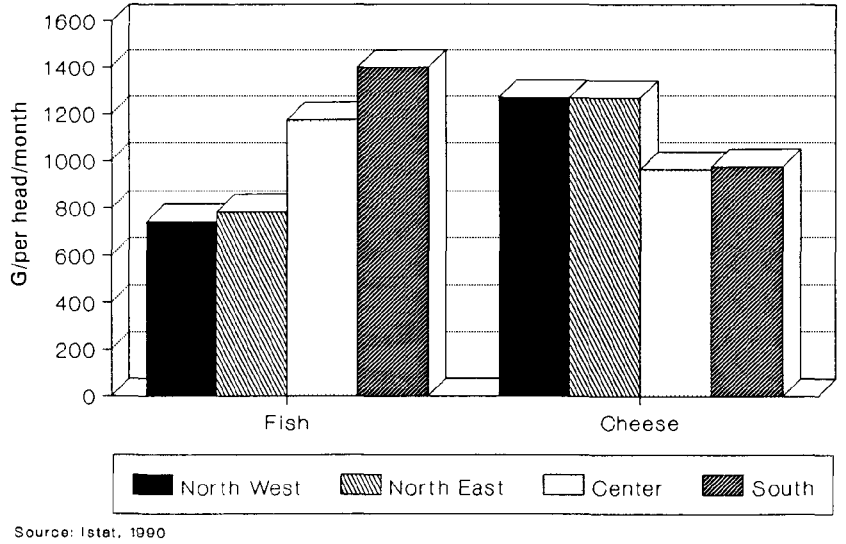


Fig. 10.3—Consumption of fish and cheese by geographical areas in Italy, 1988

	North West	North East	Centre	South
Canned tomatoes	27.0	21.8	74.7	67.1
Carrots, turnips, fennel, celery	21.9	23.1	17.1	11.1
Cucumbers, zucchine	16.8	8.0	10.7	14.0

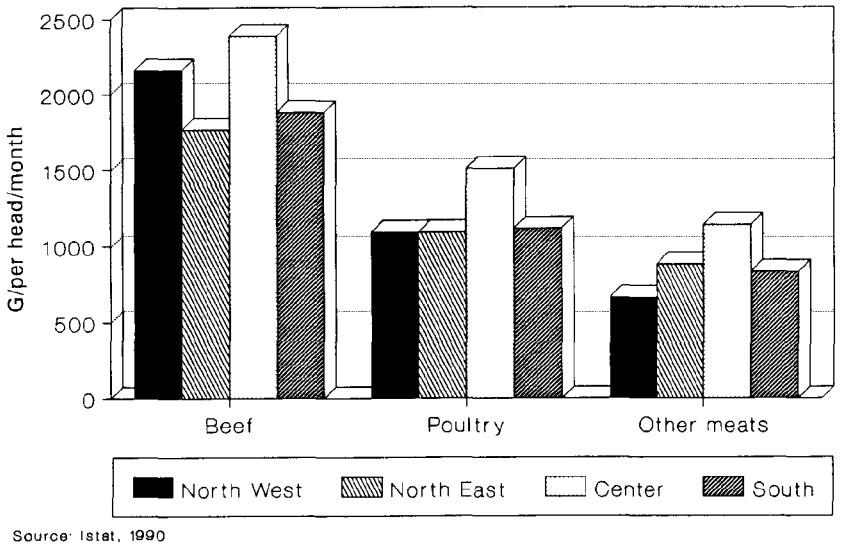


Fig. 10.4—Consumption of meats by geographical areas in Italy, 1988

	North West	North East	Centre	South
Eggplants, peppers	8.1	6.7	13.0	22.1
Garlic	0.2	0.5	1.1	0.7
Onions	8.8	15.3	7.1	7.3
Potatoes	40.6	60.1	56.3	54.7
Tomatoes	26.0	21.0	40.5	55.5
Vegetables for salad	25.3	33.2	45.5	28.5
Other vegetables	10.5	10.6	23.3	8.6

Age-standardized mortality rates for selected cancer sites for the 20 Italian regions were calculated using 1983–1985 mortality data and the resident population in each area, as published by the Italian Central Institute of Statistics (ISTAT, 1985, 1989– 1990). The following cancer sites were selected: prostate for males, breast for females and, for the general population, oropharynx, oesophagus, stomach, colon, rectum, larynx and lung.

Intake of food items in each region refers to 1973 *per capita* consumption of bread, pasta, meat (beef, chicken, and other meat, such as pork), fish, milk, cheese, eggs, oils, fruit, sugar, coffee and wine (ISTAT, 1975). These data are collected every year by the ISTAT, based on interview-based national surveys on a stratified random sample of some 38,000 families per year (3,000 households per month) selected from 140 cities with more than 50,000 inhabitants and 180 small municipalities (ISTAT, 1984). The sample units (*ie* families) are completely replaced every month, and the yearly participation rate is around 85%. Data collection is carried out through a ten day preceded and standardized

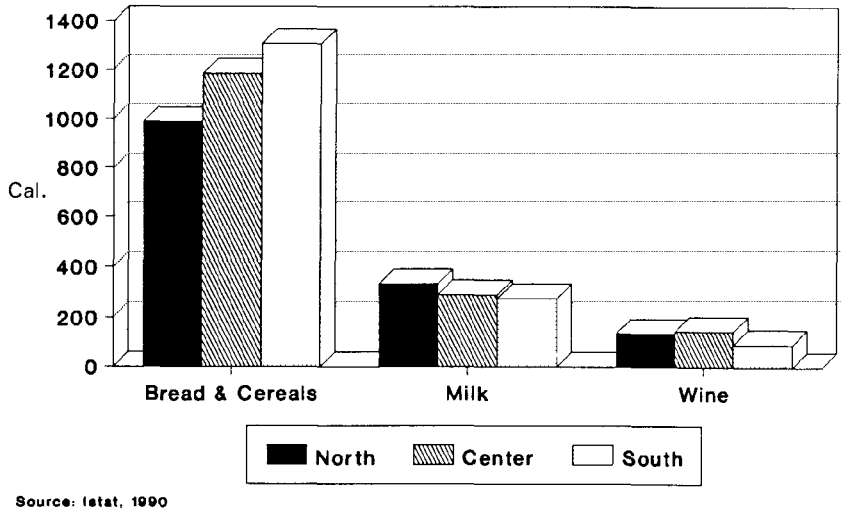


Fig. 10.5—Intake of calories from some food items by geographical areas, 1988

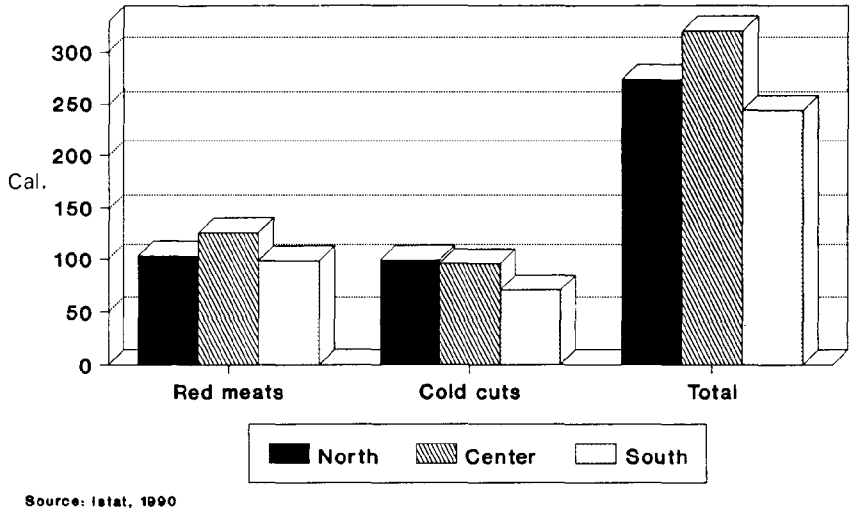


Fig. 10.6—Intake of calories from meats by geographical areas, 1988

consumption diary to be filled in daily and through a final interview performed by trained interviewers at the end of each month.

The number of cigarettes sold per inhabitant in each of the 20 regions was used as an indirect index of smoking habits: *per capita consumption* of cigarettes in each area was computed by dividing the kilograms of cigarettes sold in 1964 by the resident population of that area aged 15 years or older.

Correlation analyses show that regions with lower mortality rates for cancers of oropharynx, oesophagus, colon, lung and prostate are characterized by a higher *per capita* intake of bread, pasta and fish (the correlation coefficient (r) ranged

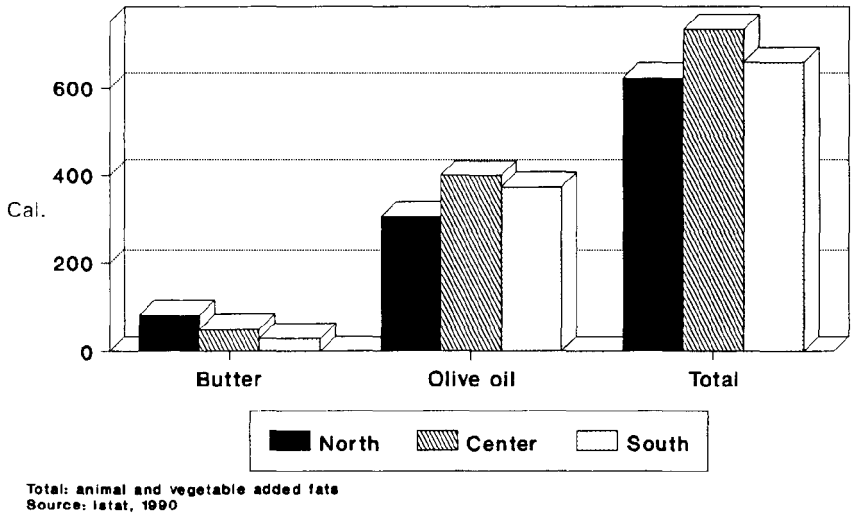


Fig. 10.7—Intake of calories from oils and other added fats by geographical areas, 1988

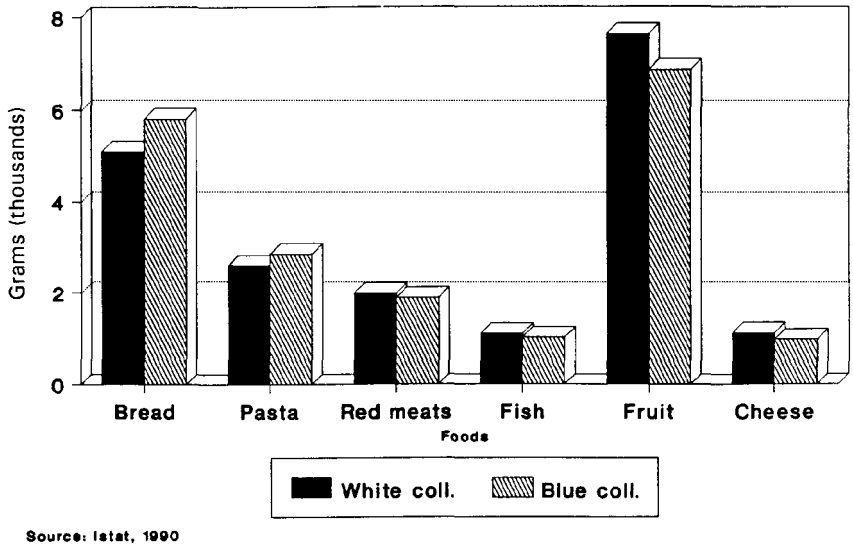


Fig. 10.8—Consumption of foods by socioeconomic condition

between −0.60 and −0.88) (Table 10.3 and Fig. 10.11–10.13). The same association, except fish, is observed for cancers of the rectum and breast (respectively r=−0.76 and r=−0.59 for bread; r=−0.61 and r=−0.63 for pasta), supporting a potential protective effect of these typically Mediterranean foods in the development of site specific cancers. In addition, stomach and larynx cancers are also negatively correlated with pasta (r=−0.60) and fish (r=−0.55)

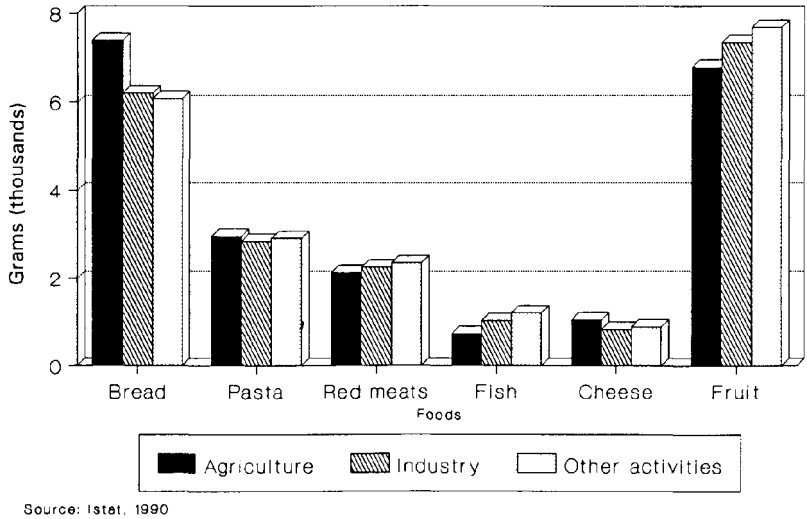


Fig. 10.9—*Per capita* consumption of foods by type of occupational activity

(Fig. 10.14). Examination of the correlation coefficients shows generally a positive link between cancer death rates and food items of animal origin. In particular, beef consumption correlates with all the abovementioned cancers except oropharynx and larynx (Fig. 10.15–10.16), while the *other meats* are linked with stomach and colon cancers. Oropharynx, oesophagus, larynx, lung, breast and prostate cancer death rates correlate positively with milk and cheese consumption (Fig. 10.17–10.18).

Cigarette consumption is positively correlated with cancers of the lung (0.70), prostate (0.68), breast (0.67) and colon (0.65) (Table 10.3).

Results from this study confirm previous findings from correlational studies (Decarli *et al*, 1986) as well as from other analytical surveys (Negri *et al*, 1991; Spiller, 1991), suggesting an association between diet and neoplastic diseases, in terms of protection or risk from specific food items.

10.2
TEMPORAL TRENDS OF DIET IN ITALY

Dietary habits have changed across time and geographic areas owing to modifications of socioeconomic status and to the influence of factors such as the increased availability of foods. In Italy, during the last 40 years there have been substantial increases in the consumption of red meats (400%), olive oil (200%), fruits (180%),

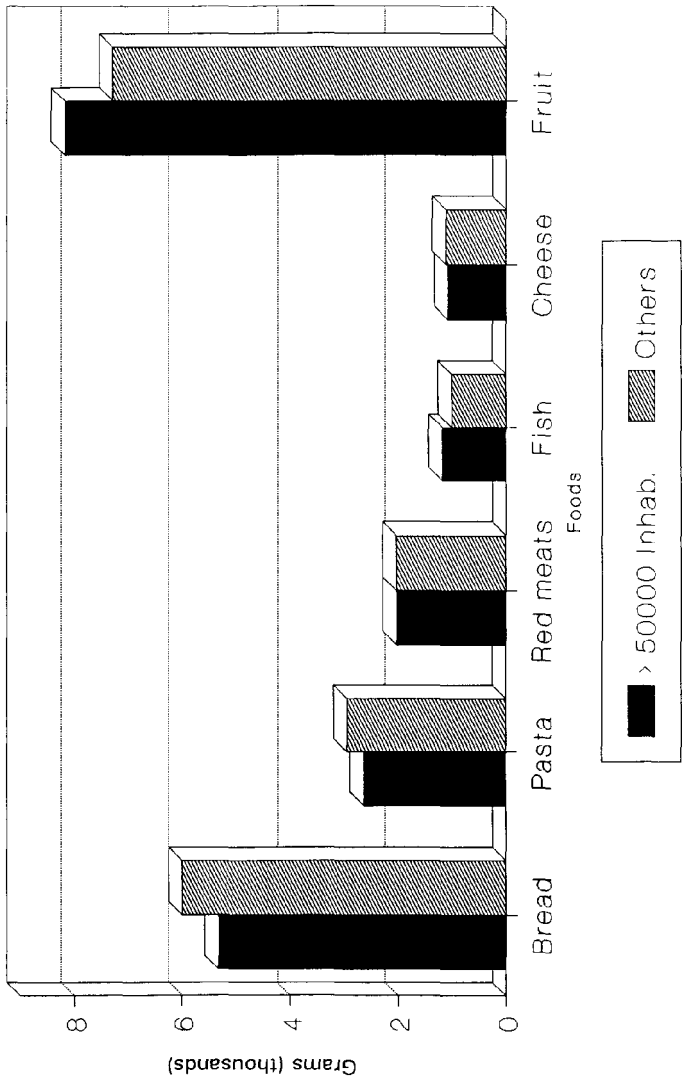


Fig. 10.10—*Per capita* consumption of foods by density of population.

Table 10.3—Estimated correlation coefficients between mortality rates for selected cancers (1985–1987) and regional consumption of some food items (1973)

	Oroph	Oesoph	Stomach	Colon	Rectum	Larynx	Lung	Breast	Prostate
Bread	**–0.601**	**–0.652**	–0.467	**–0.800**	**–0.760**	–0.416	**–0.857**	**–0.587**	**–0.871**

	Oroph	Oesoph	Stomach	Colon	Rectum	Larynx	Lung	Breast	Prostate
Pasta	**–0.726**	**–0.798**	**–0.599**	**–0.783**	**–0.605**	**–0.604**	**–0.810**	**–0.627**	**–0.877**
Beef	0.382	**0.557**	**0.645**	**0.849**	**0.626**	0.468	**0.797**	**0.728**	**0.756**
Poultry	–0.047	–0.065	**0.532**	0.504	0.425	–0.147	0.147	–0.044	0.268
Other meat	**0.077**	0.089	**0.706**	**0.595**	0.352	0.048	0.184	0.125	0.418
Fish	**–0.578**	**–0.700**	**–0.684**	**–0.664**	–0.426	**–0.548**	**–0.510**	–0.450	**–0.660**
Milk	**0.813**	**0.907**	0.297	**0.582**	0.401	**0.734**	**0.783**	**0.801**	**0.748**
Cheese	**0.652**	**0.782**	0.209	0.467	0.305	**0.725**	**0.683**	**0.735**	**0.605**
Egg	0.097	0.080	0.203	**0.513**	0.436	–0.051	0.229	0.378	0.351
Oil	**–0.536**	–0.446	–0.236	–0.108	0.161	–0.443	–0.335	–0.325	–0.157
Fruit	–0.495	–0.384	0.110	0.194	0.270	–0.343	0.123	0.179	–0.027
Sugar	**0.641**	**0.796**	0.285	**0.600**	0.334	**0.704**	**0.574**	**0.750**	**0.719**
Coffee	0.449	**0.544**	0.153	0.426	0.382	0.374	0.405	0.413	**0.568**
Wine	0.223	0.458	**0.559**	**0.580**	0.338	0.457	0.428	0.393	**0.560**
Cigarette	0.406	0.481	0.347	**0.647**	0.415	0.360	**0.698**	**0.670**	**0.683**

In bold $P<0.05$; F statistics, 1,8 degrees of freedom

particularly citrus fruit, milk (130%) and vegetables (Fig. 10.19, 10.19b). Trends for specific nutrients and for energy intake show a marked increase (around 60%) in intake of fats and calories from animal sources (Fig. 10.20, 10.21).

Changes in food consumption, nevertheless, are rather different in various areas. In general, consumption of animal derived foods in southern regions approach the higher values of northern and central areas of the country.

In 1973, consumption of meat was about 50% higher in northern and central than in southern Italy, but in 1988 this difference was clearly reduced (Fig. 10.22).

In the early 70s milk consumption was 20–50% higher in northern than in southern regions (Fig. 10.23). Recent data indicate that the differences in milk intake between geographical areas persist despite the decreasing and increasing trends (Fig. 10.23) of milk consumption observed in northern and southern regions, respectively. *Per capita* consumption of cheese has increased with time in all areas so that the differences between regions have persisted with time (Fig. 10.24).

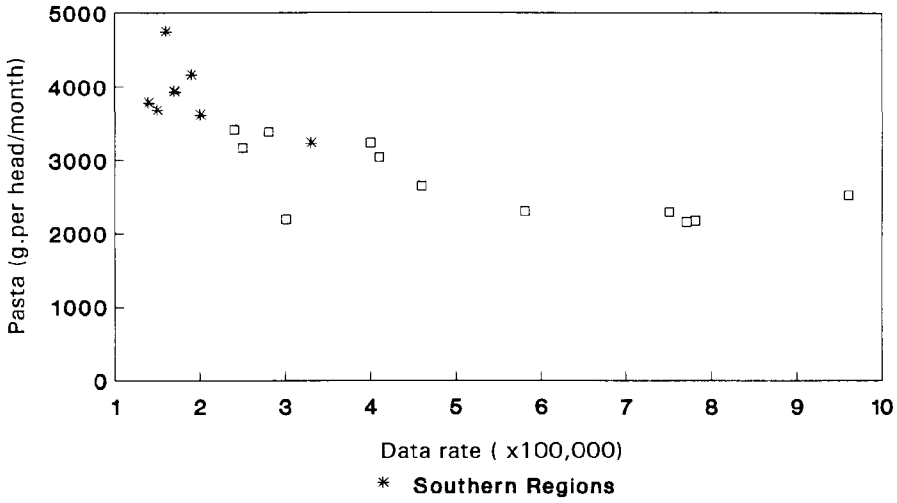


Fig. 10.11—Correlation between regional mortality rates for oesophageal cancer and regional consumption of pasta. Males.

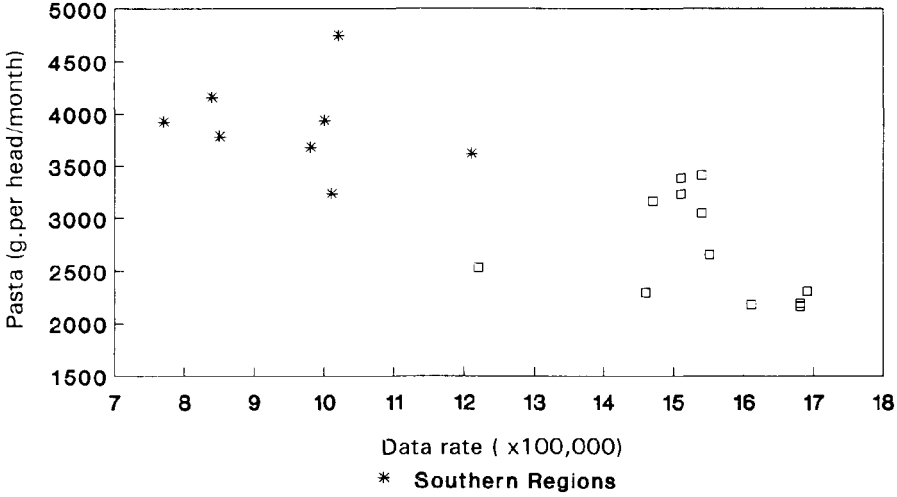


Fig. 10.12—Correlation between regional mortality rates for colon cancer and regional consumption of pasta. Males.

A negative trend is observed for intake of cereals (bread and pasta) which is consistently higher in the southern regions and has decreased in the country overall by about 13% (Fig. 10.25, 10.26). This trend, nevertheless, has not altered the marked differences between the geographical areas. *Protective* foods like fruit, fish and oils were consumed in 1973 in higher amounts in the south. The intake of these foods has increased in time with a more marked trend in northern regions (+82% for fish) (Fig. 10.27–10.29).

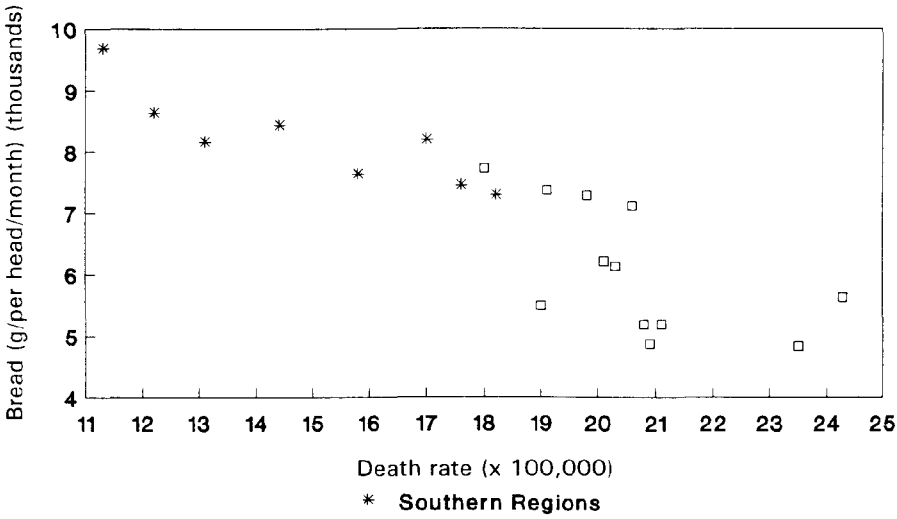


Fig. 10.13—Correlation between regional mortality rates for prostate cancer and regional consumption of bread. Males.

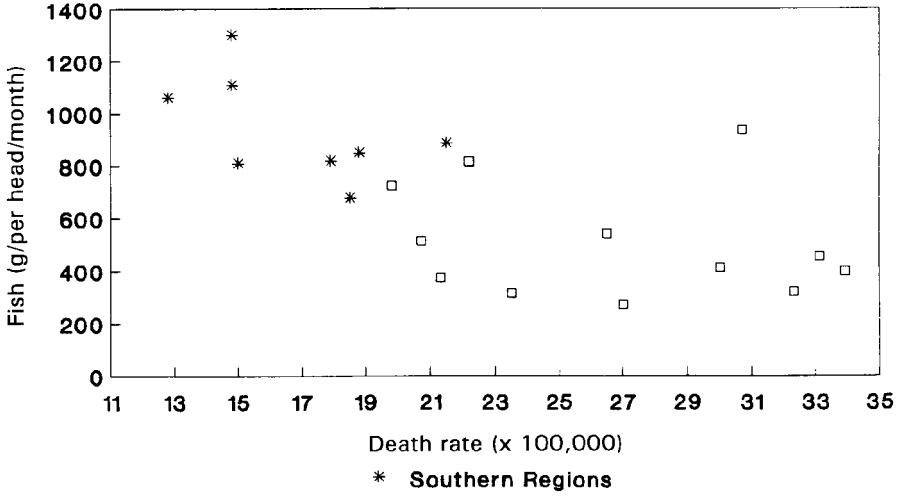


Fig. 10.14—Correlation between regional mortality rates for stomach cancer and regional consumption of fish. Males.

10.3
CONCLUSIONS

Epidemiological and experimental studies suggest that diet is likely to play a role in cancer aetiology (Armstrong and Doll, 1975). In particular, these studies support a protective effect of the so called *Mediterranean diet*, characterized by a low animal fat consumption and a higher intake of carbohydrates, fresh fruit and

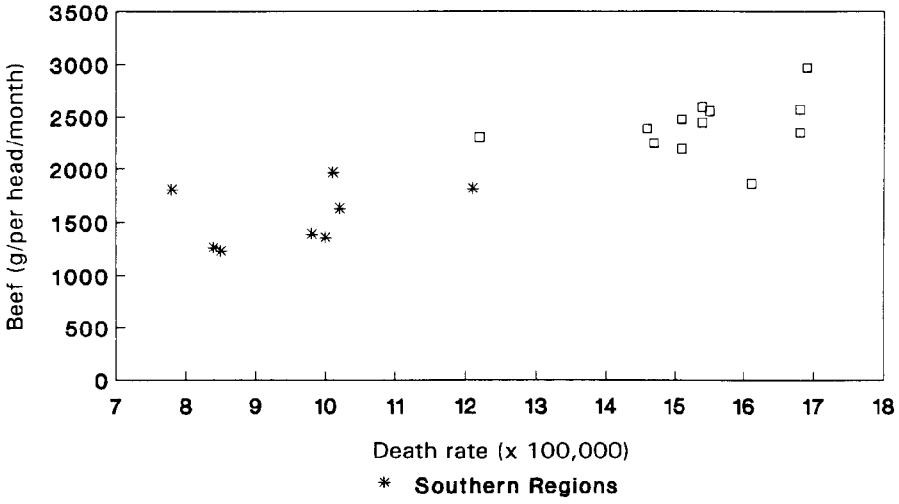


Fig. 10.15—Correlation between regional mortality rates for colon cancer and regional consumption of beef. Males.

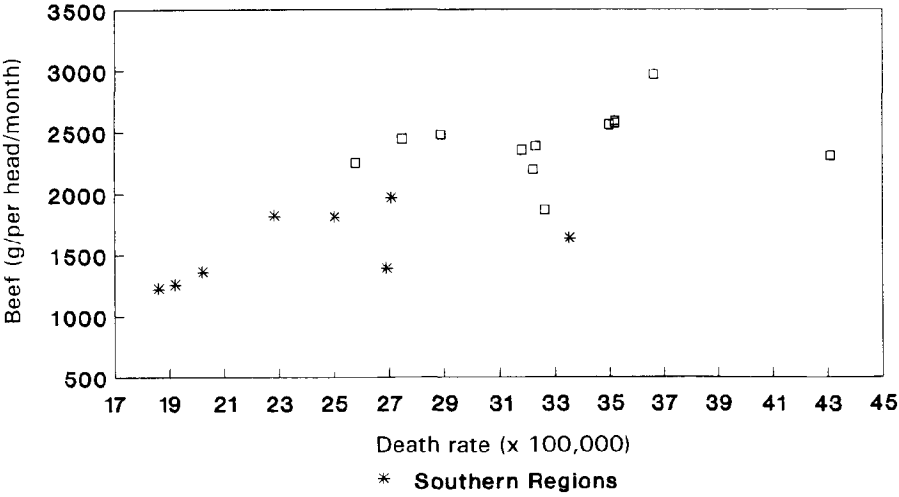


Fig. 10.16—Correlation between regional mortality rates for breast cancer and regional consumption of beef. Females.

vegetables. In Italy, this dietetic model has been commonly found in the southern regions and islands (Agradi, 1988) which are characterized also by a lower incidence of most types of cancers. Nevertheless, the differences in food consumption patterns have lessened during the past 25 years, with a tendency for southern regions, at low risk, to increase caloric intake from animal foods. A clear process toward homogenizing dietary habits is indeed evident (Kromhout *et al*, 1989). The available data seem to predict that this country will lose the

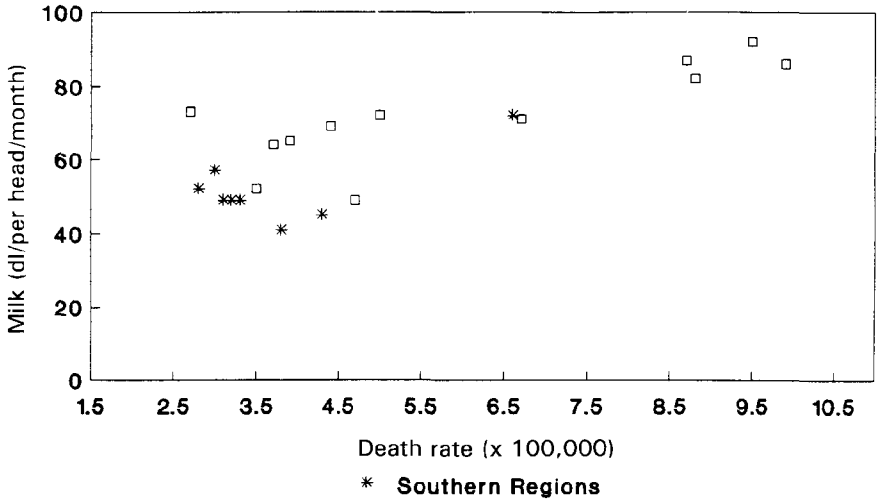


Fig. 10.17—Correlation between regional mortality rates for oropharyngeal cancer and regional consumption of milk. Males.

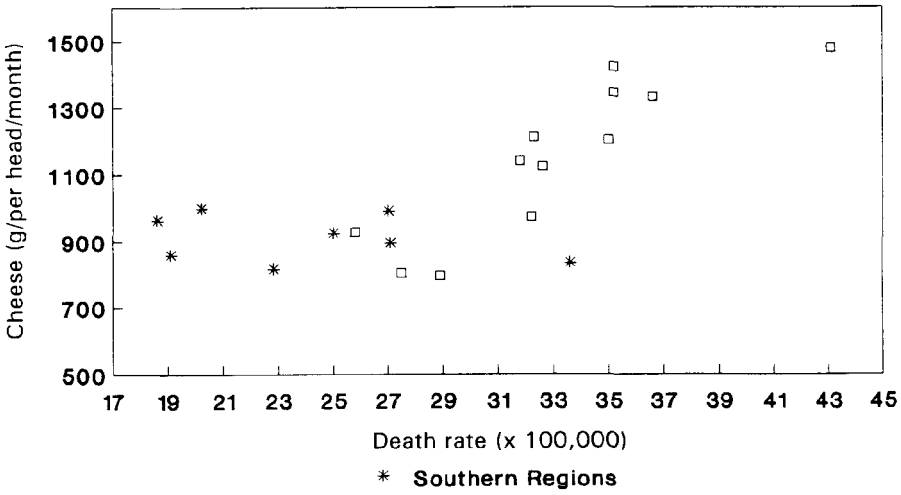


Fig. 10.18—Correlation between regional mortality rates for breast cancer and regional consumption of cheese. Females.

Mediterranean diet advantage in the future (Ferro-Luzzi *et al*, 1984; Menotti, 1991). It is possible that the influence of these changes may be reflected in cancer incidence in low risk areas, unless a nutritional policy based on information towards a healthy diet is developed. Dietary education should encourage northern areas to take the model of the Mediterranean diet into greater consideration, emphasizing the necessity for the southern population to maintain their traditional dietary patterns.

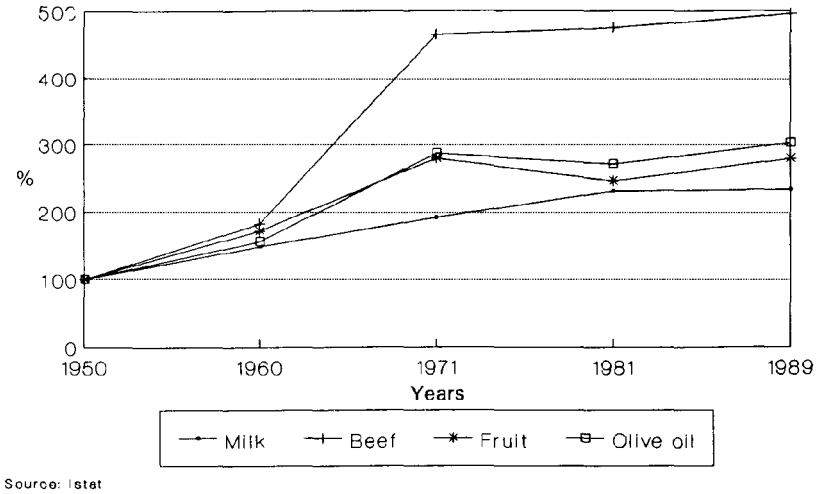


Fig. 10.19—Changes (%) in food consumption between 1950 and 1989 in Italy (1950=100).

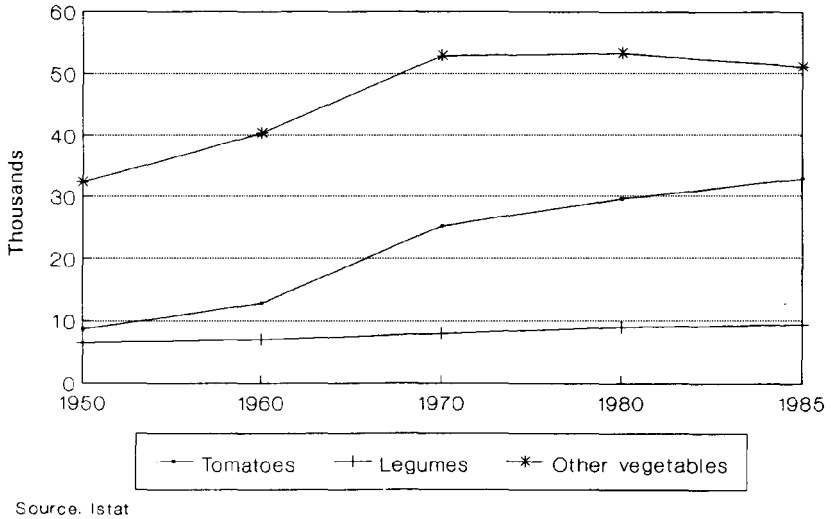


Fig. 10.19b—Consumption of vegetables between 1950 and 1985 in Italy

REFERENCES

Adlercreutz H (1990). Western diet and western diseases: some hormonal and biochemical mechanisms and associations. *Scand J Lab Clin Invest* **50 (Suppl 201):** 3–23.

Agradi E (1988). Le basi scientifiche della dieta mediterranea. *Nutrizione e Salute*. Verducci ed. Associazione Haliana Lattiero-Casearia (ASSOLATTE) (1987) Relazione de Presidente. Supplemento della Rivista II Mondo del Latte.

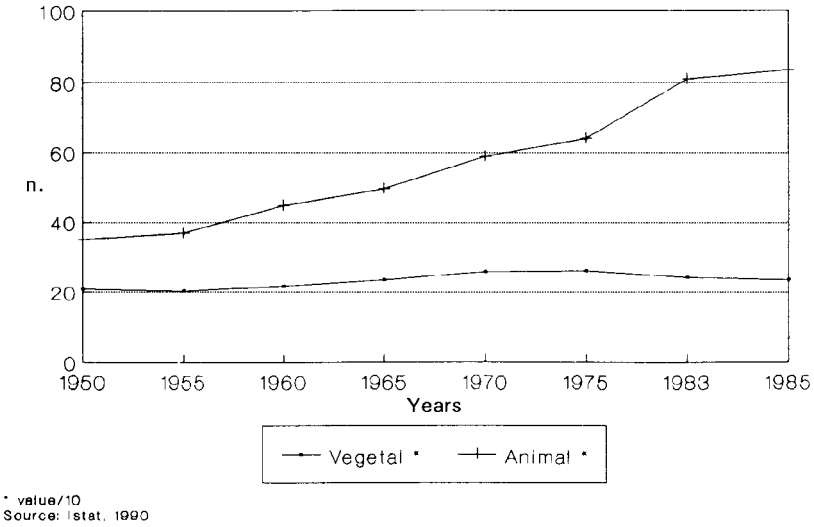


Fig. 10.20—Intake of calories in Italy, 1950–85.

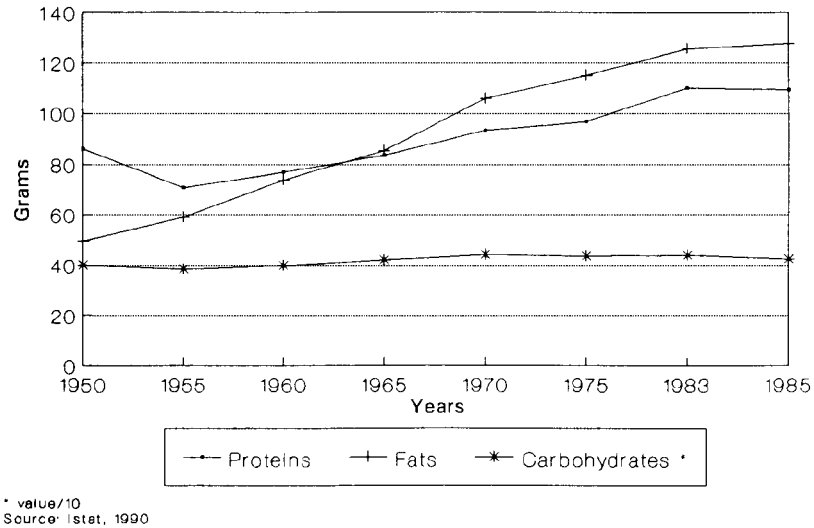


Fig. 10.21—Consumption of nutrients in Italy, 1950–85.

Armstrong B, Doll R (1975). Environmental factors and cancer incidence and mortality in different countries with special reference to dietary practices. *Int J Cancer* **15:** 617–31.

Decarli A, La Vecchia C (1986). Environmental factors and cancer mortality in Italy: correlational exercise. *Oncology* **43:** 116–26.

Ferro-Luzzi A, Maiani G, Scaccini C *et al* (1984). Changing the Mediterranean diet: effects on blood lipids. *Am J Clin Nutr* **40:** 1027–37.

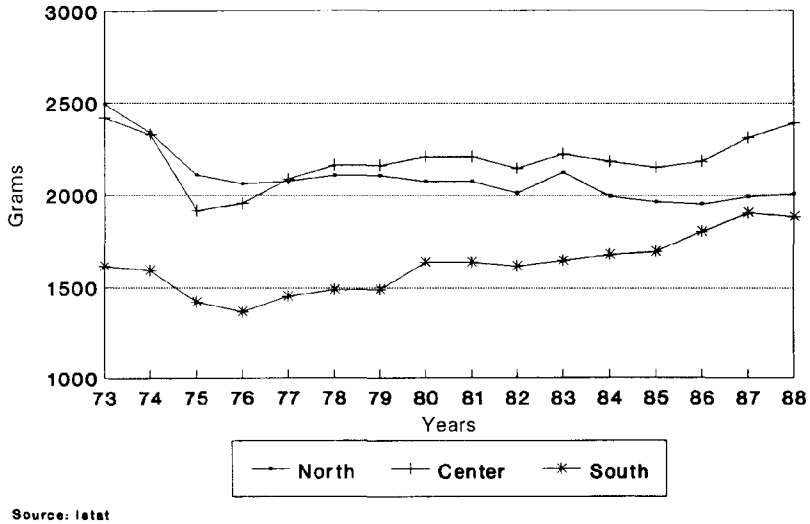


Fig. 10.22—Trends of *per capita* consumption of meat by geographical areas in Italy.

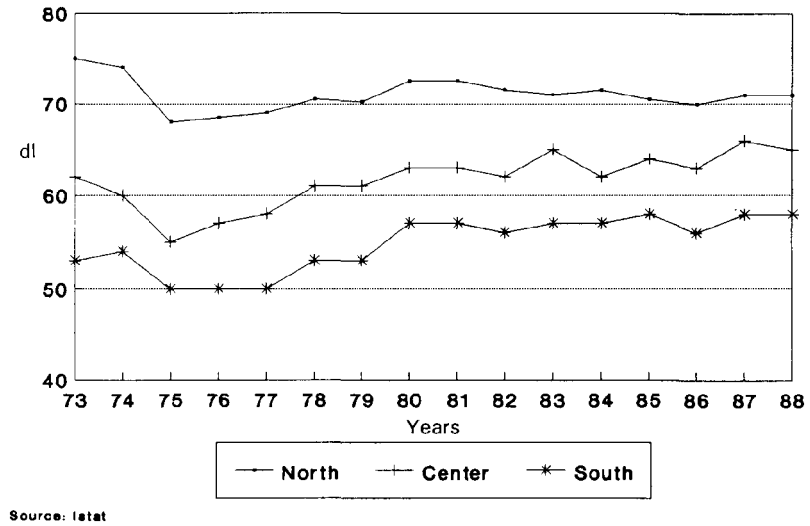


Fig. 10.23—Trends of *per capita* consumption of milk by geographical areas in Italy.

Ferro-Luzzi A, Sette S (1989). The Mediterranean diet: an attempt to define its present and past composition. *Eur J Clin Nutr* **43 (Suppl 2):** 13–29.

Henderson BE, Ross RK, Pike MC (1991). Toward the primary prevention of cancer. *Science* **254:** 1131–8.

Hill MJ (1991). Dietary fibre and human cancer. In *The Mediterranean Diet and Cancer Prevention* (eds Giacosa A, Hill MJ); ECP, Andover, UK, pp. 141–56.

ISTAT (1975). I consumi delle famiglie. Anno 1973. Supplemento al Bollettino mensile di Statistica, No. 3.

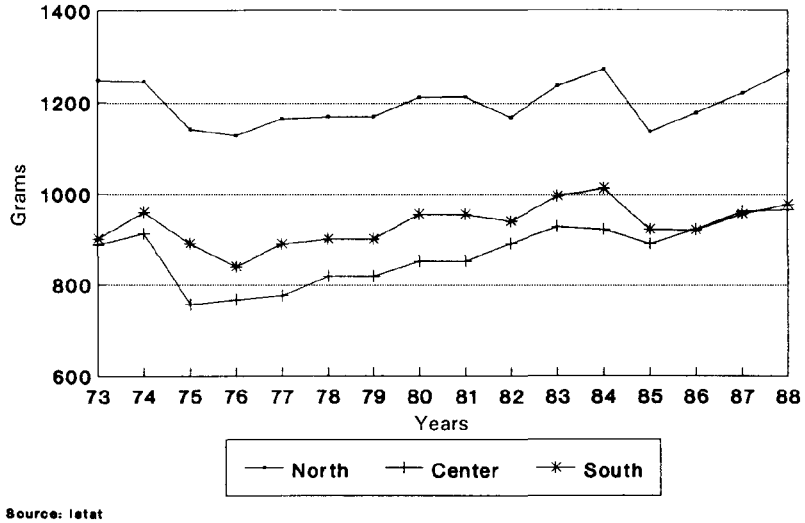


Fig. 10.24—Trends of *per capita* consumption of cheese by geographical areas in Italy.

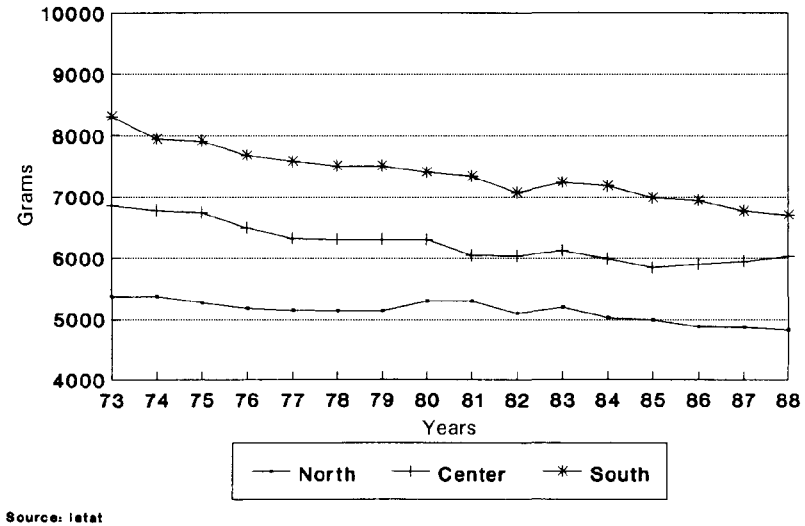


Fig. 10.25—Trends of *per capita* consumption of bread by geographical areas in Italy

ISTAT (1984). I consumi delle famiglie, 1983. Supplemento al Bollettino mensile di Statistica, No. 10.

ISTAT (1985). Popolazione residente per sesso, età e regione. Anni 1982–85. Supplemento al Bollettino mensile di Statistica, No. 21.

ISTAT (1986). Statistiche demografiche. Roma: ISTAT, Vol 34 tomo I/I.

ISTAT (1987). Statistiche demografiche. Roma: ISTAT, Vol 35 tomo I/I.

ISTAT (1989). Cause di morte, anno 1985. Ann No. 1. Roma: ISTAT.

ISTAT (1989). Cause di morte, anno 1986. Ann No. 2. Roma: ISTAT.

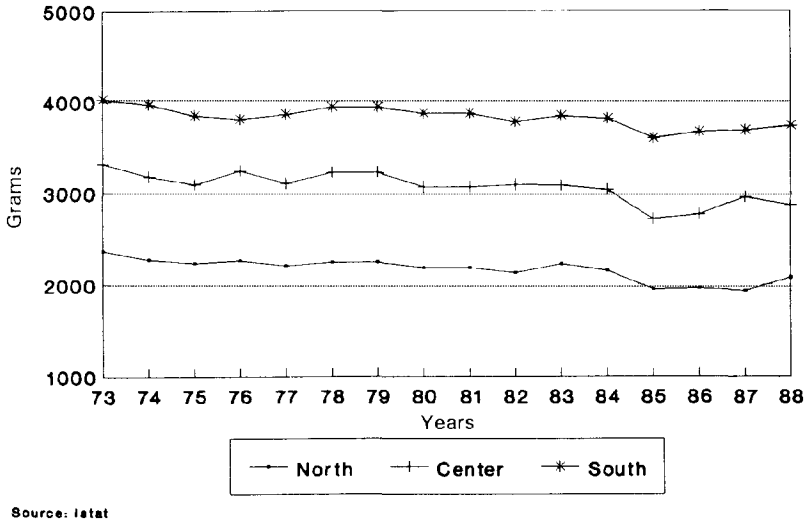


Fig. 10.26—Trends of *per capita* consumption of pasta by geographical areas in Italy.

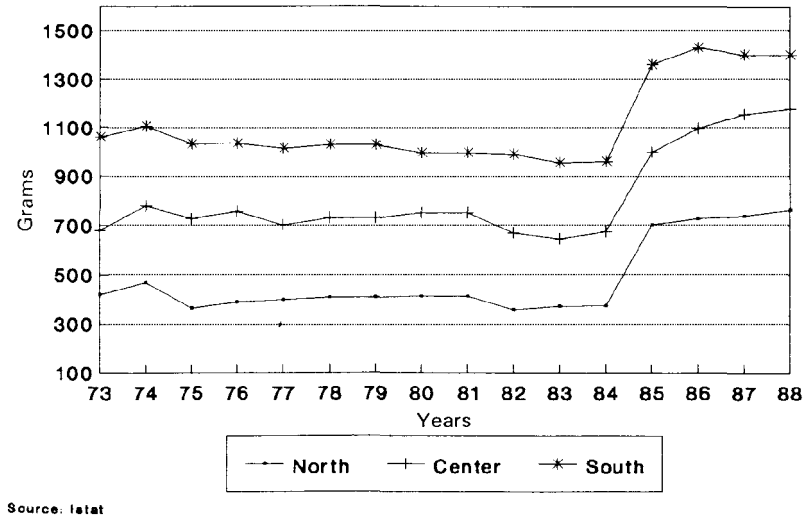


Fig. 10.27—Trends of *per capita* consumption of fish by geographical areas in Italy.

ISTAT (1990). I consumi delle famiglie, 1988. Collana d'informazione No. 30.

ISTAT (1990). Cause di morte, anno 1987. Ann 3.

Jensen OM, Esteve J, Moller H, Renard H (1990). Cancer in the European Community and its member states. *Eur J Cancer* **26:** 1167–256. Kneller RW, Guo WD, Hsing AW *et al* (1992). Risk factors for stomach cancer in sixty-five Chinese countries. *Cancer Ep Biomarkers Prev* **1:** 113–18.

Kromhout D, Keys A, Aravanis C (1989). Food consumption patterns in the 1960s in the seven countries. *Am J Clin Nutr* **49 (5):** 889–94.

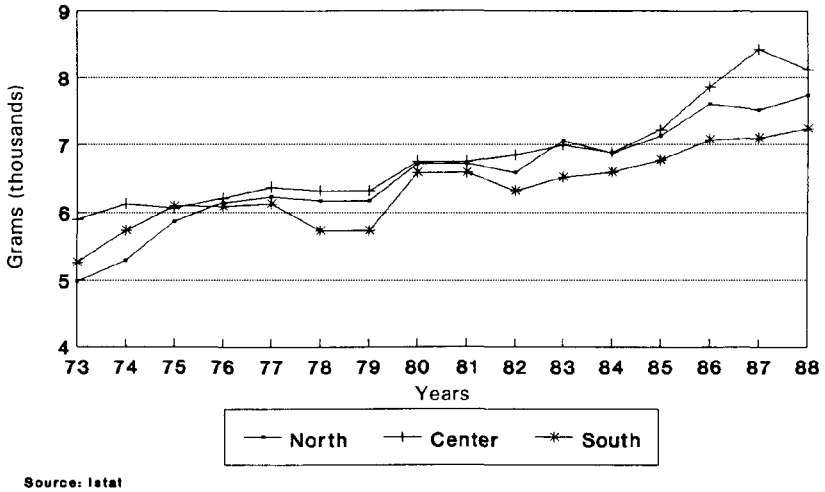


Fig. 10.28—Trends of *per capita* consumption of fresh and dried fruit by geographical areas in Italy.

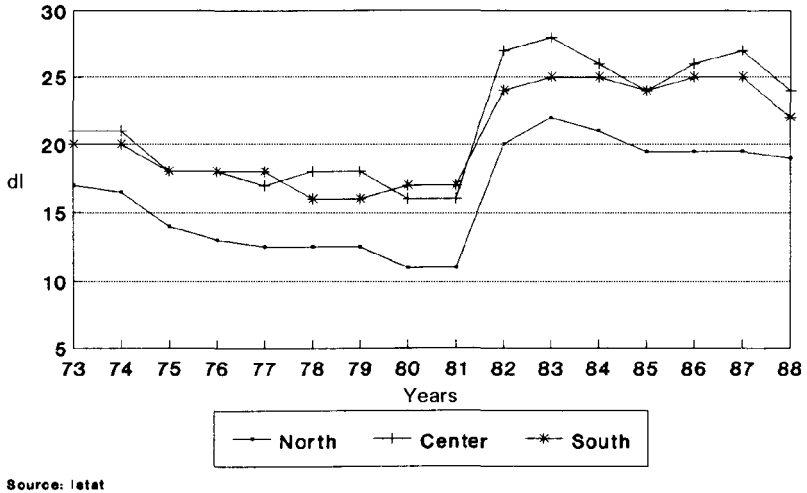


Fig. 10.29—Trends of *per capita* consumption of seed and olive oils by geographical areas in Italy.

La Vecchia C, Decarli A (1986). Cancer mortality in Italy. Temporal trends and geographical distribution. *Eur J Cancer Oncology* **22:** 1425–9.

La Vecchia C, Harris RE, Winder RL (1988). Comparative epidemiology of cancer between the United States and Italy. *Cancer Res* **48:** 7285–93.

La Vecchia C, Negri E, D'Avanzo B, Boyle P, Franceschi S (1991). Dietary indicators of oral and pharyngeal cancer. *Int J Epidemiol* **20 (1):** 39–44.

Levi F, Maisonneuve P, Filiberti R, La Vecchia C, Boyle P (1989). Cancer Incidence and Mortality in Europe. *Soz Präv* **34 (Supplement)**.

Menotti A (1991). Cardiovascular diseases. In *The Mediterranean Diets in Health and Disease* (ed Spiller GA); AVI Book, Van Nostrand Reinhold, New York, pp. 232–51.

Miller AB (1980). Nutrition and Cancer. *Prev Med* **9:** 189–96.

Negri E, La Vecchia C, Franceschi S, D'Avanzo B, Parazzini F (1991). Vegetable and fruit consumption and cancer risk. *Int J Cancer* **48:** 350–4.

Spiller GA (1991). *The Mediterranean Diets in Health and Disease*. Van Nostrand Reinhold.

Testa V, Facchini U, Bianchi A (1992). Tumore del polmone e abitudine al fumo di sigarette in Italia: differenze geografiche. *Acta Oncologica* **13 (3)**.

Turrini A, Saba A, Lintas C (1991). La dieta di riferimento. *ADI Notiziario* **3:** 5–9.

Willett WC, Stampfer MJ, Colditz AG, Rosner BA, Speizer FE (1990). Relation of meat, fat and fiber intake to the risk of colon cancer in a prospective study among women. *New Engl J Med* **323:** 1664–72.

World Health Organization (1990). Diet, nutrition and the prevention of chronic diseases. Technical Report Series 797, Geneva.

11
Mediterranean diet and cancer: a Spanish perspective

G Varela

11.1
INTRODUCTION

The Mediterranean diet (MeD) serves as a good example of the wild oscillations often seen in science's assessment of some aspects of itself: in just a short time, the MeD has turned, from being held to be boring and rather less than convenient (compared with fast food), into its present status of being considered a dietary panacea protecting against a wide range of common diseases. There are some dangers in this present position, as it is obvious that there is no single diet that is protective against all diseases. Indeed, even in the general information given to the public on the diet/health relationship it is clear that many doubts and contradictions remain. According to Brubacher (1991), in his prologue to the proceedings of the *Symposium on diet and health in Europe: the evidence*, this situation is summarized in the following paradox: *There remains no doubt about the relationship between diet and health, and yet, in spite of the many studies carried out in recent years, we have no concrete evidence of this relationship*.

For Brubacher, the reasons for this situation are that on the one hand, the healthy human has very efficient self-regulation systems, and also—often forgotten—the differences in composition and nutritive value of diets show very little effect on health, even though it is true that such effects may accumulate over time. For all these reasons, it is difficult to determine the final effect of a given dietary history on a disease, as the diet is not just an external factor which may affect the disease but is also, by itself, a very complex system. In addition, not only is the diet very complex, it is also very difficult to measure! The problem of the measurement of the actual intake of foods and nutrients will be the subject of a large proportion of this chapter.

In presenting this I write as a nutritionist who has spent many years studying the nutrition of Spaniards and the various factors affecting it. Spain is a country rich in dietary patterns and, even though the Spanish diet *in toto* conforms to the concept of the MeD, marked differences exist between the various regions and autonomous communities which constitute Spain. In our work we have attempted a multidisciplinary approach and, to this end, have cooperated with specialists in

various fields of medical pathology in order to determine the possible relationship between diet and specific diseases or conditions (*eg* obesity, cardiovascular disease, anorexia nervosa, ageing, neoplasms of various sites, mainly in the reproductive system, etc).

In trying to relate the MeD and cancer, the starting point is the observation that certain types of cancer are much less common in the Mediterranean countries than in those of central and northern Europe. This is attested to in Chapter 7 of this book and by an extensive bibliography (Brubacher, 1991; Keys, 1980; James, 1988; Moreiras-Varela, 1989). On the other hand, whilst the diets in the Mediterranean countries are different from those in countries further to the north of Europe a range of non-dietary risk factors (RF) must also be different, because of the different life styles, climate etc of the two types of populations. We should remember that, in the Mediterranean countries, the non-dietary RFs such as less stress, *siesta*, generally more physical exercise, obviously play an important role in determining risk of disease (de Groot *et al*, 1991). However, this does not negate the imporatance of the diet itself. We must also remember that many of these factors, both dietary and non-dietary, are convergent, so that the isolated influence of any one of them is very difficult to assess quantitatively.

A further problem is that diet is not a static parameter but one in constant evolution, and in this evolution many other factors intervene. A logical consequence is that knowledge of this evolution over time is of paramount interest, and particularly so in the case of the so-called degenerative diseases, which require a very long development period.

We should also keep in mind that the MeD has been most intensively studied in its possible relationship to cardiovascular disease, rather than to cancer. One of the reasons why the benefits of the MeD diet first became evident in cardiovascular disease and why knowledge of the diet/health relationship in cardiovascular diseases is so far advanced is that it is possible to quantitate the influence of definite dietary factors (for example the quantity and quality of fats) on cholesterolaemia and the distribution of cholesterol among the various serum lipoprotein fractions. Regrettably, in the case of cancer, despite the highly valuable insights represented by Wahrendorf's formulas (1987), we are still very far from the rigour of, for example, the Anderson equations (Anderson *et al*, 1976) which allow us to quantitate how changes in the energy composition of the diet, and in the energy percentages corresponding to the various families of fatty acids, may influence the cholesterolaemia levels.

Despite these difficulties we shall endeavour to find the answers to two questions:

1. Are we yet able to increase our knowledge of the possible relationship between diet and cancer?
2. Are the difficulties encountered greater or less when we concentrate our attention on the Mediterranean diet?

It is, of course, not easy to answer these questions, but while trying to do so, it will give us an opportunity to put forward some ideas about the nature of the problem. Nevertheless, a few preliminary remarks may be interesting.

11.2
PRELIMINARY REMARKS

The general problem of the study of the diet/health relationship requires background knowledge of the two components of the relation: diet and the relevant condition. With this background information, epidemiology strives to find the possible relationship between the two. It is obvious that the lack of reasonable reliability in such information, whether about the diet or about the disease, will render a rigorous scientific study of the relations between the two impossible.

The problem is further complicated by the fact that such a study involves three different types of specialists, all of them working with their own (different) methods to arrive at their own (different) objectives: dietary intake is the realm of the nutritionist, disease that of the clinician and pathologist whilst the relationships between the former and the latter is mainly the realm of the epidemiologist. Failure to note the implications of this situation may often lead to mistaken conclusions, as is often the case in this field.

In any field of science lack of data is generally thought to be preferable to wrong data. There is no need to remind anyone of the disorientations, delays and losses of precious time that have repeatedly arisen because some researcher had absolute faith in data that later turned out to be wrong. From the point of view of the nutritionist the information available on cancer morbidity and mortality seems to be more reliable than that on other conditions, such as cardiovascular diseases.

Any nutritionist with experience in the study of the nutritional status knows how difficult it is to measure the diet, and in particular its content with respect to specific components which might have a relationship to a given disease. There are many reasons for this. For example, for any biochemical or clinical determination to be valid, it must be accompanied by quality control or validation of the procedure. This is often absent in intake measurements, and this may lead to gross errors.

In any degenerative disease the possibility of the diet behaving as a risk factor will have to be considered not cross-sectionally but longitudinally in time, through the dietary history. This history should, if possible, extend back to that age at which it is suspected that the influence of the diet in the disease concerned may begin. However, whilst the measurement of the current intake is difficult, retrospective measurements are even more so, in spite of recent important improvements (Varela *et al*, 1991a). We are far from achieving reasonably good reliability in such measurements. Furthermore, over the period when the diet might influence the development of degenerative diseases changes may occur in

the quantitative and qualitative composition of that diet; these are very difficult to assess but should obviously be considered.

A single example may highlight this point: in Spain we have reasonably satisfactory information on the composition of the diet for the country as a whole, for each of the 17 autonomous communities and for each of the 50 provinces, derived from dietary surveys carried out in 1964–65 and in 1980–81 by our own Institute in cooperation with the National Institute of Statistics (Varela *et al*, 1971, 1985) and from a similar survey carried out by the Ministry of Agriculture, Fishery and Alimentation (1987). Using this database, and after adequate processing, we have recently published (Varela *et al*, 1991b) a cross-sectional study of the relationship between fat intake in the 50 Spanish provinces and the mortality and morbidity data for the various cancers of the reproductive system for the year 1982. As would be expected, the results are not satisfactory, for two reasons. Firstly, the changes in the Spanish diet in this period have been quite profound (Varela *et al*, 1988a; Moreiras-Varela *et al*, 1990). Secondly, the data from the provinces are means of all ages, and it is obvious that, for instance for breast cancer, any correlation should be looked for only for the *young female* stratum. This is quite difficult to achieve because of the methodology of the surveys. In an attempt to overcome these problems, we are currently comparing the cancer morbidity and mortality data for the year 1987 with the dietary information derived from the 1964–65 survey. We believe that the time interval between the two data collection periods might help to clarify this relationship, and it is our hope that we will thus obtain better information on the role of diet in human carcinogenesis than from a study which is cross-sectional in time.

In the meantime we have relatively good data on the fat consumption in Spain, and this has been discussed by Moreiras-Varela (1989). The mean total fat intake is 131 g per person per day (Table 11.1) and this accounts for 40% of the total energy intake. In contrast to the situation in northern Europe this is not associated with a higher incidence of colorectal or breast cancer or of cardiovascular disease. The reasons for this must be found in the types and the sources of fats consumed.

Of the 131 g per day, 73 g comes from vegetable sources (including, and principally, olive oil) and a further 2 g comes from fish, leaving only 56 g from animal sources. Thus the ratio of vegetable and fish to animal fat in Spain is 1.33 compared with UK=0.45; France=0.44; Netherlands=0.47 and even Italy= 0.94. Further, the relative amounts of saturated, monounsaturated and polyunsaturated are 36 g, 61 g and 21 g respectively, giving a P/S ratio of 0.58 (compared to 0.27 for the UK).

There have been temporal changes in the contribution of fat to the diet, which has increased from 30% to 40% during the last 15 years (Moreiras-Varela, 1989). There are great variations in fat intake between the Spanish provinces; in general, the lowest intakes of saturated fats are consumed in a broad band along the Mediterranean coast whilst the highest levels are consumed in the triangle of provinces in the north and west of Spain.

Table 11.1—Fat intake in Spain (data from Moreiras-Varela, 1989)

Total intake	131 g/person/day
% of total calories	40%
Sources:	
vegetables	73 g
fish	2 g
other animals	56 g
Fat classes:	
saturated	36 g
monounsaturated	61 g
polyunsaturated	21 g
Vegetable+fish : other animal fat	1.33
Polyunsaturated : saturated	0.58

The general pattern of food consumption in Spain (Table 11.2) is typically Mediterranean, being rich in cereals, fruit and vegetables and olive oil.

Table 11.2—The pattern of food consumption in Spain (data from Moreiras-Varela, 1989)

Cereals:	
Bread	272 g
Rice	
Vegetables:	
Potatoes	393 g
Tomatoes	
Pulses	20 g
Fruit:	
Apples	283 g
Oranges	
Meat:	
Chicken	181 g
Beef	
Fish	72 g
Oliv oil	65 g
Milk and yoghurt	383 g

11.3
DIFFICULTIES IN THE ASSESSMENT OF THE CURRENT DIET

It has been noted already that it is not easy to assess the current diet, and even less when the purpose is to look for correlations to a given disease. Since the methodological approach to the study of the diet/disease relationship is quite different when the disease is due to lack of a specific nutrient (deficiency diseases) and when its correlation with nutrition is more complex (as is the case in degenerative diseases), and since deficiency diseases have been until recently the most intensive and specialized area of nutritional study, it is inevitable that the information available about the former is both more extensive and more reliable than that for the latter.

The diagnosis of a deficiency disease generally implies knowing the recommended dietary allowances (RDA) for energy and all nutrients for a given population, and assessing the adequacy of the mean intake of the population. The problem is much more complex in the case of degenerative diseases, for a variety of reasons. These include:

(a) *The concept of diet.* Confusion sometimes arises regarding the concept of diet which may lead to errors in interpretation of its possible relationship to a given disease. Humans, in order to be adequately nourished, require a diet that contains the amount of energy and nutrients needed to fulfil the respective RDAs (Grande and Varela, 1991). These nutrients are normally obtained from foodstuffs, but no single foodstuff contains all nutrients in the quantity and quality required to cover the RDAs. Such complete coverage is, however, possible when the diet contains foodstuffs from the various different groups in which they may be classified: fruits, vegetables, cereals, meat, fish, dairy products, etc, as is the case in Spain and in all its autonomous communities (Moreira-Varela *et al*, 1990). With such a complex diet, if an adequate amount of energy is consumed for maintaining a stable body weight, this intake will also contain all the nutrients required for a balanced diet.

In this area of RDAs for energy and the various nutrients in a given population a confounding factor often arises because the RDAs are estimated on an individual and daily basis. This has been taken by some to mean that the intake for each day must be precisely adjusted to the RDAs. This is fortunately not necessary, because a reasonably well fed and nourished person generally has sufficient reserves of the various nutrients within his/her body to buffer and compensate for day-to-day maladjustments in intake (Varela, 1991). Generally speaking, in our developed societies it is estimated that it is enough that the diet/RDA assessment be performed for a period of not less than 15 days and that a *dietary indiscretion* (excess or

deficiency) on one day has no significance if it is compensated over the other days of this period.

A consequence of this is that, from the nutritional point of view there are no *good* or *bad, complete* or *incomplete* foodstuffs. All that needs to be determined is whether the diet, in terms of the energy and nutrients supplied, covers the RDAs over a period of at least 15 days.

(b) *Non-nutrient fractions of the diet.* In considering foodstuffs, and therefore diets, besides the nutrient fraction (the only one to interest nutritionists until recently) which contains about 50 nutrients, one must consider a further two non-nutrient fractions. The first one includes the so-called non-nutrient components (NNC) which are natural components of foods and have been chemically identified in quite large numbers. For instance, the potato, one of the best-studied foods in this context, contains, in addition to the already mentioned 50 nutrients, over 200 identified components which do not seem to be necessary for human nutrition, and whose role we do not yet know (Varela, 1991). The second non-nutritional fraction is that formed by additives and contaminants. According to Ames, in the average diet of persons living in the developed countries the number of NNC (to which he has given the name of natural additives) is at least 200 times greater than that of the artificial additives intentionally added to the foodstuffs.

Beyond this, however, foodstuffs are generally not consumed raw but are subjected to various industrial and culinary processes of conservation, preparation and cooking in the course of which profound changes (both quantitative and qualitative) in the composition of the nutritional fraction occur (Varela *et al*, 1990). It is logical to surmise that these changes also affect the non-nutrient fractions, causing not only quantitative changes in the amount but also in the bioavailability of the components present in the raw foods. Thus, when we want to relate diet to a given disease we should not only study the possible relationships between the components of the nutrient fraction and the disease but also the possible roles of the other two fractions. This is certainly not an easy task owing to the large number of components in the non-nutrient fractions, also to the new compounds that may be formed during the processing of the foods.

The greatest hurdle in such a study, however, derives from the novelty of this line of thinking. Until recently the nutritionists' interest was focused exclusively on the nutritional fraction, and only now, when trying to delve deeper into the diet/disease relationship, have we come to understand the importance of these non-nutritional fractions. Until we succeed in identifying and quantitating the NNC, a possible first-stage approach to the problem might be that of correlating the various diseases with the foods which are individually most important in the diet. Should such a correlation be found, the second stage would then be to try to identify the compound or compounds responsible. Yet, information about the presence in given foods

of any compound implicated in this relationship, even if chemically unidentified, would constitute substantial progress.

(c) *Regarding methodology.* In order to asses the nutritional status of a cohort we need to know the daily intake of nutrients and energy, adjusted to at least 15 days, and to ascertain if this intake is adequate for the coverage of the various RDAs. In practice it is not necessary that the period of intake measurement last for precisely 15 days; the duration of this period will be governed by the homogeneity of the diet. In general terms, our experience indicates that studying the foods consumed by a family for seven days is valid for most diets in developed countries, including Spain. However, this methodology has only been shown to be valid for the assessment of the diet's nutrient fraction and might not be valid for the non-nutrient fractions.

(d) *Substitution effect.* Another seemingly trivial fact, which is often disregarded when studying the role of a given food item in relation to health, is the so-called substitution effect of a food. When we assess the role of one given food item in the diet, that food is not consumed in addition to the usual diet, but instead of another food item. The substitution of fish for meat, for example, may have a positive effect on the risk of cardiovascular diseases. The problem now is to determine whether this is due to eating fish (with its high content of ω3 fatty acids) or to the consequent decrease intake of meat (rich in saturated fatty acids).

The problem of the diet/cancer relationship is complicated by the discovery, in the NNC fraction of the diet, of various components with marked anti-cancer action (Committee on Diet, Nutrition and Cancer, 1982). For example, vegetables of the genus *Brassica* naturally contain anti-cancer substances which would act by activating dehydrogenases and thus stimulating detoxicating actions on possible carcinogens (Wattenberg, 1977).

11.4
MEDITERRANEAN DIET AND FAT INTAKE

In a recent paper (Varela and Moreiras, 1991) on the MeD, we pointed out the difficulties in defining it. The diet is not uniform among the various countries surrounding the Mediterranean, nor the various regions within these countries. Further, the traditional diets in these countries are changing markedly, often in different directions and at different rates. In spite of these difficulties, however, there seems to be clear dietary differences between these countries and those of central and northern Europe. Further, it seems to be equally clear that these dietary differences are somehow associated with differences in mortality and morbidity of some major diseases, particularly cardiovascular diseases and possibly also some cancers. Among the various components of the MeD, fat is receiving the most attention.

Estimation of fat intake is generally difficult, and particularly so in the case of the MeD. For example, the beneficial effects of consumption of specific components of fat on cardiovascular diseases are known and are mainly due to the polyunsaturated omega-3 fatty acids. However, it is not enough to speak about overall consumption of fish since there are marked seasonal variations, both quantitative and in the composition of the various fatty acid families (Table 11.3) and these variations may influence the fat/health relationship.

Nevertheless, the greatest difficulty in the assessment of the true lipid intake derives from other sources. Most of the information on the dietary fat/health relationship stems from experimental or epidemiological studies in which the fat intake is calculated from the foodstuffs consumed, with the help of food composition tables. However, in most of these tables the fat content and composition given is that in the raw foodstuffs, while most of these are consumed after being subjected to various cooking processes. In the course of these procedures, the composition of the foodstuffs, including the fat composition, undergoes important quantitative and qualitative changes (Varela *et al*, 1990; Varela, 1988; Varela *et al*, 1988b). The intake from the MeD (Table 11.4) depend therefore not only on its food composition, but also on the form in which those foods are consumed. One of the characteristics of the MeD is that about 50% of the total fat intake is now derived from the cooking fats with which they are prepared. This immediately poses the question, *how is this cooking fat consumed?* A small fraction of this cooking fat is consumed raw, in dressings; most of it comes from fried foods. We first studied fat penetration during deep-frying (DF, a major cooking technique in Spain), then turned to other procedures, both home-cooking (stir-frying, stewing) and industrial (canning), where various different types of cooking fats are used (Varela *et al*, 1988b; Perez Alvarez-Quiñones, 1990; Varela, 1990).

Table 11.3—Seasonal changes in the fatty composition of 100 g of sardines*

	Total (g)	SFA (g)	MUFA (g)	PUFA	
	ω6	ω3			
Summer	20.40	8.49(41.6%)	6.02(29.5%)	1.68(8.2%)	4.22(20.6%)
Winter	5.4	2.25(41.6%)	1.23(22.7%)	0.49(9.1%)	1.16(21.4%)

SFA=saturated fatty acids; MUFA=monounsaturated fatty acids; PUFA= polyunsaturated fatty acids. *Sardines represent approximately 5–10% of total fish intake in Spain.

The process of DF foodstuffs is a highly complex one (Varela *et al*, 1988b), in which many factors have a role. In principle DF essentially consists in replacing part of the water contained in the foodstuff with the cooking (frying) fat which penetrates into it. For this penetration of the hot fat (at about 180°C) to occur, most of the water must first evaporate, and in potatoes during this phase, the core temperature within the foodstuff remains at about 100°C (Varela *et al*, 1988b).

When the process is correctly carried out, the fat penetrating the food builds a peripheral crust which prevents its deeper penetration into the mass of the food. Olive oil (OO) has shown itself to be particularly appropriate for this form of frying.

Table 11.4—Differential characteristics of the Mediterranean diet fat intake

Composition	Low cholesterol
	Low sat fatty acids
	High monounsaturated fatty acids
Intakes of particular foods	Low butter and margarine
	High vegetable oil (mainly olive oil)
	50% of total fat is culinary, most of which comes from deep frying

Some of the practical consequences of this form of frying are:

(a) The action time of the hot fat on the interior of the food is very short, and occurs in the absence of oxygen. The consequence of these two factors is that DF is a less aggressive process to the heat-labile components of the food (such as vitamin C) than other cooking procedures.
(b) The replacement of water by fat and the formation of the surface crust markedly increase the palatability of the fried food.
(c) Because of its peculiar penetration kinetics, the amount of fat ingested with the fried foodstuffs is not greater than with other cooking procedures.
(d) During the DF process important qualitative changes occur in the fat composition of the foodstuff, and the composition of the lipid in fried food is quite different from that of the raw food.

There are changes in lipid composition of foods when frying lean or fatty meat in olive oil. For lean meat, the total lipid content increases with a marked decrease of the SFA fraction while the MUFA increase and the PUFA decrease (Table 11.5). When fatty meat is fried the quantitative changes are non-significant, as the amount of fat lost into the bath and that penetrating from the bath are practically the same. As expected the proportion of SFA decreases, the MUFA increase, and there is no variation in the PUFA fraction.

We have also studied the fat penetration patterns into foodstuffs when using other cooking techniques or industrial processes, such as canning fish in various types of oil. The results observed have been in the same general direction, though not of the same magnitude (Perez Alvarez-Quiñones, 1990; Varela, 1990).

11.5
CONCLUSION

We have tried to present and discuss some of the difficulties encountered in the assessment of food intake, which is the first step in establishing scientifically the relation between diet and different diseases including cancers. These difficulties increase when we try to study lipid intake, which is one of the main features of the Mediterranean diet that has been linked to disease risk.

Table 11.5—Changes in the lipidic composition of lean and fat beef meat, raw and fried in olive oil

	Olive Oil	BEEF MEAT			
	FAT			LEAN	
	Raw	Un-cooked	1st frying	Un-cooked	1st frying
SFA	15.7	43.8	42.0*	41.2	28.6*
MUFA	74.4	49.5	52.0*	43.2	61.5*
PUFA (g/ 100 g total fat)	9.7	2.3	2.0	15.6	9.6*
Total fat (g/ 100 g food)	100	41.0	40.8	3.1	6.4*

Total fat expressed as g/100 g of food and fatty acids families in g/100 g of fat. *Significant when compared to raw ($P<0.05$)

It is important to identify these difficulties and to overcome them in order to push forward our knowledge of the interrelationships between diet and cancer.

REFERENCES

Anderson JT, Grande F, Keys A (1976). Independence of the effects of cholesterol in man. *Am J Clin Nutr* **28:** 1184.

Brubacher GB (1991). Preface Diet and Health in Europe: the evidence. *Ann Nutr Metab* **35(Suppl 1):**

Committee on Diet, Nutrition and Cancer (1982). National Research Council, National Academy Press, Washington DC.

de Groot L, van Stavaren W, Hautvast JGAJ (1991). Nutrition and the elderly in Europe. EURONUT-SENECA (CEE). *Eur J Clin Nutr* **45(Suppl 3):**

Grande F, Varela G (1991). En busca de la Dieta Ideal. Publicaciones de la Fundación Española de la Nutrición. Serie Divulgación No 12, Madrid.

James WPT (1988). *Healthy Nutrition. Preventing nutrition-related diseases in Europe*. WHO. Regional Office for Europe European Series No 24. Copenhagen.

Keys A (1980). *Seven Countries. A multivariate study of death and coronary heart diseases*. Cambridge (USA), Harvard University Press.

Ministerio de Agricultura, Pesca Y Alimentation. Consumo alimentario en España (1987). Publicaciones de la Dirección General de Politica Alimentaria, Madrid.

Moreiras-Varela O (1989). The Mediterranean diet in Spain. *Eur J Clin Nutr* **43(Suppl 2):** 83–7.

Moreiras-Varela O, Perez I, Carbajal A (1990). Evolución de los hábitos alimentarios en España. Publicaciones del Ministerio de Sanidad y Consumo, Madrid.

Perez Alvarez-Quiñones M (1990). El proceso de enlatado de sardinas. Repercusiones nutricionales y sensoriales de la fritura y de las diferentes fases de elaboración y maduración. Tesis Doctoral. Facultad Farmacia, Universidad Complutense, Madrid.

Varela G, Garcia D, Moreiras-Varela O (1971). La Nutrición de los españoles. Diagnóstico y Recomendaciones. Publicaciones del Institute de Desarrollo Económico, Madrid.

Varela G, Moreiras-Varela O, Requejo A (1985). Estudios sobre Nutricion (2 Volumenes). Publicacioines del Institute Nacional de Estadistica, Madrid.

Varela G (1988). Role de l'huile d'olive dans la preparation des aliments. *Rev Franc Corp Grass* **35:** 215–222.

Varela G, Moreiras O, Carbajal A (1988a). Evolución del estado nutritivo y de los hábitos alimentarios de la población española. Publicaciones de la Fundación Española de la Nutrición. Seri Divulgación No. 9, Madrid.

Varela G, Bender AE, Morton ID (1988b). Frying of food. Principlal changes, new approaches. Ellis Horwood, Chichester, UK.

Varela G (1990). Changes in fat composition due to industrial and culinary processing. Possible consequences in prevention of cardiovascular diseases. 4th International Colloquium on Mono-unsaturated fatty acids. Congress on the biological value of olive oil. Boston, USA.

Varela G, Perez M, Ruiz-Roso B (1990). Changes in the quantitative and qualitative composition of fat from fish, due to seasonality and industrial and culinary processing. *Bibl Nutr Dieta* **46:** 104–9.

Varela G (1991). Dietary Salud. *Rev Sanidad e Higiene Pública* **65:** 77–81.

Varela G, Moreiras O (1991). Mediterranean diet. *Cardiovascular Risk Factors* **1:** 313–321.

Varela G, Moreiras O, Carbajal A, Belmonte S (1991a). Estudio transversal entre la cantidad y calidad de la grasa consumida en España y la mortalidad por diferentes tipos de neoplasias del aparato reproductor . *Rev Clin Española* **189:** 55–9.

Varela G, Moreiras O, Carbajal A, Belmonte S (1991b). Estudio de la relación entre la grasa de la dieta y el cáncer de mama en España. Informe a la Fundación Banco Exterior, Madrid.

Wahrendorf J (1987). An estimate of the proportion of colo-rectal and stomach cancer which may be prevented by certain changes in dietary habits. *Int J Cancer* **40:** 625–8.

Wattenberg LW (1977). Naturally occurring inhibitors of chemical carcinogenesis. In *Naturally Occurring Carcinogens-Mutagens and Modulators of Carcinogenesis*; (ed Miller), Jap Soc Scien Press, Tokio, pp. 315–29.

12
Temporal changes of Mediterranean diet: possible effects on cancer risk

A Giacosa, F Merlo, R Filiberti, P Visconti, M J Hill, M Gerber for the ECP Mediterranean Diet Group

12.1
THE MEDITERRANEAN DIET AND CANCER

Cancer is among the most frequent causes of death in the EC countries, killing 726,244 (22%) out of 3,270,173 European citizens who died in 1982 (Table 12.1) (Europe against Cancer, 1988; Moller Jensen, 1990). Cancer mortality rates differ greatly within the EC, both within and between single member states (Table 12.1). These differences are, to some extent, attributable to specific life style, such as smoking habits and diet, as well as to working conditions.

Epidemiological data suggest that about one third of cancer deaths is due to tobacco and alcohol consumption, while diet may play a role in the aetiology of another 35% (Table 12.2) (Europe against Cancer, 1988). Thus, although other risk factors are likely to be involved in cancer aetiology, dietary habits, alcohol intake and smoking are largely responsible for the epidemiology of cancer in Europe.

By definition, the Mediterranean diet (Keys, 1975; Giacco *et al*, 1991) is basically characterized by a low animal fat content (with low meat, high fish and olive oil consumption); a high content of carbohydrates, mostly represented by starch (pasta, bread, etc); a high consumption of fresh fruit and vegetables (Ferro-Luzzi *et al*, 1989).

Since the 1960s several studies have shown that the diet which is typically followed in the Mediterranean countries is associated with lower risk of cardiovascular diseases, particularly atherosclerotic coronary heart disease (Menotti, 1991; Keys *et al*, 1954a, 1954b, 1955, 1957, 1963). This dietary profile has also been associated with a longer life expectancy in the Mediterranean countries, compared to that characterizing North European countries (James *et al*, 1989). Indeed, in the Mediterranean area, besides the lower incidence of cardiovascular

Table 12.1—Number and aged standardized rates of cancer deaths in Europe

Country	Total deaths 1982	Cancer deaths 1982	Cancer rate* males 1980–4	Cancer rate* females 1980–4
Belgium	112428	26821	211.9	112.4
Denmark	55114	13774	181.6	135.0
FDR	715857	159958	180.7	113.7
Greece	86349	17035	144.3	80.2
Spain (1)	290672 (1)	56854	148.5	80.4
France (2)	554823 (2)	126632	199.9	91.5
Ireland	32877	6220	164.5	122.7
Italy (2)	545291 (2)	123717	187.5	99.3
Luxembourg	4171	1036	215.6	121.1
The Netherlands	117264	31811	199.0	108.0
Portugal	192551	14727	134.4	84.3
United Kingdom	662802	147659	184.6	124.9
EEC	3270173	726244	182.2	104.7

(1)=1979; (2)=1981; *=Age-standardized mortality rates×100.000.

Table 12.2—Cancer risk factors in Europe

Factors (%)	Best evaluation (%)	Range of evaluations	Evaluation of the number of yearly deaths
Tobacco	30	25–35	220,000
Alcohol	4	2–5	30,000
Food	30?	10–50	220,000?
Work	4	2–8	30,000
Infections	3?	1–10	22,000?
Geophysics (1)	3	2–4	22,000

(1)=Ionizing and solar radiations.

(specifically atherosclerotic coronary hearth disease) (Keys *et al*, 1986), it has been observed that some cancers, such as those of the large bowel, breast and other hormonal dependent organs, are less frequent than in northern Europe (Europe against Cancer, 1988; Moller Jensen *et al*, 1990; DeCarli *et al*, 1991; Berrino *et al*, 1989; Levi *et al*, 1989). It has been hypothesized that a low dietary intake of saturated fat accompanied by a higher intake of unrefined carbohydrates and other protective nutrients, particularly vitamin C, E and ß-carotene and minerals, could explain the observed differences (Berrino and Muti, 1989). Moveover, the abovementioned differences between countries can be

observed within countries as well. As is shown in Chapter 6 examination of Italian mortality data shows higher cancer death rates in the northern than in the southern regions (DeCarli *et al*, 1985; La Vecchia *et al*, 1986).

For some site specific cancers these differences are particularly striking: the gastric cancer mortality rate is about 50% lower in the south of Italy than in the central and northern regions of the country (Europe against Cancer, 1988; Decarli *et al*, 1986), a difference that is clearly associated with dietary habits, as illustrated by the Italian case-control study on gastric cancer (Buiatti *et al*, 1989b). Indeed, several investigations performed in Italy in the last 30 years have revealed that the *typical Mediterranean diet* is not actually followed in the whole country but is most commonly found in the southern regions and in the islands (Sicily and Sardinia) (Agradi, 1988; Istituto di Tecnica e Propaganda Agraria, 1987). Also the Italian incidence data for breast, colon, rectum, oesophagus and stomach cancer differ according to geographical areas (Table 12.3) (Zanetti *et al*, 1990).

Examination of incidence data for site specific cancers reveals variations also within France (Table 12.4), as well as within other European Countries (Levi *et al*, 1989).

Table 12.3—Age-standardized site specific cancer incidence in selected Italian geographical areas, by gender (rates/100.000)

Site	Varese		Geneva		Parma		Ragusa	
M	F	M	F	M	F	M	F	
Stomach	55.6	34.9	30.7	22.3	62.8	40.3	27.3	18.1
Colon	29.6	35.0	33.4	30.1	26.6	23.5	17.9	19.0
Rectum	25.1	15.7	17.6	12.5	19.3	14.0	10.9	9.4
Breast	-	88.2	-	93.7	-	84.0	-	65.2

Standard population: Italy 1981.

Table 12.4—Age-standardized site specific cancer incidence in selected French geographical areas, by gender (rates/100.000)

Site	Calvados		Doubs		Isere		Bas-Rhin		Tarn		Herault	
M	F	M	F	M	F	M	F	M	F	M	F	
Stomach	23.5	11.6	23.6	10.5	17.3	8.4	21.7	10.6	13.4	6.1	15.8	5.9
Colon	18.9	14.0	28.3	21.5	24.2	19.5	32.5	20.5	32.8	22.0	25.3	19.6
Rectum	21.9	11.8	27.7	13.9	23.2	12.2	25.6	12.1	24.4	11.0	20.8	10.6
Breast	0.9	72.2	0.7	72.5	0.9	79.1	1.0	82.1	2.3	75.5	0.7	88.6

Site	Calvados		Doubs		Isere		Bas-Rhin		Tarn		Herault
M	F	M	F	M	F	M	F	M	F	M	F

Standard population: Europe.

12.2
TREND OF FOOD CONSUMPTION IN EUROPE

Toward the end of the 1950s the Seven Countries Study was designed to investigate the relationship between diet and cardiovascular diseases. Sixteen cohorts were selected in Finland, Greece, Italy, Yugoslavia, the Netherlands, Japan and the USA.

During the 1960s food consumption data were collected among subjects randomly selected from these cohorts by using a standardized questionnaire (Menotti, 1991; Kromhout *et al*, 1989). In Finland and in the Netherlands, the intake of milk, potatoes, edible fats and sugar products was very high. Fruit, meat and pastry consumption was high in USA; bread consumption was high in Yugoslavia. Cereal, wine, olive oil and fresh fruit consumption was high in two Mediterranean Countries, (Italy and Greece); the Japanese cohort was characterized by a high consumption of fish, rice and soy products (Kromhout *et al*, 1989).

A reason of great concern among nutritionists is the fact that across European sub-populations the differences in food consumption patterns have lessened during the past 25 years with a clear progress towards homogenizing dietary habits (Kromhout *et al*, 1989; Istituto Centrale di Statistica Italia, 1981). This is of particular relevance in the Mediterranean countries. Indeed, the available data seem to predict that these countries will lose the *Mediterranean diet advantage* in a few years (Menotti, 1991; Ferro-Luzzi *et al*, 1984; Istituto Centrale di Statistica, 1981). An example of this new *dietary trend* is given by the observation that serum cholesterol is slightly increasing progressively in the southern regions of Italy, while it is decreasing in the north of Italy (Ferro-Luzzi *et al*, 1984; Laurenzi *et al*, 1989).

Similar observations come from Spain: a survey on dietary habits showed an increased consumption of fats, during the last 15 years (Moreiras-Varela, 1989). The effects of life style changes on the nutrition was investigated in a Mediterranean city of Spain (Fernandez-Ballart *et al*, 1989). In younger people there was a remarkable energy excess derived from lipids (compared with the recommended allowances), which did not occur in old subjects. Among all social/cultural characteristics, the life style was shown to be the main explanation for the different food intakes. Elderly (males) who lived with young people consumed more energy ($P<0.01$), lipids ($P<0.001$) and carbohydrates ($P<0.05$) than those who lived with old individuals. In elderly living with younger ones, the energy sources become umbalanced in the same way as in the young people.

These observations clearly indicate that there is a real risk that a potentially preventive dietary model for cardiovascular diseases and possibly for some cancers, which is traditionally followed in the Mediterranean regions, could be lost in the near future if a nutrition policy based on information and education is not promptly developed.

12.3
RATIONALE OF THE STUDY

Time trends and differences in mortality from specific cancers reported both at country as well as international level indicate the existence of associations between food consumption and dietary habits and cancer risk. The evidence which has been reported so far is the subject of scientific debate, particularly in regards to the identification of the nutritional components which may increase or reduce cancer risk. Given the relevance of providing clear guidelines for public health, it is urgent to explore in a scientific and standardized way the dietary habits of sub-populations which differ in terms of cancer risk.

Europe shows relevant differences in cancer mortality with generally higher rates in northern countries and lower rates in the so called Mediterranean countries (Moller Jensen *et al*, 1990; Levi *et al*, 1989). This north/south gradient in cancer rates is also found within the Mediterranean countries, suggesting possible within country life style differences, particularly dietary habits (Levi *et al*, 1989; La Vecchia *et al*, 1986). A detailed evaluation of these relationships is particularly relevant in terms of public health not only at the European level but also worldwide, since a protective health effect of the *Mediterranean diet* is generally claimed without any final and consistent scientific basis.

For knowledge of population characteristics and dietary patterns between European countries, as well as within them, it is crucial to properly address the potential role of diet, and specific dietary components, in the occurrence of neoplasms.

12.4
AIMS OF THE STUDY

On the basis of what has been previously mentioned, ECP (European Cancer Prevention Organzation) is planning a study with the following main aims:

(a) To investigate whether there are differences of dietary habits between selected European countries which are known to have different mortality rates from site specific cancers which have been reported to be associated with diet.
(b) To investigate whether there are dietary differences within the participating European countries, between areas characterized by different mortality from site-specific cancers.

(c) To investigate the modifications of dietary habits in the participating European countries and within them in terms of nutritional components and of reasons and factors influencing these changes.
(d) To investigate in the participating European countries the individual knowledge concerning nutrition in terms of food components and of a *healthy diet*.

12.5 BACKGROUND OF THE STUDY

12.5.1 Dietary surveys in Europe

Despite large persistent difference in the dietary habits of European countries, remarkable changes, chiefly in the direction of a greater homogeneity of eating and drinking patterns, have been recorded in the last decade (Kromhout *et al*, 1989; Ferro-Luzzi *et al*, 1984; Laurenzi *et al*, 1989; La Vecchia *et al*, 1988). Although dietary surveys are routinely conducted in most European countries, their number and quality vary substantially from one country to another. Further, most dietary statistics and surveys show important weaknesses concerning the possibility of disaggregating data into age- and/or sex-specific strata or, even more, at an individual level. This obviously hampers the opportunity for more sophisticated analysis (*eg* age and sex standardization) and of better designed interventions.

To improve this situation more investment should be made in the organization of specific questionnaire-based investigations on the dietary habits of selected samples of the general population. The difficulties of collecting reliable dietary information on a large scale are well known. They can probably be alleviated by taking advantage of the vast experience in terms of design and validation of dietary questionnaires, which has stemmed from multi-year aetiological investigations, particularly in the cancer field (Willett, 1990).

12.5.2 Motivations for changes in dietary habits

It is already clear that changes in dietary habits are due to several factors other than typical nutritional variables. Factors that can motivate changes in diet habits are socioeconomic factors, availability of food items, health or ethical-aesthetic reasons, work (timing and site of meals), quality of products, advertisement, mass media, etc. Food consumption and dietary habits in the Mediterranean areas have changed since the 1950s along with changes in socioeconomic status determined by the industrialization of the country, particularly the northern

regions, and a more ready availability of foodstuffs over greater distances and for longer periods.

In order to plan any large scale prevention policy concerning dietary habits, it is fundamental to know not only food consumption patterns for specific populations, but also motivations that are behind changes in dietary habits (James *et al*, 1988). To acquire this knowledge several attempts have been proposed, each one sharing pros and cons.

12.5.3
Nutrition and healthy diet: individual knowledge

Very little is known concerning the level of knowledge of individuals about nutritional requirements/healthy diet. Given the variation which is detected within the European countries in terms of dietary habits, it would be desirable to develop a common instrument for data collection on the individual awareness of what is good to eat for a healthy way of living. This common tool would provide precious information to plan future educational campaigns on diet and diseases, including cancer.

12.6
METHODS AND SUBJECTS

The study will involve Italy, Spain, UK, France, Greece, Portugal, Sweden and possibly other European countries. In Italy, France, Spain and Portugal the study will include various regions with different dietary patterns and different cancer rates. A particular effort will concern the inclusion of areas showing high and low risk for site specific cancers, *eg* stomach, breast, colon, etc.

A specifically designed standardized questionnaire form will be developed and validated through feasibility/pilot studies to be conducted in selected participating countries/areas. Such a questionnaire will include specific queries concerning (a) individual dietary habits; (b) changes in food consumption, and motivations behind them; (c) knowledge about nutritional components/healthy diet.

The questionnaire will also be designed to gather other information including individual demographic variables that will be used to disaggregate the collected information according to gender, age, social status, occupation, level of education, etc.

Since previous studies have been conducted in several European countries, it is possible to identify groups of epidemiologists-nutritionists able to provide background information for the performances of well comparable, albeit distinct, dietary surveys. In fact, research teams in Italy and France are already using independently designed questionnaires which have been (Buiatti *et al*, 1989a; Franceschi *et al*, 1991; Gerber *et al*, 1989; Benito, 1990; Benito *et al*, 1990) and are actually being used to collect specific information on dietary habits,

including both qualitative and quantitative assessments of specific food items, fat intake or calorie adjusted fat intake.

The proposed research project will include the following steps:

1. The design and validation of a comprehensive self-administered dietary questionnaire. Such a questionnaire should include simple and unambiguous questions and should be able to (a) investigate several quantitative and qualitative aspects of the recent individual eating and drinking pattern; (b) provide a valid and reproducible estimate of both total calories, macronutrients, micronutrients, alcohol and fibres; (c) investigate individual changes in food consumption that have occurred during the last five years, and motivation behind these changes; (d) investigate individual knowledge on specific foods associated with health risk.
2. The identification for each European country participating in this ECP study of at least two geographical areas which differ in terms of cancer incidence/mortality, dietary habits and cultural tradition (Moller Jensen *et al*, 1990).
3. The identification in each selected geographical area of a random sample of subjects representative of the whole population of the area as far as age and gender distribution are concerned.
4. The development of a mathematical algorithm for computerized evaluation of nutritional components of individual diets.

12.7
SAMPLE SIZE

Sample size requirements will be computed using *Power* (Power Statistical Software) according to the nutritional data available in each country (Agradi, 1988; Ottogalli *et al*, 1991; International Dairy Federation, 1982, 1989; Associazione Italiana Lattiero-Casearia (ASSOLATTE), 1987), considering the possibility of detecting statistically significant differences between means for selected dietary components/nutrients.

12.8
TIMING OF THE STUDY

The proposed research will last four years and will be carried out in 3 phases.

12.8.1
Phase 1: feasibility/pilot study

During the first 12 months the research team involved in the project will develop the self-administered questionnaire and arrange its validation through specific pilot studies to be carried out within each participating country. In the meantime each participating country will identify sub-areas (at least two)—to be included

in the study—from which age-sex representative population samples will be selected. This feasibility phase will require two meetings of the identified study group.

12.8.2
Phase 2: data collection

The second and third year of the study will consist of the data collection, quality control and storage. In the meantime the study group will develop the mathematical algorithm required for translating questionnaire-based information in terms of calories and nutrients.

12.8.3
Phase 3: statistical analyses/writing reports

This is the final stage of the study which we expect will take approximately 6 months.

ACKNOWLEDGEMENTS

The names of the participants in the ECP Mediterranean Diet Group (in addition to the authors) are: H Barroca (Portugal), E Benito (Spain), A Benos (Greece), S Franceschi (Italy), I Giordanelli (Italy), L E Holm (Sweden), P Judd (UK), H Saldanha De Oliveira (Portugal), A Hubert (France).

REFERENCES

Agradi E (1988). Le basi scientifiche della Dieta Mediterranea. Nutrizione e salute. Verducci Editore.

Associazione Italiana Lattiero-Casearia (ASSOLATTE) (1987). Relazione del Presidente. Supplemento della Rivista II Mondo del Latte.

Benito E (1990). La dieta como factor de riesgo en el cancer colorrectal. Conselleria de Sanitat i Seguretat Social. Govern Balear. Prensa Universitaria, ed.

Benito E *et al* (1990). A population-based case-control study of colorectal cancer in Majorca. I. Dietary factors. *Int J Cancer* **45:** 69–76.

Berrino F *et al* (1989). Dietary fat, nutritional status and endocrine associated cancers. In *Diet and Cancer Etiology* (ed Miller AB); ESO Monograph, New York Heidelberg: Springer Verlag, pp. 1–10.

Berrino F, Muti P (1989). Mediterranean diet and cancer. *Eur J Clin Nutr* **43 Suppl 2:** 49–55.

Buiatti E *et al* (1989a). Methodological issues in a multicentric study of gastric cancer and diet in Italy: study design, data sources and quality controls. *Tumori* **75:** 410–19.

Buiatti E *et al* (1989b). A case-control study of gastric cancer and diet in Italy. *Int J Cancer* **44:** 611–6.

DeCarli A *et al* (1985). Cancer Mortality in Italy, 1979. *Tumori* **71:** 519–26.

DeCarli A, La Vecchia C, Cislaghi C, Mezzanotte G, Marubini E (1986). Descriptive epidemiology of gastric cancer in Italy. *Cancer* **58(11):** 2560–9.

DeCarli A *et al* (1991). Diet and cancer. In *The Mediterranean Diets in Health and Disease* (ed Spiller GA); AVI Book, Van Nostrand Reinhold, New York, pp. 287–303.

Europe against Cancer (1988). Commission of European Communities. March 1988; 5–6/88.

Fernandez-Ballart J *et al* (1989). Nutrition of the elderly in a Mediterranean city in Spain: effects of life-style patterns. *Int J Vitam Nutr Res* **59(1):** 8–13.

Ferro-Luzzi A *et al* (1984). Changing the Mediterranean diet: effects on blood lipids. *Am J Clin Nutr* **40:** 1027–37.

Ferro-Luzzi A *et al* (1989). The Mediterranean diet: an attempt to define its present and past composition. *Eur J Clin Nutr* **43 (Suppl 2):** 13–29.

Franceschi A *et al* (1991). Validation of a dietary questionnaire for case-control studies. 9th Annual ECP Symposium on Public Education and Cancer, Madrid 17– 19 October 1991.

Gerber M *et al* (1989). Relationship between vitamin E and polyunsaturated fatty acids in breast cancer. Nutritional and metabolic aspects. *Cancer* **64:** 2374–5353.

Giacco R *et al* (1991). Comparison of current eating habits in various Mediterranean countries. In *The Mediterranean Diets in Health and Disease* (ed Spiller GA); AVI Book, Van Nostrand Reinhold, New York, pp. 3–9.

International Dairy Federation (1982). Consumption statistics for milk and milk products including summary 1966–80. Document 144. Brussels: IDF.

International Dairy Federation (1989). Consumption statistics for milk and milk products. Document 237. Brussels: IDF.

Istituto Centrale di Statistica Italia 1978 (1981). Alcuni dati sugli aspetti demografici, sociali ed economici . Roma: ISTAT.

Istituto Centrale di Statistica (1981). Le regioni in cifre. Roma: ISTAT.

Istituto di Tecnica e Propaganda Agraria (1987). Per una sana alimentazione italiana. Monografia, Roma.

James WP *et al* (1988). Healthy nutrition. Preventing nutrition-related diseases in Europe. WHO EURO European Series, No 24. Copenhagen, WHO Regional OFFICE for Europe.

James WP *et al* (1989). Mediterranean diet: protective or simply non toxic? *Eur J Clin Nutr* **43 Suppl 2:** 31–41.

Keys A *et al* (1954a). Studies on the diet, body fatness and serum cholesterol in Madrid, Spain. *Metabolism* **3:** 195.

Keys A *et al* (1954b). Studies on serum cholesterol and other characteristics on clinically healthy men in Italy. *Arch Int Med* **93:** 328.

Keys A *et al* (1955). Further studies on serum cholesterol of clinically healthy men in Italy, *Voeding* **16:** 492.

Keys A (1957). Diet and epidemiology of coronary heart disease. *JAMA* **164:** 1912.

Keys A *et al* (1963). Coronary heart disease among Minnesota business and professional men followed fifteen years . *Circulation* **28:** 381.

Keys A *et al* (1975). How to eat well and stay well: the Mediterranean way. New York: Doubleday.

Keys A *et al* (1986). The diet and 15 years death rate in seven countries studies. *Am J Epidemiol* **124:** 903–915.

Kromhout D *et al* (1989). Food consumption pattern in the 1960s in the seven countries. *Clin Nutr* **49(5):** 889–94.

Laurenzi M *et al* (1989). Is Italy losing the *Mediterranean advantage?*. Report on the Gubbio population study: cardiovascolar risk factors at baseline. Gubbio Collaborative Study Group. *Prev Med* **18(1):** 35–44.

La Vecchia C *et al* (1986). Cancer Mortality in Italy: Temporal trends and geographical distribution. *Eur J Cancer Oncol* **22:** 1425–9.

La Vecchia C et al (1988). Comparative epidemiology of cancer between the United States and Italy. *Cancer Res* **48:** 7285–93.

Levi F *et al* (1989). Cancer incidence and mortality in Europe. *Medicine Sociale et preventive* 34.

Menotti A (1991). Cardiovascular diseases. In *The Mediterranean Diets in Health and Disease* (ed Spiller GA); AVI Book, Van Nostrand Reinhold, New York, pp. 232–251.

Moller Jensen O *et al* (1990). Cancer in the European Community and its Member States. *Eur J Cancer* **26:** 1167–1256.

Moreiras-Varela O (1989). The Mediterranean diet in Spain. *Eur J Clin Nutr* **43 Suppl 2:** 83–7.

Ottogalli G *et al* (1991). Dairy products. In *The Mediterranean Diets in Health and Disease* (ed Spiller GA); AVI Book, Van Nostrand Reinhold, New York, pp. 287– 303.

Power Statistical Software. Epicenter Software, Pasadena, California Testolin G *et al* (1991). Vegetables and fruits. In *The Mediterranean Diets in Health and Disease* (ed Spiller GA); AVI Book, Van Nostrand Reinhold, New York, pp. 110–124.

Willet W (1990). Nutritional Epidemiology. Monographs in Epidemiology and Biostatistic. Vol 15, New York Oxford, Oxford University Press.

Zanetti R *et al* (1990). Incidenza dei tumori in Italia. *Federazione Medica* **XLIII:** 2.

13
Olive oil and cancer
M Gerber

13.1
INTRODUCTION

It is well known that a title has to be provocative in order to appeal to the readers. This one is a little more than provocative, it is presumptuous. In spite of an increasing number of reports suggesting a relationship between nutritional factors and cancer, it has been extremely difficult indeed to pinpoint a specific food or nutrient responsible for a protective or deleterious effect with respect to cancer incidence and/or mortality.

Fruit and vegetables often appear protective (Katsouyanni *et al*, 1986; Iscovich *et al*, 1989; Van't Veer *et al*, 1990b; Negri *et al*, 1991). Fibre is one nutrient often reported negatively associated with colorectal cancer (reviewed in Freudenheim and Graham, 1989) and also, more seldomly, with breast cancer (Lubin *et al*, 1986; Van't Veer *et al*, 1990b). Vitamin C especially is credited with a protective effect against gastric cancer (Buiatti *et al*, 1989) because of its role in lowering the gastric pH, hence in inhibiting the synthesis of nitrosamines. Beta-carotene or other carotenoids are also serious candidates for a protective role in epithelial cancer related to tobacco, like lung cancer (Colditz *et al*, 1987; Harris *et al*, 1991) and bladder cancer (Helszouer *et al*, 1989). In contrast, foods rich in fat have often been associated with increasing incidence and/or mortality of some cancers, principally breast and colon.

Colon cancer was among the first to be found associated with fat consumption in international correlation studies (Wynder and Shigematsu, 1967; Armstrong and Doll, 1975). International comparisons of mortality rates showed a correlation with animal fat intake (Rose *et al*, 1986). Increased relative risks with increasing intake of food rich in animal fats like dairy products (Benito *et al*, 1990), of total fat (Graham *et al*, 1988) or saturated fat (Whittemore *et al*, 1990) were shown in case-control studies. In a prospective study, Willett *et al* (1990) also showed that a high intake of animal fat increases the risk of colon cancer.

For breast cancer the controversy is still open. Most international or national correlation studies reviewed by Goodwin and Boyd (1987) support the association of fat intake and breast cancer mortality or incidence rates. But other

epidemiological studies have led to inconsistent results (Goodwin and Boyd, 1987). This is mostly true for prospective studies, although they are expected to produce strong evidence because they are supposed to avoid the recall bias of nutritional data collection. The earliest one (Hirayama, 1978) shows an association as well as the most recent one by Howe *et al* (1991). The prospective study on a nurse cohort in the USA (Willett *et al*, 1987) brought about negative results with regards to the relationship between breast cancer and fat. However, the sample of population was probably aware of health problems related to fat, and showed rather low limits for the highest quintile of absolute intake of total fat and cholesterol. Goodwin and Boyd (1987) suggested that the range of fat intake observed in this population was too narrow to allow for emergence of a significant relative risk. These authors, by an analysis based upon their results from international correlation studies, calculated that Willett's study could at the best demonstrate a relative risk of 1.4, which could be reduced to 1.16 if misclassification were to occur. However, the same study reported a positive association between fat intake and colon cancer, as mentioned above, which would imply that either the negative association with breast cancer is real or that the association fat intake-colon cancer is stronger than that between fat intake and breast cancer. Case-control studies tip the scale towards a positive association. In a combined analysis of 12 case-control studies from several countries, Howe *et al* (1990) showed a significant association between saturated fat and postmenopausal breast cancer. In addition, Van't Veer *et al* (1990a,b) found a significant positive association with total fat intake in the Netherlands as well as Richardson *et al* (1991) in Southern France. It is noteworthy that in a Greek case-control study (Katsouyanni *et al*, 1986) there was no association between fat intake and breast cancer risk.

Whereas some findings strongly suggest that olive oil can be protective against cardiovascular diseases (Sirtori *et al*, 1986), data are rather scarce with regard to the relationship between olive oil and cancer. Some of the studies quoted above tried to discriminate among the various types of fatty acids found in fat-rich food, saturated, monunsaturated or polyunsaturated. The findings of these studies will be presented in the last section of this chapter as the basis of the discussion on the eventual effect of olive oil on cancer. Before that, the chemical characteristics of olive oil will be depicted, followed by an evaluation of olive oil intake in various countries, and the effect of olive oil on various blood lipid parameters.

13.2
OLIVE OIL CHARACTERISTICS

The major fatty acid of olive oil (72%) is oleic acid. It is a long chain of 18 carbon atoms with one double bond in the *cis*-configuration. But this fatty acid is also found in the fat of mammals and poultry (30 to 45% respectively). A genetic manipulation of sunflower oil resulted in an oil with 74% of oleic acid (oleisol),

which is not yet very much used. There exists a *trans*-monounsaturated fatty acid, elaidic acid, which

Table 13.1—Composition of the main vegetable oils. Fatty acids g per 100 g total fatty acids

	Saturated							Monounsaturated				Polyunsaturated	
	12:0	14:0	16:0	18:0	20:0	22:0	24:0	16:1	18:1	20:1	22:1	18:2	18:3
Maize, corn	0	0.6	14.0 (6–22)	2.3	0.3	Tr	Tr	0.3	30.0 (19–50)	0.2	0.2	50.0 (34–62)	1.6
Olive	0	Tr	12.0 (7–20)	2.3	0.4	0	0	1.0	72.0 (65–85)	0	0	11.0 (4–20)	0.7
Palm	0.2	1.1	41.5 (32–51)	4.3	0.3	0	0	0.3	43.3 (35–52)	0	0	8.4 (5–12)	0.3
Peanut	0.1	0.5	10.7 (6–15)	2.7	1.2	3.4	1.1 (35–72)	Tr	49.0	1.1	Tr (13–45)	29.0	0.8
Safflowerseed	0	Tr	8.0	2.5	0.2	Tr	0 (7–42)	0.1	13.0 (55–81)	0.10	75.0	0.5	
Soyabean	0.1	0.2	10.0 (6–19)	4.0	0.3	0.1	Tr	0.2	25.0 Tr (14–35)	0.2	52.0	7.4 (40–62)	(4–11)
Sunflowerseed	0	0.1	5.8	6.3 (0.2–12)	0.6	0.7	0.2	0.1	33.0 Tr (5–60)	0.2	52.0	0.3	(17–78)

Ref: McCance and Widdowson's. *The Composition of Food*, revised by Paul and Southgate. Elsevier, 1976.

is very seldom found in nature, but more often in foods containing hydrogenated linoleic acid for solidifying purposes.

The fatty acid content of the main vegetable oils used in western societies is shown in Table 13.1. Olive oil is by far the richest in total monounsaturated fatty acids (73%), especially oleic acid (18:1) and the lowest in polyunsaturated fatty

acid (11.7%), especially linoleic acid (18:2). The total content of saturated fatty acids is very comparable among these vegetable oils (between 12 and 15%); however, whereas the content in palmitic acid (16:0) and stearic acid (18:0) is very similar between corn, olive and peanut oils, the proportion is reversed for sunflower oil.

The antioxidant capacity of olive oil is maintained by compounds very different from those of other vegetable oils. Table 13.2 shows that the tocopherol content is very low, in contrast to the other oils. Squalene and phenolic compounds (hydroxytyrosol and oleuropeine) are responsible for the low oxidability of olive oil. They are characterized by their solubility which allows for their equal distribution between the hydrophobic cell membrane and the hydrophilic cytosol (Driss *et al*, 1991). It is noteworthy that oleisol, in spite of an amount of oleic acid close to that of olive oil, retains the same content of tocopherols as sunflower oil.

Table 13.2—Tocopherol content of the main vegetable oils mg/100g

	→	→	→	→T3
Maize	11.2	60.2	1.8	0
Olive	5.1	Tr	0	0
Palm	25.6	31.6	7.0	14.3
Peanut	13.0	21.4	2.1	0
Safflowerseed	38.7	17.4	24.0	0
Soyabean	10.1	59.3	26.4	0
Sunflowerseed	48.7	5.1	0.8	0

Ref: McCance and Widdowson's. *The Composition of Food*, revised by Paul and Southgate. Elsevier, 1976.

13.3
OLIVE OIL INTAKE

So far, olive oil is essentially consumed in the olive tree-growing areas, namely in the Mediterranean regions, Table 13.3 gives an indication of the mean amount of olive oil consumed in these countries. The consumption varies within the countries themselves. For example, in Italy the consumption is decreasing from South to North and in Spain from East to West. In the region Languedox-Roussillon, in southern France, the mean consumption is much higher than the national mean value: 1,650 kg/year. This is a little more than 10 % of the total of the vegetable oils and less than 5% of the total lipids, whereas in Greece, the mean olive oil consumption is 99.4% of the total of vegetable oil consumption and 39% of the total lipids (calculated after Rose *et al*, 1986).

However, there is a trend for a change in every one of these countries, either towards saturated fat (*eg* butter and other animal fat in Southern Italy) or other vegetable oils (*eg* sunflower oil and grape-seed oil in southern France). In other

countries, the nutritional intakes of monounsaturated fatty acids and oleic acid refer only to an animal source. In that case, oleic acid generally contributes between one-fourth and one-third of total fat intake (Fisher *et al*, 1985).

Table 13.3—Olive oil consumption in Mediterranean countries

Country	kg/person/year
Greece	20
Lybia	16
Italy	12
Spain	10
Portugal	5
Algeria	1.2
France	0.4

Ref: International Centre for Olive Trees.

13.4 EFFECT OF OLIVE OIL ON BLOOD LIPID PARAMETERS

Changes in some lipid levels, especially total cholesterol, have been shown in the blood of cancer patients compared to controls. In colon cancer the plasma cholesterol level is generally lower in cancer patients than in controls (Feinleib, 1981; Wallace *et al*, 1982) whereas it is higher in breast cancer patients (Basu *et al*, 1975; Wallace *et al*, 1982; Gerber *et al*, 1988). High-density lipoprotein-cholesterol (HDL-C) has been proposed as a marker for breast cancer (Boyd and McGuire, 1990) although no modifications have been observed (Gerber *et al*, 1988; Ferraroni *et al*, manuscript in preparation). Because of this relationship between some cancers and lipid parameters, our study on olive oil and cancer requires that these parameters be reviewed.

Population and intervention experimental studies are sources of information with regards to the effect of olive oil on blood lipids. Population studies generally compare analyses in populations with different contents of fat in their diet (Knuiman *et al*, 1980). One study (Aravanis *et al*, 1988) was conducted in young boys in Crete, whose fat intake and oleic acid intake was high (45% and 27.2% of energy, respectively) and saturated fat intake low (10% of energy), reflecting a high consumption of olive oil. Contrary to what was expected, low density lipoprotein-cholesterol (LDL-C) was not lower and HDL-C not higher than that of North American boys and even lower than that from northern Europe boys. But body mass indexes of the Cretan boys are higher than those of Northern American boys and there was no allowance for this variable in the analysis.

Among the 6 intervention studies discussed below, two are based on olive oil intake (Chang and Huang, 1990; Masana *et al*, 1991), one on an intake of olive oil and avocados (Berry *et al*, 1991), one on a mixture of olive oil and oleisol (Mensink and Katan, 1990) and two exclusively on oleisol (Wardlaw and Snook, 1990; Delplanque *et al*, 1991). Two studies compare the blood lipid parameters after a diet rich in oleic acid to a previous baseline of the lipid parameters (Berry *et al*, 1991; Masana *et al*, 1991). It is found that when changing to a diet rich in olive oil, triglycerides (TG), total cholesterol (TC) and LDL-C are lowered, whereas HDL-C shows little variation. The same results are found when a diet rich in oleic acid (mainly from oleisol) is compared to a diet rich in saturated fat (Mernsink and Katan, 1990; Wardlaw and Snook, 1990) except for HDL-C which tends to increase in the study by Wardlaw and Snook (1990). Compared to men submitted to a diet rich in PUFA, identical groups submitted to a diet rich in oleic acid, with olive oil (Chang and Huang, 1990) or oleisol (Delplanque *et al*, 1991) show higher TG, TC and LDL-C plasma levels. Oleisol diets also induced an increase in HDL-C, whereas olive oil diets, in this experiment, tended to induce a lower HDL-C level than in the PUFA group. In an experimental study (Masi *et al*, 1986) rabbits were submitted to diets rich in butter, olive oil and corn oil. They confirmed the previous human observations, namely that olive oil has an intermediary lipid-lowering effect (the highest levels are found with the saturated fatty acid diet and the lowest with the polyunsaturated one) but that olive oil maintains a higher level of HDL-C than corn oil.

Thus, it is obvious that olive oil has a protective effect on cardiovascular diseases, also that it preserves arterial PGI_2 production (Masi *et al*, 1986). With regard to cancer, so far the picture is not clearcut, since some findings are similar to those found in cancers (low cholesterol, as in colon cancer, elevated HDL-C which can be a marker in BC) whereas others are antagonistics (cholesterol-lowering activity of olive oil against high cholesterol in BC).

13.5
OLIVE OIL AND CANCER

Several studies discriminate among the lipid rich food with respect to cancer risk. Dairy products, rich in saturated fat, are the most often incriminated for breast cancer (Lé *et al*, 1986; Richardson *et al*, 1991) together with meat (Toniolo *et al*, 1989). In contrast, a population study on Eskimos shows that cancer incidence is lower in this population whose diet is rich in fish (Nielsen *et al*, 1980). Experimental studies have shown that olive oil did not increase tumour incidence or growth in murine models, contrary to corn and sunflower oil (Cohen *et al*, 1986; Katz and Boylan, 1986; Lasekan *et al*, 1990).

International correlation studies have differentiated between per capita animal and vegetable fat consumption (Carroll and Braden, 1985; Rose *et al*, 1986). There is a strong correlation between colon, prostate, breast and ovary cancer mortality rates and animal fat consumption per capita. It is interesting to note that Israel,

whose animal fat consumption is low (around 40 g/day, 14.6 kg/year) shows a breast and ovarian cancer mortality rate as elevated as Canada where animal fat consumption is twice as high. There is no correlation between vegetable fat consumption and the various cancers. Data are only shown in relation to breast cancer, and it is noteworthy that Israel which consumes high amounts of vegetable oil (around 60 g/day, 21.9 kg/year), mostly sunflower oil (Berry *et al*, 1986), shows a much high mortality rate than Greece in spite of the higher animal fat intake (60 g of animal fat/day, 21.9 kg/year) and the higher vegetable fat intake consumed in this country (80 g of vegetable fat/day, 29.2 kg/year) which is olive oil.

There are some studies which discriminate between the three types of fatty acids. Most of saturated and monounsaturated fats are of animal origin, except for the oleic acid of olive oil. Polyunsaturated fatty acids of the n-6 series are largely of vegetable origin, whereas fatty acids from some fishes especially those with coloured meat are the major source of the n-3 series. Saturated fatty acids are the most often associated with breast cancer risk (Knekt *et al*, 1990; Howe *et al*, 1991; Richardson *et al*, 1991) whereas it is very infrequent for polyunsaturated fatty acids (Van't Veer, 1990a). On the contrary, experimental *in vivo* and *in vitro* studies have shown that PUFA are inhibitors of tumour cell proliferation. Moreover, this effect can be counteracted by the antioxidant action of vitamin E (Begin *et al*, 1988; Najid *et al*, 1989; Zhu *et al*, 1989; Gerber *et al*, 1990; Conzales *et al*, 1991).

Coming to monounsaturated fatty acids, three studies have shown a positive risk association with breast cancer (Knekt *et al*, 1990; Shun-Zhang *et al*, 1990; Richardson *et al*, 1991). In the Shanghai study it is obvious that monounsaturated fatty acids are of animal origin since olive oil is not used in this country, whereas poultry is the main animal food. In our study, olive oil consumption was evaluated. As such it was consumed in a larger amount by cases than by controls; however, after allowance for the index of socioeconomic level (length of studies), the difference was no longer statistically significant (Richardson *et al*, 1991; Gerber and Richardson, this book). On the contrary, monounsaturated fatty acids were significantly associated with an elevated relative risk. When oleic acid of vegetable origin was subtracted, there was no change in the relative risk, indicating that the risk was associated with monounsaturated fatty acids of animal origin.

What can we conclude from this scattered information about olive oil and cancer? First, that not all vegetable oils carry the same risk-reduction effect against cancer. Looking at Israel and Greece, according to Rose *et al* (1986), we note that in Israel the total consumption of fat is around 100 g/day (36.5 kg/year), with 40 g of animal fat (14.6 kg/year) and 60 g of vegetable fat (21.9 kg/year) which is mainly sunflower oil (Berry *et al*, 1986) whereas in Greece the total consumption of fat is around 140 g/day (51.1 kg/year) with 60 g of animal fat (21.9 kg/year) and 80 g of vegetable fat (29.2 kg/year) which is mainly olive oil (Table 13.3). This suggests that a larger intake of fat is not detrimental if it is

mainly constituted of olive oil. It could be objected that Israel data are difficult to interpret because of the large proportion of migrant populations who eventually carry with them genetic and cultural factors other than dietary. However, in their recent study, Parkin *et al* (1990) indicate that migrant populations all show an increasing risk of breast cancer with time and especially an increase in risk with duration of residence; this is small but statistically significant for Jews from Europe and much more marked for Jews from North Africa, stressing the importance of a change in the environmental factors. Among other factors, North African migrants may have changed from the use of olive oil to that of sunflower oil. This could be an indication that, among vegetable oils, olive oil appears more associated with a reduced risk than those with polyunsaturated fatty acids. In the same line, the study by Katsouyanni *et al* (1986) should be recalled with the indication of a negative association of breast cancer and fat intake, fat being mainly olive oil in Greece.

Second, that monounsaturated fats when they are of animal origin are associated with breast cancer risk. Since oleic acid is chemically identical whatever its origin, some other explanations must be searched for. Some reports indicate that the proteic context has an influence on the distribution of fatty acids in plasma and tissues (Koba and Sugano, 1990; Gerber, unpublished work). This may be so, since the membrane fatty acid composition of the cancer cells is quite different than those from the normal cells (Masotti *et al*, 1988; Pritchard *et al*, 1989; Szabados *et al*, 1989; Lanson *et al*, 1990).

Another explanation could be that the responsible element for the eventual protective factor in olive oil would be not the oleic acid but other compounds of the oil. It has been shown in the second section that the antioxidant content of olive oil and of other vegetable oils is quite different. There are some indications (Burton *et al*, 1983; Slater *et al*, 1984; Cheeseman *et al*, 1986, 1988; Gerber *et al*, 1988, 1989, 1990, 1991) that antioxidants and especially vitamin E, are elevated in plasma and tumour tissues of cancerous patients and tumour-bearing animals. The accumulation of antioxidants could be a self-serving feature facilitating either promotion (Cerutti, 1989) or growth (Slater *et al*, 1984). Thus vitamin E could facilitate tumour growth, and the different effect of the various vegetable oils on cancer could also lie in their antioxidant content.

ACKNOWLEDGEMENTS

The work from our laboratory quoted in this article has been financially supported by Ligue National contre le Cancer and INSERM contract number 911006.

REFERENCES

Armstrong B, Doll R (1975). Environmental factors and cancer incidence and mortality in different countries, with special reference to dietary practices. *Int J Cancer* **15:** 617–31.

Aravanis C, Mensink RP, Karalias N (1988). Christodoulou B, Kafatos A, Katan MB (1988). Serum lipids, apoproteins and nutrient intake in rural Cretan boys consuming high-olive oil diets. *J Clin Epidemiol* **41:** 1117–23.

Basu TK, Williams DC (1975). Plasma and body lipids in patients with carcinoma of the breast. *Oncology* **31:** 172–76.

Begin ME, Ellis G, Horrrobin DF (1988). Polyunsaturated fatty acid-induced cytotoxicity against tumour cells and its relationship to lipid peroxidation. *J Natl Cancer Inst* **80:** 188–94.

Benito E, Obrador A, Stiggelbout A, Bosch FX, Mulet M, Munoz N, Kaldor J (1990). A population-based case-control study of colorectal cancer in Majorca. I. Dietary factors. *Int J Cancer* **45:** 69–76.

Berry EM, Zimmerman J, Peser M, Ligumsky M (1986). Dietary fat, adipose tissue composition and the development of carcinoma of the colon. *J Natl Cancer Inst* **77:** 93–97.

Berry EM, Eisenberg S, Haratz D, Friedlander Y, Norman Y, Kaufmann N, Stein Y (1991). Effect of diets rich in monounsaturated fatty acids in plasma lipoproteins—the Jerusalem nutrition study: high MUFAs versus high PUFAs. *Am J Clin Nutr* **53:** 899–907.

Boyd NF, McGuire V (1990). Evidence of association between plasma high-density lipoprotein cholesterol and risk factors for breast cancer. *J Natl Cancer Inst* **82:** 460–8.

Buiatti E, Palli D, Decarli A *et al* (1989). A case-control study of gastric cancer and diet in Italy. *Int J Cancer* **44:** 611–16.

Burton GW, Cheeseman KH, Doba T *et al* (1983). vitamin E as an anti-oxidant *in vitro* and *in vivo.* In Ciba Foundation symposium 101 (ed), Biology of Vitamin E, London, Pitman, pp 4–14.

Carroll KK, Braden LM (1985). Dietary fat and mammary carcinogenesis. *Nutr Cancer* **6:** 254–9.

Cerutti PA (1989). Response modification in carcinogenesis. *Env Health Persp* **81:** 39–43.

Chang NW, Huang PC (1990). Effect of dietary monounsaturated fatty acids on plasma lipids in humans. *J Lipid Res* **31:** 2141–7.

Cheeseman KH, Collins M, Proudfoot K *et al* (1986). Studies on lipid peroxidation in normal and tumour tissues. The Novikoff rat liver tumour. *Biochem J* **235:** 507–14.

Cheeseman KH, Emery S, Maddix SP *et al* (1988). Studies on lipid peroxidation in normal and tumour tissues. The Yoshida rat liver tumour. *Biochem J* **250:** 247– 52.

Cohen LS, Thompson DG, Maueura Y, Choi K, Blank ME, Rose DP (1986). Dietary fat and mammary cancer. I Promotion of effect of different fats on N-nitrosomethylurea-induced rat mammary tumorigenesis. *J Natl Cancer Inst* **77:** 33–42.

Colditz GA, Stampfer MJ, Willett WC (1987). Diet and lung cancer. *Arch Int Med* **147:** 157–60.

Delplanque B, Richard JL, Jacotot B (1991). Effet de 1'enrichissement progressif en monoinsaturés due régime sur les acides gras, lipides, apoproteines et particules lipoprotéiques du serum d'une population d'hommes normolipémiques. Coll Int "Caractéristiques nutritionnelles des régimes alimentaires méditerranéens, prévention des maladies cardio-vasculaires" pp 48–9, Monastir, October 1991.

Driss F, Duranthon V, Viard V, Darcet Ph (1991). Activités biologiques ds sustances mineures de 1'olivier. Coll Int "Caractéristiques nutritionnelles des régimes alimentaires méditerranéens, prévention des maladies cardio-vasculaires" p 14, Monastir.

Feinleib M (1981). On a possible inverse relatinship between serum cholesterol and cancer mortality. *Am J Epidemiol* **114:** 5–10.

Fischer DR, Morgan KJ, Zabik ME (1985). Cholesterol, saturated fatty acids, polyunsaturated fatty acids, sodium and potassium intakes of the United States population. *J Am Coll Nutr* **4:** 207–24.

Freudenheim JL, Graham S (1989). Toward a dietary preventon of cancer. *Epidemiologic Rev* **11:** 229–35.

Gerber M, Cavallo F, Marubini E *et al* (1988). Liposoluble vitamins and lipid parameters in breast cancer. A joint study in Northern Italy and Southern France. *Int J Cancer* **42:** 489–94.

Gerber M, Richardson S, Crastes de Paulet P, Pujol H, Crastes de Paulet A (1989). Relationship between vitamin E and polyunsaturated fatty acids in breast cancer. Nutritional and metabolic aspects. *Cancer* **64:** 2347–53.

Gerber M, Richardson S, Favier F, Crastes de Paulet A (1990). Vitamin E and tumor growth. In *Antioxidants in Therapy and Medicine* (eds Emerit I *et al*); Plenum Press, New York, pp 129–32.

Gerber M, Richardson S, Chappuis P, Salkeld R (1991). Anti-oxidants in breast-cancer female patients. *Cancer Investigation* **9:** 421–8.

Gonzales MJ, Schemmel RA, Gray JE *et al* (1991). Effect of dietary fat on growth of MCF-7 and MDS-MB231 human breast carcinomas in athymic nude mice: relationship between carcinoma growth and lipid peroxidation product levels. *Carcinogenesis* **12:** 1231–5.

Goodwin PJ, Boyd NF (1987). Critical appraisal of the evidence that dietary fat intake is related to breast cancer risk in humans. *J Nat Cancer Inst* **79:** 473–85.

Graham S, Marshall J, Haughey B *et al* (1988). Dietary epidemiology of cancer of the colon in western New York. *Amer J Epidemiol* **128:** 490–503.

Harris RWC, Key TJA, Silcocks PB, Bull D, Wald NJ (1991). A case-control study of dietary carotene in men with lung cancer and in men with other epithelial cancers. *Nutr Cancer* **15:** 63–8.

Helszouer KJ, Comstock GW, Morris JS (1989). Selenium, lycopene, →tocopherol, ß-carotene, retinol and subsequent bladder cancer. *Cancer Res* **49:** 6144–8.

Hirayama T (1978). Epidemiology of breast cancer with special reference to the role of diet. *Prev Med* **7:** 173–95.

Howe GR, Griedenreich CM, Jain M, Miller AB (1991). A cohort study of fat intake and risk of breast cancer. *J Natl Cancer Inst* **83:** 336–40.

Howe GR, Hirohata T, Hislop TG *et al* (1990). Dietary factors and risk of breast cancer: combined analysis of 12 case-control studies. *J Nat Cancer Inst* **82:** 561– 9.

Iscovich JM, Iscovich RB, Howe G, Shiboski S, Kaldor JM (1989). A case-control study of diet and breast cancer in Argentina. *Int J Cancer* **44:** 770–6.

Katsouyanni K, Trichopoulos D, Boyle P *et al* (1986). Diet and breast cancer. A case-control study in Greece. *Int J Cancer* **38:** 815–20.

Katz EB, Boylan ES (1989). Effect of the quality of the dietary fat in tumor growth and metastasis from a rat mammary adenocarcinoma. *Nutr Cancer* **12:** 343–50.

Knekt P, Albanes D, Seppanen R *et al* (1990). Dietary fat and risk of breast cancer. *Am J Clin Nutr* **52:** 903–8.

Knuiman JT, Hermus RJJ, Hautvast JGAJ (1980). Serum total and high-density lipoprotein cholesterol concentrations in rural and urban boys from 16 countries. *Atherosclerosis* **36:** 529–37.

Koba K, Sugano M (1990). Dietary protein influences polyunsaturated fatty acid patterns of rat tissue lipids. *J Nutr Sci Vitaminol* **36:** S-173–6.

Lasekan JB, Clayton MK, Gendron Fitzpatrick A, Ney DM (1990). Dietary olive and Safflower oils in promotion of DMBA-induced mammary tumorigenesis in rats. *Nutr Cancer* **13:** 153–63.

Lanson M, Bougnoux P, Besson P *et al* (1990). n-6 Polyunsaturated fatty acids in human breast carcinoma phophatylethanolamine in early relapse. *Brit J Cancer* **61:** 776–8.

Lé MG, Moulton LH, Hill C, Kramar A (1986). Consumption of dairy produce and alcohol in a case-control study of breast cancer. *J Nat Cancer Inst* **77:** 633–6.

Lubin F, Wax Y, Modan B (1986). Role of fat, animal protein and dietary fiber in breast cancer etiology: a case-control study. *J Nat Cancer Inst* **77:** 605–12.

Masana L, Camprubi M, Sarda P, Sola R, Joven J, Turner PR (1991). The Mediterranean-type diet: is there a need for further modification? *Am J Clin Nutr* **53:** 886–9.

Masi I, Giani E, Galli C, Tremoli E, Sirtori CR (1986). Diets rich in saturated, monounsaturated and polyunsaturated fatty acids differently affect plasma lipids, platelets and arterial wall eicosanoids in rabbits. *Ann Nutr Metab* **30:** 66–72.

Masotti L, Casali E, Galeotti T (1988). Lipid peroxidation in tumour cells. *Free Radical Biology and Medicine* **4:** 377–86.

Mensink RP, Katan MB (1990). Effects of dietary trans fatty acids on high-density and low density lipoprotein cholesterol levels in healthy subjects. *N Engl J Med* **323:** 439–45.

Najid A, Beneytout JL, Tixier M (1989). Cytotoxicity of arachidonic acid and of its lipoxygenase metabolite 15-HPETE on human breast cancer MCF-7 cells in culture. *Cancer Letters* **46:** 137–41.

Negri E, La Vecchia C, Franceschi S, D'Avanzo B, Parazzini F (1991). Vegetable and fruit consumption and cancer risk. *Int J Cancer* **48:** 350–4.

Nielsen NH, Hansen JPH (1980). Breast cancer in Greenland—selected epidemiological, clinical and histological features. *J Cancer Res Clin Oncol* **98:** 287–99.

Parkin DM, Steinitz R, Khlat M, Kaldor J, Katz L, Young J (1990). Cancer in Jewish migrants to Israel. *Int J Cancer* **45:** 614–21.

Pritchard GA, Jones DL, Mansel RE (1989). Lipids in breast carcinogenesis. *Br J Surg* **76:** 1069–73.

Richardson S, Gerber M, Cénée S (1991). The role of fat, animal protein and vitamin consumption in breast cancer. A case-control study in Southern France. *Int J Cancer* **48:** 1–9.

Rose DP, Boyar AP, Wynder EL (1986). International comparisons of mortality rates for cancer of the breast, ovary, prostate and colon and per capita food consumption. *Cancer* **58:** 2363–71.

Slater T, Benedetto C, Burton GW *et al* (1984). Lipid peroxidation in animal tumours: a disturbance in the control of cell division? In *Icosanoids and Cancer* (eds Thaler-Dao H, Paoletti R, Crastes de Paulet A); Raven Press, New York, pp 21–29.

Szabados GY, Tretter L, Horvath I (1989). Lipid peroxidation in liver and Erlich ascites cell mitochondria. *Free Rad Res Comms* **7:** 161–70.

Shu YP, Su ZW, Li CH (1989). Growth-inhibition effects of oleic acid, linoleic acid and their methyl esters on transplanted tumors in mice. *J Natl Cancer Inst* **81:** 1302–06.

Shun-Zhang Y, Rui-Fang I, Da-Dao X, Howe GR (1990). A case-control study of dietary and nondietary risk factors for breast cancer in Shangai. *Cancer Res* **50:** 5017–21.

Sirtori CR, Tremoli E, Gatti E *et al* (1986). Controlled evaluation of fat intake in the Mediterranean diet: comparative activities of olive oil and corn oil on plasma lipids and platelets in high-risk patients. *Am J Clin Nutr* **37:** 355–60.

Toniolo P, Riboli E, Protta F, Charrel M, Cappa AP (1989). Calorie-providing nutrients and risk of breast cancer. *J Nat Cancer Inst* **81:** 278–86.

Van't Veer P, Kok FJ, Brants HAM, Ockhuizen T, Sturmans F, Hermus RJJ (1990a). Dietary fat and the risk of breast cancer. *Int J Epidemiol* **19:** 12–18.

Van't Veer P, Kolb C, Verhoef P, Kok FJ, Schouten EG, Hermus RJJ, Sturmans F (1990b). Dietary fiber, beta-carotene and breast cancer: results from a case-control study. *Int J Cancer* **45:** 825–8.

Wallace RB, Rost C, Burmeister LF, Pomrehn PR (1982). Cancer incidence in humans: relationship to plasma lipids and relative weight. *J Natl Cancer Inst* **68:** 915–8.

Wardlaw GM, Snook JT (1990). Effect of diets high in butter, corn oil, or high oleic acid sunflower oil on serum lipids and apolioproteins in men. *Am J Clin Nutr* **51:** 815–21.

Whittemore AS, Wu-Williams AH, Lee M *et al* (1990). Diet, physical activity and colorectal cancer among Chinese in North-America and China. *J Natl Cancer Inst* **82:** 915–26.

Willett WC, Stampfer MJ, Colditz GA, Rosner BA, Hennekens CH, Speizer FE (1987). Dietary fat and the risk of breast cancer. *N Engl J Med* **316:** 22–8.

Willett WC, Stampfer MJ, Colditz GA, Rosner BA, Speizer FE (1990). Relation of meat, fat and fiber intake to the risk of colon cancer in a prospective study among women cancer. *N Engl J Med* **323:** 1664–72.

Wynder EL, Shigematsu T (1967). Environmental factors of cancers of the colon and the rectum. *Cancer* **20:**1520–61.

14
Dietary fat, obesity and cancer
C La Vecchia

14.1
INTRODUCTION

Fats are a major component of energy intake in populations from developed countries, and the observation that energy intake, and consequently body weight, have a role in the process of carcinogenesis was already made in the early 1940s on the basis of animal experiments: rodents fed at libitum had a higher cancer incidence than animals with restricted calorie intake (Tannenbaum, 1940). Still, the evidence linking obesity with cancer risk in humans is now much stronger than that related to dietary fat intake.

Epidemiological knowledge and open problems in the issue of dietary fat, obesity and cancer risk will be reviewed in this chapter, on the basis of two published reviews on the topic (La Vecchia, 1992; La Vecchia *et al*, 1992).

14.2
DIETARY FAT

The association between fat intake and several common cancers, including colorectum, breast, endometrium, ovary and prostate, received its strongest support from correlation studies on populations. On an international scale, strong direct correlations were observed between breast cancer mortality in various countries and fat consumption (Carroll, 1975). Armstrong and Doll (1975) systematically reviewed incidence rates in 23 countries and mortality rates in 32 countries, and found coefficients above 0.6 for mortality and above 0.5 for incidence for fat intake and cancers of the colorectum, breast, corpus uteri and ovary; for prostatic cancer mortality, the correlation coefficient was 0.7.

Similar correlations were observed also on a national level, and persisted after allowance for major identified covariates. Table 14.1 gives, as an example, the crude and partial correlation coefficients between selected food items and breast cancer rates in various regions of Italy, a country with marked differences in dietary habits and cancer rates: foods rich in animal fats were positively correlated with breast cancer mortality, and the coefficients remained

significantly positive after allowance for age at first birth (La Vecchia and Pampallona, 1986).

Table 14.1—Correlation between breast cancer mortality and selected dietary variables in various Italian regions*

Food items	Correlation coefficients	
Crude	Adjusted for age at first birth	
Milk	0.81	0.52
Cheese	0.74	0.52
Meat	0.39	–0.25
Sugar	0.66	0.15
Wine	0.37	–0.45
Pasta	–0.78	–0.31

*From La Vecchia and Pampallona, 1986.

Inspection of the geographical differences in mortality from cancers of the breast or colon in areas like Italy (Fig. 14.1a,b) with substantial variability in diet composition is also of interest since it suggests that not only total fat intake, but also type of fat may be of relevance. In northern Italy, in fact, where colon and breast cancer rates are uniformly elevated, butter is the main type of seasoning fat, while in southern Italy olive oil is most commonly used (La Vecchia *et al*, 1988b).

Observational studies on populations are useful to formulate hypotheses, but cannot provide convincing evidence of a cause-effect relationship. Unfortunately, however, the evidence from analytic epidemiological studies is much less convincing, and the correlation between fat intake and cancer has been described as weak in individuals as opposed to populations.

14.2.1 Cancer of the colorectum

Diets rich in fat (and particularly meat) have been associated with high colorectal cancer risk in several case-control studies, and in some of the studies that specifically considered types of fats positive associations were found with saturated fats. Diets rich in vegetables, fruits and possibly fibres tended to be associated with a low risk (Miller *et al*, 1983; Manousos *et al*, 1983; Potter and McMichael, 1986; Reddy, 1987; Graham *et al* 1988; La Vecchia *et al*, 1988c; Lee *et al*, 1989). Two cohort studies (Morgan *et al*, 1988; Willet *et al*, 1989) on diet and colon cancer found positive associations with fat.

A high-fat diet may induce colorectal carcinogenesis by increasing synthesis and secretion of cholesterol and bile acids. These are converted by colonic bacteria to secondary bile acids, which may promote tumours. While saturated and unsaturated fats have similar effects on bile acid secretion and synthesis, it

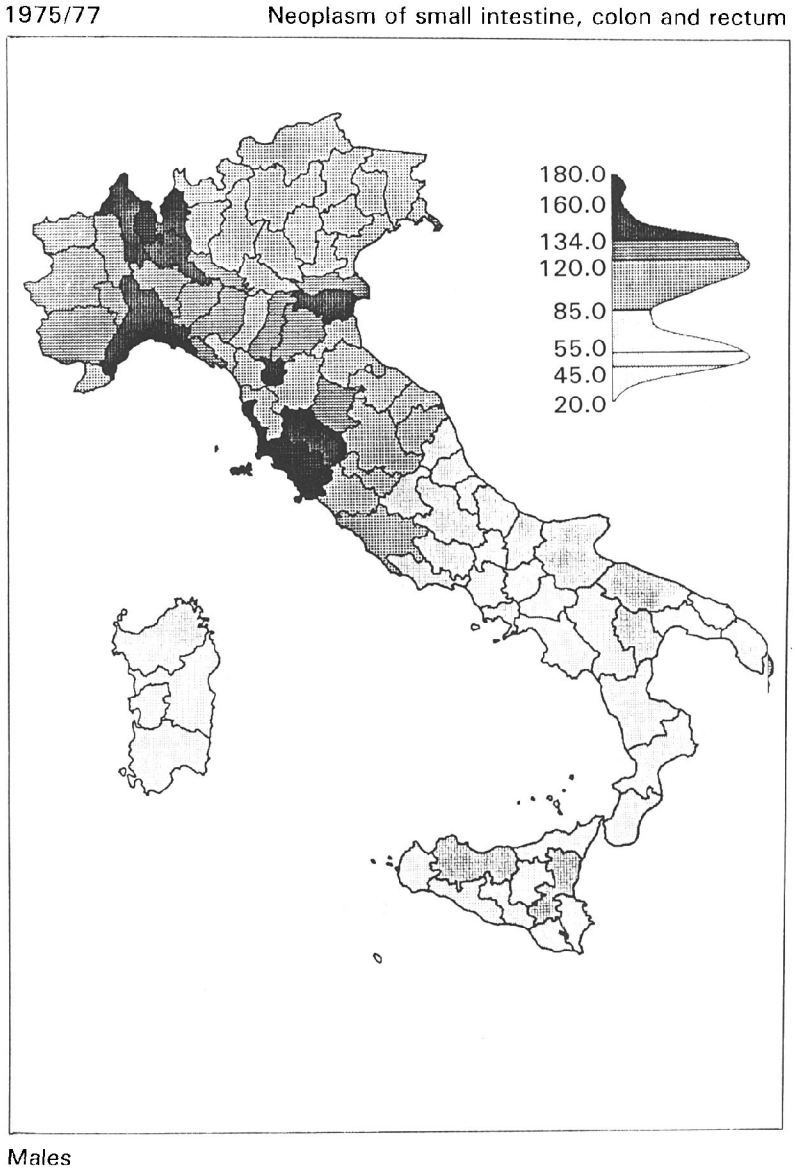


Fig. 14.1a—Colon cancer mortality in Italy in males

has been suggested that the promotional effect may be less for mono-unsaturated fats (Reddy, 1987).

Although the overall pattern from case-control studies on dietary patterns related to elevated colorectal cancer risk is fairly consistent, the strength of the association with fats is generally moderate. Table 14.2 gives, as an example, the

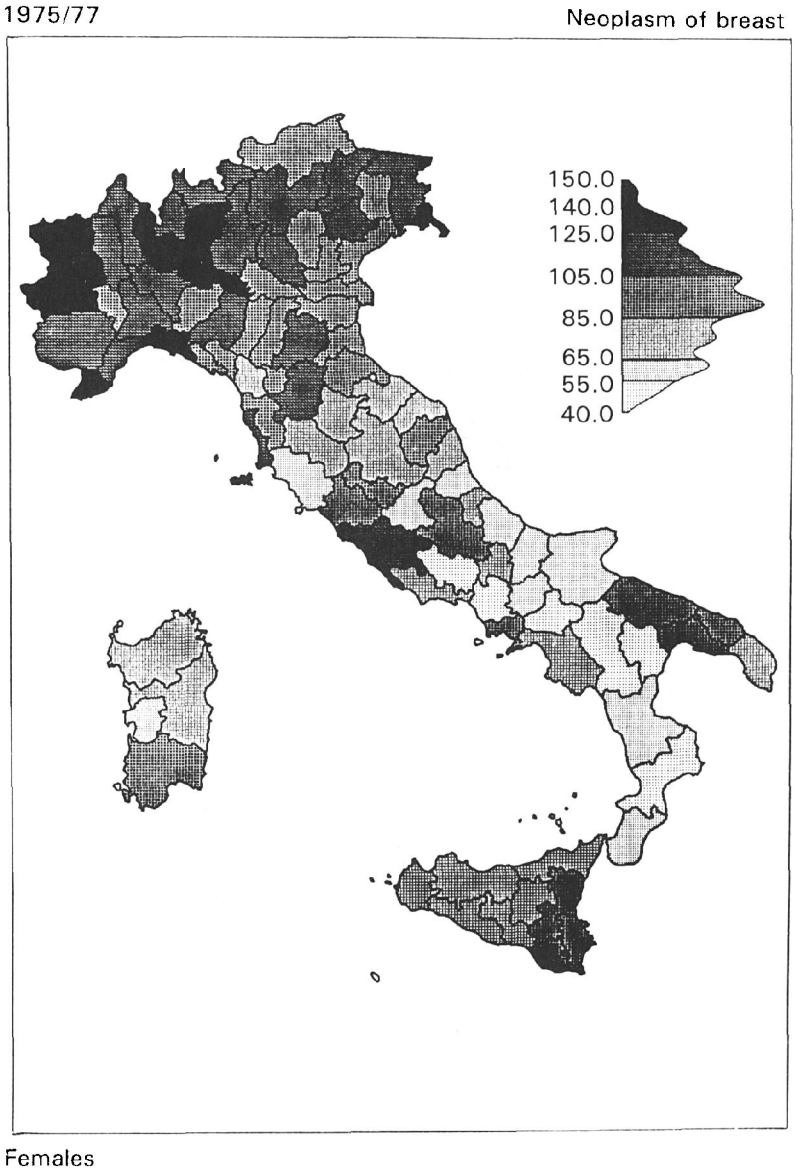


Fig. 14.1b—Breast cancer mortality in Italian females

relative risk estimates from various fat-rich foods from an Italian case-control study (La Vecchia *et al*, 1988c). Most of the relative risk estimates were moderate (*eg* between 1 and 2), and some inconsistencies were apparent either for various intestinal subsites or in the two sexes.

Table 14.2—Relationhip between intake of selected fats and meat and colorectal cancer risk in Italy*

Study and source or type of fat	Relative risk for the highest *vs* lowest consumption level for	
Colon cancer	Rectal cancer	
Butter	2.0	1.7
Margarine	0.9	1.5
Olive oil	1.9	1.3
Other oils	0.8	0.8
Meat	2.0	2.2

*From La Vecchia *et al* 1988c.

These and other inconsistencies and difficulties do not totally eclipse the evidence of an association between fat and colorectal cancer in humans, although they do impede any precise assessment of the association in quantitative terms.

14.2.2 Breast cancer

Again, most of the initial evidence linking breast cancer to diet came from animal experiments and from ecological studies on diet and breast cancer risks in different populations.

Unfortunately, the evidence from analytical epidemiology to date is largely confused. Case-control studies have reported associations with fats and specific food items such as fried foods, dairy products, beef and other red meat, pork and desserts (Phillips, 1975; Miller *et al*, 1978; Lubin *et al*, 1981; Graham *et al*, 1982; Katsouyanni *et al*, 1986; Lubin *et al*, 1986; Hirohata *et al*, 1987; La Vecchia *et al*, 1987a; Willett *et al*, 1987; Rohan *et al*, 1988; Iscovich *et al*, 1989; Mills *et al*, 1989; Toniolo *et al*, 1989; Vant Veer *et al*, 1990). The associations, however, were moderate and inconsistent. Published evidence from case-control studies is summarized in Table 14.3. Some of these found a direct association with fats, such as those from Canada (Miller *et al*, 1978), Israel (Lubin *et al*, 1986) and the Netherlands (Vant Veer *et al*, 1990); in an Italian study, the relative risk for the highest saturated fat intake was 2.8 (Toniolo *et al*, 1989). In other studies the association was weak and inconsistent, although the point estimates were above 1 (Miller *et al*, 1978; Lubin *et al*, 1981; Katsouyanni *et al*, 1986; La Vecchia *et al*, 1987a; Iscovich *et al*, 1989; Vant Veer *et al*, 1990), whereas studies from the United States (Graham *et al*, 1982), Hawaii (Hirohata *et al*, 1987) and Australia (Rohan *et al*, 1988) showed no evidence of a positive association. To further complicate the issue, three prospective studies from the United States (Jones *et al*, 1987; Willett *et al*, 1987; Mills *et al*, 1989) found no evidence of any positive association with total fat intake, or with any specific type of fat.

Thus, the relationship between fat and breast cancer remains more obscure and uncertain than that for colorectal cancer. Nonetheless, even if the increased risk for the upper levels of fat intake were of the order of 1.2–1.5, as found in most case-control (but not prospective) investigations, this would represent an association of magnitude similar to that observed for most established reproductive and hormonal breast cancer risk factors (La Vecchia *et al*, 1989), and would have major public health and preventive implications.

14.2.3 Cancers of the endometrium and ovary

Although strong positive correlations were observed between fats, oils and endometrial cancer incidence, the issue is clearly complicated by the close correlation between fat and energy intake which, in turn, is the major determinant of obesity, a consistently recognized risk factor for endometrial cancer (La Vecchia, 1989).

Few analytical studies have directly addressed the role of diet in the aetiology of endometrial cancer. Preliminary results from a case-control study (Armstrong, 1979) based on 24 hour recall suggested that intake of carbohydrates and total calories (but not proteins or fats) was higher in cases than in controls.

A study from Italy (La Vecchia *et al*, 1986; La Vecchia, 1989), including a total of 567 cases and 2113 controls, reported strong direct associations with subjective intake scores for fats and oils (Table 14.4), and significant protections by green vegetables and fresh fruit. However, information on only a small number of food items was collected in that study, and it was not possible to allow for total energy intake.

As for endometrial cancer, most of the links between diet and ovarian cancer are indirect, and based on international differences or ecological studies. Correlations with fats are in the same direction as those for endometrial cancer, although somewhat weaker in relation to incidence (La Vecchia, 1989).

Table 14.3—Relation of total fat* intake and breast cancer risk in selected case-control studies

Study, year	Level of fat intake**			
I+	II	III	IV	V
Phillips, 1975	1	1.2		
Miller *et al*, 1978	1	1.7	1.2	1.8
Lubin *et al*, 1981	1	1.6	1.5	1.8
Graham *et al*, 1982	1	1.1	1.2	0.9

Study, year	Level of fat intake**				
I+	II	III	IV	V	
La Vecchia *et al*, 1987	1	1.3	1.3		
Hirohata *et al*, 1987° (Japanese)	1	1.1	1.0	1.3	
Hirohata *et al*, 1987° (Caucasian)	1	0.7	0.5	0.8	
Katsouyanni *et al*, 1986°°	1	1.4			
Rohan *et al*, 1988	1	0.9	1.1	1.1	0.9
Toniolo *et al*, 1989	1	1.9	1.6	1.8	
Iscovich *et al*, 1989	1	1.4	0.7	3.6	
Van't Veer *et al*, 1990	1	1.5	1.6	1.3	2.6

*Animal fat, when only available; **As reported in the original studies. Thus, the data in this table allow within, but not between, studies comparisons; +Reference category; °Study based on Japanese and Caucasian population separately; °° 90th *vs* 10th centile.

Information from follow-up studies is scanty and controversial. In a cohort of British nuns (Kinlen, 1982), with low intake of meat and fats, no reduction in risk was apparent. Populations of Mormons (Lyon *et al*, 1980) or Seventh-day Adventists (Phillips *et al*, 1980) are not necessarily informative, since they differ in several aspects linked to ovarian cancer.

The findings of case-control studies are somewhat more consistent. Among five studies which considered various measures of fat intake (Byers *et al*, 1983; Cramer *et al*, 1984; La Vecchia *et al*, 1987b; Shu *et al*, 1989; Slattery *et al*, 1989) (Table 14.5), three found significant direct associations. In one of these, based on a Chinese population with wide ranges of consumption of various nutrients, the effect of fat persisted after adjustment for total calories, whereas no significant association persisted with calories or proteins after allowance for animal fat intake (Shu *et al*, 1989).

As for breast cancer, the range of relative risks shown in Table 14.5 is comparable with that of the best recognized hormonal and reproductive risk factors for ovarian cancer and, if due to a causal association, could have appreciable public health relevance in developed countries (La Vecchia, 1989).

Table 14.4—Relationship between level of fat intake and endometrial cancer risk. Milan, Italy, 1983–1990

Total fat intake subjective score	Endometrial cancer	Controls	Ralative risk (95% CI)*
Low	262	1134	1[+]
Intermediate	196	708	1.2 (0.9–1.4)
High	109	271	1.8 (1.4–2.3)
p (trend)	567	2113	<0.01

*Mantel-Haenszel estimates adjusted for age; [+]Reference category.

Table 14.5—Fats and ovarian cancer: summary results from case-control studies

Study	Level of fat intake			
1*	2	3	4	
Byers *et al*, 1983	1	1.3	1.2	–
Cramer *et al*, 1984	1	1.1	1.9	1.8
La Vecchia *et al*, 1987	1	1.2	2.1	–
Shu *et al*, 1989	1	1.1	1.8	1.9
Slattery *et al*, 1989	1	0.9	1.3	–

*Reference category.

14.2.4 Cancer of the prostate

Two case-control studies from Northern Italy (Talamini *et al*, 1986; La Vecchia *et al*, 199la) found elevated risks for milk and/or dairy product consumption. A more detailed dietary investigation from the Rosewell Park Memorial Institute (Mettlin *et al*, 1989) found a trend towards a higher risk for intake of fat from meats and a strong direct association with whole milk (*rr* 2.5 for three or more glasses per day), but not with skimmed milk. This again was interpreted as supporting the hypothesis that animal fat is related to increased prostatic cancer risk. The results of selected case-control studies considering the relationship between fats and prostatic cancer are given in Table 14.6 (Graham *et al*, 1983; Ross *et al*, 1987; Kolonel *et al*, 1988; Ohno *et al*, 1988; Mettlin *et al*, 1989). Although the interpretation of most single studies may be open to debate, the overall pattern is consistent with an elevated risk for highest levels of fat intake.

Table 14.6—Fats and prostatic cancer: summary results from selected case-control studies

	Age/Race Group	Level of fat intake**				
	1*	2	3	4	5	
Graham *et al*, 1983	<70	1	1.0	0.8	0.9	2.2
	~~≥~~70	1	1.4	0.8	1.8	1.9
Kolonel *et al*, 1988	<	1	0.9	0.8	1.0	–
	~~≥~~70	1	1.0	1.1	1.5	–
Mettlin *et al*, 1989	–	1	1.1	0.9	1.2	1.3
Ohno *et al,* 1988	–	1	0.8	–	–	–
Ross *et al*, 1987		1	1.8	1.6	–	–
	Whites	1	1.4	1.9	–	–
	Blacks					

*Reference category; **As reported in the original studies. Thus, the data in this table allow within, but not between, studies comparisons.

Thus, although it is difficult to make any precise quantitative assessment of cancers associated with a high-fat diet in humans, available epidemiological evidence is reasonably consistent for colorectal cancer, for which the relative risk across extreme levels of (saturated) fat intake can be of the order of two, and a plausible biological framework is available. Epidemiological data are more scanty, but seem to support a positive relationship for ovarian and endometrial cancer, too, while the evidence of a potential role of dietary fat in breast and prostatic cancer is still largely uncertain and controversial, despite a substantial amount of research, at least in relation to breast cancer.

14.3 OBESITY

There is substantial evidence that overweight and obesity are related to at least three cancer sites: gallbladder, endometrium and breast in post-menopausal women (Lew *et al*, 1979). The relative risks are of the order of five for obese individuals as compared to leaner ones for gallbladder and endometrium, but only about 30–50% higher for breast cancer (Table 14.7). Still, since mortality rates from breast cancer are substantially higher than from gallbladder and endometrial neoplasms, the public health implications of elevated breast cancer

rates in overweight individuals are probably greater than for any other neoplasms.

Table 14.7—Mortality ratios for selected sites of cancer The American Cancer Society One Million Cohort Study (Lew and Garfinkel, 1979)

Site	Weight index						
<80	80–89	90–109	110–119	120–129	130–139	→140	
Males							
Stomach	134	61	100	122	97	73	188
Colorectum	90	86	100	126	123	153	173
Pancreas	120	82	100	91	88	76	162
Kidney	106	96	100	163	139	191	–
Prostate	102	92	100	90	137	133	129
Females							
Stomach	74	95	100	107	126	126	103
Colorectum	93	84	100	96	110	130	122
Breast	82	86	100	119	116	122	153
Cervix	76	77	100	124	151	142	239
Endometrium	89	109	100	136	185	230	542
Ovary	86	98	100	115	99	88	163
Kidney	112	70	100	109	130	185	203

The underlying aetiological mechanisms are different for gallbladder as compared to breast or endometrial cancer. Obesity, in fact, is a major cause of gallstones (La Vecchia *et al*, 1991b), and this is likely to be the basis of the elevated risk of gallbladder cancer, too, while for cancers of the breast and mostly of the endometrium the underlying biological mechanisms are related to the increased oestrogen levels in post-menopausal obese women, due to aromatization of androgens to oestrogens in the adipose tissue (La Vecchia *et al*, 1988a).

A hormonal mechanism, although still largely undefined, is probably at the basis of the possible association between overweight and cancer of the prostate, which is of similar magnitude (and public health importance) to that with breast cancer, although published evidence is not totally consistent (Table 14.8) (La Vecchia *et al*, 1988a).

Further, the American Cancer Society One Million Cohort Study (Lew and Garfinkel, 1979), the cohort of 50,000 American alumni (Whittemore *et al*, 1985) and some (Goodman *et al*, 1986) though not all (Talamini *et al*, 1990) case-control studies found a direct association between measures of body weight and renal cell adenocarcinoma. Besides epidemiological confirmation, this possible association lacks clear understanding of potential biological mechanism (s), but would be of

Table 14.8—Relation of body mass index with cancer of the breast, endometrium and prostate from a series of case-control studies conducted in Northern Italy (La Vecchia *et al*, 1988)

Body mass index (kg/m^2)	Relative risk (95% confidence interval for:		
Breast cancer	Endometrial cancer	Prostatic cancer	
<20	1*	1*	1*
20–24	1.3 (0.9–1.0)	1.6 (1.0–2.5)	
25–29	1.2 (0.9–1.7)	2.4 (1.5–3.8)	2.0 (1.2–3.5)
≥30	1.6 (1.1–2.4)	6.4 (3.9–10.4)	2.5 (1.2–5.2)

*Reference category.

interest, particularly since little is known on the causes of adenocarcinoma of the kidney, besides an association with smoking (La Vecchia *et al*, 1990).

It is more difficult, particularly using a case-control approach, to study the relationship between measures of body weight and digestive tract sites, since early symptoms of these neoplasms induce modifications of dietary patterns and hence body weight changes (La Vecchia, 1989; La Vecchia and Negri, 1992). It is thus conceivable, though not proven, that overweight may have some influence on colorectal cancer, too, as well as on other tumours linked to neoplastic cachexia, such as pancreas and ovary. All these sites, in fact, were linked to overweight in the American Cancer Society One Million Cohort Study (Lew and Garfinkel, 1979) (Table 14.7).

These uncertainties and the limitations of published work still cannot eclipse the importance, on a public health scale, of overweight and obesity as a cause of human cancer. In the United States, in fact, it has been estimated that approximately 2% of all cancer deaths are due to overweight (Doll and Peto, 1981). Although in Europe this proportion may be somewhat lower, it is nonetheless not only relevant from a public health viewpoint, but also has important and immediate implications for prevention.

Overweight is thus the single aspect of nutrition and diet to be so well-defined in epidemiological terms as to open immediate perspectives for intervention and prevention, and on which public education could have useful effects. Besides cancer, moreover, education and campaigns against overweight and obesity also have major consequences for other major groups of diseases, from diabetes to cardiovascular to digestive tract conditions (Garfinkel and Stellman, 1988).

ACKNOWLEDGEMENTS

This work was conducted within the framework of the Italian National Research Council (CNR) Applied Projects *Clinical Applications of Oncological Research* (Contract No 92.02384.PF 39) and *Risk Factors for Disease* (Contract No 91. 00285.PF41), with the contributions of the Italian Association for Cancer

Research and the Italian and Swiss Leagues against Tumours. The author wishes to thank Mrs Hanne-Christine Janin for editorial assistance.

REFERENCES

Armstrong B, Doll R (1975). Environmental factors and cancer incidence and mortality in different countries, with special reference to dietary practices. *Int J Cancer* **15:** 617–31.

Armstrong BK (1979). Diet and hormones in the epidemiology of breast and endometrial cancer. *Nutr Cancer* **1:** 90–95.

Byers T, Marshall J, Graham S, Mettlin C, Swanson M (1983). A case-control study of dietary and nondietary factors in ovarian cancer. *JNCI* **71:** 681–6.

Carroll KK (1975). Experimental evidence of dietary factors and hormone-dependent cancers. *Cancer Res* **35:** 3374–83.

Cramer DW, Welch WR, Hutchinson GB, Willett WC, Scully RE (1984). Dietary animal fat in relation to ovarian cancer risk. *Obstet Gynecol* **83:** 833–8.

Doll R, Peto R (1981). The causes of cancer: quantitative estimates of avoidable risks of cancer in United States today. *JNCI* **66:** 1191–1308.

Garfinkel L, Stellman SD (1988). Mortality by relative weight and exercise. *Cancer* **62:** 1844–50.

Graham S, Marshall J, Mettling C *et al* (1982). Diet in the epidemiology of breast cancer. *Am J Epidemiol* **116:** 68–75.

Graham S, Haughey B, Marshal J *et al* (1983). Diet in the epidemiology of carcinoma of the prostate gland. *JNCI* **70:** 687–92.

Graham S, Marshall J, Haughey B *et al* (1988). Dietary epidemiology of cancer of the colon in western New York. *Am J Epidemiol* **128:** 490–503.

Goodman MT, Morgenstern H, Wynder EL (1986). A case-control study of factors affecting the development of renal cell cancer. *Am J Epidemiol* **124:** 926–941.

Hirohata T, Nomura A, Hankin JH *et al* (1987). An epidemiologic study on the association between diet and breast cancer. *JNCI* **78:** 595–600.

Iscovich JM, Iscovich RB, Howe G *et al* (1989). A case-control study of diet and breast cancer in Argentina. *Int J Cancer* **44:** 770–6.

Jones DY, Schatzkin A, Green SB *et al* (1987). Dietary fat and breast cancer in the National Health and Nutritional Examination Survey I Epidemiologic Follow-up Study. *JNCI* **79:** 465–71.

Katsouyanni K, Trichopoulos D, Boyle P *et al* (1986). Diet and breast cancer: a case-control study in Greece. *Int J Cancer* **38:** 815–20.

Kinlen LJ (1982). Meat and fat consumption and cancer mortality: a study of strict religious orders in Britain. *Lancet* **i:** 946–9.

Kolonel LN, Yoshizawa CN, Hankin JH (1988). Diet and prostatic cancer: a case-control study in Hawaii. *Am J Epidemiol* **127:** 999–1012.

La Vecchia C, Decarli A, Fasoli M, Gentile A (1986). Nutrition and diet in the etiology of endometrial cancer. *Cancer* **57:** 1248–53.

La Vecchia C, Pampallona S (1986). Age at first birth, dietary practices and breast cancer mortality in various Italian regions. *Oncology* **43:** 1–6.

La Vecchia C, Decarli A, Franceschi S *et al* (1987a). Dietary factors and the risk of breast cancer. *Nutr Cancer* **10:** 205–14.

La Vecchia C, Decarli A, Negri E *et al* (1987b). Dietary factors and the risk of epithelial ovarian cancer. *JNCI* **79:** 663–9.

La Vecchia C, Decarli A, Negri E, Parazzini F (1988a). Epidemiological aspects of diet and cancer: a summary review of case-control studies from Northern Italy. *Oncology* **45:** 364–70.

La Vecchia C, Harris RE, Wynder EL (1988b). Comparative epidemiology of cancer between the United States and Italy. *Cancer Res* **48:** 7285–93.

La Vecchia C, Negri E, Decarli A *et al* (1988c). A case-control study of diet and colorectal cancer in Northern Italy. *Int J Cancer* **41:** 492–8.

La Vecchia C (1989). Nutritional factors and cancers of the breast, endometrium and ovary. *Eur J Cancer Clin Oncol* **25:** 1945–51.

La Vecchia C, Negri E, Boyle P (1989). Reproductive factors and breast cancer: an overview. *Soz Praeventivmed* **34:** 101–07.

La Vecchia C, Negri E, D'Avanzo B, Franceschi S (1990). Smoking and renal cell carcinoma. *Cancer Res* **50:** 5231–3.

La Vecchia C, Negri E, D'Avanzo B, Franceschi S, Boyle P (1991a). Dairy products and the risk of prostatic cancer. *Oncology* **48:** 406–10.

La Vecchia C, Negri E, D'Avanzo B, Boyle P (1991b). Risk factors for gallstone disease requiring surgery. *Int J Epidemiol* **20:** 209–15.

La Vecchia C (1992). Cancers associated with high-fat diets. *J Natl Cancer Inst Monogr* **12:** 79–85.

La Vecchia C, Negri E (1992). Public education on diet and cancer: calories, weight and exercise. In *Public Education on Diet and Cancer* (eds Benito E, Giacosa A, Hill MJ); Dordrecht, Kluwer, pp. 91–9.

Lee HP, Gourley L, Duffy SW *et al* (1989). Colorectal cancer and diet in an Asian population—A case-control study among Singapore Chinese. *Int J Cancer* **43:** 1007–16.

Lew EA, Garfinkel L (1979). Variations in mortality by weight among 750,000 men and women. *J Chronic Dis* **32:** 563–76.

Lubin JH, Burns PE, Blot WJ *et al* (1981). Dietary factors and breast cancer risk. *Int J Cancer* **28:** 685–9.

Lubin F, Wax Y, Modan B (1986). Role of fat, animal protein, and dietary fiber in breast cancer etiology: a case-control study. *JNCI* **77:** 605–12.

Lyon JL, Gradner JW, West DW (1980). Cancer risk and life-style: cancer among Mormons from 1967–1975. In *Cancer Incidence in Defined Populations* (eds Cairns J, Lyon FL, Stolnick M); Cold Spring Harbor Laboratory, (Banbury Report No 4), pp. 93–8.

Manousos O, Day NE, Trichopoulos D, Gerovassilis F, Tzonou A, Polychronopoulou A (1983). Diet and colorectal cancer: a case-control study in Greece. *Int J Cancer* **32:** 1–5.

Mettlin C, Selenskas S, Natarajan N, Huben R (1989). Beta-carotene and animal fats and their relationship to prostate cancer risk. A case-control study. *Cancer* **64:** 605–12.

Miller AB, Kelly A, Choi NW *et al* (1978). A study of diet and breast cancer. *Am J Epidemiol* **107:** 499–509.

Miller AB, Howe GR, Jain M *et al* (1983). Food items and food groups as risk factors in a case-control study of diet and colo-rectal cancer. *Int J Cancer* **32:** 155–61.

Mills PK, Beeson WL, Phillips RL *et al* (1989). Dietary habits and breast cancer incidence among Seventh-day Adventists. *Cancer* **64:** 582–90.

Morgan JW, Fraser GE, Phillips RL, Andress MH (1988). Dietary factors and colon cancer incidence among Seventh-day Adventists. *Am J Epidemiol* **128:** 918.

Ohno Y, Yoshida O, Oishi K *et al* (1988). Dietary beta-carotene and cancer of the prostate. A case-control study in Kyoto, Japan. *Cancer Res* **48:** 1331–6.

Phillips RL (1975). Role of life-style and dietary habits in risk of cancer among Seventh-day Adventists. *Cancer Res* **35:** 3513–22.

Phillips RL, Garfinkel L, Kuzma JW, Beeson WL, Lotz T, Brin B (1980). Mortality among California Seventh-day Adventists for selected cancer sites. *JNCI* **65:** 1097–1107.

Potter JD, McMichael AJ (1986). Diet and cancer of the colon and rectum: a case-control study. *JNCI* **76:** 557–69.

Reddy BS (1987). Dietary fat and colon cancer: animal models. *Prev Med* **16:** 460– 7.

Rohan TE, McMichael AJ, Baghurst PA (1988). A population-based case-control study of diet and breast cancer in Australia. *Am J Epidemiol* **128:** 478–89.

Ross RK, Shimizu H, Paganini-Hill A, Honda G, Henderson BE (1987). Case-control study of prostate cancer in blacks and whites in Southern California. *JNCI* **78:** 869–74.

Shu XO, Gao YT, Yuan JM, Ziegler RG, Brinton LA (1989). Dietary factors and epithelial ovarian cancer. *Br J Cancer* **59:** 92–6.

Slattery ML, Schuman KL, West DW, French TK, Robinson LM (1989). Nutrient intake and ovarian cancer. *Am J Epidemiol* **130:** 497–502.

Talamini R, La Vecchia C, Decarli A, Negri E, Franceschi S (1986). Nutrition, social factors and prostatic cancer in a Northern Italian population. *Br J Cancer* **53:** 817–21.

Talamini R, Baron AE, Barra S *et al* (1990). A case-control study of risk factors for renal cell cancer in Northern Italy. *Cancer Causes Control* **1:** 125–31.

Tannenbaum A (1940). Relationship of body weight to cancer incidence. *Arch Pathol* **30:** 509–17.

Toniolo P, Riboli E, Protta F *et al* (1989). Calorie-providing nutrients and risk of breast cancer. *JNCI* **81:** 278–86.

Van't Veer P, Kok FJ, Brants Ham *et al* (1990). Dietary fat and the risk of breast cancer. *Int J Epidemiol* **19:** 12–18.

Whittemore AS, Paffenbarger RS Jr, Anderson K, Lee JE (1985). Early precursors of site-specific cancers in college men and women. *JNCI* **74:** 43–51.

Willett WC, Stampfer MJ, Colditz GA *et al* (1987). Dietary fat and the risk of breast cancer. *N Engl J Med* **316:** 22–28.

Willett WC, Stampfer MJ, Colditz GA, Rosner BA, Speizer FE (1989). A prospective study of diet and colon cancer in women. *Am J Epidemiol* **130:** 820.

15
Dietary fibre and human cancer
M J Hill

15.1
INTRODUCTION

It has long been claimed that a vegetarian diet can protect against major diseases such as heart disease, colorectal cancer, breast cancer etc (*eg* Kinlen *et al*, 1983; Phillips *et al*, 1980) but it is usual for nutritionists to try to focus on specific components of the diet in an effort to rationalize the observations. By focusing on dietary fibre, for example, the epidemiology of disease can be simplified and hypotheses for the mechanism of the protective effect proposed, tested and refined or rejected. Further, it allows the effects of diets based on rice, wheat, bananas, maize or potatoes to be rationally compared.

The concept that colorectal cancer (and a range of other intestinal diseases) could be prevented by the consumption of a high-fibre diet was recently popularized by Burkitt (1971) although the value of fibre had been recognized by Hippocrates in the 4th Century BC. Burkitt argued on the basis of his long experience in Africa (where colon cancer is rare) and most frequently cited the matoke-eating Ugandans as his example. The protective effect was hypothesized to be due to the effect of the high fibre intake on the rate of colonic transit and on stool bulk. It had been hypothesized by others (Aries *et al*, 1969; Hill *et al*, 1971) that bowel cancer was caused by bacterial metabolites produced *in situ* in the colon from benign substrates; Burkitt argued that a faster transit time allowed less time for the bacteria to produce their metabolites and less time for the metabolites to act, whilst stool bulking diluted carcinogens in the bowel lumen. Matoke is, essentially, boiled mashed bananas which is rich in resistant starch, serotonin and fibre, all of which will have a major effect both on stool bulk and on transit time; matoke-eaters in Uganda are said to produce 700 g stools per day (compared with 100–150 g in most western populations). The message about fibre was delivered in Scandinavia, UK, USA and Australasia where the main source of fibre is in the form of cereals, rather than the fruit fibre consumed in East Africa and on which the hypothesis was based. The contrast between the original source of evidence, the perceived active agent (fruit fibre) there and the message translated from this in terms of total of cereal fibre caused considerable

confusion in the early 1970s, and this was supplemented by the loose terminology. For example, Irving and Drasar (1973), in a comparison of diet and colorectal cancer in 37 countries, observed no correlation at all with total *fibre*; within this there was a statistically significant protective effect of cereals, offset by a positive correlation with fruit fibre. Armstrong and Doll (1975) saw a similar protective effect of cereals. The confusion over terminology has now been largely resolved as a result of the careful studies of numerous groups, principally in Europe but some in the United States.

Much of the discussion has been of *fibre*, because this is the component that was assumed to be active. *Fibre* was assumed to be the dietary polysaccharide *not* digested in the small bowel. Later reports avoided the use of the term fibre as being too imprecise; since it included cereal fibre (stool bulking) and fruit fibre (no stool bulking) it was a major cause (rather than a resolver) of confusion. Many groups have therefore used the alternative, and more precise, chemical terms of non-starch polysaccharide (NSP), cellulose, pentosan etc (*eg* Bingham *et al*, 1985). More recently, it has been realized that some starch reaches the colon and so the term *complex carbohydrate* to include all polysaccharides that escape digestion has been proposed.

In this chapter I will first give a brief outline of the terms used and their interrelationship, then progress to a review of the epidemiological studies and then a discussion of the mechanisms that have been proposed for their anticancer action. Finally I will propose a return to food groups (rather than nutrients) as being a more sensible basis for discussion in this field of research. Particular attention will be paid to the role of cereals, but these cannot be discussed in isolation, because much of the literature has concerned the nutrient *fibre* rather than the cereal food group.

15.2
PLANT CELL WALLS AND DIETARY FIBRE

Plant materials are rich in simple and complex carbohydrate. The polysaccharide within the cell tends to be either simple sugars or starches readily digestible by plant or intestinal amylases. Cell wall polysaccharide, which has a protective role and so needs to be relatively resistant to, for example, microbial enzymes, contains a range of complex carbohydrates the composition of which has been reviewed excellently on numerous occasions elsewhere (*eg* Southgate, 1976; Selvendran and Verne, 1990).

The major polysaccharide in all plant products is starch, and this is readily analysed as glucose following enzymic hydrolysis to its monosaccharides by amylases etc. The major problem has been to assay the non-starch polysaccharide, which was thought until relatively recently to be *unavailable carbohydrate*. The earliest assays were of the fraction resistant to digestion by dilute acid and dilute alkali; this *crude fibre* was essentially cellulose and lignin (Fig. 15.1) and omitted a wide range of polysaccharides that escape small bowel

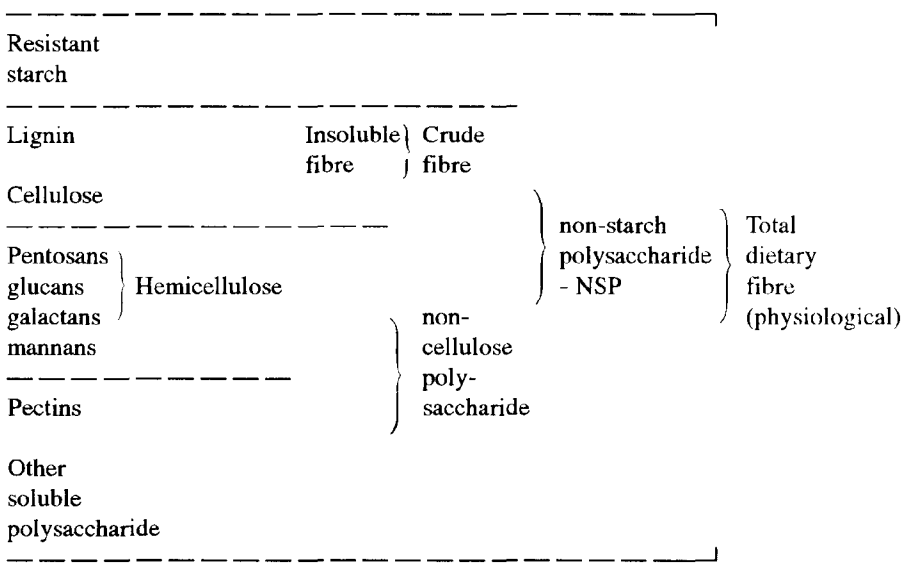


Fig. 15.1—The interrelationship between different *fibre* fractions

digestion and enter the colon. Van Soest (1967) used detergents to fractionate the cell; the acid-detergent fraction (ADF) was essentially crude fibre whilst the neutral detergent fibre (NDF) was essentially the insoluble fibre fraction but omitted the soluble fibre. More modern analytical techniques are based on gravimetric methods (*eg* Prosky *et al*, 1984) which give information on total fibre but no information on the composition of the fibre, or on chemical or colorimetric methods (Southgate, 1969; Englyst *et al*, 1983; Englyst and Kingman, 1990), which are more time consuming but which give detailed information on the relative amounts of the different components of fibre. The interrelationship between the different fibre fractions is illustrated in Fig. 15.1. Fruit fibre is rich in pectins and soluble fibres. Vegetable fibre is rich in hemicellulose and with little crude fibre when the vegetables are young; the proportion of crude fibre increases as the vegetables age. Cereal fibre is largely insoluble, with the hemicellulose *protected* by the cellulose and rendered relatively resistant to digestion by gut bacterial enzymes whereas the fibre from young vegetables is readily digested by the gut bacterial flora.

A key factor in our understanding of dietary fibre has been the realization that a proportion of the starch intake is not digested during small bowel transit and so enters the colon; there it behaves as non-starch polysaccharide. In a study of potato starch Englyst *et al* (1987) demonstrated that the proportion of starch digested during small bowel transit is very high if the potato is well cooked and is consumed hot, but is lower if the potato is less well cooked or if it is allowed to cool before consumption. The amount of starch resisting small bowel digestion is likely to be

very much higher than the amount of dietary fibre, making interpretation of the previous analytical result very equivocal.

The relative digestibility by the colonic bacterial flora of various fibre fractions is illustrated in Table 15.1; vegetable and fruit fibre is almost completely digested during colonic transit whilst wheat bran is largely undegraded.

Table 15.1—Relative degree of degradation of complex carbohydrates during colonic transit

Source	Intake	Subjects	% Digestion
Cellulose	2.2g	Young men	6
Hemicellulose	12.2g	Adults	96
Pectin	5.1g	Adults	96
Vegetable sources			
Carrot	7.8g	Young men	84
Peas	2.4g	Young men	84
Cabbage	6.9g	Young men	80
Ispaghula husk	37.4g	Adults	87
Cereal sources			
Wheatbran	21.4g	Adults	42

15.3 CONTRIBUTION OF PLANT FOOD TO THE TOTAL DIET

In many studies of colon carcinogenesis an attempt to estimate the total fibre intake is made. Table 15.2 illustrates the importance of cereals to the total intake of plant material in European countries. Fruit contributes a relatively small amount, the principal non-cereal sources being green vegetables and potatoes. In Italy and Spain rice is a major contributor to the total cereals whilst in the northern countries the major cereal is wheat, with smaller amounts of oats. In 1972 Robertson estimated the changes in total fibre intake in the UK diet. The figures were calculated from old data and would be based on crude fibre assays; however, they illustrate the changes in intake of the relevant foods with decreases in the staple foods (cereals and potatoes) not compensated for by the increases in fruit and vegetables (Table 15.3). More recent data on the sources of *unavailable carbohydrate* (Table 15.4) illustrate the changes in interpreting old data; Robertson (1972) estimated that only about 12% of the fibre intake was from cereal whereas modern analyses suggest that the true figure would be nearer to 50%. From these two sources it can be seen that (a) currently cereals contribute 45% of the fibre (NSP) and 50% of the unavailable carbohydrate; (b) this figure has fallen to that level steadily during that 100 years except for

periods of war; (c) potatoes currently contribute 10% of the fibre and 9% of the unavailable carbohydrate and this too has steadily decreased during the last century; (d) fruit currently contributes similarly to potatoes to both variables; (e) vegetables, the second major source of carbohydrate to the colon, contribute 30% of the fibre and slightly less of the unavailable carbohydrate in the UK diet.

Table 15.2—The relative contribution of vegetables and cereals to the total intake of complex carbohydrate in a number of European countries (data from BNF, 1990)

Country	Contribution of carbohydrate Intake		% of total energy from carbohydrate
	Cereals	Vegetables*	
Finland	150	45	27
UK	170	60	27
Ireland	190	65	26
Germany	150	45	22
France	165	50	30
Spain	160	70	28
Italy	235	35	32
Turkey	395	85	57

*Includes green and root vegetables, potatoes, pulses and nuts.

15.4
EPIDEMIOLOGICAL STUDIES

Epidemiological studies of the relation between complex carbohydrate intake and malignant or cardiovascular disease can be divided into population or ecological studies, case-control or analytical studies and cohort or prospective studies.

Table 15.3—Changes in the fibre content of the UK diet between 1860 and 1970 (data from Robertson, 1972)

	1860	1880	1910	1938	1942	1944	1957	1970
Potatoes	1.3	1.3	1.0	0.8	1.0	1.2	0.9	0.9
Other vegetables	NA	NA	1.1	1.4	1.4	1.5	1.6	1.6
Fruit and nuts	NA	NA	0.6	1.1	0.8	0.8	1.0	1.1
Cereal products	1.1–2.8	0.9	0.9	0.5	2.1	1.5	0.6	0.5
Total	2.4–4.1	2.2	3.6	3.8	5.3	5.0	4.1	4.1

Table 15.4—The major sources of carbohydrate in the UK diet for 1988; adapted from BNF (1990)

Food group	Starch	Res starch	Total NSP	Unavailable carbohydrate
Bread and flour	65.8	1.0	3.4	6.9
Other cereal products	35.9	0.4	2.2	3.4

Food group	Starch	Res starch	Total NSP	Unavailable carbohydrate
Fruit and fruit products	0.4	0.2	1.3	1.8
Potatoes	18.6	0	1.3	1.8
Other vegetables	10.5	0	3.7	5.9
Total—all foods	138.9	1.6	12.5	21.0

In the ecological studies the diet of populations is determined from WHO statistics and compared with the cancer mortality or incidence rates for those same populations. Such studies have the advantage that large numbers of widely divergent populations can be compared; the major disadvantages are the relative lack of precision of the data, the use of mean diet intakes and the fact that the populations differ in many other respects as well as diet and so are poorly controlled. Nevertheless the studies carried out tend to support strongly the concept of a protective role for cereals (Table 15.5); this is in contrast to the lack of correlation with intakes of fruit and vegetables (Irving and Drasar, 1973; Armstrong and Doll, 1975). However, the problem has been complicated by the perceived need to implicate fibre. In consequence in the first study by Drasar and Irving (1973) all fibre containing foods were considered together (and no correlation was seen). When separate food groups were considered there was an inverse correlation with intake of cereals (−0.30), a positive association with fruit consumption (+0.22) and no association with vegetables, pulses, potatoes etc (Irving and Drasar, 1973). Armstrong and Doll (1975) found a significant inverse correlation between cereal intake and cancer of the colon, breast, corpus uteri and prostate (Table 15.6); when partial regressions were calculated after controlling for the item most strongly correlated (*ie* meat for colon cancer, total fat, corpus uteri and prostate, gross national product for breast) the correlation was no longer significant (as were almost all other dietary correlations). Armstrong and Doll (1975), like Irving and Drasar (1973), found very much weaker correlations for other plant foods and positive correlations for fruits. Liu *et al* (1979) observed a strong inverse correlation with cereal and other sources, which disappeared when they were controlled for cholesterol intake. Similarly the strong protective effect of cereals and pulses observed by Eyssen and Bright-See (1984) was greatly weakened after controlling for fat intake. Dietary items are highly intercorrelated and so a (causal) correlation with item A inevitably leads to (coincidental) correlations with items B and C. The loss of significance observed by Armstrong and Doll (1975), Liu *et al* (1979) etc could therefore suggest that the observed protective effect of cereals was spurious. For this reason it is necessary to search for mechanisms to rationalise any epidemiological observation. Lack of such a mechanism (for example, for the observed correlation between the proportion of persons with television sets and risk of colorectal cancer, observed by Drasar and Irving, 1973) should prompt caution in interpretation of the observed association. This will be dealt with in more detail later.

Table 15.5—Studies of fibre and colon cancer mortality

Study	Fibre source	Correlation coefficient
Irving and Drasar (1974)	Cereals	–0.30
	Vegetables/Potatoes	0.05
	Fruit	+0.22
Armstrong and Doll (1975)	Cereals	–0.70
	Pulses	–0.39
Howell (1975)	Cereals	–0.84
	Pulses	–0.76
Schrauzer (1976)	Cereals	–0.70
Yanai *et al* (1979)	Cereals	–0.50
Eyssen and Bright-See (1984)	Cereals	–0.73
	Pulses	–0.70
Bingham *et al* (1979)	Cereals	–0.96
Malhotra (1977)	Cereals	Protective
Liu *et al* (1979)	Cereals and other fibre sources	–0.77

Table 15.6—Correlation between food group intakes and the incidence or mortality from cancer at various sites (figures in parentheses are partial regressions after controlling for the most highly correlated item)

	Colon incidence	Breast incidence	Endometrium incidence	Prostate mortality
	Males	Females	Females	Males
Cereals	–0.52* (–0.20)	–0.64* (–0.29)	–0.58* (–0.20)	–0.60* (–0.10)
Potatoes	–0.32 (0.06)	–0.39 (–0.08)	–0.24 (0.02)	0.40* (0.22)
Pulses	–0.31 (0.29)	–0.43* (–0.16)	–0.62* (–0.08)	–0.59* (–0.32)
Veg	0.28 (0.06)	0.11 (–0.09)	0.10 (0.07)	o0 (0.03)
Fruit	0.47* (0.38)	0.64* (0.60*)	0.54* (0.49)	0.34 (0.13)
Sugar	0.55* (0.05)	0.70* (0.45*)	0.62* (0.13)	0.63* (0.16)

*Highest correlation seen. Data adapted from Armstrong and Doll, 1975.

A common complaint about the studies cited in Table 15.5 was that they did not have good data with which to calculate fibre intakes. Bingham *et al* (1979) therefore took UK diet data from the National Food Survey and calculated the intake of fibre fractions, using their own food tables; from that they were able to obtain a very high inverse correlation (r=–0.96) between colon cancer mortality and the intake of pentosan (which is mainly from cereal sources). A later and more rigorous assay which totally excluded all starch led to new calculations (Bingham *et al*, 1985) in which the apparent strong protective effect of pentosan-rich fibre (cereal) disappeared to be replaced by a strong protective effect of uronic acid-rich fibre (vegetables). However, with the realization of the importance of

resistant starch (discussed later) this reappraisal may now require its own reappraisal. Eyssen and Bright-See (1984) observed that the inverse correlation with colon cancer was much stronger for intake of cereals than for intakes of cereal fibre. This could suggest that the *active component* of cereal may include other factors in addition to fibre. Alternatively it could illustrate the lack of precision of food tables, especially when comparing foods grown in different climates.

A large number of case-control (analytical) studies have been reported. The main advantage of such an approach is that non-dietary variables can be taken into account, and this should make the results very much more reliable. However, in the case of malignant disease of the intestine, where the onset of symptoms is insidious, a major disadvantage of case-control studies is that, since the symptoms of colon cancer will affect the current diet, recall methods have to be used to determine the diet before the onset of symptoms. Such methods are notoriously inaccurate and it is not surprising that the results from such studies have been highly variable. Thus Potter and McMichael (1986) observed a *positive* correlation with fibre intake in one Australian study whilst in another Kune *et al* (1987) found a strong protective effect. A number of case-control studies in southern Europe have observed a protective effect of vegetables but not of cereals (reviewed by Boutron *et al*, 1991). However Bidoli *et al* (1992) have observed a protective effect of whole grain bread and pasta against colorectal cancer in a case control-study in northeast Italy.

Animal studies have a number of advantages over human experiments, largely related to the degree of control that the experimenter retains. Animals do not normally get colorectal cancer and so they need to be given specific carcinogens. These can therefore be administered at a specified age, and by specified routes. Diet can be closely controlled in terms of amount, composition, timing in relation to pre-or post-carcinogen treatment etc. The length and mode of follow-up can be standardized exactly. Genetically pure strains of animal can be used to control for specific predispositions. In summary, all of the problems associated with the population studies or the case-control experiments can be controlled. Unfortunately there are disadvantages with animal models as well. Because it is a model, you need to know *what* you are modelling and so a set of assumptions is built into the model from the beginning. Table 15.7 illustrates the effect of changing the nature of the initiator or the route of administration or the sex of the animal on the relation between diet and cancer risk. By varying the model bran can appear to give promotion, a protection or no effect; similarly for pectin. In consequence, all results from animal studies must be questioned on the grounds that the criteria used to select which of the models was to be used will have contributed to the determination of which result was obtained.

15.5
MECHANISM OF PROTECTION AGAINST COLORECTAL CANCER

When Burkitt (1971) proposed a role for dietary fibre in protection against colorectal cancer, the postulated mechanism was that:

(a) Fibre causes stool bulking which dilutes luminal carcinogens.
(b) Fibre causes an increased rate of transit through the colon and this decreases the time available for bacterial production of carcinogens and for carcinogen action.
(c) Increased colonic carbohydrate provides nutrients for gut bacteria causing a change in the composition and the metabolic activity of the gut flora and a change in the physicochemical environment in the colon.
(d) Metabolism of complex carbohydrate in the colon results in the production of metabolites (particularly butyrate) with antineoplastic properties.

Table 15.7—The effect of variations in animal models on the relation observed between diet and cancer risk (Hill, 1989)

Rat model used			Type of fibre	Observed effect
Carcinogen	Route	Sex		
Changes in carcinogen				
AOM	Sc	M	Cellulose	None
DMH	Sc	M	Cellulose	Protection
DNU	Sc	F	Pectin	None
AOM	Sc	F	Pectin	Protection
Change in route of administration				
DMH	Sc	M	Cellulose	Protection
DMH	Oral	M	Cellulose	None
DMH	Sc	M	Hemicellulose	None
DMH	Oral	M	Hemicellulose	Protection
DMH	Sc	F	Bran	Promotion
DMH	Oral	F	Bran	None
Change in sex of animal				
DMH	Oral	M	Bran	Protection
DMH	Oral	F	Bran	None
DMH	Sc	M	Bran	None
DMH	Sc	F	Bran	Promotion

Much of this has been investigated and has been reviewed by Hill and Fernandez (1990). The hypothesis was generated before the mechanism for the histopathological sequence was proposed by Hill *et al* (1978); this hypothesis has

been discussed in detail in Chapter 21 of this volume. The postulated mechanisms will be discussed in turn.

(a) *Stool bulking.* Cereal fibre has potent stool bulking properties (Table 15.8) with a 65–70% increase in stool mass being produced by 16 g, 39 g and 54 g of wheat bran in three separate studies of healthy young English males. These each had a direct diluting effect on two types of stool marker compounds—the acid and the neutral steroids. When a very high dose (100 g) of wheat bran was used it produced a trebled stool mass but also caused non-specific washout of all steroids, and so no extra dilution over that achieved by half the amount. Oat bran produces a similar stool bulking effect and a similar dilution of neutral compounds. However, oat bran stimulates faecal loss of bile acids and so, despite the stool bulking, the faecal acid steroid concentration actually increases. Similarly fruit fibre (pectin) offers relatively little stool bulking, but this is more than offset by a non-specific increase in faecal steroid output leading to an increased faecal concentration of all steroids. Of the fibre sources studied only wheat bran and cellulose have the desired effect of decreasing the stool concentration of both acidic and neutral steroids, and of meeting the criteria postulated.

Table 15.8—The effect of cereal and other fibres on stool bulk, and on the faecal concentration of two marker compounds—the acid steroids and the neutral steroids. All figures are expressed as a percentage of the control value

Dietary fibre		Faecal Weight	Acid steroids		Neutral steroids	
Source	Dose	Daily	Conc	Daily	Conc	
Wheat	16g	167	100	60	100	60
	39g	170	104	63	108	64
	54g	165	91	55	97	58
	l00g	300	171	57	168	56
Oat	l00g	230	290	125	–	–
Cellulose	36g	167	100	60	100	60
Pectin	36g	125	146	117	141	113
Sugar cane	10g	167	165	99	100	60
Lignin	10g	110	168	153	–	–

(b) *Rate of transit.* While it is well established that cereal fibre increases the rate of colonic transit, it is not clear that this results in a decreased extent of bacterial metabolism. The lack of linkage between transit time and extent of bacterial metabolism is well documented (Hill and Fernandez, 1990) and could have many possible explanations. The suggested relation between transit and mean contact time is, I believe, falacious and was discussed in detail by Hill (1974). Briefly the *faecal stream* is not continuous; slow transit of faecoliths also implies slow transit of the spaces between faecoliths so that the net contact time with faeces is unchanged.

(c) *Bacterial flora.* The relation between diet and the bacterial flora appears self evident so that when during the 1970s and 1980s, repeated studies failed to detect any effect of fibre on the faecal bacterial flora, it caused considerable concern. Later studies by Fernandez *et al* (1984) and Berghouse *et al* (1984) showed, in contrast, a considerable effect of diet on the flora of ileostomy effluent, indicating that the major site of bacterial metabolism of fibre was the proximal colon. In retrospect this should have been predicted. In the proximal colon the fibre concentration would be maximal and the conditions sufficiently fluid to enable maximal metabolism of any substrate, including fibre. By the time the distal colon and rectum is reached the amount of readily metabolized carbohydrate has been greatly decreased and so its effect on the balance of the flora will have been similarly decreased. This analysis is consistent with the results obtained in canulated pigs by Fadden *et al* (1984). Fermentation of carbohydrate yields volatile fatty acids and this can lead to an acidification of the proximal colon (Bown *et al*, 1974; Pye, 1988). This can be such that putrefactive metabolism may be inhibited and could lead to decreased production of carcinogens and mutagens. This is consistent with the hypothesized mechanism of the protective effect of cereals against colorectal carcinogenesis.

(d) *Anticarcinogenic metabolites.* Much has been made of the possible role of butyrate both as a colonocyte nutrient and as an antineoplastic agent. Carbohydrate is metabolized in the large bowel (particularly in the proximal colon) to volatile fatty acids including butyric acid. Studies by Roediger (1982) showed that butyrate is taken up by colonocytes from the gut lumen in preference to nutrients from the vascular system, and this led to a general belief that butyrate was *good* for the colon. The next phase was the demonstration in cultured colonocytes that butyrate can improve cell differentiation and so should have anticarcinogenic properties (*eg* Gum *et al*, 1987; Kim *et al*, 1980). In contrast, Berry and Paraskevo (1988) while studying markers of progression from adenoma to carcinoma in cultured cell lines, obtained evidence that butyrate can act as a tumour promoter in the colon by favouring growth of malignant clones at the expense of normal tissue. Thus, the evidence from cultured cells is confused; tests in simple systems suggest protection whilst those that attempt relevance to the situation in the large bowel suggest the opposite.

In this situation, studies of patients are relevant. In case-control studies comparing patients with colorectal cancer, or adenomas or controls, if butyrate is protective then colonic butyrate levels should be notably higher in controls than in adenomas; if it is promoting then the levels should be higher in cancer than in adenoma cases. In fact there was a non-significant tendency for both of these when faecal butyrate levels were measured (Table 15.9). However, these levels are the result of differential rates of production and of absorption between the groups; when production rates were assayed there were no differences between the three patient groups ($P = 0.40$). Clearly much more work needs to be done if butyrate is to be shown to be responsible for the protective effect of cereals.

Table 15.9—Concentrations of butyrate in faeces (mmol/litre) of various patient groups on their normal diet and on a high carbohydrate diet (data adapted from Claesen *et al*, 1991).

	Control diet	Rate of butyrate production*	
	Control	Wheat bran	
Control patients	10.9±1.0	1.6±0.2	3.1±0.3
Adenoma patients	8.0±0.9	1.2±0.9	2.2±0.3
Cancer patients	14.6±3.0	1.3±0.2	2.7±0.4
	P=0.07	P=0.40	P=0.18

*Rate of production during 6 hours in a faecal homogenate incubated with and without external substrate.

15.6
DIETARY FIBRE AND BREAST CANCER

Interest in the possible role of cereal fibre in breast carcinogenesis initially arose because of the strong association between breast cancer and colorectal cancer in geographical distribution, and because of the known association between the two cancers in second primaries. In the latter case, a woman who survives a primary breast cancer has an increased risk of a later primary colorectal cancer and *vice versa*. There was initially, however, no obvious mechanism for a role for fibre in breast carcinogenesis as immediately attractive as those proposed by Burkitt for colon carcinogenesis.

The relationship has been studied extensively by Gorbach. He noted that there is considerable evidence of a role for circulating oestrogens in the promotion of oestrogen-dependent breast cancers. The serum levels of oestrogens in vegetarians are much lower than in omnivorous women (Goldin *et al*, 1982), and so is the risk of breast cancer. Gorbach (1984) has postulated that the serum levels of oestrogens are dependent on the enterohepatic circulation of the steroids. This latter is determined by the gut bacterial flora, the composition of which is dependent on diet. In addition Adlercreutz (1990) has proposed that

lignans, which are formed from indigestible plant components by gut bacterial action, have antioestrogenic properties.

There is now a growing body of epidemiological evidence (reviewed by Rose, 1990) of an association between low intake of dietary fibre, particularly cereal fibre, and breast cancer risk. Van't Veer *et al* (1991), in a case-control study, noted that the combination of high fibre and low fat gave good protection against breast cancer. Zaridze *et al* (1991) observed a dose-response relation with high cellulose intake (the only measure of dietary fibre in the report). La Vecchia *et al* (1987) carried out a large case-control study directed to a few selected dietary items; they observed a dose-response related protective effect of whole grain bread or pasta which was not statistically significant. In breast cancer studies it may be important to differentiate between pre- and post-menopausal cases and between oestrogen-dependent and oestrogen-independent cases. On the hypothesis of Gorbach (1984) the post-menopausal oestrogen-dependent tumours are the most likely to exhibit a protective effect of fibre; because of its known effect on the colonic bacterial flora, cereal fibre is more likely than vegetable fibre to be protective.

15.7
CONCLUSIONS

In general consumption of cereals is associated with a lower risk of colorectal and breast cancer in populations living in North America, northern Europe and Australasia. However, unfortunately most groups have concentrated their studies on the dietary fibre component of cereals and, because of analytical difficulties (Leeds, 1992) this has tended to confuse the issue. Future studies should concentrate on food groups rather than on food components. There has been a lot of work in animals testing the *Fibre* theory. Although these models are widely open to misinterpretation (as discussed by Hill, 1989) they tend to support strongly a protective role for wheat bran (but not other vegetable or fruit fibres). Several possible mechanisms of action of fibre in protecting against colorectal cancer have been discussed. These fit cereal fibre much better than other fibre sources; the hypotheses with most support are the effect on carcinogen concentration of stool bulking and the effect on carcinogen production of caecal acidification. Other hypotheses, such as the effect of transit rate and the protective effect of butyrate, remain unsupported *in vivo*.

REFERENCES

Aldercreutz H (1990). Western diet and western diseases: some hormonal and biochemical mechanisms and associations. *Scand J Lab Clin Invest* **50 (Suppl 201):** 3–23.

Aries VC, Crowther JS, Drasar BS, Hill MJ (1969). Degradation of bile salts by human intestinal bacteria. *Gut* **10:** 575–7.

Armstrong B, Doll R (1975). Environmental factors and cancer incidence in different countries, with special reference to dietary practices. *Int J Cancer* **15:** 617–31.

Berghouse L, Hori S, Hill MJ *et al* (1984). Comparison between the bacterial and oligosaccharide content of ileostomy effluent in subjects taking diets rich in refined or unrefined carbohydrate. *Gut* **25:** 1071–77.

Berry RD, Paraskevo C (1988). Expression of CEA by adenoma and carcinoma derived epithelial cell lines: possible markers of tumour progression and modulation of expression by sodium butyrate. *Carcinogenesis* **9:** 447–50.

Bidoli E, Franceschi S, Talamini R, Barra S, La Vecchia C (1992). Food consumption and cancer of the colon and rectum in north east Italy. *Int J Cancer* **50:** 223–9.

Bingham S, Williams DR, Cole TJ, James WPT (1979). Dietary fibre and regional large bowel cancer mortality in Europe. *Br J Cancer* **40:** 456–63.

Bingham S, Williams DR, Cummings JH (1985). Dietary fibre consumption in Britain: new estimates and their relation to large bowel cancer mortality. *Br J Cancer* **52:** 399–402.

Boutron MC, Wilpart M, Faivre J (1991). Diet and colorectal cancer. *Eur J Cancer Prevention* **1 (Suppl 1):** 13–20.

Bown RL, Gibson A, Sladen G *et al* (1974). Effects of lactulose and other laxatives on ileal and colonic pH as measured by a radiotelemetry device. *Gut* **15:** 999– 1004.

British Nutrition Foundation Task Force (1990). Complex Carbohydrates in Foods. BNF.

Bruce WR, McKeown-Eyssen G, Ciampi A, Dion PW, Boyd N (1981). Strategies for dietary intervention studies in colon cancer. *Cancer* **47:** 1121–5.

Burkitt DP (1971). Some neglected leads to cancer causation. JNCI **47:** 913–6.

Claesen MR, Bonnen H, Mortensen PB (1991). Colonic fermentation of dietary fibre to short chain fatty acids in patients with adenomatous polyps and colonic cancer. *Gut* **32:** 923–8.

De Cosse J, Miller HH, Lesser ML (1989). Effect of wheat fiber and vitamins C and E on rectal polyps in patients with familial adenomatous polyposis. *JNCI* **81:** 1290–7.

Drasar BS, Irving D (1973). Environmental factors and cancer of the colon and breast. *Br J Cancer* **27:** 167–72.

Englyst H, Wiggins HS, Cummings JH (1982). Determination of the non-starch polysaccharide in plant foods by gas-liquid chromatography of constituent sugars as alditolacetates. *Analyst* **107:** 307–18.

Englyst H, Cummings JH (1987). Digestion of polysaccharides of potato in the small intestine of man. *Am J Clin Nutr* **45:** 423–31.

Englyst H, Kingsman SM (1990). Dietary fiber and resistant starch. In *Dietary Fiber* (eds Kritchevsky D, Bonfield C, Anderson J).

Eyssen G, Bright-See E (1984). Dietary factors in colon cancer: international relationships. *Nutr Cancer* **6:** 160–70.

Fadden K, Owen R, Hill MJ *et al* (1984). Steroid degradation along the gastrointestinal tract: the use of the canulated pig as a model system. *Trans Biochem Soc* **12:** 1105–6.

Fernandez F, Kennedy H, Hill M, Truelove S (1985). The effect of diet on the bacterial flora of ileostomy fluid. *Microbiol Aliments Nutrition* **3:** 47–52.

Goldin B, Adlercreutz H, Gorbach SL *et al* (1982). Estrogen excretion patterns and plasma levels in vegetarian and omnivorous women. *N Eng J Med* **307:** 1542–7.

Gorbach SL (1984). Estrogens, breast cancer and intestinal flora. *Rev Infect Dis* **6:** 85–90.

Gum JR, Kam WK, Byrd JC *et al* (1987). Effects of sodium butyrate on human colonic adenocarcinoma cells. *J Biol Chem* **262:** 1092–7.

Hill MJ (1974). Colon cancer: a disease of fibre depletion or dietary excess? *Digestion* **11:** 293–306.

Hill MJ (1989). Experimental studies of fat fibre and calories in carcinogenesis. In *Diet and Aetiology of Cancer* (ed Miller AB); Springer, Heidelberg, p. 31–8.

Hill MJ, Drasar BS, Aries VC *et al* (1971). Bacteria and etiology of cancer of large bowel. *Lancet* **1:** 95–100.

Hill MJ, Morson BC, Bussey HJR (1978). Etiology of adenoma-carcinoma sequence in large bowel. *Lancet* **1:** 245–7.

Hill MJ, Fernandez F (1990). Bacterial metabolism, fiber and colorectal cancer. In *Dietary Fiber* (eds Kritchevsky D, Bonfield C, Anderson J); Plenum, New York, p. 417–29.

Howell MA (1975). Diet and an etiological factor in the development of cancers of the colon and rectum. *J Chronic Dis* **28:** 67–80.

Irving D, Drasar BS (1973). Fibre and cancer of the colon. *Br J Cancer* **28:** 462–3.

Kirn YS, Tsao D, Siddigui B *et al* (1980). Effects of sodium butyrate and dimethylsulfoxide on biochemical properties of human colon cancer cells. *Cancer* **45:** 1185–92.

Kinlen L, Hermon C, Smith PG 91983). A proportionate study of cancer mortality among members of a vegetarian society. *Br J Cancer* **48:** 355–61.

Kune S, Kune GA, Watson LF (1987). Case-control study of dietary etiological factors: the Melbourne colorectal cancer study. *Nutr Cancer* **7:** 21–42.

La Vecchia C, De Carli A, Franceschi S *et al* (1987). Dietary factors and risk of breast cancer. *Nutr Cancer* **10:** 205–14.

Leeds AR (1992). Fibre and resistant starch and cancer. In *Public Education on Diet and Cancer* (eds Benito E, Giacosa A, Hill M); Kluwer, Lancaster, pp. 85–90.

Liu K, Moss M, Persky V *et al* (1979). Dietary cholesterol, fat and fibre and colon cancer mortality. *Lancet* **2:** 782–5.

Malhotra SL (1967). Geographic distibution of gastrointestinal cancers in India with special reference to causation. *Gut* **8:** 361–72.

Phillips RL, Garfinkel L, Kuzma J, Beeson WL, Terry L, Brin B (1980). Mortality among California Seventh Day Adventists for selected cancer sites. *JNCI* **65:** 1097–1107.

Potter J, McMichael AJ (1986). Diet and cancer of the colon and rectum. A case-control study. *JNCI* **76:** 557–69.

Prosky L, Asp N, Furda I *et al* (1984). Determination of total dietary fiber in foods, food products and total diets: International study. *JAOAC* **67:** 1044–52.

Pye G (1988). Gastrointestinal pH and colorectal neoplasia. PhD Thesis University of Nottingham.

Robertson J (1972). Changes in the fibre content of the British diet. *Nature* **238:** 290–2.

Roediger W (1982). Utilization of nutrients by isolated epithelial cells of the rat colon. *Gastroenterology* **83:** 424–9.

Rose DP (1990). Dietary fiber and breast cancer. *Nutr Cancer* **13:** 1–8.

Selvendran R, Verne A (1990). The chemistry and properties of plant cell walls and dietary fiber. In *Dietary Fiber* (eds Kritchevsky D, Bonfield C, Anderson J); Plenum, New York, p. 1–13.

Shrauzer GN (1976). Cancer mortality correlation studies. II. Regional associations of mortalities with the consumption of food and other commodities. *Med Hypoth* **2:** 39–49.

Southgate DAT (1969). Determination of carbohydrates in foods. II. Unavailable carbohydrates. *J Sci Food Agric* **20:** 331–5.

Southgate DAT (1976). Determination of food carbohydrates. Applied Science, London.

Van Soest P, Wine RH (1967). Use of detergents in the analysis of fibrous foods. IV. Determination of plant cell wall constituents. *JAOAC* **50:** 50–55.

Van't Veer P, Van Leer E, Rietduk A *et al* (1991). Combination of dietary factors in relation to breast cancer occurrence. *Int J Cancer* **47:** 499–503.

Yanai H, Inaba Y, Takagi H, Yamomoto S (1979). Multivariate analysis of cancer mortalities for selected sites in 24 countries. *Env Hlth Perspect* **32:** 83–101.

Zaridze D, Lifanova Y, Maximovitch D, Day N, Duffy S (1991). Diet, alcohol consumption and reproductive factors in a case-control study of breast cancer in Moscow. *Int J Cancer* **48:** 493–501.

16
Alcohol and cancer in the Mediterranean
S Franceschi

16.1
INTRODUCTION

The identification of Mediterranean countries is often made following different criteria and often coincides substantially with the south of Europe. Geographically speaking, Portugal should, however, be excluded and Albania and other non-EC should be added (Menotti, 1991). Further, there are in-built limitations in the analysis of health problems when national boundaries are taken as reference. The inclusion of France is questionable, since a large part of its territory and population shares the characteristics of central Europe. This is true also for some areas of northern Italy, while the inner parts of Yugoslavia would be better associated with eastern Europe.

These problems are particularly relevant to the assessment of aspects such as dietary habits or, as in the present review, alcohol consumption. For the purpose of this presentation attention will be concentrated on Portugal, Spain, France, Italy, Yugoslavia and Greece. The basic characteristics of these countries, at least until 25– 30 years ago and with the exception of France, include being largely agricultural societies whose industrial and post-industrial development is relatively recent as compared to the countries of central and northern Europe. In respect to alcoholic beverages, features shared by Mediterranean countries are the substantial internal production, chiefly of wine, the tendency towards intermediate-to-high levels of chronic alcohol consumption, mostly during meals and relatively evenly spread across the days of the week, and a wide social acceptance of such drinking pattern even in women and young individuals.

16.2
QUANTITATIVE ASPECTS OF THE PRODUCTION AND CONSUMPTION OF ALCOHOLIC BEVERAGES IN THE MEDITERRANEAN

Commercial production of the three most important alcoholic beverages is shown in Table 16.1 (IARC, 1988). For each beverage the ten largest producing

countries are listed, according to their volume of production in the most recent available year (*ie* 1980 or 1981). It is clear that among the ten largest wine producing countries, which account altogether for 81% of total world production of wine, there are four of the Mediterranean countries considered in this chapter. Greece, which does not appear in Table 16.1, is also a substantial producer of wine and ranks twelfth in the complete

Table 16.1—Commercial production of alcoholic beverages. Ten major producing countries (IARC, 1988)

Wine		Beer		Spirits	
Country	Million hecto-litres	Country	Million hecto-litres	Country	Million hecto-litres
1 Italy	75.0	USA	227.3	USSR	22.0
2 France	69.1	Germany, Federal Republic	93.7	USA	14.9
3 Spain	42.6	USSR	62.9	Japan	6.4
4 USSR	32.2	UK	61.7	Poland	5.3
5 Argentina	23.3	Japan	46.4	Republic of Korea	5.1
6 USA	18.0	Mexico	29.3	UK	4.9
7 Portugal	9.4	Brazil	24.3	Germany, Federal Republic	3.9
8 Romania	7.6	Germany, Democratic Republic	24.1	Spain	3.1
9 Germany, Federal Republic	7.1	Czechoslovakia	23.9	France	2.8
10 Yugoslavia	6.9	Canada	22.7	Germany, Democratic Republic	2.1

list (IARC, 1988). While no Mediterranean country is present among the largest producing countries in respect to beer, Spain and France are eight and ninth, respectively, as far as the production of spirits is concerned (Table 16.1). This relationship between the different types of alcoholic beverages is well reflected in the respective proportion of individual consumption attributable to wine, beer and spirits (not shown) (IARC, 1988).

Trends in per head consumption of commercial alcohol in European countries for the period 1960–85 are considered in Table 16.2. Portugal (13.1/litre per head), Spain (11.8), France (13.3) and Italy (11.6) remain among the European countries which show the heaviest per head intake of alcoholic beverages

overall. It is, however, worth noting that, also on account of the already massive consumption in the 1960s, Mediterranean countries are among the countries where consumption of commercial alcohol and, to an even larger extent, wine (not shown, IARC, 1988) has not increased for the last decade or is even decreased (*eg* France and Italy) (Table 16.2).

As already mentioned, it is important to remember that national consumption data often obscure substantial variation in within-country consumption of alcoholic beverages. This is a feature of several Mediterranean countries whose history and geographical shape include both coastal and continental areas. Italy has been chosen to provide an example of the wide range of alcohol consumption which can be revealed by analysing smaller areas (*ie* regions). Table 16.3 considers the average yearly consumption of wine per family and shows that the ratio between the region with heaviest wine intake (Valle d'Aosta in the north-western part of Italy, 86.4 litres) and the region with lowest consumption (*ie* Sicily, a southern island, 30.0 litre) is 2.9. By and large, substantial amounts of alcohol (*ie*>70 litres per family) are consumed especially in the north-east (Veneto region) and in central Italy (Toscana and Marche) which are also well-known wine-producing areas.

16.2
ALCOHOL AND CANCER IN THE MEDITERRANEAN

Table 16.4 summarises the cancer sites for which a direct association with alcohol intake is well established and indicates the proportion of cancer attributable to alcohol. Alcohol-related cancers tend to be particularly common in southern European countries and this pattern has already been reviewed (Tuyns, 1990; Jensen *et al*, 1990). Briefly, some of the highest incidence and mortality rates for cancer of the upper aero-digestive tract (*ie* oral cavity, pharynx, oesophagus and larynx) in European men are found in southern European countries where the production and consumption of wine has traditionally been high: France, Italy and Portugal, in addition to other European countries such as Luxembourg and Germany (Levi *et al*, 1989; Jensen *et al*, 1990). The range of variation of incidence and mortality rates for cancers of the upper aero-digestive tract is narrower among European women than men and the geographic pattern is also different, partly on account of substantially lower alcohol consumption in females than males in southern European countries and partly because the prevalence of smoking, the other dominating risk factor for these neoplasms, is higher in women in northern and central Europe. In fact, the geographic pattern of cancers of the upper aerodigestive tract in women resembles that of cancer of the lung (Jensen *et al*, 1990).

Table 16.2—Consumption of commercial alcohol (as ethanol) per head Europe. 1960–1985 (IARC, 1988)

Country	Ethanol (litres per head)			
1960	1970	1977	1985	
Albania	–	0.6	0.6	–
Austria	8.7	11.9	11.5	9.9
Belgium	6.4	8.9	10.1	10.5
Bulgaria	3.8	7.2	–	8.7
Czechoslovakia	5.5	9.1	9.9	9.1
Denmark	4.2	6.3	8.8	9.9
Faröe Islands	–	2.5	3.8	–
Finland	1.8	4.5	6.9	6.5
France	17.3	19.6	17.3	13.3
German, Democratic Republic	4.6	6.3	9.1	10.3
German, Federal Republic	6.9	11.2	12.2	10.8
Greece	–	5.9	6.3	–
Hungary	6.2	10.1	13.6	11.5
Iceland	1.7	2.7	3.2	4.0
Ireland	3.4	4.2	5.8	6.2
Italy	12.2	14.5	12.4	11.6
Luxembourg	8.3	10.2	14.4	13.0
Malta	–	2.3	3.3	–
The Netherlands	2.5	5.7	8.9	8.5
Norway	2.6	3.6	4.5	4.1
Poland	3.8	5.1	8.2	7.0
Portugal	10.4	9.9	14.0	13.1
Romania	4.1	6.3	–	–
Spain	10.3	11.3	12.8	11.8
Sweden	3.7	5.6	6.0	5.0
Switzerland	9.8	10.5	10.6	11.2
United Kingdom	5.1	5.2	6.8	7.1
Yugoslavia	4.7	7.6	6.9	7.7

Table 16.3—Wine consumption in Italian regions per year per family (ISTAT, 1991)

Region	Wine (litres)
Piemonte	66.0
Valle d'Aosta	86.4
Lombardia	62.4
Trentino-Alto Adige	42.0
Veneto	78.0

Region	Wine (litres)
Friuli-Venezia Giulia	63.6
Liguria	56.4
Emilia-Romagna	61.2
Toscana	79.2
Umbria	58.8
Marche	76.8
Lazio	60.0
Abruzzo	51.6
Molise	67.2
Campania	45.6
Puglia	58.8
Basilicata	44.4
Calabria	40.8
Sicilia	30.0
Sardegna	39.6
ITALY	57.6
NORTH-CENTRE	66.0
SOUTH	44.4

Table 16.4—Cancer and alcohol

Causally-related sites	Proportion attributable to alcohol
Oral cavity	(>85%)
Pharynx	(>85%)
Oesophagus	(>85%)
Larynx	(>75%)
Liver	(>70%)

Liver cancer is an uncommon disease in most European countries. The southern part of Europe, however, has higher rates, with a maximum in Spain. The pattern in men and women is similar, with marginally higher occurrence in men (Levi *et al*, 1989; Jensen *et al*, 1990). Differences in diagnosis and classification of the cause of death between European countries may have an important influence on the observed pattern, since in relatively less medically developed countries liver cancer rates are likely to be inflated by the inclusion of liver metastases (Jensen *et al*, 1990).

Interestingly, although cancers of the upper aero-digestive tract and the liver are similarly alcohol-related, their distribution patterns in Europe do not overlap. The high rates of liver cancer, at least in some Mediterranean countries, have been suggested to be associated with chronic hepatitis B infection (Trichopoulos

et al, 1978). Indeed, a descriptive analysis of the features of mortality from liver cirrhosis (a disease very close epidemiologically to liver cancer) in Italy suggests that it is made up of two components which are characterized by different age trends (Capocaccia and Farchi, 1988). It appears that only one of these components is associated with the consumption of alcohol. For males, this is 40% (47% for the north, 30% for central Italy, and 33% for the south/islands). For females, the average is 25% (37% for the north, 16% for central Italy and 12% for the south/islands) (Capocaccia and Farchi, 1988).

16.3 SPECIAL RESEARCH OPPORTUNITIES ON ALCOHOL-RELATED CANCER IN THE MEDITERRANEAN

On account of the high alcohol intake and social acceptability of alcohol drinking in the Mediterranean, and of a few specific characteristics of drinking patterns in this area (*eg* long-term heavy drinking rather than *binges*; wine predominance, etc), present and future epidemiological data from Mediterranean countries offer a special opportunity to explore further several open issues concerning the relationship between alcohol and cancer.

The effect of alcohol in nonsmokers: In Mediterranean countries the search for heavy drinkers who are not, at the same time, heavy smokers is relatively more successful than elsewhere. Table 16.5 considers the risk of oral and pharyngeal cancer (Talamini *et al*, 1990) related to alcohol among nonsmokers. There was a significant trend toward increasing risk with increasing alcohol consumption. Whereas among males no difference was seen between abstainers and moderate drinkers, among females an elevated risk emerged also for those who drank fewer than 14 drinks per week. Overall, ORs for 1–14 and>56 drinks per week were 1.5 and 2.2, respectively. Twenty-one out of twenty-five nonsmoking cases and 298/519 nonsmoking controls who described themselves as drinkers reported drinking only wine. All cases and 98 % of controls said they drank wine predominantly.

These results on the effect of alcohol in 27 lifetime nonsmoking cases of oral and pharyngeal cancer and 572 nonsmoking (Talamini *et al*, 1990) controls represents a contribution to a debate which is still open. Owing to insufficient numbers of non-smoker cancer cases, in many previous investigations nonsmokers and light smokers (*ie*<10 cigarettes per day) had to be combined (Graham *et al*, 1977; Olsen *et al*, 1985; De Stefani *et al*, 1988; Merletti *et al*, 1989) thus making it difficult to interpret the 2- to 20-fold increased risk of oral and pharyngeal cancer in those individuals who reported variously defined heavy alcohol consumption.

Table 16.5—Alcohol and cancer of the oral cavity/pharynx in nonsmokers. Northern Italy (Talamini *et al*, 1990)

Alcohol (drinks/wk)	Males		Females		Odds ratio* (95% CI)
cases	controls	cases	controls		
0	1	27	1	97	1+
<14	–	28	9	70	
14–55	3	191	11	115	1.5 (0.6–3.7)
>55	2	42	–	2	2.2 (0.2–27.9)
					4.08 (*P*=0.04)

*Mantel Haenszel estimates and 95% confidence interval (CI) adjusted for age and sex;
+reference category.

Among those investigators who had been able to report on alcohol-related risk in strictly defined nonsmokers, Wynder *et al* (1957) found no difference in drinking habits among 16 cases of cancer of the oral cavity and pharynx and nine controls who did not smoke, while an approximate doubling of risk was seen by Rothman and Keller (1972) and Elwood *et al* (1984) among nonsmokers who consumed approximately 300 grams of alcohol per week. Also Tuyns *et al* (1988) in a large study which showed an effect of alcohol on pharyngeal cancer risk across all strata of smoking habits, were able to report on only 9 cases of lifetime nonsmokers with tumours of the hypopharynx or epilarynx (and in whom they found higher alcohol consumption than among controls). Blot *et al* (1988) observed a trend toward increasing risk with drinking among 50 nonsmoking male cases of oral and pharyngeal cancer (OR for>=30 drinks per week=5.8). Their suggestion that lower risks may be associated with intake of wine compared to liquor or beer are, however, not supported by the Italian study in which, at variance with the US data, virtually all drinkers drank wine predominantly and two thirds drank wine only.

Table 16.6 shows the effect of alcohol consumption on risk of cancer of the oesophagus in nonsmokers (La Vecchia and Negri, 1989). There was no difference in risk between abstainers and moderate drinkers (<4 drinks per day, about 50 g of pure ethanol, combined in Table 16.4 in the reference category in order to give more stable estimates) but the risk increased markedly for higher levels of alcohol consumption. The point estimates were 2.1 for 4 to 8 drinks per day and 3.6 for over 8 drinks per day, with a clear dose-effect relation and a significant trend in risk (P= 0.01). These results (La Vecchia and Negri, 1989) therefore confirm the findings of a study from Calvados, France (Tuyns, 1983), which included a sufficient number of nonsmokers to show a substantial effect of alcohol alone, but in which the number of non-drinking smokers (11 males) was probably too small to provide reliable estimates for tobacco alone.

Table 16.6—Alcohol and cancer of the oesophagus in nonsmokers. Northern Italy (La Vecchia and Negri, 1989)

Alcohol (drinks/wk)	Males		Females		Odds ratio* (95% CI)
cases	controls	cases	controls		
0	2	26	8	77	1+
<28	3	90	14	114	
28–55	3	66	4	9	2.1 (0.8–5.3)
–55	3	21	1	1	3.6 (0.9–13.6)
					6.09 (*P*=0.01)

*Mantel Haenszel estimates and 95% confidence interval (CI) adjusted for age and sex;+ reference category.

Finally, in order to further confirm the independent effect of alcohol in upper digestive tract carcinogenesis, it is worth noting that the ORs for alcohol in nonsmokers (Talamini *et al*, 1990; La Vecchia and Negri, 1989) were very similar to those emerging from the overall data set, after adjustment for smoking and drinking habits, respectively (Franceschi *et al*, 1990). In conclusion, especially in data from the Mediterranean area, tobacco does not seem to be a requisite cofactor for alcohol-related cancers.

The effect of wine as compared to other alcoholic beverages: Wine, in contrast to the situation in northern European and North American countries, is cheap in Mediterranean countries and therefore represents by far the chief source of alcohol-intake in light as well as heavy drinkers. Table 16.7 shows the distribution of oral and pharyngeal cancers and controls according to different drinking patterns (Barra *et al*, 1990). Moderate drinkers (*ie*<55 drinks/week) did not show a significant elevation of cancer risk regardless of which type(s) of alcoholic beverage they consumed. Increased ORs clearly emerged in heavy and very heavy (*ie*>84 drinks/week) drinkers which, although ranging from 4.1 for drinkers of a combination of wine, beer and spirits to 11.2 for drinkers of wine only, were not statistically heterogeneous.

Table 16.7—Cancer of the oral cavity and pharynx and type(s) of alcoholic beverage. Northern Italy (Barra *et al*, 1991)

Type(s) of beverage	Odds ratio*+ Alcohol (drinks/wk)		
–55	56–83	–84	
Wine only	1.9	4.00	11.2
Wine and beer	0.7	3.9	7.4
Wine and spirits	1.1	3.5	9.9
Beer only			
Spirits only		0.8	
Beer and Spririts			

Type(s) of beverage	Odds ratio*+ Alcohol (drinks/wk)		
–55	56–83	–84	
All three	0.8	1.8	4.1

*Estimates from multiple logistic regression equations including terms for age, area of residence, occupation, smoking and drinking habits; +seventeen cases and 386 controls who were abstainer or drinker of>=20 glasses of wine/week were used as reference category.

A very similar risk pattern emerged as concerns cancer of the oesophagus, where ORs for moderate drinkers tended to be low (1.7 to 2.5) and either non-significant or of borderline statistical significance. The elevation of ORs in heavy and very heavy drinkers (ORs from 6.0 to 15.0) appeared also to be substantially independent of the type(s) of alcoholic beverage habitually consumed. The aforementioned tendency of individuals who reported only consumption of wine to show higher risk increases as compared to individuals who consumed combinations of alcoholic beverages was seen in oesophageal cancer as well (Table 16.8). Since wine consumption was very common in the present series and virtually no heavy or very heavy drinkers described themselves as consumers of beer and/or spirit only, such categories had to be grouped both for oral and pharyngeal cancer and oesophageal cancer, thus providing an estimate of risk which did not compare well with the others.

Table 16.8—Cancer of the oesophagus and type(s) of alcoholic beverage. Northern Italy (Barra *et al*, 1991)

Type(s) of beverage	Odds ratio*+ Alcohol (drinks/wk)		
–55	56–83	–84	
Wine only	1.7	5.4	15.0
Wine and beer	1.8	4.3	4.3
Wine and spirits	1.8	3.6	10.0
Beer only			
Spirits only		1.6	
Beer and Spririts			
All three	2.5	5.0	6.0

*Estimates from multiple logistic regression equations including terms for age, area of residence, occupation, smoking and drinking habits; +thirty-five cases and 386 controls who were abstainers or drinkers of<=20 glasses of wine/week were used as reference category.

Some studies have attempted to estimate the effect of specific beverages on the upper digestive tract. The results of these studies are in agreement with the possibility that all types of beverages contribute to cancer risk in proportion of their alcoholic content. A predominant role of spirits in oral, pharyngeal and

oesophageal cancer causation has, however, emerged in some instances. Wynder *et al* (1957) reported higher relative risks for oral cancer among whisky drinkers when compared to beer and/or wine drinkers. They failed, however, to find very heavy drinkers among individuals who abstained from whisky. Higher proportions of drinkers of whisky, beer or combinations of these, but not of wine only, were found among cases of cancer of the oral cavity and pharynx by Keller and Terris (1965) in a case-control study in New York City. Williams and Horm (1977) found similar risk estimates in alcohol drinkers, regardless of the type of beverage, in the United States Third National Survey, while Kabat and Wynder (1989) reported increased risks only in drinkers of beer and whisky. In a large population-based study of oral and pharyngeal cancer conducted in four areas of the US, the trends were strongest for consumption of beer and spirits and persisted after adjustment of one for the other. Conversely, there was little or no excess risk for wine drinkers of up to 5 drinks/day.

In a cohort of Danish brewery workers, beer appeared to exert the strongest effect on causation of oesophageal cancer (Jensen, 1979). Similar suggestions concerning a predominant effect of beer came also from the United States (Mashbert *et al*, 1981; Mettlin *et al*, 1981; Graham *et al*, 1990) and South Africa (Segal *et al*, 1988). In an area of northern France with very high cider intake, Tuyns *et al*, (1977, 1979) reported the specific role played by cider and apple jack (distillates of apple cider) in the aetiology of oesophageal cancer. However, in the same country, no significant increases in risk for the oral cavity and pharynx were reported by Leclerc *et al* (1987) for any alcoholic beverage, including cider. In Latin American countries, Martinez (1969) and De Stefani *et al* (1988) found no differences in the deleterious effect of red wine, beer and hard liquors on the causation of oral and pharyngeal cancer.

According to the data in Tables 16.7 and 16.8, ORs both for cancer of the oral cavity and pharynx and for oesophageal cancer tended to be lower, alcohol intake being equal, in those individuals who described themselves as habitual drinkers of two or three types of alcoholic beverage, as compared to drinkers of wine only (Barra *et al*, 1990). Such heterogeneity, however, in addition to not being statistically significant, can probably be explained by the tendency of self-reports to underestimate alcohol intake, particularly at high levels of consumption (Boland and Roizen, 1973). Futhermore, as shown by questionnaire-based dietary studies (Pietinen *et al*, 1988) as well as investigations on smokers who used a variety of kinds of tobacco (Doll and Peto, 1976), the possibility of reporting different sources of the relevant exposure (*eg* wine, beer and/or spirits) may well have reduced the phenomenon of under-reporting among drinkers of combinations of alcoholic beverages compared to drinkers of wine only.

In conclusion, the results from the aforementioned study (Barra *et al*, 1990) from the northern part of Italy, an area with very high wine intake, confirm that wine *per se* can cause very large excesses of tumours of the oral cavity, pharynx and oesophagus. It appears, therefore, from this and previous studies, that the most

frequently used alcoholic beverage in each area tends to emerge, in turn, as the most important determinant of upper digestive tract tumours. In fact, heavy and very heavy drinkers who avoid the consumption of the locally commonest (and consequently cheapest) alcoholic beverages are extremely rare. This suggests that all the various types of alcoholic beverage are carcinogenic and that the apparent differences in the risk estimates of each single study are partly or totally due to different levels and/or socio-cultural correlates of drinking patterns in various populations.

Other opportunities of assessment of the (still little understood) qualitative aspects of the relationship between alcohol intake and cancer onset, which are offered especially by Mediterranean countries, include the study of potential differences in the adverse impact of alcohol according to whether it is drunk only during meals or between meals as well. The interaction of alcohol with dietary habits can also be better elucidated. In fact, Mediterranean countries show a wide range of food consumption habits, ranging from the so called *Mediterranean diet*, in which intake of fresh fruit and vegetables and starch is very high (Ferro-Luzzi and Sette, 1989) to various degrees of dietary habits closer to those of central and northern Europe.

16.4 CONCLUSIONS

Two major conclusions can be drawn from the present review of alcohol consumption patterns and occurrence of selected alcohol-related cancers in the Mediterranean. The first, relevant to Mediterranean countries themselves, is that the incidence and mortality of alcohol-related cancers is greater in these countries than in most other industrialized countries. If the classical estimate of the proportion of alcohol-attributable cancer provided by Doll and Peto (1981) for the United States is taken as reference, it is essential to appreciate that such proportions have to be multiplied at least by three in order to reflect the situation of South Europe. A careful attempt to estimate the number of deaths due to alcohol drinking in France (Pignon and Hill, 1991) reached the conclusion that 9% of the overall mortality (3% in women and 15% in men) was attributable to alcohol. In respect to cancer deaths, such proportions were 19% in males and 3% in females (Pignon and Hill, 1991).

There are, indeed, variations in the excess observed both between- and within-Mediterranean countries, but overall the burden of disease and death stemming from alcohol drinking is heavier, from a public health viewpoint, than commonly appreciated. The situation may be further aggravated if the shift to a more international drinking pattern would imply, for at least substantial subsets of younger generations of women and men, an increase in habitual consumption of beer and spirits in excess of the reduction of wine intake.

The second conclusion is relevant to Europe as a whole. In spite of the purported and, at least partly, well documented advantages of *Mediterranean*

diet, more attention must be paid to the issue of alcohol consumption within the European Community. In this respect the situation of Mediterranean countries is not as favourable as in other dietary habits. The most effective way to reduce alcohol consumption is to raise prices (Dillner, 1991). To this extent the harm associated with alcohol is a job for politicians at least as much as for health professionals. The concern that price increases would not touch *addicts* was refuted by a study which showed that an increase in price led heavy drinkers to reduce their consumption as much as light drinkers (Dillner, 1991).

At present, however, a threat to the level of alcohol consumption comes from the European Community. All member countries are committed to the harmonization of duty within the single market. This, however, will entail, besides the probable favourable effects in respect to several Mediterranean healthy foods, a fall in the retail prices of most alcoholic beverages in north European countries. It is, therefore, essential that the European Community reconcile its policy to the target of the World Health Organization Health for All by Year 2000, which recommends *significant decrease in health damaging behaviours such as the use of alcohol*.

ACKNOWLEDGEMENTS

This work was conducted within the framework of the CNR (Italian National Research Council) Applied Project *Clinical Application of Oncological Research* and with the contribution of the Italian Association for Research on Cancer and the Italian League against Tumours. We thank Dr Anna E Baron for her useful suggestions and Mrs Ilaria Calderan for editorial assistance.

REFERENCES

Barra S, Franceschi S, Negri E, Talamini R, La Vecchia C (1990). Type of alcoholic beverage and cancer of the oral cavity, pharynx and oesophagus in an Italian area with high wine consumption. *Int J Cancer* **46:** 1017–20.

Blot WJ, McLaughlin JK, Winn DM *et al* (1988). Smoking and drinking in relation to oral and pharyngeal cancer. *Cancer Res* **48;** 3282–7.

Boland B, Roizen R (1973). Sales slips and survey responses: new data on the reliability of survey consumption measures. *Drinking Drug Pract Surv* **8:** 5–10.

Capocaccia R, Farchi G (1988). Mortality from liver cirrhosis in Italy: proportion associated with consumption of alcohol. *J Clin Epidemiol* **41:** 347–57.

De Stefani E, Correa P, Oreggia F *et al* (1988). Black tobacco, wine and maté in oropharyngeal cancer. A case-control study from Uruguay. *Rev Epidémiol Santé Publique* **36:** 389–94.

Dilner L (1991). Alcohol abuse, *Br Med J* **302:** 859–60.

Doll R, Peto R (1976). Mortality in relation to smoking: 20 years observation on male British doctors. *Br Med J* **2:** 1525–36.

Doll R, Peto R (1981). The causes of cancer. *J Natl Cancer Inst* **66:** 1191–308.

Elwood JM, Pearson JCG, Skippen DH, Jackson SM (1984). Alcohol, smoking, social and occupational factors in the aetiology of cancer of the oral cavity, pharynx and larynx. *Int J Cancer* **34:** 603–12.

Ferro-Luzzi A, Sette S (1989). The Mediterranean diet: an attempt to define its present and past composition. *Eur J Clin Nurition* **43:** 13–29.

Franceschi S, Talamini R, Barra S *et al* (1990). Smoking and drinking in relation to cancers of the oral cavity, pharynx, larynx and esophagus in northern Italy. *Cancer Res* **50:** 6502–7.

Graham S, Dayal H, Rohrer T *et al* (1977). Dentition, diet, tobacco and alcohol in the epidemiology of oral cancer. *J Natl Cancer Inst* **59:** 1611–8.

Graham S, Marshall J, Haughey B *et al* (1990). Nutritional epidemiology of cancer of the esophagus. *Am J Epidemiol* **131:** 454–67.

International Agency for Research on Cancer (1988). *Alcohol Drinking.* IARC Monographs **44:** Lyon.

ISTAT (1991). Le regioni in cifre. Rome.

Jensen OM (1979). Cancer morbidity and causes of death among Danish brewery workers. *Int J Cancer* **23:** 454–63.

Jensen OM, Estéve J, Moller H, Renard H (1990). Cancer in the European Comunity and its member States. *Eur J Cancer* **26:** 1167–256.

Kabat GC, Wynder EL (1989). Type of alcoholic beverage and oral cancer, *Int J Cancer* **43:** 190–4.

Keller AZ, Terris M (1965). The association of alcohol and tobacco with cancer of the mouth and pharynx. *Am J Publ Health* **55:** 1578–85.

La Vecchia C, Negri E (1989). The role of alcohol in oesophageal cancer in non-smokers and tobacco in non-drinkers. *Int J Cancer* **43:** 784–5.

Leclerc A, Brugère J, Luce D, Point D, Guenel P (1987). Type of alcoholic beverage and cancer of the upper respiratory and digestive tract. *Eur J Cancer Clin Oncol* **23:** 529–34.

Levi F, Maisonneuve P, Filiberti R, La Vecchia C, Boyle P (1989). Cancer Incidence and Mortality in Europe. *Soz Praeventivmed* **34 (Suppl 2):** S1–S84.

Martinez I (1969). Factors associated with cancer of the esophagus, mouth, and pharynx in Puerto Rico. *J Natl Cancer Inst* **42:** 1069–94.

Mashberg A, Garfinkel L, Harris S (1981). Alcohol as a primary risk factor in oral squamous carcinoma. *CA* **31:** 146–55.

Menotti A (1991). Food patterns and health problems: health in southern Europe. *Ann Nutr Metab* **35 (Suppl 1):** 69–77.

Merletti F, Boffetta P, Ciccone G, Mashberg A Terracini B (1989). Role of tobacco and alcoholic beverages in the etiology of cancer of the oral cavity/oropharynx in Torino, Italy. *Cancer Res* **49:** 4919–24.

Mettlin C, Graham S, Priore R, Marshal J, Swanson M (1981). Diet and cancer of the esophagus. *Nutr Cancer* **2:** 143–7.

Olsen J, Sabroe S, Ipsen J (1985). Effect of combined alcohol and tobacco exposure on risk of cancer of the hypopharynx. *J Epidem Community Health* **39:** 304–7.

Pietinen P, Hartman AM, Haapa E *et al* (1988). Reproducibility and validity of dietary assessment instruments. *Am J Epidemiol* **128:** 655–76.

Pignon JP, Hill C (1991). Nombre de décès attributable à 1'alcool, en France, en 1985. *Gastroenterol Clin Biol* **15:** 51–6.

Rothman K, Keller A (1972). The effect of joint exposure to alcohol and tobacco on risk of cancer of the mouth and pharynx. *J Chronic Dis* **25:** 711–6.

Segal I, Reinach SG, deBeer M (1988). Factors associated with oesophageal cancer in Soweto, South Africa. *Br J Cancer* **58:** 681–6.

Talamini R, Franceschi S, Barra S, La Vecchia C (1990). The role of alcohol in oral and pharyngeal cancer in non-smokers and of tobacco in non-drinkers. *Int J Cancer* **46:** 391–3.

Trichopoulos D, Tabor E, Gerety RJ *et al* (1978). Hepatitis B and primary hepatocellular carcinoma in a European population. *Lancet* **ii:** 1217–9.

Tuyns AJ, Péquignot G, Jensen OM (1977). Le cancer de 1'oesophage en Ille-et-Vilaine en fonction des niveaux de consommation d'alcool et de tabac. Des risques qui se multiplient. *Bull Cancer* **64:** 45–60.

Tuyns AJ, Péquignot G, Abbatucci JS (1979). Oesophageal cancer and alcohol consumption; importance of type of beverage. *Int J Cancer* **23:** 443–7.

Tuyns AJ (1983). Oesophageal cancer in non-smoking drinkers and in non drinking smokers. *Int J Cancer* **32:** 443–4.

Tuyns AJ, Estève J, Raymond L *et al* (1988). Cancer of the larynx/hypopharynx, tobacco and alcohol: IARC International case-control study in Turin and Varese (Italy), Zaragoza and Navarra (Spain), Geneva (Switzerland) and Calvados (France) . *Int J Cancer* **41:** 483–91.

Tuyns AJ (1990). Alcohol-related cancers in Mediterranean countries. *Tumori* **76:** 315–20.

Wynder EL, Bross IJ, Feldman RM (1957). A study of etiolgoical factors in cancer of the mouth. *Cancer* **10:** 1300–23.

Williams RR, Horm JW (1977). Association of cancer sites with tobacco and alcohol consumption and socioeconomic status of patients: inteview study from the Third National Cancer Survey. *J Natl Cancer Inst* **58:** 525–47.

17
The role of vegetables and fruit in cancer risk

E Negri, B D'Avanzo, A Tavani

17.1
INTRODUCTION

The consumption of high amounts of fresh and raw vegetables and fruit and of low amounts of proteins and fats has been associated with lower risk of cancer and other important diseases, including cardiovascular diseases. In various ecological studies, populations consuming less vegetables and fruit are from high risk areas for cancers of the oesophagus (Iran, Japan and others), stomach (Poland) and colon (Great Britain and North America) and those consuming high amounts of fats and proteins have high incidence of colon and breast cancer (Doll and Peto, 1981).

As reported in a comprehensive review by Steinmetz and Potter (1991), results from analytical studies are in the same direction, although the relationship between diet and cancer is difficult to detect and the evidence is not always consistent. However, several studies report inverse associations between vegetable consumption and various cancer sites, and to a smaller extent, between fruit consumption and cancer. Analytical studies most commonly showed inverse associations between cancer and consumption of tomatoes, soy products, legumes and green and yellow vegetables (*ie* carrots, spinach, pumpkin, green peppers, green lettuce, chives, green leeks, turnip leaves, chicory, parsley and green asparagus, broccoli and brussel sprouts) (Table 17.1). Vegetable consumption appears to protect from most common epithelial cancers, whereas the protection conveyed by fruit is apparently limited to the upper digestive and respiratory tract.

A summary of the epidemiological evidence related to several specific cancer sites derived from Steinmetz and Potter (1991) is given in the following section.

Table 17.1—Case-control studies reporting negative associations between vegetable and fruit consumption and risk of cancer*

Type of vegetable and fruit	Total number of studies	Studies showing negative associations	
No	No	%	
Raw or fresh vegetables	15	13	87
Leafy green vegetables	43	32	74
Cruciferous vegetables	24	17	71
Carrots	34	27	79
Broccoli	10	7	70
Cabbage	19	12	63
Lettuce	18	15	83
Raw or fresh fruit	18	11	61
Citrus fruit	17	12	71

*Modified from K A Steinmetz, J D Potter, 1991.

17.2
ASSOCIATIONS BETWEEN FOODS AND SPECIFIC CANCER SITES

Risk of *mouth and pharynx* cancers is approximately halved by consumption of fresh fruit. Citrus fruit, dark yellow fruit and green leafy vegetables appear to be protective possibly because of their high content of vitamins A and C and other micronutrients. Fruit and vegetables have been shown to be protective also in the presence of other risk factors for cancers of the upper digestive tract (mainly alcohol and tobacco) and the inverse associations remained after adjustment for major confounding factors, such as alcohol and smoking, often associated with a poor diet.

For cancer of the *oesophagus* the relative risk seems to be inversely related to both green vegetables and fruit intake. In a study from Iran (Cook-Mozaffari *et al*, 1979) where, as in China and some parts of USSR, oesophageal cancer is highly correlated to life style habits other than smoking and alcohol, a protective association was observed for several types of fruits and vegetables. Vitamin C has been indicated as the protective agent, although a higher consumption of fruit has often been associated with a higher consumption of milk and meat, suggesting that a more affluent diet may be responsible for the protection. In a study from Italy the combination of a low intake of fresh vegetables and fruit with alcohol and tobacco consumption substantially increased the risk of oesophageal cancer (Negri *et al*, 1992) (Table 17.2).

For cancer of the *stomach* the strong declines in mortality registered in most countries in the last fifty years are almost certainly due to dietary improvements,

including increased consumption of vegetables and fruit, besides better food storage and preservation (La Vecchia *et al*, 1990). Fruit and some vegetables, such as lettuce, onions, tomatoes, celery and squash, have been associated with decreased risk of stomach cancer. Vegetables and fruit consumed raw, rather than cooked or preserved, seem to be particularly protective.

Table 17.2—Relative risks for combinations of consumption of alcohol, tobacco and of low level of beta-carotene for oesophageal cancer. Italy, 1983–91*

Alcohol	Tobacco	ß-carotene (low level of intake)	Relative risks
No	No	No	1
No	No	Yes	2.5
Yes	No	Yes	9.0
No	Yes	Yes	10.9
Yes	Yes	Yes	38.6

*Modified from E Negri *et al*, 1991.

Cruciferous and fibre-rich vegetables probably protect against *colon* cancer. Little relation emerges with fruit and there is some suggestion of a positive association with consumption of legumes. Similar associations have been reported for *rectal* cancer, although data from published studies appear less consistent.

For *pancreatic* cancer, carrots, fruit and cruciferous vegetables have been often related to a decrease in risk, although risk estimates are often modest and not significant.

The evidence of a lower risk of cancer of the *larynx* for high intake of vegetable is not particularly strong, but fruit appears to convey an appreciable protection as for other upper digestive and respiratory tract neoplasms. Cohort and case-control studies show that consumption of carrots and green leafy vegetables, both rich in sources of beta-carotene, are protective against *lung* cancer.

A diet poor in fresh vegetables and fruit, and probably also in several other foods and nutrients, has been linked to increased risk of primary *liver* cancer.

Risk of *cutaneous melanoma* seems to be reduced by high consumption of lettuce, yellow squash, tomatoes and carrots.

Studies from Greece and Italy (Katsouyanni *et al*, 1986; La Vecchia *et al*, 1987) have observed a protective effect on *breast* cancer provided by green vegetables. Risk of cancer of the *cervix uteri* is lowered by high intake of carrots, green vegetables and vegetables rich in beta-carotene, while the association with other vegetables and fruit is not very consistent. For *ovarian* and *endometrial* cancers a positive association with intake of fruit and a negative one with green vegetables has been observed.

Green vegetables and carrots, more clearly than fruit, are protective against *bladder* cancer. Less consistent information is available for risk of cancer of the

kidney, which has been, however, directly related to a low intake of green vegetables.

Scanty information is available on dietary correlates of *prostatic* cancer but the few analytical studies suggest a potential protection of fruit.

Consumption of cruciferous vegetables and fresh fruit has been related to reduce risk of *thyroid* cancer in an Italian study (Franceschi *et al*, 1990), although the mechanism of the protective action is not clear. A study from the United States suggested a protection from cabbage, brussell sprouts, cauliflower, broccoli and potatoes (Ron *et al*, 1987).

There is no evidence, in contrast, of any protective effect of fruit or vegetables against *lymphomas, myeloma* or other lympho-related neoplasms.

17.3 RESULTS FROM AN ITALIAN NETWORK OF CASE-CONTROL STUDIES

Data from a network of case-control studies conducted in Italy in the period 1983–90 in the Greater Milan area have been analysed in order to examine the relationship between cancer risk and frequency of consumption of green vegetables and fruit (Negri *et al*, 1991). The cancer sites under study were oral cavity and pharynx, oesophagus, stomach, colon, rectum, liver, gallbladder, pancreas, larynx, breast, endometrium, ovary, prostate, bladder, kidney, thyroid, Hodgkin's disease, non-Hodgkin lymphomas and multiple myeloma, for a total of 8,077 cancer cases and 6,147 controls. Consumption of green vegetables and fruit was divided into (approximate) tertiles, and relative risks, adjusted for several risk factors, were computed.

The results confirmed that elevated green vegetables consumption is inversely related to the risk of a number of common epithelial cancers, whereas the relationship with hormone-dependent cancers was weaker and absent for non-epithelial tumours. Fruit consumption was less consistently associated than green vegetables to risk reduction, which appeared more specific for the upper digestive and respiratory tract and a few other sites such as liver, pancreas, prostate and urinary tract. As shown in Table 17.3, risks were reduced for all cancers except myeloma and lymphomas. All the trends in risk were in the same direction and significant for all carcinomas except gallbladder (and even then, probably only because of the small number of cases).

Elevated fruit consumption was related to significantly reduced risk of cancers of the oral cavity and pharynx, oesophagus, stomach, colon, liver, pancreas, larynx, prostate, bladder and kidney. The protection was somehow directly related to the level of the location of the tumour in the digestive tract: the relative risk was 0.2 for oral cavity, 0.3 for oesophagus, 0.4 for stomach, 0.6 for colon and 0.9 for rectum. No association emerged for thyroid cancer, lymphomas or for multiple myeloma (Table 17.4).

Table 17.3—Relative risk of selected cancers according to green vegetable consumption. Milan, Italy, 1983–1990

Type of cancer	Relative risk estimate for tertile of vegetable consumption		
1# (Low)	2	3 (High)	
Oral cavity and pharynx	1	0.6	0.3
Oesophagus	1	0.5	0.2
Stomach	1	0.8	0.4
Colon	1	1.0	0.5
Rectum	1	1.0	0.6
Liver	1	0.8	0.2
Gallbladder	1	0.8	0.5
Pancreas	1	0.7	0.4
Larynx	1	0.7	0.2
Breast	1	0.9	0.7
Endometrium	1	0.9	0.6
Ovary	1	0.8	0.6
Prostate	1	0.8	0.3
Bladder	1	0.9	0.3
Kidney	1	1.0	0.4
Thyroid	1	0.7	0.5
Hodgkin's disease	1	1.1	1.3
Non-Hodgkin lymphomas	1	1.0	1.5
Multiple myeloma	1	0.8	1.1

*Modified from Negri *et al*, 1990; #reference category.

17.4
BIOLOGICAL INFERENCES AND PUBLIC HEALTH IMPLICATIONS

The observed pattern of risk for fruit suggests some non-specific action of fruit on the upper digestive tract and urinary tract, through which most of the substances or metabolites are excreted, whereas the general protection provided by green vegetables may imply a systemic action.

Although the effect of dietary items and components on hormone-related cancers is still uncertain, a high intake of green vegetables has been found protective towards breast cancer. The mechanism of action might involve the modification of oestradiol metabolism by dietary indoles contained in cruciferous vegetables.

Table 17.4—Relative risk of selected cancers according to fruit consumption. Milan, Italy, 1983–1990*

Type of cancer	Relative risk estimate for fertile of fruit consumption		
1# (Low)	2	3 (High)	
Oral cavity and pharynx	1	0.6	0.2
Oesophagus	1	0.5	0.3
Stomach	1	0.7	0.4
Colon	1	1.0	0.6
Rectum	1	1.3	0.9
Liver	1	1.3	0.6
Gallbladder	1	1.7	0.8
Pancreas	1	0.7	0.5
Larynx	1	0.4	0.3
Breast	1	0.9	1.1
Endometrium	1	1.2	1.3
Ovary	1	1.1	1.5
Prostate	1	0.8	0.4
Bladder	1	1.0	0.4
Kidney	1	1.1	0.6
Thyroid	1	1.4	1.6
Hodgkin's disease	1	0.7	0.8
Non-Hodgkin lymphomas	1	0.8	0.7
Multiple myeloma	1	0.6	0.8

*Modified from Negri *et al*, 1990; #reference category.

For tobacco-related cancers, the synergism between low consumption of vegetables and smoking may have important public health implications, since the relationship seems to be particularly strong for these cancers, such as lung and urinary tract carcinomas. In fact, potential anticarcinogenic agents in vegetables and fruit may block initiating or promoting agents, exposure to which is provided by smoking (Doll and Peto, 1981). The protective effect of fruit and vegetables against several epithelial cancers may, at least in part, be due to the antioxidant effect of some micronutrient, such as beta-carotene (pro-vitamin A) or ascorbic acids (vitamin C). Pro-vitamin A and its esters and analogues can reduce the probability that partially altered cells will become totally transformed and successfully proliferate into a pathological tumour. It is also possible that frequent consumption of fruit and vegetables implies a lower intake of fats, proteins or total calories, which are likely to increase the risk of some cancers, like breast and colon carcinomas, or it simply might be an indicator of a health-oriented attitude towards diet and other life style habits. In several studies,

however, the negative association between cancer and fruit and vegetables persisted even after several other risk factors were taken into account.

In epidemiological studies on diet, confounding with social status must be carefully considered. Lower social status is in fact associated with smoking and alcohol drinking, which are major risk factors for several cancers. Also, in many non-Mediterranean countries fresh fruit and vegetables are more difficult to obtain and consequently lower social groups have a diet poorer in these items.

From an epidemiological point of view, methodological difficulties in investigating dietary habits may lead to underestimated risks related to diet, so that the association appears weaker than for other factors. Attenuation of estimates of risks might depend on the narrow range of exposure to dietary factors within most populations and may also derive from the inability of dietary assessment methods to classify dietary habits with great precision. In spite of these methodological problems and cautions, the general epidemiological evidence suggests a protective effect of vegetables and fruit consumption, which is stronger and more consistent for vegetables than for fruit. Agreement is more complete for raw and fresh vegetables than any other item while evidence for legumes and potatoes is less consistent.

Southern European populations, which show an appreciable range of variation in intake of several foods and nutrients, including fresh fruit and vegetables, may provide a useful opportunity for further investigation and quantification of the role of diet on cancer risk.

ACKNOWLEDGEMENTS

This work was conducted within the framework of the National Research Council (CNR) Applied Project Oncology (Contract No 91.00285, PF41) and with the contributions of the Italian Association for Cancer Research, the Italian League against Tumours and Mrs A Marchegiano Borgomainerio. The authors wish to thank Mrs J Baggott and the GA Pfeiffer Memorial Library.

REFERENCES

Cook-Mozaffari PJ, Azordegan F, Day NE *et al* (1979). Oesophageal cancer studies in the Caspian Littoral of Iran: results of a case-control study. *Br J Cancer* **39:** 293–309.

Doll R, Peto R (1981). The causes of cancer. Oxford University Press, Oxford.

Franceschi S, Talamini R, Fassina A *et al* (1990). Diet and epithelial cancer of the thyroid gland. *Tumori* **76:** 331–8

Katsouyanni K, Trichopoulos D, Boyle P *et al* (1986). Diet and breast cancer: a case-control study in Greece. *Int J Cancer* **38:** 815–20.

La Vecchia C, Decarli A, Franceschi S *et al* (1987). Dietary factors and the risk of breast cancer. *Nutr Cancer* **10, 4:** 205–14.

La Vecchia C, Negri E, D'Avanzo B *et al* (1990). Electric refrigerator use and gastric cancer risk. *Br J Cancer* **62:** 136–7.

Negri E, La Vecchia C, Franceschi S *et al* (1991). Vegetable and fruit consumption and cancer risk. *Int J Cancer* **48:** 350–4.

Negri E, La Vecchia C, Franceschi S *et al* (1992). Attributable risks for oesophageal cancer in Northern Italy. *Eur J Cancer* in press.

Ron E, Kleinerman RA, Boice JD *et al* (1987). A population based case-control study of thyroid cancer. *JNCI* **79:** 1–12.

Steinmetz KA, Potter JD (1991). Vegetables, fruit and cancer. I. Epidemiology. *Cancer Causes and Control* **2:** 325–57.

18
Food additives and contaminants
M J Hill

18.1
INTRODUCTION

Of all the cancer risks to which humans are exposed, those from food additives and contaminants have probably received the most attention in western countries. Despite this attention, it is clear that they represent only a very minor part of the total carcinogen load and are responsible for only a small proportion of the total cancer risk.

The food additives and contaminants, generally termed *chemicals* by the media and pressure groups, can be divided into those deliberately added for a defined purpose (the *additives*) and those that are present accidentally as a result of other human activity or of geology, climate etc. (the *contaminants*). Many plants contain toxic compounds *naturally*: cycads produce the potent colon carcinogen cycasin and secrete it into the cycad nuts as a matter of course; similarly the cycanogenic glucosides linamarin and amygdalin are present in certain grasses and in cassava roots naturally, as are the cardioactive glycosides and the cathartic glycosides in other plants. These naturally occurring pharmaco-active compounds are present regardless of the activities of the grower or the food processors and so are not included in the food additives and contaminants.

The main aim of the food supplier is to satisfy the demand of the public for food that is appetizing and which satisfies the nutritional requirements. With fresh fruit and vegetables this is relatively simple; the tastes of the public are known and it is simply necessary to produce the fruit/vegetables in sufficient quantity. This leads the producer to apply quantities of pesticide and fungicide to prevent spoilage and blemishing of the fruit/vegetables and to maximize saleable yield; these agents then enter the food as contaminants, usually in trace amounts. This attempt to maximize production and to minimize pest or fungal damage to the product is the main cause of food contamination. The contaminants are usually present only in trace amounts but it is axiomatic that any compound which is lethal to insects, microbes etc is likely to have some effect on the health of humans if consumed in sufficient quantity. Avoidance of the use of antifungal agents is not without hazard since many products such as nuts, grains, seeds etc

that are stored under cool dry conditions can suffer severe contamination with fungi if the conditions are not sufficiently dry. This can cause visible spoilage or, more seriously, contamination with fungal toxins. Nevertheless, in general fruits, nuts and salads eaten raw are usually considered to be very good for health.

Foods can only be eaten raw when in season; out of season they need to be treated in some way to preserve them. Traditionally vegetables and meats were preserved with salt; this acted by decreasing the water activity to levels that inhibit bacterial growth and so prevent spoilage. In addition, sea salt is rich in nitrate which is reduced by bacteria to the potent antibacterial agent nitrite. Fruit was traditionally preserved bottled in sucrose syrup solutions whose major action, as with salt, was to decrease water activity. Meats may also be preserved by smoking or by curing in nitrate brines; the former results in residual polycyclic aromatic hydrocarbon carcinogens whilst the latter leaves high residual nitrite concentrations. Historically the next preservation methods were canning and then vacuum packing, drying and, most recently, freezing. In canning the essential process includes heating to kill bacteria and then sealing in a metal container to prevent reinfection. Air is excluded in order to prevent oxidation and rancidity of unsaturated fats; nitrite is added if contamination with clostridia is suspected. Vacuum packing achieves the same aim as canning, but the heated product is sealed in a plastic container under vacuum to exclude the air. Dried foods are preserved simply by removal of water to decrease water activity and prevent spoilage. Frozen foods are prepared and stored at a temperature below that which permits bacterial growth.

More recently, in order to increase product production rate or to reduce costs, industrial processes have been developed which mimic older traditional preservation methods. Most notable of these is the production of artificially *smoked* food which has the appearance and taste of smoked food but which has never been exposed to smoke. This artificial smoking process is much quicker and cheaper than the traditional method and so commercially has almost totally replaced it.

Clearly the main aim of food processing and preservation is to prevent bacterial growth and so prevent spoilage or, more seriously, food-borne infection. Food poisoning by *Clostridium* spp is often fatal even in countries with good medical services; infection with *Salmonella, Shigella* and *Campylobacter* whilst not normally fatal, nevertheless causes considerable discomfort and can be serious especially in the young and the old. It is very well worth preventing and most would consider that in any risk-benefit analysis, the benefits of an additive that prevented bacterial disease would count very highly indeed.

The subsidiary aims of food additives are to improve the storage properties (the shelf life) and the organoleptic properties of the food by the use of food colours, flavour enhancers etc.

In this chapter we will briefly consider the types of food additives and contaminants, why they are present in the food and under what circumstances they present a health hazard. Finally an attempt will be made to

quantitate the level of hazard, to put it into the perspective and context of the other cancer risks.

18.2
FOOD ADDITIVES

The major classes of food additives are:

(a) Antibacterial and antioxidant agents, the function of which is to prevent food spoilage.
(b) Agents whose function is to modify the appearance of a product (*eg* food colours).
(c) Organoleptic agents (*eg* flavour enhancers, artificial flavouring agents, texturing agents such as carrageenan etc).
(d) Nutritional fortifying agents (*eg* added vitamins, trace metals etc).
(e) Other agents whose function is to improve shelf life.

18.2.1
Antibacterial and antioxidant agents

Bacterial spoilage of food can be minimized in the short term by heat treatment but for long term storage either bacteria must be excluded or antibacterial agents must be used. Traditionally the agents that have been most widely used have been salt, smoke products and nitrate.

A wide range of organisms cannot tolerate high salt concentrations but many others are resistant and so the action of salt as a preservative is the more general one of reducing water activity. When the food is to be consumed it is necessary first to rinse away the salt; this is not easy and the use of this preservative results in a high salt intake.

During the smoking process the meat product becomes impregnated with the products of wood pyrolysis including a range of bacteriostatic phenolic compounds, polycyclic aromatic hydrocarbons etc. Many of these are carcinogenic in animal studies, and epidemiological studies, particularly from Iceland (reviewed by Sigurjonsson, 1967), have shown a strong association between consumption of smoked food and gastric cancer. Interestingly, those consuming the *artificially smoked* industrially produced products did not have an increased risk of gastric cancer.

It has been claimed that the traditional value of salt as a preservative was due to the nitrate contamination. Bacteria present in the food to be preserved would then reduce the nitrate to nitrite—a potent antibacterial agent which would then kill the bacteria present and prevent further contamination. This is utilized in curing of meats. In Europe there is a wide range of cured meat products including hams, sausage, salami, wursts etc, the storing properties of which are due to their nitrite content. France is the only country in Europe where nitrate/

nitrite is *not* used in the curing process as used in private farms etc, and this is also the only country where botulism following consumption of ham has been regularly reported. The common food poisoning organisms such as *Salmonella, Shigella, Campylobacter* and *Clostridium* spp are commonly present in the intestines of food animals and carcase handling. In consequence red meat and poultry are common sources of food poisoning. However, curing of the meat largely eliminates the risk of such infection (Tompkin, 1980); further, for the long term prevention of clostridial infection at room temperature there is little alternative to nitrite. The value of curing of meats and its mode of action has been reviewed recently by Roberts and Dainty (1991).

Oxidative spoilage is second only to microbial spoilage in importance, and a wide variety of antioxidant agents are available. The most common problem is the rancidity of fat as a result of oxidative degradation of unsaturated fatty acids; the problem is greatest therefore in foods that are rich in fats, particularly the polyunsaturated fats. The antioxidant agents include naturally occurring agents such as ascorbic acid, tocopherols, plant quinones and tannins etc. In addition there are synthetic antioxidants, the most widely used of which are butylated hydroxyanisole (BHA) and butylated hydroxytoluene (BHT). In the absence of such protective agents fat-rich foods become rancid in a few days and take on the characteristic noxious taste and smell.

18.2.2
Agents which modify the appearance of foods

The use of appearance-enhancing additives is the subject of considerable criticism by pressure groups and the media but in fact there is considerable commercial pressure for their use. Traditionally butter is yellow but when, as a first step towards more intensive farming, cows were fed large amounts of clover the butter from such animals was very pale and, consequently, customers would not buy it. For this reason a yellow dye, butter yellow, was added and the product then became saleable. Butter yellow was one of the first food colours to be shown to be carcinogenic. When herrings are smoked in the traditional way to produce kippers the product is brown. When an industrial (artificial) kippering process was introduced it was necessary to add a colour (Brown FK) to give them the appearance of true kippers. Brown FK has also been shown to be carcinogenic in animal tests and was therefore banned. When peas are canned the heat process destroys their green colour and so a green dye is added to restore the *correct* appearance. In other examples dyes are added not to restore a colour but to give a distinctive appearance to the product (*eg* sweets, cake decoration etc).

A number of artificial food colours have been shown to be carcinogenic in animal and *in vitro* tests and consequently banned from use; in no case has this been supported by human epidemiology but that is because of the crudeness of epidemiological methods and the widespread use of such colours. No food colour is completely above suspicion and so the EC has a permitted list of

colours, none of which can be used at a level likely to result in a total intake of colours exceeding a *safe* dose.

Colour can be *improved* in a product by other methods. The pinkness of ham can be enhanced by the addition of nitrite, which reacts with the myoglobin in the ham to enhance the natural colour.

18.2.3
Improvers of organoleptic properties

The palatability and attractiveness of a food can depend on many qualities including the appearance and colour, the taste, the *structure* etc.

A number of compounds have the property of enhancing the taste of a product. The most notable of these is sodium glutamate, which is widely used in east Asia and in Chinese and Polynesian foods.

Carrageenan—a polysaccharide from seaweed—is widely used as a food bulking agent and to improve its structure in, for example, ice cream, confectionery products. Malted wheat is added to some breads, as is pea fibre, to improve the taste and increase the fibre content. Sugar is a vital component of chocolate not because of its sweetness (which is easily replaced) but because of its bulking properties giving a much bigger bar of chocolate for a given weight when compared with diabetic chocolate.

18.2.4
Other agents

The EC-approved list of food additives includes a range of miscellaneous food additives. Bread, when produced by traditional methods, rapidly becomes stale (*ie* has a short shelf-life) and cannot be sold more than 24 hours after production. However, techniques are available to extend the shelf life so that even sliced loaves remain relatively fresh for many days.

18.3
FOOD CONTAMINANTS

The major contaminants in food that give rise to concern are the pesticides and fungicides present in the raw materials of food production, the microbial metabolites formed during food spoilage, and contaminants permeating into foods from packaging materials.

18.3.1
Pesticides/fungicides

In EC countries there are strict regulations regarding the levels of such contaminants; in general they should not be detectable at specified detection

limits. It is necessary to specify such detection limits because analytical techniques have now reached the stage where the determined analyst is likely to be able to detect almost any potential contaminant.

A major problem with the storage of grains, nuts, seeds etc is that in hot and humid conditions fungal contamination can be a major problem. In particular many fungi produce mycotoxins that are potent carcinogens such as the *Fusarium* toxins (Schoental, 1979), aflatoxins (Hsieh *et al*, 1977).

Fusarium spp and other field fungi produce a range of mycotoxins that have been described by Schoental (1979) and implicated in a range of gastrointestinal tumours in human and in laboratory and domestic animals. Their acute toxic effects have been recognized for many decades. For example acute alimentary toxic aleukia occurred in a groups of people who ate bread made from wheat contaminated with *Fusarium* toxin. In animals given repeated doses of the toxin benign and malignant tumours developed in the stomach and upper small intestine. No long term follow-up has been made of persons known to have been exposed to the mycotoxins (*eg* from their acute effects).

Aflatoxins have been the subject of many reviews and their role in human primary hepatic carcinoma is well established. They have been the subject of many reviews during the last 20 years (*eg* Wogan, 1975; Hsieh *et al*, 1977; Wei *et al*, 1981). They are produced by a wide range of fungi, particularly the *Aspergillus* spp, characterized by being ubiquitous in nature in soils in all except the extreme arctic and antarctic regions. They are normal contaminants on all vegetable products and are of particular importance as contaminants of grains, seeds, nuts etc that are stored in anything other than cool dry conditions. Analytical techniques are such that aflatoxin can be detected in any food source (including human breast milk). The amount of aflatoxin produced depends on the storage time, temperature and humidity, and so is clearly likely to be very much higher in tropical hot humid climates than in the cooler temperate zones.

The aflatoxins are extremely potent hepatotoxins and hepato carcinogens in animals; they have also been very strongly associated with human primary hepatic carcinoma (PHC). As reviewed by Linsell and Beers (1977) the evidence shows a good dose response between PHC risk and aflatoxin exposure within countries but not between countries (Table 18.1); it is only a major risk factor in developing countries

Table 18.1—The relation between aflatoxin intake and primary hepatic carcinoma incidence (for details see Hill, 1986)

Population	Daily aflatoxin intake (ng/kg body wt/day)	PHC incidence per 100,000 per year
Kenya		
High altitude	3.5	1.2
Middle altitude	5.9	2.5
Low altitude	10.0	4.0

Population	Daily aflatoxin intake (ng/kg body wt/day)	PHC incidence per 100,000 per year
Swaziland		
High veld	5.1	2.2
Mid veld	8.9	3.8
Low veld	43.1	9.2
Mozambique	222.4	13.0
Thailand		
Sohgkhla	5.0	2.0
Ratburi	45.0	6.0

(Enwonwu, 1984) and then in conjunction with hepatitis B virus infection. Within the EC there is legislation to limit the amount of aflatoxin in food to trace levels.

Pesticides are used to limit disease and so maximize crops before harvesting, and residual levels are to be found in the foods. Again, as with the mycotoxins, their detection can be seen as a challenge to the analyst and, with modern technology, a wide range of agents can often be detected in foods but at levels that are extremely unlikely to have any significance.

18.3.2
Soil-derived contaminants

Plants take up a range of minerals, ions etc as part of their normal physiological processes. For example, plants take up nitrate from the soil, and one of the determinants of the nitrate content of plants is the nitrate content of the soil in which they were grown. Plants also take up molybdenum from the soil; this trace element is an essential co-factor of the nitrate-reductase system that controls the level of nitrate in the plant tissues. Numerous other anions and cations are taken up by the same mechanisms and, as a result of this process, plants grown on industrial waste sites can contain toxic contaminants derived from the soil. The most notable of these are arsenic (from the soil or as a pesticide residue) and cadmium. Arsenic is also present in some fish products—indeed this is often the major source in the human diet.

18.3.3
Meat contaminants

A range of meat contaminants has been described, in addition to the microbial contaminants that cause food spoilage or food poisoning. A number of veterinary drugs (*eg* growth promoting hormones, copper salts) can leave low level residues

in the meat. In addition, where meat is packaged there is often transfer of carcinogens (*eg* vinyl chloride, urethane) from the packaging material.

18.4
ADDITIVES AND CONTAMINANTS AND CANCER

Many food contaminants are known carcinogens, the most prominent being the aflatoxins and some other mycotoxins, the heavy metal complexes from pesticide and insecticide residues (principally arsenic) and the polymerizing agents (*eg* vinyl chloride, urethane) used in packaging materials. However Lutz and Schlatter (1992) have attempted to quantitate the risk associated with such carcinogens and found them to be only small contributors to the overall cancer risk. They extrapolated from existing animal and human data to deduce a figure for the carcinogenic potency of each of the major contaminants, then multiplied this by the life time exposure to calculate the number of cases likely to be caused. Even using the upper limit of the range of potency and the upper limit of the range of calculated lifetime exposure, the food-borne carcinogens could only account for at most 1 or 2% of the total cancer load (Table 18.2). However, by limiting the analyses to food-borne carcinogens there is the risk of ignoring the importance of precursors of carcinogens. Nitrite can, under suitable conditions, react with secondary nitrogen compounds to yield N-nitroso compounds—an extremely potent group of carcinogens (Preussman and Tricker, 1988). Secondary amines yield N-nitrosamines which are usually volatile and easily assayed; most meat and fish products to which nitrate has been added contain detectable levels of volatile nitrosamines, but usually at very low concentrations (Table 18.3). The carcinogenic potential of such low exposures is difficult to estimate but is likely to be very low. However, Fine (1979) has assayed volatile N-nitrosamines in kitchen fumes (*eg* when cooking ham, bacon, sausage etc) and this is likely to much greater than that from the food itself. In addition, nitrite can N-nitrosate suitable substrates after ingestion in, for example, the acid stomach, the bacterially colonized stomach, the infected urinary bladder in amounts that are many orders of magnitude greater than those present preformed in the food (Table 18.4). This has been implicated in the causation of gastric cancer in hypochlorhydric patients and in bladder cancer in patients with bladder infections (Hill, 1991).

Table 18.2—Estimated life time risk of cancer per million persons due to dietary carcinogens (Lutz and Schlatter, 1991)

Compound	Estimated intake ng/kg/day	Life time risk per million
Arsenic	150–500	150–1,200
N-nitroso compounds	160	135
Aromatic amines	1,500	15–150

Compound	Estimated intake ng/kg/day	Life time risk per million
Polycyclic aromatic hydrocarbons	130–270	6–14
Ethyl carbamate	1,100	100
Mycotoxins	1–3	5–20
Other known carcinogens		<100
Ethanol	4×10^8	<4,000
Total diet-related cancer incidence per million		80,000

Although it is clear from the analysis by Lutz and Schlatter (1992) that the risks from carcinogenic food additives and contaminants are very much smaller than the general public perceives them to be, it is also clear that they are finite and could in principle be decreased. In order to discuss this rationally it is necessary to divide the food additives and contaminants into 3 groups, namely:

(a) Contaminants (*ie* compounds that should not be present).
(b) Additives that prevent microbial spoilage.
(c) Other additives.

Table 18.3—N-nitroso compound concentration in various foodstuffs (data from various sources)

Food sample	Concentration (µg/kg)	Food sample	Concentration (µg/kg)
Cured meats		*Alcoholic beverages*	
Ham	<1	Beer/ale (general)	0–5
Salami	0–10	Whisky	0–1
Pepperoni	0–2	Pale strong lager	0–8
Smoked meats	0–8	Dark strong lager	0–47
Corned beef	0–7		
Fried bacon (lean)	2–65	*Fermented foods*	
Meat and sausages	0–45	Salt fermented veg	1–32
		Japanese sake	0–3
Dairy products			
Cheese	0–5		

Table 18.4—Concentrations of N-nitroso compounds endogenously formed compared with preformed in food

Endogenously formed		Preformed in food	
Site	Concentration (µM)	Source	Concentration (µM)
Saliva	ND - 0.12	Cured meats	ND - 1.22

Endogenously formed		Preformed in food	
Site	Concentration (μM)	Source	Concentration (μM)
Gastric juice	ND - 6.0	Bacon	ND - 0.13
pH 3–7	mean 1.4	Fish	ND - 0.13
Urine -		Cheese	ND - 0.13
sterile	ND - 0.024		
infected	ND - 0.56		
bilharzia	ND - 0.20		
Faeces	ND		
Vaginal exudate	NS - 0.5		

ND=not detectable; NS=non significant.

Contaminants. Since contaminants, by definition, should not be present, it is axiomatic that their levels should be minimized. Nevertheless, this should not be done at the expense of food quality. Some of the contaminants are from packaging materials that help to protect the meat etc from microbial contamination. Some of the fungicide residues are present as a result of attempts to prevent mycological overgrowth with its associated risk of mycotoxin contamination.

Antimicrobial additives. The major hazard associated with food is microbial infection (food poisoning); an associated problem is food spoilage by microbial action. A range of antimicrobial agents is used to prevent microbial proliferation with varying levels of effectiveness. The most serious cause of food poisoning is *Cl. botulinum*, and this is almost unknown in most western populations because of the effectiveness of nitrite additives. Of western countries only in France is botulism regularly reported and this is also a country where home curing of ham (without the use of nitrite) is common. Sockett (1991) reviewed the food poisoning outbreaks associated with manufactured foods in England and Wales between 1980 and 1989. He concluded that such outbreaks accounted for less than 5% of the total food poisoning cases and more than 95% were from unprocessed foods to which no antimicrobials had been added. Whereas in food poisoning in general the most common infecting organism is *Campylobacter* (Table 18.5) which is twice as common as *Salmonella*, the cases associated with manufactured foods were dominated by *Salmonella* (53%) with all other bacteria accounting for only 21% and viruses (less than 2% mainly from processed fish and shellfish); scombrotoxin accounted for 2.4% of cases, all from processed or tinned shellfish or fish. Clearly the antimicrobial procedures are highly effective and their use as additives is justified; in any cost-benefit analysis, protection against food poisoning on a continuing basis must outweigh the long term risk of cancer.

Table 18.5—The major causes of food poisoning in the UK

	Number of cases, 1991	
Causal organism	Weeks 48–51	Whole year
Campylobacter	2,050	32,285
Shigella	1,546	10,416
Salmonella enteritidis	959	12,000
Other salmonella	721	8,000
Cl. difficile	806	
Yersinia	441	
Aeromonas	313	
Vibrio	83	

Other additives. The situation with respect to the *other food additives* gives a much more difficult cost-benefit analysis. All estimates of risk suggest that it is a small one, but is it necessary at all? The answer depends entirely on views on the cosmetic and organoleptic properties of foods; is food colour of sufficient importance to justify the risks associated with food colours, for example? Do we really need flavour enhancers? These are matters for public debate.

REFERENCES

Enwonwu C (1984). The role of dietary aflatoxin in the genesis of hepatocellular cancer in developing countries. *Lancet* **ii:** 956–8.

Fine D (1979). N-nitroso compounds in the environment. In *Advances in Environmental Science and Technology, Vol 10* (eds Pitts J, Metcalf R); John Wiley, New York, pp. 39–123.

Hsieh DP, Wong JJ, Wong ZA *et al* (1977). Hepatic transformation of aflatoxin and its carcinogenicity. In *Origins of Human Cancer* (eds Hiatt H, Watson J, Winsten J); Cold Spring Harbor Lab Press, New York, pp. 697–707.

Linsell CA, Beers FG (1977). Field studies on liver cell cancer. In *Origins of Human Cancer* (eds Hiatt H, Watson J, Winsten J); Cold Spring Harbor Lab Press, New York, pp. 549–56.

Lutz WK, Schlatter J (1991). Carcinogens and mutagens in the diet. In *Public Education on Diet and Cancer* (eds Benito E, Giacosa A, Hill MJ); Kluwer, Lancaster, pp. 13–24.

Preussmann R, Tricker AR (1988). Endogenous nitrosamine formation and nitrate burden in relation to gastric cancer epidemiology. In *Gastric Carcinogenesis* (eds Reed P, Hill M); Excerpta Medica, Amsterdam, pp. 147–61.

Roberts TA, Dainty RH (1991). Nitrite and nitrate as food additives: rationale and mode of action. In *Nitrates and nitrites in foods and water* (ed Hill MJ); Ellis Horwood, Chichester, pp. 113–30.

Schoental R (1979). The role of fusarium mycotoxins in the aetiology of tumours of the digestive tract of certain other organisms in man and animals. *Front Gastrointest Res* **4:** 17–24.

Sigurjonsson J (1967). Occupational variations in mortality in gastric cancer in relation to dietary differences. *Br J Cancer* **21:** 651–6.

Sockett PN (1991). Food poisoning outbreaks associated with manufactured foods in England and Wales: 1980–89. *Communicable Disease Reports* **1:** Review No 10, 105–9.

Tompkin RB (1980). Botulism from meat and poultry products—a historical perspective. *Fd Technol* **34:** 229–36.

Wei C, Macy J, Hsieh DP (1981). Biotransformation of aflatoxin B_1 and its conjugated metabolites by rat gastrointestinal microfloras. *Appl Env Microbiol* **41:** 549–51.

Wogan GN (1975). Dietary factors and special epidemiological situations of liver cancer in Thailand and East Africa. *Cancer Res* **35:** 3499–3502.

19
Dietary anticarcinogens and cancer

M J Hill

19.1 INTRODUCTION

The human diet, as well as containing a wide array of carcinogens (Lutz, 1992) also contains a similarly wide array of anticarcinogens. These latter are detected in model systems by their ability to inhibit carcinogenesis and so, of necessity, their detailed study has had to await a detailed understanding of the test systems. Nevertheless, despite early work by, for example, Crabtree (1947) and later interest from such leaders as Ames (1983) there has been relatively little interest in experimental anticarcinogenesis.

Anticarcinogens have been defined as including *any factor, extrinsic or intrinsic, which delays or prevents the emergence of malignant characters in any tissue of any species of organism* (Crabtree, 1947). Such a wide definition is likely to include a wide array of compounds, the vast majority of which will be irrelevant in practice to human cancer. The dietary anticarcinogens most widely studied have been the antioxidant vitamins and trace elements, because support for their relevance has been obtained from epidemiological studies. However, the lignans and phytoestrogens (Adlercreutz, 1987) have also received a lot of attention as have plant indoles, thiocyanates, flavones etc (Wattenberg, 1985) and phytate (Shamsuddin *et al*, 1988). Further, on the definition given above, dietary fibre would qualify as an anticarcinogen.

The major mechanisms of anticarcinogenesis are illustrated by a discussion of the broader aspects of the carcinogenesis process.

19.2 MECHANISMS OF CARCINOGENESIS/ ANTICARCINOGENESIS

Chemical carcinogenesis involves, ultimately, the formation of alkylated or modified nucleic acid bases. For this to occur the carcinogen must be metabolized to a high-energy intermediate (the ultimate carcinogen) which is then able to react with the nucleic acid. Included amongst these high-energy

intermediates are the free radicals; the oxygen radicals formed during oxidative metabolism are a rich source of initiators of radical formation and have been reviewed by Diplock (1988). Such radicals are inactivated and "scavenged" by the antioxidant vitamins ascorbic acid, tocopherol and carotene, by antioxidant food additives such as butylated hydroxytoluene (BHT), by a range of compounds found in cruciferous vegetables (Virtanen, 1962) and studied by Wattenberg (1979), and by phytic acid (Shamsuddin *et al*, 1988; Babbs, 1990).

The carcinogen, before it can interact with its target DNA, must first gain entry into the cell and in many cases this is achieved through interaction with specific receptor sites, specific transport mechanisms etc. Anticarcinogens can therefore act by blocking such receptors etc; an important mechanism by which the lignans and phytoestrogens are able to inhibit carcinogenesis might be their ability to bind to, and block, the hormone binding sites in breast, endometrial and prostate tissues. These compounds have been studied in some detail by Adlercreutz (*eg* Adlercreutz, 1990). Entry to the cell can also be modulated by modifying exposure levels (*eg* of colonocytes by increasing stool bulk with dietary fibre; of hepatocytes by interfering with enterohepatic circulation of compounds).

After or during entry to the cell the carcinogen is beset by a range of host-defence mechanisms which detoxify compounds entering the cell. These include a range of mixed function oxidation systems (MFO) which are maximal in the liver (as the main organ responsible for detoxification of xenobiotics) but are found in all tissues. These are inducible systems, which can be induced by a range of plant components which have, themselves, low toxicity such as flavones (Wattenberg, 1978), indoles (Loub *et al*, 1975), coumarins and lactones (Wattenberg, 1977).

Because of the range of host defence mechanisms, the normal tissues, particularly in exposed organs (such as the oesophagus, stomach and liver) display considerable resistance to carcinogenesis. However, precancerous lesions have been identified, in which the normal tissue is first modified to an atypical morphology (*eg* Barrett's oesophagus, intestinal metaplasia of the stomach, ulcerative colitis, liver cirrhosis) which while not malignant, is much more sensitive than normal tissue to the range of carcinogens to which it is exposed. Thus, a mechanism by which anticarcinogens could act would be by stabilizing or reversing these precancerous changes. An example of this might be ascorbic acid, low serum levels of which are associated with intestinal metaplasia of the stomach and which therefore might have an anticarcinogenic action by preventing intestinalization of the gastric mucosa.

19.3
DIETARY SOURCES OF ANTICARCINOGENS

A number of foods are associated in epidemiological studies with decreased cancer risk, including fresh fruit, vegetables and cereals. Although the evidence

for these effects is secure in the literature and is reviewed in Chapters 15 and 17 of this book, the mechanism by which they act is far from clear, as will be illustrated by some examples.

19.3.1 Wheat bran

Wheat bran has been found in animal model systems to protect against colorectal carcinogenesis whilst consumption of cereals has also been correlated inversely with risk of that tumour. A variety of mechanisms has been proposed to explain this; these include:

(a) Stool bulking—cereal fibre is a potent stool bulking agent and this results in dilution of the colonic contents and of any luminally-delivered carcinogen or tumour promoter (Hill and Fernandez, 1990); there is good evidence that luminal factors are important in colorectal carcinogenesis (Hill, 1986).
(b) Carbohydrate fermentation—colonic carbohydrate is fermented to a range of volatile fatty acids resulting in caecal acidification (Bown *et al*, 1974) and the establishment of an environment too acidic for the efficient activity of the bacterial enzymes likely to be implicated in colon carcinogenesis; there is a consequent amelioration of the effects of the products of such metabolism (Rafter *et al* 1986).
(c) Butyrate production—a great deal of excitement has been generated from tissue culture studies, some of which suggest anticarcinogenic properties for butyrate, a major metabolite of carbohydrate metabolism in the colon. There is a similar body of evidence (Berry and Paraskevo, 1988; Williams *et al*, 1990) indicating that butyrate can act as a tumour promoter; this has generated less excitement.
(d) Phytate action as free-radical scavenger—Babbs (1990) has argued plausibly that the protective effect of cereals could be due to the scavenging of free radicals in the colon by inositol hexaphosphate (phytic acid). In support of this Shamsuddin *et al* (1988) have shown inhibition of experimental carcinogenesis in rats by phytic acid—evidence that is noticeably absent from the butyrate story. The phytic acid also caused a decreased concentration of oxygen radicals in the colon of those rats.
(e) Lignan production—the production of lignans in the colon by bacterial action on (unidentified) substrates of plant origin has been studied extensively by Adlercreutz (1990). This probably has no relevance to the protection against colon carcinogenesis but may explain a similar protection against breast cancer (Adlercreutz, 1984).
(f) Conclusions—at present we have no clear evidence of the mechanisms by which wheat bran protects against colorectal or breast carcinogenesis.

19.3.2
Vegetables

The analysis of the mechanism by which consumption of vegetables protects against a range of cancers is complicated by the presence in such foods of a host of anticarcinogens including a range of antioxidant vitamins (ascorbic acid, carotene, tocopherol) and other compounds (flavones, isothiocyanates, indoles, phenols, coumarins, lactones) in addition to dietary fibre. The current situation is that the evidence for protection against human cancer is better for the food group of fresh vegetables than it is for any of the putative anticarcinogens present in such foods. This may be because we have yet to identify the main active agent, or because the food analyses have not been sufficiently precise to give us accurate analytical data with which to carry out the epidemiological studies, or because the action is due to a combination of factors.

19.4
CONCLUSIONS

In studying the beneficial effects of the Mediterranean diet we should concentrate our efforts on the study of food groups rather than on micronutrients or anutrients.

REFERENCES

Adlercreutz H (1984). Does fiber-rich food containing animal lignan precursors protect against both colon and breast cancer? An extension of the fiber hypothesis. *Gastroenterology* **86:** 761–6.

Adlercreutz H (1990). Western diet and western diseases: some hormonal and biochemical mechanisms and associations. *Scand J Lab Invest* **50 (Suppl 201):** 3– 23.

Aldercreutz H, Hoverstedt K, Bannwart C, *et al* (1987). Effect of dietary components, including lignans and phytoestrogens on enterohepatic circulation and liver metabolism of estrogens and on sex hormone binding globulin (SHBG). *J Ster Biochem* **27:** 1135–44.

Ames BC (1983). Dietary carcinogens and anticarcinogens. *Science* **221:** 1256–64.

Babbs CF (1990). Free radicals and the etiology of colon cancer. *Free Rad Biol Med* **8:** 191–200.

Bown RL, Gibson A, Sladen G (1974). Effects of lactulose and other laxatives on ileal and colonic pH as measured by a radiotelemetry device . *Gut* **15:** 999–1004.

Berry RD, Paraskevo C (1988). Expression of CEA by adenoma and carcinoma derived epithelial cell lines: possible markers of tumour progression and modulation of expression by sodium butyrate. *Carcinogenesis* **9:** 447–50.

Crabtree HG (1947). Anticarcinogenesis. *Br Med Bull* **4:** 345–7.

Diplock AT (1988). Micronutrients and trace elements in cancer prevention. In *Gastric Carcinogenesis* (eds Reed PI, Hill MJ); Elsevier, Amsterdam, pp 99–104.

Hill MJ (1986). Microbes and human Carcinogenesis. Edward Arnold, London.

Hill MJ, Fernandez F (1990). Bacterial metabolism, fiber and colorectal cancer. In *Dietary Fiber* (eds Kritchevsky D, Bonfield C, Anderson J); Plenum, New York, pp 417–30.

Loub WD, Wattenberg LW, Davis DW (1975). Arylhydrocarbon hydroxylase induction in rats by naturally occurring indoles of cruciferous vegetables. *JNCI* **54:** 985.

Lutz W, Schlatter J (1992). Carcinogens and mutagens in the diet. In *Public Education on Diet and Cancer* (eds Benito E, Giacosa A, Hill M); Kluwer, Lancaster (in the press).

Rafter JJ, Eng VWS, Furrer R, Medline A, Bruce WR (1986). Effects of calcium and pH on the mucosal damage produced by deoxycholic acid in the rat colon. *Gut* **27:** 1320–9.

Shamsudden AM, Elsayed AM, Ullah A (1988). Suppression of large intestinal cancer in F344 rats by inositol hexaphosphate. *Carcinogenesis* **9:** 577–80.

Virtanen AI (1962). Some organic sulfur compounds in vegetables and fodder plants and their significance in human nutrition. *Angew Chem Int Ed Engl* **1:** 299.

Wattenberg LW (1977). Naturally occurring inhibitors of chemical carcinogenesis. In *Naturally Occurring Carcinogens-Mutagens and Modulators of Carcinogenesis* (eds Miller EC *et al*). *Jap Soc Sci Press,* Tokyo, pp 315–29.

Wattenberg LW (1978). Inhibitors of chemical carcinogenesis. *Adv Cancer Res* 197–223.

Wattenberg LW (1979). Naturally occurring inhibitors of chemical carcinogenesis. In *Naturally Occurring Carcinogens-Mutagens and Modulators of Carcinogenesis* (eds Miller EC *et al*); Jap Sci Soc Press, Tokyo, pp 315–21.

Wattenberg LW (1985). Inhibitors of carcinogenesis and their implications for cancer prevention in humans. In *Diet and Human Carcinogenesis* (eds Joossens J, Hill M, Geboers J); Excerpta Medica, Amsterdam, pp 49–61.

Williams A, Harper S, Paraskevo C (1990). Neoplastic transformation of a human colonic epithelial cell line: *in vitro* evidence for the adenoma to carcinoma sequence. *Cancer Res* **50:** 4724–30.

20
Nutritional factors and breast cancer in a French Mediterranean region

S Richardson, M Gerber

20.1
INTRODUCTION

The association of dietary factors and breast cancer (BC) has been widely discussed during the past decade (Miller, 1981; Willett and MacMahon, 1984; Wynder, 1980). Most of the interest has been centred around the role played by fat, animal protein and alcohol intake.

Although most international or national correlation studies reviewed by Goodwin and Boyd (1987) as well as more recent studies like the one by Rose *et al* (1986), Taioli *et al* (1991) and Yu *et al* (1991) suggest a positive association between total fat or saturated fat intake and BC mortality or incidence rates, epidemiological studies have led to inconsistent results (Goodwin and Boyd, 1987). A recent report (Howe *et al*, 1990) discussing the last epidemiological studies showed in a combined analysis of 12 case-control studies from several countries a significant association between saturated fat and postmenopausal BC. In addition Van't Veer *et al* (1990a) found a significant positive association with total fat intake. More recently two case-control studies gave opposite results; no association between fat and the risk of breast cancer (Graham *et al*, 1991) and an attributable risk for breast cancer of 14.9% for the highest quartiles of saturated fat intake (Hankin *et al*, 1992). The prospective cohort studies, expected to give the best answers to the question of fat and breast cancer association, are the more inconcsistent, showing negative results (Willett *et al*, 1987; Jones *et al*, 1987) and positive results (Knekt *et al*, 1990; Howe *et al*, 1991).

In some case-control studies, the risk of BC was also positively associated with the intake of protein rich foods and more specifically animal protein (Nomura *et al*, 1978; Lubin *et al*, 1981, 1986; Hislop *et al*, 1986; La Vecchia *et al*, 1987; Iscovitch *et al*, 1989; Toniolo *et al*, 1989). Three prospective studies (Hirayama, 1978, 1979; Phillips, 1983) examined also the relationship with meat intake and the two Japanese studies showed a positive association.

Recently the risk of BC has been inversely associated with fibre intake or vegetable consumption (Katsouyanni *et al*, 1986; La Vecchia *et al*, 1987; Iscovitch *et al*, 1989; Van't Veer *et al*, 1990b) or ß-carotene (Rohan *et al*, 1988;

Iscovitch *et al*, 1989). One study (Graham *et al*, 1982) found an inverse association with retinol in older women whilst others did not (La Vecchia *et al*, 1987; Rohan *et al*, 1988; Iscovitch *et al*, 1989).

The case-control study reported here was designed to study specifically the role of dietary fat, animal protein, vitamin intake and alcohol on BC in an area of Europe where there is a large variability in the diet due to the existence of both a rural population with traditional dietary habits and an urbanized population. Like the abovementioned Greek and Italian studies (Katsouyanni *et al*, 1986; La Vecchia *et al*, 1987; Toniolo *et al*, 1989) it is a Mediterranean area, extending from the south of the Rhône river to the Pyrenees mountains by the Spanish boundary. Some changes already affected this traditional diet especially with regard to olive oil consumption which decreased for economic reasons. A subset of the patients involved in this study has undergone a thorough biological investigation which was also used for validation of the nutritional questionnaire (Gerber *et al*, 1988, 1989). Results regarding alcohol intake have already been reported (Richardson *et al*, 1989) and here we present results regarding both specific food items and nutrients. Alcohol, being a dietary component which was shown to be positively associated with BC in our study, will be specifically taken into account in our analysis.

20.2
SUBJECTS AND METHODS

Patients were interviewed between February 1983 and April 1987. Cases were women aged between 28 and 66 with histologically confirmed primary carcinoma of the breast who were hospitalized in a cancer institute (Centre Régional de Lutte Contre le Cancer, CRLC, Montpellier) and had not previously undergone any therapy. Controls in the same age groups were all the women admitted for the first time to three wards (neurological, neurosurgical and a nearby hospital) or hospitalized for general surgery in a large clinic. All these women came for a first diagnosis and hence were not currently treated for chronic diseases. These wards were chosen at first because the pathologies which they treat are, on the whole, not related to nutritional factors. We excluded from the controls only women admitted to these wards for neoplasic or cardiovascular diseases. The cardiovascular diseases were excluded from the hospital wards because in neurology about half of the patients come because of ischemic accidents and hence not excluding them would lead to over-representation of this pathology which is related to diet. For the clinic which treats a variety of diseases the only exclusions were neoplastic diseases.

The CRLC is the main cancer treatment centre in the area and is attended by patients, irrespective of social class, mainly from the Languedox-Roussillon region. For other diseases, patients can choose to be treated either in a hospital or in a private clinic approved by their health insurance plan. For this reason, we chose as control wards, two hospital wards (neurology and neurosurgery) and a

private clinic carrying out general surgery. Before the start of the study a check was made that the wards from which the cases and controls were recruited had patients of similar age and coming from the same geogrpahical area of residence. In our sample the proportions of cases and controls from rural and urban areas are similar (rural: 19% of cases *vs* 22% of controls, small towns: 48% *vs* 41%, large cities: 33% *vs* 29%, chi^2_2=2.25 NS).

Each week, a coordinator visited the wards and selected for interview all women satisfying the inclusion criteria of the study on the new admission list. Periodically the age distribution for cases and controls was compared and, if necessary, the recruitment of controls in particular age groups was stopped for a while. The interviews were carried out by trained medical staff, who questioned cases and controls. The interviews, presented as an enquiry on living conditions and health, lasted between 30 and 40 minutes. Medical and reproductive history was recorded, as well as general information regarding socioeconomic status.

Part of the questionnaire was of dietary history type (Block, 1982). It started by a recall of the usual structure of the meals and then the dietary interview covered 55 key-food items in lipid, animal protein, retinol, ß-carotene and vitamin E consumption. For each item, a unit quantity was specified (weight, spoon, etc) and each subject told the interviewer her daily weekly or monthly frequency of consumption of the item. In this questionnaire the grouping of food items was similar to that originally designed by the Nutrition Unit of the French National Institute for Health and Medical Research (Pequignot and Cubeau, 1973). The overall duration of the nutritional habits described in the questionnaire was also requested. If the subjects, eating habits had changed over the last 12 months, they were asked to refer to their former diet. The weekly vitamin, animal protein and lipid consumption was evaluated from these data by means of nutritional tables (Paul and Southgate, 1978; Randouin *et al*, 1985). Seasonal consumption was taken into account by multiplying by the proportion of months where the specific food item was usually consumed. When data were missing on some food items for a patient, the nutrient consumption related to this food item could not be evaluated. This explains the slight reduction of the sample size occurring when nutrient consumption is analysed. Questions concerning alcoholic beverages (wine, beer, fortified wines and spirits) were included among questions concerning consumption of non-alcoholic beverages in order to minimize under-declaration (Tuyns *et al*, 1975). It was decided to evaluate the total alcohol consumption per week by summing the number of glasses of the different types of alcoholic beverage consumed (see Richardson *et al*, 1989 for details).

The dietary questionnaire was centred on key items for lipid, animal protein and some vitamin consumption and did not include information on carbohydrates. Consequently, a total caloric intake could not be evaluated.

Analyses of variance and covariance for testing the null hypothesis concerning the difference between the mean value of the weekly consumption of food items of cases and controls was carried out after logarithmic transformation of the data

and using the GLM procedure of SAS. This transformation was adopted because the distribution of values recorded in the original scales of measurements was widely dispersed and skewed. Table 20.1 gives simple data description in the original scale of measurements whilst *P* values refer to the analysis carried out after logarithmic transformation and adjustment on age and menopausal status.

For each food item or nutrient, classes corresponding to tertiles of the control distribution were chosen. The odds ratios (ORs) corresponding to the second and third tertile will be referred to as OR_2 and OR_3. For some food items (olive oil and nuts) the first class corresponds to no consumption and the next two classes are separated by the median of the controls; for margarine consumption only two classes (yes/no) were considered. If interactions were suspected chi^2 tests of homogeneity were calculated following Breslow and Day (1980).

Both univariate and multivariate analyses were systematically carried out but we report here only the results from the multivariate analysis using logistic regressions (Breslow and Day, 1980) performed with BMDP programmes (1985). To compute adjusted ORs each food or nutrient was included in turn in a model including all the adjustment variables as a categorical variable with 3 independent levels, and 95% CI were derived from the standard error of the corresponding regression coefficient. The chi^2 value of the test for linear trend after adjustment was computed as the difference between the deviance of the model without and with the variable of interest coded as a single variable taking values 1, 2 or 3.

To measure the independent effect of each nutrient, a multivariate stepwise logistic regression including all the different nutrients was carried out. In view of the existing correlations between several nutrient intakes, the stability of the results was checked by computing both ascending and descending stepwise procedures. For this multivariate nutrient analysis, the sample size was constituted of 379 cases and 474 controls for whom there were no missing nutrient values. Since total caloric intake could not be calculated in our study, the difference between an overall caloric effect and the effect of individual nutrients could not be tested by the methods discussed in Howe (1989).

20.3 RESULTS

Altogether 932 interviews were completed during the study period. All cases replied and 8 controls refused to answer. The analysis presented thus comprises 409 cases and 515 controls. The number of controls is larger than the number of cases because during the defined study period all cases and all controls satisfying the inclusion criteria in the 3 wards were interviewed.

The control group was composed of 156 women (30%) admitted for neurosurgery (mostly sciatic neuritis, more seldomly traumatism or benign tumours), 41 women (8%) admitted for abdominal surgery (gynaecological or digestive), 97 women (19%) admitted for neurological conditions (mainly

peripheral peresias and parasthesias, epilepsy), 61 women (12%) admitted for neurological diseases (multiple sclerosis and Parkinson's disease), 71 women (14%) with slight psychological disorders, 63 women (12%) admitted for headaches, asthenia and sleep disorders, 15 women (3%) admitted for cardiovascular disease. For 11 women (2%), the diagnoses were unknown.

The mean age of cases and controls were respectively 52.4 and 50.4 years [standard deviation (SD) 8.6 and 9.4]. Nutritional habits were long standing, averaging 26.9 years for cases and 24.4 years for controls [SD 12.2 and 12.5 respectively].

20.3.1
Risk factors for breast cancer

To assess comparability with previous studies, the ORs relating to generally recognized determinants of breast cancer are given in Table 20.2 after adjustment on age and menopausal status (except for age at menopause). They are in general agreement with those found in the literature (Sattin *et al*, 1985). There is a statistically significant elevated risk for a family history of breast cancer (mother or sister), a past history of benign breast disease, a late menopause and a higher education level. There is a borderline significant protective effect for a late age at menarche. The risk associated with a late pregnancy does not reach statistical significance.

When pre- (N=348) and postmenopausal (N=575) women were considered separately, the risks relating to a later age at first pregnancy become significant among premenopausal women (OR_2=1.95 [1.1–3.6] and OR_3=2.05 [0.9–4.8], chi^2 test for trend=4.4, P=0.04) as well as that related to an elevated Quetelet index among postmenopausal women (OR_2=1.58 [1.0–2.6] and OR_3=1.77 [1.1–2.8], chi^2 test for trend=6.0, P=0.01). Variables in Table 20.2, except Quetelet index and age at menopause, will be taken as adjustment variables in multivariate analysis of the nutritional factors in addition to other appropriate variables.

20.3.2
Food items

Mean weekly consumption of 21 groups of key items is shown in Table 20.1 separately for cases and controls as well as the level of significance of the test of comparison after adjustment on age and menopausal status. The overall food intake of the cases is significantly higher than that of the controls and this is equally true for the consumption of high fat cheese, desserts and chocolate, olive oil and alcohol. There are weaker differences concerning the consumption (higher in cases than in controls) of meat, processed pork, citrus fruits, fruits rich in ß-carotene and nuts, whilst that of margarine is somewhat lower in cases than in controls.

Adjusted odds ratio on the classical risk factors of Table 20.2, age, menopausal status and alcohol consumption, were then computed for the food items (cited above) which show some differences between cases and controls. There are significantly elevated ORs for processed pork meat, high fat cheese, citrus fruits, fruits rich in ß-carotene, desserts and chocolates and overall food consumption. The test for linear trend is non significant for processed pork meat and only borderline for both categories of fruits. On the other hand there is a clearly significant increasing trend for high fat cheese, desserts and chocolate and total food consumption. For meat, olive oil and nuts neither ORs nor trends are significant. Note that all the ORs are moderate and never exceed 1.7. For margarine the adjusted OR is significantly below 1.

Table 20.1—Weekly intake of food groups for cases and controls

g/week	Cases 409		Controls 515		
Mean	sd	Mean	sd	*P**	
Meat	930	595	896	613	0.08
Offal	73	174	64	130	NS
Processed pork meat	103	127	99	174	0.08
Fish	81	217	75	202	NS
Eggs	194	142	196	148	NS
Milk (litre)	1.457	1.675	1.492	1.777	NS
Butter and cream	108	88	108	97	NS
Low fat cheese	64	93	70	103	NS
High fat cheese	298	251	264	251	0.006
Yogurt	420	511	422	538	NS
Margarine	22	46	27	53	0.08
Olive oil	40	78	32	63	0.04
Other oils	200	140	190	150	NS
Salads	139	90	137	102	NS
Vegetables	1092	569	1064	557	NS
Citrus fruits	544	505	484	421	0.08
Fruits rich in ß-carotene	984	795	889	726	NS
Desserts and chocolate	376	383	320	374	0.002
Nuts	28	65	22	48	0.07
Alcohol (glasses)	6.5	9.3	3.9	8.2	0.001
Total food	7167	2585	6848	2619	0.03

*After logarithmic transformation of the data and adjustment on age and menopausal status.

Olive oil is generally considered as a healthy source of fat, therefore a non-significant relative risk estimate was expected. However, because of the peculiar

place of olive oil in the Mediterranean diet, we further investigated which confounding factor could be responsible for the higher consumption of olive oil in the case group. It was shown (Table 20.3) that in the class of women with higher

Table 20.2—Relative risk estimates for generally recognized determinants of breast cancer

		Cases 409	Controls 515	OR*	95% CI
Family history of	No	383	501	1	
breast cancer (mother, sister)	Yes	26	14	2.5	(1.3–4.9)
Past history of	No	350	481	1	
benign breast disease	Yes	59	33	2.9	(1.8–4.6)
Age at menopause	<50	123	192	1	
(years)	≥50	142	117	1.8	(1.3–2.6)
Age at menarche	<12	89	112	1	
(years)	12–14	258	298	1.1	(0.8–1.6)
	>14	62	103	0.6	(0.4–1.0)
chi² test for trend (P value)				*2.79*	*(0.095)*
Parity	0	54	74	1	
	1–3	298	229	1.2	(0.8–1.8)
	≥4	57	102	0.8	(0.5–1.3)
chi² test for trend (P value)				*1.63*	*NS*
Age at first	<21	67	111	2	
full-term pregnancy	21–27	221	255	1.4	(0.9–1.9)
	>27	67	73	1.4	(0.9–2.2)
chi² test for trend (P value)				*2.25*	*NS*
Education level	<15	157	248	1	
(age at the end	15–18	175	179	1.7	(1.3–2.3)
of education)	>18	75	83	1.7	(1.1–2.5)
chi² test for trend (P value)				*7.71*	*(0.005)*
Quetelet index	<21.3	106	165	1	
(weight/height²)	21.3–24.2	132	166	1.2	(0.8–1.6)
	>24.2	170	182	1.3	(0.9–1.8)
chi² test for trend (P value)				*2.31*	*NS*

*Adjusted OR on age and menopausal status.

education, the number of low and high consumers of olive oil is strictly equal, and very comparable in the less educated women. In this last class, the largest number of high olive oil consumers, and symmetrically the lowest number of low consumers, is in the control group.

Table 20.3—Distribution of cases and controls according to the level of education and to olive oil consumption

Age at end of studies	Olive oil consumption (g/week)	Cases (*N*=399) %	Controls (*N*=504) %
–18	–34.6	67	60
	>34.6	33	40
>18	–34.6	27	27
	>34.6	73	73

In a multivariate analysis, all food items of Table 20.1 were simultaneously considered as well as the adjustment variables (classical risk factors, age, menopausal status and alcohol consumption). The only significant items are processed pork meat: OR_3=1.5 [1.0–2.2], *t*=1.92, high fat cheese: OR_3=1.4 [1.0–2.0], *t*=2.05, desserts and chocolate: OR_3=1.6 [1.1–2.4], *t*=2.63 and margarine: OR=0.65 [0.5–0.9], *t*=2.72, thus confirming overall the results of Table 20.4. When the multivariate analysis of all food items is carried out separately for pre- and postmenopausal women, the same items (processes pork meat, high fat cheese, desserts and chocolate and margarine) exhibit significant ORs for postmenopausal women whilst for premenopausal women the only statistically significant OR is that for margarine.

20.3.3 Nutrients

Table 20.5 shows the risk of BC for 3 levels of weekly consumption of animal protein, total fat and its constituents after adjustment on the classical risk factors of Table 20.2, age and menopausal status. The risk was increased significantly for total, animal, saturated and monounsaturated fat with a clearest trend for saturated fat. The ORs for the third fertile were all significant staying nevertheless below two. For animal protein the ORs were borderline significant and the test for trend was not significant.

Table 20.4—Relative risk estimates for the association between breast cancer and selected foods or food items+

	#	Cases	Controls	OR*	95% CI
	–510	134	184	1	
Meat	510–1080	127	153	1.0	(0.7–1.4)
	>1080	148	177	1.0	(0.7–1.4)
chi² test for trend (P value)				*0.01*	*NS*
	–25	100	173	1	
Processed pork	25–87.5	154	168	1.4	(1.0–2.0)
meat	>87.5	155	173	1.4	(0.9–2.0)

	#	Cases	Controls	OR*	95% CI
chi² test for trend (P value)				*2.81*	*(0.094)*
	–90	126	204	1	
High fat cheese	90–210	116	128	1.3	(0.9–1.8)
	>210	167	182	1.4	(1.0–1.9)
chi² test for trend (P value)				*5.25*	*(0.022)*
	No	278	313	1	
Margarine	Yes	127	193	0.7	(0.5–0.9)
	0	171	244	1	
Olive oil	–34.614	97	130	0.9	(0.6–1.3)
	>34.614	131	130	1.3	(0.9–1.8)
chi² test for trend (P value)				*1.33*	*NS*
	<300	111	154	1	
Citrus fruits	300–525	119	167	1.0	(0.7–1.4)
	–525	177	193	1.4	(1.0–2.0)
chi² test for trend (P value)				*3.50*	*(0.061)*

	#	Cases	Controls	OR*	95% CI
	<491	114	171	1	
Fruits rich in	491–963	135	170	1.0	(0.7–1.5)
ß-carotene	–963	158	172	1.4	(1.0–2.0)
chi² test for trend (P value)				*3.76*	*(0.052)*
	–125	108	176	1	
Desserts and	125–315	133	170	1.4	(1.0–2.0)
chocolate	>315	166	166	1.7	(1.2–2.5)
chi² test for trend (P value)				*10.4*	*(0.001)*
	0	207	288	1	
Nuts	–25	98	111	1.2	(0.8–1.6)
	>25	103	113	1.1	(0.8–1.5)
chi² test for trend (P value)				*0.40*	*NS*
	–5377	98	161	1	
Total food	5377–7447	143	159	1.5	(1.1–2.2)
	>7447	144	161	1.7	(1.1–2.4)

	#	Cases	Controls	OR*	95% CI
chi² test for trend (P value)				*6.95*	*(0.008)*

[+]Foods or food items which had different mean weekly intake for cases and controls; #classes are defined with respect to weekly consumption, units as defined in Table 20.1; *OR: Adjusted OR by logistic regression on age, menopausal status, alcohol consumption and all variables of Table 20.2 except Quetelet index.

The same nutrients were then investigated separately for pre- and postmenopausal women (Table 20.6). For premenopausal women there exists significant increasing trends for total, animal and monounsaturated fat intake after adjustment. Saturated fat shows a weaker trend. The ORs for animal protein intake are non-significant. No significant ORs were observed for polyunsaturated fat or cholesterol intake (results not shown). For postmenopausal women, only saturated fat shows a significant

Table 20.5—Relative risk estimates for the association between breast cancer and the intake of protein, fat and cholesterol

	#	Cases	Controls	OR*	95% CI
	–326	107	162	1	
Protein	326–4680	145	164	1.4	(1.0–1.9)
	>468	134	159	1.4	(1.0–2.0)
chi² test for trend (P value)				*3.34*	*(0.068)*
	–650	104	165	1	
Total fat	650–896	132	160	1.3	(0.9–1.9)
meat	>896	150	158	1.6	(1.1–2.2)
chi² test for trend (P value)				*6.06*	*(0.014)*
	–328	103	163	1	
Animal fat	328–491	149	166	1.5	(1.0–2.1)
	>491	141	159	1.6	(1.1–2.2)
chi² test for trend (P value)				*5.73*	*(0.017)*
	–190	96	166	1	
Saturated FA	190–268	133	159	1.4	(1.0–2.0)
	>268	158	158	1.9	(1.3–2.6)

	#	Cases	Controls	OR*	95% CI
chi² test for trend (P value)				*12.13*	*(<0.001)*
	–203	93	164	1	
Monounsaturated FA	203–289	142	160	1.6	(1.1–2.3)
	>289	152	159	1.7	(1.2–2.5)
chi² test for trend (P value)				*9.54*	*(0.002)*
	<183	112	161	1	
Polyunsaturated #	183–283	133	161	1.2	(0.9–1.7)
FA	–283	142	161	1.2	(0.9–1.7)
chi² test for trend (P value)				*1.28*	*NS*
	<0.82	127	162	1	
Polyunsaturated/	0.82–1.23	133	160	1.0	(0.7–1.4)
Saturated FA	–1.23	127	161	0.9	(0.6–1.3)
chi² test for trend (P value)				*0.23*	*NS*
	–2.68	115	162	1	
Cholesterol	2.68–3.81	145	165	1.4	(1.0–1.9)
	>3.81	159	159	1.3	(0.9–1.9)
chi² test for trend (P value)				*2.68*	*NS*

*OR: Ajusted OR by logistic regression on age, menopausal status and all variables of Table 20.2 except Quetelet index. The tertile classes correspond to grams per week; #including linoleic acid (18.2) which accounts for about 48% of the total polyunsaturated intake.

increasing trend after adjustment (which included age at menopause) as well as significant ORs for the third tertile. Monounsaturated fat exhibits a significant OR for the second tertile but no clear trend.

Table 20.7 displays the adjusted ORs for breast cancer related to the vitamin consumption found in our study. For ß-carotene and vitamin E intake there is no significant variation in the risk. For retinol a significant increasing trend is shown which is essentially related to postmenopausal women.

A multivariate analysis of all the nutrients including alcohol consumption was then carried out. Beforehand, possible interactions were investigated and a significant negative interaction was found between alcohol and total fat intake (see Richardson *et al*, 1989). The ORs for a high intake of total fat (–896 g/ week) are only significantly elevated (2, CI 1.2–3.4) for the women in the lowest class of alcohol consumption (<1 glass of alcoholic beverage per week). This interaction was taken into account in the logistic regressions.

A logistic regression model was fitted with the following independent variables: age, classical risk factors of Table 20.2 and menopausal status which were forced, alcohol intake, total fat, protein, cholesterol, retinol, ß-carotene and vitamin E intake and an interaction term between alcohol and total fat intake. All variables were categorized in 3 classes except age. The interaction term (4 coefficients) was simplified by assuming equality of all the interaction coefficients in line with the pattern shown in Table 20.8. This assumption is also justified as the improvement of the likelihood between a model with 4 interaction coefficients and a model assuming equality of all the interaction coefficients is non-significant (chi^2_3=1.54, NS).

In this first model, we found a significant negative interaction term between alcohol and total fat intake and significant ORs only for the main effect of total fat intake and alcohol intake (Table 20.9). All the other nutrients have non significant ORs; in particular the ORs for animal protein adjusted on total fat and alcohol intake have clearly decreased in comparison to the univariate analysis: OR_2=1.2 [0.8–1.7], OR_3=1.0 [0.6–1.6]. Fat and animal protein intake, which were both assessed comprehensively in our study, are important sources of calories. The ORs for this combined fat and protein calorie intake are significant (OR_2=1.4 [1.0–2.0], OR_3= 1.5 [1.1–2.2]) but weaker than those for total fat intake alone indicating that this variable is not particularly relevant in our study.

The constituents of total fat were then considered separately for pre- and postmenopausal women in a logistic regression including age, the classical risk factors of Table 20.2, age at menopause and Quetelet index for postmenopausal women only, alcohol intake, animal protein, saturated, monounsaturated and polyunsaturated fat intake, retinol, ß-carotene and vitamin E intake and two interaction terms between alcohol and saturated fat intake and between alcohol and monounsaturated fat intake. The results are different for pre- and postmenopausal women. For premenopausal women the only significant nutrient is monounsaturated fat with ORs similar to those of Table 20.6. In contrast for postmenopausal women, the ORs of saturated fat intake are significantly increased for both tertile with a clear trend. Those for monounsaturated fat do not show a trend with the OR for the second tertile only

Table 20.6—Relative risk estimates for the association between breast cancer and protein and fat intake in premenopausal and postmenopausal women

		Cases	Controls	OR*	95% CI
Premenopausal women					
	–326	28	51	1	
Protein	326–468	50	65	1.4	(0.7–2.6)
	>468	60	79	1.5	(0.8–2.8)
chi² test for trend (P value)				*1.08*	*NS*
	–650	30	62	1	
Total fat	650–896	45	61	1.5	(0.8–2.9)
	>896	63	71	1.8	(1.0–3.3)
chi² test for trend (P value)				*3.33*	*(0.068)*
	–328	26	57	1	
Animal fat	328–491	45	63	1.5	(0.8–2.5)
	>491	68	77	1.8	(1.0–3.5)
chi² test for trend (P value)				*3.21*	*(0.073)*
	–190	29	57	1	
Saturated FA	190–268	47	66	1.2	(0.6–2.3)
	>268	63	71	1.7	(0.9–3.2)
chi² test for trend (P value)				*3.16*	*(0.075)*
	–203	27	59	1	
Monounsaturated	203–289	46	67	1.4	(0.7–2.7)
FA	>289	66	68	2.0	(1.1–3.7)
chi² test for trend (P value)				*5.03*	*(0.025)*

		Cases	Controls	OR*	95% CI
Postmenopausal women					
	<326	79	111	1	
Protein	326–468	95	99	1.3	(0.9–2.1)
	>468	73	80	1.3	(0.8–2.1)
chi² test for trend (P value)				*1.3*	*NS*
	–650	74	103	1	
Total fat	650–896	87	99	1.2	(0.8–1.9)
	>896	86	87	1.4	(0.9–2.2)
chi² test for trend (P value)				*1.9*	*NS*
	–328	77	106	1	
Animal fat	328–491	104	103	1.6	(1.0–2.5)

	>491	72	82	1.3	(0.8–2.1)
chi² test for trend (P value)				*1.3*	*NS*
	–190	67	109	1	
Saturated FA	190–268	86	93	1.6	(1.0–2.5)
	>268	94	87	2.0	(1.2–3.1)
chi² test for trend (P value)				*8.3*	*(0.004)*
	–203	66	105	1	
Monounsaturated	203–289	96	93	1.7	(1.1–2.6)
FA	>289	85	91	1.5	(1.0–2.4)
chi² test for trend (P value)				*3.1*	*(0.078)*

*OR adjusted by logistic regression on age, all variables of Table 20.2 except Quetelet index and age at menopause for the postmenopausal group.

borderline significant and there is a significant negative interaction between alcohol intake and monounsaturated fat intake. The OR for the third fertile of retinol is borderline significant and those for animal protein show an inverse trend. As previously the OR for the third fertile of Quetelet index is significantly elevated. In view of the inverse trend shown between saturated fat and animal protein intake, it did not seem relevant to consider their combined calorie intake.

20.4 DISCUSSION

Overall in our study we have found some evidence that BC risk was associated with lipid intake.

As in all hospital-based case-control studies, selection bias cannot be totally excluded. The first to be addressed is a referral bias since the recruitment of neither cases or controls is exhaustive for their respective diseases. The questionnaire elicited information on the site of residence, characterized as rural, small towns or cities (>100,000 inhabitants); there is no difference between cases and controls in the distribution of the sample among these three classes, indicating that the control recruitment from the three hospitals had a similar origin to the case recruitment. There was also no difference in the proportion of cases and controls coming from the Languedox-Roussillon region or from farther departments, indicating comparable geographic coverage. Further the neurology

and neurosurgery wards belong to the same hospital group as the cancer treatment centre.

The second potential bias arises from the disease for which the controls were hospitalized. Our main concern was to avoid over-representation of a disease which could affect dietary practices. Care was taken to include only patients coming for a first diagnosis and not under treatment, and interviews were conducted shortly after diagnosis. Furthermore, the interviewers assessed the usual dietary history of the patients and not the recent diet. For patients declaring recent changes in dietary habits, they were asked to recall their previous dietary habits. The average duration of nutritional habits reported by cases was similar to that of controls. There is no evidence that selective under-declaration took place. Both cases and controls were patients in a hospital and had similar motivation for answering.

In their critical appraisal of the evidence that dietary fat intake is related to BC risk in humans, Goodwin and Boyd (1987) noted that in one case-control study which showed a positive association (Sarin *et al*, 1985), among the exclusion criteria for the controls were coronary heart diseases and diabetes mellitus. They suggested that this could bias the results toward finding a positive association since the same exclusions were not applied in the case group. We have only excluded cardiovascular diseases in the wards where they are clearly over-represented, leaving a percentage of 3% of cardiovascular pathologies in our controls. Further, medical history of hypertension and diabetes mellitus was recorded in our questionnaire and found to be comparable among cases and controls: 16% for cases *vs* 15% for controls for hypertension; 5.4% for cases *vs* 5. 8% for controls for diabetes. Therefore our positive results are not likely to be due to this bias.

Table 20.7—Relative risk estimates for the association between breast cancer and retinol, ß-carotene and vitamin E intake in the total study population and in premenopausal and postmenopausal women

		Cases	Controls	OR*	95% CI
Total women					
	–3.11	102	162	1	
Retinol	3.11–11.37	152	161	1.5	(1.1–2.1)
	>11.37	139	163	1.5	(1.0–2.1)
chi^2 test for trend (P value)				*5.34*	*(0.021)*
	–52	126	162	1	
ß-carotene	52–86	122	163	1.0	(0.7–1.4)
	>86	140	164	1.0	(0.7–1.5)
chi^2 test for trend (P value)				*0.01*	*NS*
	–98	111	162	1	
Vitamin E	98–170	129	163	1.2	(0.8–1.7)

		Cases	Controls	OR*	95% CI
	>170	145	158	1.3	(0.9–1.8)
chi² test for trend (P value)				*2.20*	*NS*
Premenopausal women					
	–3.11	32	56	1	
Retinol	3.11–11.37	60	63	1.8	(1.0–3.3)
	>11.37	47	78	1.3	(0.7–2.4)
chi² test for trend (P value)				*0.324*	*NS*
	–52	43	61	1	
ß-carotene	52–86	44	63	1.1	(0.6–2.0)
	>86	51	73	1.0	(0.6–1.8)
chi² test for trend (P value)				*0.002*	*NS*

		Cases	Controls	OR*	95% CI
	–98	39	66	1	
Vitamin E	98–170	52	69	1.2	(0.6–2.1)
	>170	47	59	1.2	(0.7–2.2)
chi² test for trend (P value)				*0.352*	*NS*
Postmenopausal women					
	–3.11	70	106	1	
Retinol	3.11–11.37	92	98	1.4	(0.9–2.2)
	>11.37	91	86	2.8	(1.2–2.8)
chi² test for trend (P value)				*6.96*	*(0.008)*
	–52	83	101	1	
ß-carotene	52–86	78	100	0.9	(0.6–1.5)
	>86	88	91	1.0	(0.6–1.5)
chi² test for trend (P value)				*0.15*	*NS*
	–98	72	96	1	
Vitamin E	98–170	77	94	1.2	(0.7–1.8)
	>170	97	99	1.3	(0.8–2.0)
chi² test for trend (P value)				*0.87*	*NS*

*OR adjusted by logistic regression on age, all variables of Table 20.2 except Quetelet index and age at menopause for the postmenopausal group. The fertile classes correspond to grams per week.

Purposely, we recruited controls in wards characterized by different diagnosis referral: neurology, neuro-surgery and general visceral surgery in order to dilute the potential effect of specific disease. Moreover, it has been checked that with regard to lipid intake, the three wards had comparable consumption which was always lower

Table 20.8—Relative risk estimates of total fat intake and alcohol consumption given by logistic regression

Variable	Category	OR*	95% CI	*t*
Alcohol consumption	1–7	3.1	1.8–5.4	4.0
(glasses/week)	>7	4.0	2.2–7.3	4.5
Total fat intake	651–896	1.8	1.1–3.0	2.4
	>896	2.0	1.2–3.3	2.8
Interaction term alcohol x total fat		0.5	0.3–1.0	–2.1

*Adjustment was made for age, the classical risk factors of Table 20.2 and menopausal status.

Table 20.9—Relative risk estimates of fat, protein, retinol intake and alcohol consumption given by logistic regression among postmenopausal women

Variable	Category	OR*	95% CI	*t*
Alcohol consumption	1–7	4.6	2.2–9.6	4.0
(glasses/week)	>7	6.0	2.6–13.9	4.2
Saturated fat	190–268	1.9	1.0–3.6	1.9
	>268	3.3	1.4–7.8	2.7
Monounsaturated fat	203–289	1.8	0.9–3.7	1.7
	>289	1.3	0.6–2.9	0.6
Interaction term alcohol x mono-unsaturated fat		0.3	0.1–0.8	–2.5
Protein	326–468	0.8	0.4–1.4	–0.9
	>468	0.4	0.2–0.9	–2.1
Retinol	3.11–11.37	1.2	0.7–2.0	0.7
	>11.37	1.7	1.0–2.8	1.9
Quetelet	21.3–24.2	1.2	0.7–2.1	0.6
	>24.2	1.8	1.1–3.1	2.2

*Adjustment was made for age, the classical risk factors of Table 20.2 and age at menopause. The tertile classes of the nutrients correspond to grams per week.

than that of the cases. We also attempted to compare the average intake for some food items or nutrients of our controls with those reported in other studies. The

average lipid intake per week of the controls is 812 gr, which is compatible with that found by Pequignot *et al* (1980) on a representative sample of French families living in urban areas of different sizes. The recent study of Toniolo *et al* (1989) was conducted in a Mediterranean population with somewhat similar nutritional habits to the population studied here. The daily meat (including poultry) consumption of controls in our study is comparable to that found by Toniolo (128 g in our study *vs* 133 g) and similarly for saturated fat (34 g in our study *vs* 32 g) and monounsaturated fat (38 g in our study *vs* 39 g for the controls).

Several arguments support the validity of the studied nutritional data. The dietary instrument used in our study was a list-based dietary history of similar design to the one described in Block *et al* (1986) and adapted to our country according to Pequignot and Cubeau (1973) except that the food list was restricted to key items for animal protein, lipid and some vitamin consumption. An evaluation of portion size either directly in grams for instance for meat or by reference to a stated medium serving was carried out enabling a satisfactory quantification and comparability between individuals. Interviewers were clearly aware of the case or control status of the patient but not of the specific objectives of the study. Since a large number of related food items are the source of a given nutrient, it is unlikely that any interviewing bias could influence the nutrient differences found between cases and controls.

The validity and reproducibility of such dietary questionnaires has been much discussed and some of the issues have been recently reviewed by Block and Hartman (1989). There is evidence that quantitative history interviews restricted to key items are capable of capturing to a large extent the variation of a particular nutrient in a population (Willett *et al*, 1985). Our questionnaire was administered by an interviewer and a recent study of Sobell *et al* (1989) indicated that this improves the correlation with past diet. It is difficult to compare the variability of lipid intake between our study and others since it is most often expressed as a variation of the proportion of calories derived by fat. This same proportion cannot be evaluated in our study since we could not calculate a total energy intake. Between the median of the lowest tertile and the highest tertile there is nevertheless a twofold increase or more for total fat, saturated fat and monounsaturated fat.

Another aspect of validation of a dietary instrument is the finding of some significant correlations between blood measurements and nutritional intake. This was discussed for a subsample of our study in Gerber *et al* (1988, 1989). It should nevertheless be assumed that the assessment of dietary intake by questionnaire leads to some measurement errors and some subjects being misclassified in the categorical analysis. Wu *et al* (1988) have shown that errors in reported dietary intake may account for a large part of the observed variation. Even if these measurement errors and misclassification are non-differential between cases and controls, the estimates will be biased conservatively and the control for confounding variables can be ineffective (Savitz and Baron, 1989).

Our study supports the hypothesis of an association between BC risk and dietary fat intake which was shown to be particularly strong for saturated fat and postmenopausal women BC. We come to this final result through successive steps, at first considering food groups, then nutrients and finally carrying out a multivariate analysis. As shown in Tables 20.1 and 20.3, the overall food intake of the cases (even that of citrus fruits) is larger than that of the controls but all the clearly significant ORs concern food items containing lipids. Note further that the ORs are increased for food items containing animal fat (high fat cheese, dessert and chocolate and to a less degree processed pork). In contrast the consumption of margarine, a vegetable fat, carried a lower risk. It has been demonstrated that in our region olive oil is an index of socioeconomic level, since as many cases as controls in the group with high level of education consume high level of olive oil. Since there are more highly educated cases than controls, the mean consumption is higher in the case group. However, adjustment on length of education allowed the calculation of a non-significant OR.

The same food items remain significantly associated after multivariate adjustment, especially for postmenopausal women. With regard to high fat cheese, our results can be compared to those of Nomura *et al*, 1978; Lê *et al*, 1986; Toniolo *et al*, 1989 and Van't Veer *et al*, 1990a. This last study as well as that of Lubin *et al* (1981) and Iscovitch *et al* (1989) also report on the association of BC risk with desserts and biscuits. Some studies (Nomura *et al*, 1978; Lubin *et al*, 1981) have quoted a positive association of BC with margarine intake but this item was always included in a grouping with other fatty foods. Among our controls, we checked that the dietary pattern of margarine users involved less animal fat, a pattern which could explain the inverse association.

Concerning the different fat constituents, the most significant ORs are related to saturated fat for postmenopausal women and to monounsaturated fat for premenopausal women (Table 20.5). This can be explained by the specific dietary patterns of these two groups. The differences in consumption between cases and controls are larger for items rich in monounsaturated fat (meat, olive oil) for the premenopausal group than for the postmenopausal group. On the contrary, for postmenopausal women, the main differences concern high fat cheese and processed pork. This might reflect an age-related dietary pattern. It is interesting to note that monounsaturated fat (essentially oleic acid) is also found to be a risk factor for BC in other population samples. Besides our study, this has been reported by Knekt *et al* (1990) and Shun-Zhang *et al* (1990) who showed monounsaturated fat to be a risk factor for BC both in Scandinavian and Chinese populations. But it contradicts the hypothesis proposed by Katsouyanni *et al* (1986) that olive oil (made up essentially of oleic acid) may be protective since they reported an OR<1 for fat in their study and since olive oil is the major source of lipid in Greece. However, there is an essential difference between the oleic acid ingested in the various countries. In Scandinavia, meat is the source of oleic acid (42%) with 45% of saturated fatty acids. In China poultry provides the oleic acid (52%) together with saturated fatty acids (29%) whereas in Greece,

olive oil (72% of oleic acid and 15% of saturated fatty acids) is the main source of monounsaturated fatty acids. Whether the difference with regard to BC risk is due to the different amount of saturated fatty acid or to the animal origin *vs* the vegetable origin of the oleic acid is not clear. But it is obvious that, in nutritional studies, olive oil should be considered as a food in its globality and not only by its nutrient content in fatty acids. This may give the clue for the understanding of the beneficial effect of Mediterranean diet. Further investigations on animal models are in progress in our laboratory to address this question.

Among the liposoluble vitamins, only retinol intake shows a significant increasing trend with elevated ORs for the third fertile especially for postmenopausal women.

In Tables 20.6 and 20.7, no adjustment was made for alcohol consumption and its negative interaction with lipid intake. Only when this interaction is taken into account does the effect of total fat become significant in the multivariate analysis. This negative interaction was necessary for the adjustment of a multiplicative model for the joint effect of alcohol and lipid intake whereas in our data, an additive model could seem to be more appropriate: the OR for women in the highest class of alcohol and total fat intake is 4.5 which corresponds indeed to the sum minus one of an OR equal to 2 for the sole effect of total fat and an OR equal to 3.5 for the sole effect of alcohol.

Total calorie intake could not be evaluated with our data hence we were unable to consider calorie adjustment of the relationship for fat intake by the methods usually taken (Willett and Stampfer, 1986; Howe, 1989). Testing for a difference of effect between the calories of fat and animal protein could have been done but was not deemed to be relevant in our data set since there is no evidence of increased risk associated with the intake of animal protein. Besides, it has been shown that the effects of different energy-adjustment methods may account, in part, for the varying interpretations in the cohort studies of dietary fat and breast cancer (Kushi *et al*, 1992).

Our results concerning the association with lipid and especially on the role of saturated fat in postmenopausal women are in line with the combined analysis of 12 case-control studies (Howe *et al*, 1990). Some of these studies have also found an increasing risk of BC in relation with the intake of animal protein contrary to our study where the borderline association with animal protein intake in the total sample disappeared when lipid intake was taken into account in the multivariate analysis. We have no indication of any risk reduction with increased consumption of either vegetables (total or green) or ß-carotene which does not confirm the results of Katsouyanni *et al* (1986), La Vecchia *et al* (1987), Rohan *et al* (1988), Iscovich *et al* (1989) and Van't Veer *et al* (1990b). The trend found for retinol in postmenopausal women was the opposite to that described by Graham *et al* (1982) and is only weakly significant after the multivariate analysis as expected in view of the higher consumption by the cases of food items which are rich both in saturated fat and retinol.

Although several case-control studies and most prospective studies did not find any evidence of an association between BC and dietary fat intake, there exist underlying biological mechanisms which give plausibility to the existence of this association. The main mechanisms suggested concern hormones especially oestrogens because of the importance of hormone-related risk factors in BC and of the experimental evidence that estrogen promotes tumour growth and can induce transforming factors in BC cells (Dickson *et al*, 1986). One of the most likely mechanisms involves an endogenous synthesis of oestrogens from steroids in adipose tissues owing to the presence in adipocytes of the aromatase enzyme (Siiteri, 1978). This explanation is supported by the results of an intervention trial showing that by reducing dietary fat intake from near 40% to 20% of kilocalories, there was a 17% reduction in the average estradiol blood concentration (Prentice *et al*, 1990). In addition, large amounts of fat in the gut content might alter estrogen-metabolizing intestinal flora (Hill, 1971). Some studies have found that the association of energy intake with BC risk was stronger than the one with lipid. Since it is known that the lipid-related calories are the last to metabolize, the net result of a high energy intake is lipid storage (Schutz *et al*, 1989). Thus the risk association with high energy intake is not in contradiction with the risk associated with high lipid storage or Quetelet index as we have found in our multivariate analysis of postmenopausal women. Finally, a mechanism has been invoked concerning the specific role of saturated fatty acids. They could modulate the peripheral activity of oestrogens through the oesterification of oestradiol by fatty acids of the peripheral tissue. The estradiol esters formed with saturated fatty acids have more potent organ action than those formed with polyunsaturated fatty acids (Horrobin and Manku, 1989). Thus normal plasma concentrations of oestradiol may result in increased hormonal effect when there exists an excess of saturated fat in the peripheral tissue.

In conclusion we have found evidence in our study of a positive association between dietary fat and BC in women and especially saturated fat in postmenopausal women. The findings support the rationale for dietary recommendations and intervention studies.

ACKNOWLEDGEMENTS

This work was supported by the *Ligue National contre le Cancer*. The authors thank Dr Cadillac, Dr Frerebeau, Dr Labauge and Dr Vlahovitch from Neurology and Neuro-Surgery wards (Hôpital Gui-de-Chauliac) and their nursing staff for collaboration in control sample recruitment and all medical secretarial and nursing staff of Professor Pujol, CRLC.

REFERENCES

Block G (1982). A review of validations of dietary assessment methods. *Amer J Epidemiol* **115:** 492–505.

Block G, Hartman AM, Dresser CM, Carroll MD, Cannon J, Gardner L (1986). A data-based approach to diet questionnaire design and testing. *Amer J Epidemiol* **124:** 453–69.

Block G, Hartman AM (1989). Issues in reproducibility and validity of dietary studies. *Amer J Clin Nutr* **50:** 1133–8.

BMDP (1985). Statistical software. University of California Press, Berkeley.

Breslow NE, Day NE (1980). Statistical methods in cancer research. Vol. 1. The analysis of case control studies. IARC Scientific Publication No. 32, IARC, Lyon, p. 5–338.

Dickson RB, McManaway MF, Lippman ME (1986). Estrogen induced factors of BC cells partially replace estrogen to promote tumor growth. *Science* **232:** 1540– 5.

Gerber M, Cavallo F, Marubini E *et al* (1988). Liposoluble vitamins and lipid parameters in breast cancer. A joint study in Northern Italy and Southern France. *Int J Cancer* **42:** 489–94.

Gerber M, Richardson S, Crastes de Paulet P, Pujol H, Crastes de Paulet A (1989). Relationship between vitamin E and polyunsaturated fatty acids in breast cancer. Nutritional and metabolic aspects. *Cancer* **64:** 2347–53.

Goodwin PJ, Boyd NF (1987). Critical appraisal of the evidence that dietary fat intake is related to breast cancer risk in humans. *J Nat Cancer Inst* **79:** 473–85.

Graham S, Marshall J, Mettlin C, Rzepka T, Nemoto T, Byers T (1982). Diet in the epidemiology of breast cancer. *Amer J Epidemiol* **116:** 68–75.

Hankin JH, Zhao LP, wilkens LR, Kolonel LR (1992). Attributable risk of breast, prostate and lung cancer in Hawaii due to standard fat. *Cancer Causes Control* **3:** 17–23.

Hill MJ, Goddard P, Williams REO (1971). Gut bacteria and etiology of cancer of large bowel. *Lancet* **1:** 95–100.

Hirayama T (1978). Epidemiology of breast cancer with special reference to the role of diet. *Prev Med* **7:** 173–95.

Hirayama T (1979). Diet and cancer. *Nutr Cancer* **1:** 67–81.

Hislop TG, Coldman AJ, Elwood JM, Brauer G, Kan L (1986). Childhood and recent eating patterns and risk of breast cancer. *Cancer Detect Prev* **9:** 47–58.

Horrobin DF, Manku MS (1989). Premenstrual syndrome and premenstrual breast pain (cyclical mastalgia): disorders of essential fatty acid (EFA) metabolism. *Prostaglandins leukotrienes and essential fatty acids: Reviews* **37:** 255–61.

Howe G (1989). Total energy intake: implications for epidemiolgoic analyses. *Amer J Epidemiol* **129:** 1315.

Howe GR, Freidenreich CM, Jain M *et al* (1991). A cohort study of fat intake and risk of breast cancer. *J Natl Cancer Inst* **83:** 336–40.

Howe GR, Hirohata T, Hislop TG *et al* (1990). Dietary factors and risk of breast cancer: combined analysis of 12 case-control studies. *J Nat Cancer Inst* **82:** 561– 9.

Iscovich JM, Iscovich RB, Howe G, Shiboski S, Kaldor JM (1989). A case-control study of diet and breast cancer in Argentina. *Int J Cancer* **44:** 770–6.

Jones DY, Shatzkin A, Green SB *et al* (1987). Dietary fat and breast cancer in the National Health and Nutrition Examination Survey I epidemiology follow-up study. *J Natl Cancer Inst* **79:** 475–7.

Katsouyanni K, Trichopoulos D, Boyle P *et al* (1986). Diet and breast cancer. A case-control study in Greece. *Int J Cancer* **38:** 815–20.

Knekt P, Albanes D, Seppanco R *et al* (1990). Dietary fat and risk of breast cancer. *Am J Clin Nutr* **52:** 903–8.

Kushi LH, Sellers TA, Potter JD *et al* (1992). Dietary fat and post-menopausal breast cancer. *J Natl Cancer Inst* **84:** 1092–9.

La Vecchia C, Decarli A, Franceschi S, Gentile A, Negri E, Parazzini F (1987). Dietary factors and the risk of breast cancer. *Nutr Cancer* **10:** 205–14.

Lê MG, Moulton LH, Hill C, Kramar A (1986). Consumption of dairy produce and alcohol in a case-control study of breast cancer. *J Nat Cancer Inst* **77:** 633–6.

Lubin JH, Burns BE, Blot WJ, Ziegler RG, Lees AW, Fraumeni JF (1981). Dietary factors and breast cancer risk. *Int J Cancer* **28:** 685–9.

Lubin F, Wax Y, Modan B (1986). Role of fat, animal protein and dietary fiber in breast cancer etiology: a case-control study. *J Nat Cancer Inst* **77:** 605–12.

Miller AB (1981). Breast cancer. *Cancer* **47:** 1109–13.

Nomura AM, Henderson BE, Lee J (1978). Breast cancer and diet among the Japanese in Hawaii. *Amer J Clin Nutr* **31:** 2020–5.

Paul AA, Southgate DAT (1978). In *The composition of food* (eds McCance, Widdowson); 4th edition, Elsevier, North Holland, Amsterdam.

Péquignot G, Cubeau J (1973). Enquêtes méthodologiques comparant chez les memes sujets la consommation alimentaire appréciée par interrogatoire à la consommation mesurée par pesée. *Rev Epidémiol Med Soc Santé Publique* **21:** 585–608.

Péquignot G, Serville Y, Cubeau J, Guilloud-Bataille MM, Guggenbuhl-Péquignot F (1980). La consommation alimentaire des Francais en fonction de la taille des agglomérations, reflet de l'évolution longitudinale. *Rev Epidémiol Santé Publique* **28:** 169–83.

Phillips RL, Snowdon DA (1983). Association of meat and coffee use with cancers of the large bowel, breast and prostate among Seventh-day Adventists: preliminary results. *Cancer Res* **43:** 2403–8.

Prentice R, Thompson D, Clifford C, Gorbach S, Goldin B, Byar D (1990). Dietary fat reduction and plasma estradiol concentration in healthy postmenopausal women. *J Nat Cancer Inst* **82:** 129–34.

Randouin L, Legalic P, Dupuis Y, Bernardin J (1985). Tables de composition des aliments. Institut scientifique d'Hygiéne Alimentaire. J Lanore, Paris.

Richardson S, De Vincenzi I, Pujol H, Gerber M (1989). Alcohol consumption in a case-control study of breast cancer in Southern France. *Int J Cancer* **44:** 84–89.

Rohan TE, McMichael AJ, Baghurst PA (1988). A population based case-control study of diet and breast cancer in Australia. *Amer J Epidemiol* **128:** 478–89.

Rose DP, Boyar AP, Wynder EL (1986). International comparisons of mortality rates for cancer of the breast, ovary, prostate and colon and per capita food consumption. *Cancer* **58:** 2363–71.

Sarin R, Tandon RK, Paul S, Gandhi BM, Kapur BML, Kapur K (1985). Diet, body fat and plasma lipids in breast cancer. *Indian J Med Res* **81:** 493–8.

Schutz Y, Flatt JP, Jéquier E (1989). Failure of dietary fat intake to promote fat oxidation: a factor favoring the development of obesity. *Amer J Clin Nutr* **50:** 307–14.

Schun-Zhang Y, Rui-Fang L, Da-Dao X, Howe GR (1978). A case-control study of dietary and nondietary risk factors for breast cancer in Shanghai. *Cancer Res* **50:** 5017–21.

Siiteri PK (1978). Steroid hormones and endometrial cancer. *Cancer Res* **38:** 4360– 5.

Sobell J, Block G, Koslowe P, Tobin J, Andres R (1989). Validation of a retrospective questionnaire assessing diet 10–15 years ago. *Amer J Epidemiol* **130:** 173–87.

Toniolo P, Riboli E, Protta F, Charrel M, Cappa AP (1989). Calorie-providing nutrients and risk of breast cancer. *J Nat Cancer Inst* **81:** 278–86.

Tuyns AJ, Péquignot G, Jensen OM, Pomeau Y (1975). La consommation individuelle de boissons alcoolisées et de tabac dans un échantillon de la populaiton en Ille et Vilaine. *Rev Alcool* **21:** 105–50.

Van't Veer P, Kok FJ, Brants HAM, Ockhuizen T, Sturmans F, Hermus RJJ (1990a). Dietary fat and the risk of breast cancer. *Int J Epidemiol* **19:** 12–18.

Van't Veer P, Kolb C, Verhoef P, Kok FJ, Schouten EG, Hermus RJJ, Sturmans F (1990b). Dietary fiber, beta-carotene and breast cancer: results from a case-control study. *Int J Cancer* **45:** 825–8.

Willett WC, MacMahon B (1984). Diet and cancer—an overview. *N Engl J Med* **310, 10:** 633–8.

Willett WC, Sampson L, Stampfer MJ *et al* (1985). Reproducibility and validity of a semiquantitative food frequency questionnaire. *Amer J Epidemiol* **122:** 51–65.

Willett WC, Stampfer MJ (1986). Total energy intake: implications for epidemiologic analyses. *Amer J Epidemiol* **124:** 17–27.

Willett W, Stampfer MJ, Colditz GA *et al* (1987). Dietary fat and the risk of breast cancer. *N Eng J Med* **316:** 22–8.

Wu ML, Whittemore AS, Jung DL (1988). Errors in reported dietary intakes. *Amer J Epidemiol* **128:** 1137–45.

Wynder EL (1980). Dietary factors related to breast cancer. *Cancer* **46:** 899–904.

Yu H, Harris RE, Gao YT (1991). Comparative epidemiology of cancers of the colon, rectum, prostate and breast in Shanghai, China versus the United States. *Int J Epidemiol* **20:** 76–81.

21
Diet and colorectal carcinogenesis
M J Hill

21.1
INTRODUCTION

Colorectal cancer is one of the so-called *diseases of Western affluence*, being common in North America, Australasia, north and western Europe and the River Plate region of South America, and relatively rare in Africa, Asia and the Andean countries of South and Central America. Within Europe the disease has a relatively low incidence in the south and relatively high in the central European countries such as Czechoslovakia, Hungary, Austria, Switzerland and Germany, as well as in the Benelux countries and the British Isles. This has been discussed in detailed in Chapter 4.

Since all of the African and Asian countries have low incidences of the disease, this suggested an important role for racial/genetic factors. However, this was disproved by the studies of migrants within and between countries, which showed that the risk of colorectal cancer was related to the current place of residence and not to the country of origin. In this respect colorectal cancer contrasted with gastric and breast cancer, where the risk of the disease is related to the country of origin unless the person migrated early in life before the age of 20. The migrant studies suggested that colorectal cancer is caused by environmental factors associated with geographical place of residence; such environmental factors can be divided into (a) the physical factors dependent solely on geograph (*eg* air pollution, attitude, climate, etc) and which are necessarily shared with neighbours, and (b) the cultural factors which are chosen by the individual and which need not necessarily be shared with the rest of the local population (*eg* religious practices, diet). These types of factors can be distinguished by studying populations with a shared physical environment and different cultures (*eg* the racial groups in Johannesburg, the religious subgroups in Bombay, the subgroups of Chinese in Singapore, the religious subgroups in southern California). In all of these situations the distinct cultural groups have distinct colorectal cancer incidences. The epidemiology of colorectal cancer has been reviewed in detail elsewhere (Faivre *et al*, 1985; Hill, 1986; DeCosse and Bayle, 1985).

It is generally accepted that the total epidemiology of colorectal cancer is consistent with a key role for dietary factors in the aetiology of the disease. However, it is recognized also that the epidemiology of cancer of the proximal colon, distal colon and rectum differ in important respects (Faivre *et al*, 1985; Jensen, 1985). It is also recognized that colorectal cancers arise via the adenoma-carcinoma sequence and have a multistage aetiology (Hill *et al*, 1978); the role of diet may differ at the different stages of the disease.

In this chapter I will review the evidence relating colorectal cancer risk to specific dietary items and in particular the role of diet in the individual steps of the adenomacarcinoma sequence.

21.2 POPULATION STUDIES

Very many population (or *ecological*) studies of diet and colorectal cancer have been carried out, particularly in the 1970s and early 1980s. In such studies the risk of cancer in a group of populations is correlated with the mean diet of those populations. In many such population correlations, the incidence of colon or colorectal cancer was taken from the tables produced by the International Agency for Research on Cancer (*eg* Doll *et al*, 1970; Waterhouse *et al*, 1976, 1982; Muir *et al*, 1987) from registries that meet the standards of quality control set by IARC; in many other studies mortality statistics of the type compiles by Segi (*eg* Segi, 1984). The major problem with the mortality data, which are usually for countries (see, for example, Table 4.3 and 4.4) is that they are influenced by the quality of medical services and the consequent success rate in treatment of cancers. The incidence data from IARC are reliable and accurate but are from registries that do not necessarily cover the whole, or even a large part, of a country. This latter is important because the diet data are usually taken from tables compiled by the WHO-Food and Agriculture Organization; these are for whole countries and so rarely correspond exactly to the populations used for the cancer statistics. The FAO data suffer further from being based on food sold in shops and take no account of food wastage, food grown in gardens etc. Nevertheless, despite these problems, there is considerable concordance between the various studies (Table 21.1). Almost all show a strong correlation between colon cancer and intake of animal fat, total fat or meat. Many show a protective effect of cereals (and of cereal fibre) and vegetables. The correlation coefficients observed usually are well above r=0.70, which is remarkably high for dietary studies and should have been difficult to dismiss. The data *have* been dismissed, however, by many epidemiologists because of the shortcomings of the data used and for the reasons discussed below. An important observation by Gregor *et al* (1969) has not been repeated by others; they correlated the risk of colon cancer with current diet and with the diet 20 years earlier. The correlations were much stronger with current diet, suggesting a role in tumour promotion rather than tumour initiation.

Table 21.1—Population studies of diet and colorectal cancer

Reference	Observation
Gregor *et al* (1969)	In a study of 28 populaitons, showed a strong correlation with dietary protein. The strongest correlation was with current diet and not diet of 20 years earlier.
Drasar and Irving (1973)	In a study of 37 populations, observed very strong correlations with fat (particularly animal and hidden fat) and protein.
Armstrong and Doll (1975)	In a study of 23 populations, observaitons similar to those above. No relation with fibre.
Liu *et al* (1979)	Major correlation with fat and cholesterol.
Enstrom (1977)	Study of 47 countries showed correlation with beer and rectal cancer.
Hill *et al* (1979)	Three social classes in Hong Kong showed correlation with fat, meat and fibre.
Eyssen and Bright-See (1984)	Strong correlation with fat and meat; weak inverse correlation with fibre.

21.3 CASE-CONTROL STUDIES

The populations compared in the studies in Table 21.1 were usually taken from the whole world (in order to provide the greatest range in cancer incidence and diet data) and so they differ in many other respects in addition to diet; in case-control studies these can be controlled, in principle, and so the correlations obtained should be much more reliable. In fact the problems and shortcomings encountered with the population studies pale into insignificance in comparison with those seen with case-control studies of digestive tract disease. This is because the onset of symptoms may be slow and insidious and, during that time, patients modify their diet in order to ameliorate symptoms. It is necessary therefore to attempt to determine the diet corresponding to the period before the onset of symptoms using diet recall techniques. These are notoriously unreliable and in consequence older case-control studies correlated the risk of colon cancer with a wide range of dietary components (Table 21.2). The lack of clear and strong correlations with fat and meat from the majority of these early case-control studies has been widely used as the reason for rejecting the results of the population studies.

Table 21.2—Early case-control studies of diet and colorectal cancer

Reference	Observation
Perau (1960)	Strong correlation with fat.
Higginson (1966)	No correlations.

Reference	Observation
Wynder and Shigematsu (1967)	No correlation.
Moclan *et al* (1975)	Correlation (inverse) with crude fibre.
Haenszel *et al* (1973)	Correlatin with intake of meat and string beans.
Haenszel *et al* (1980)	No correlations.
Bjelke (1974)	Protective effect of vitamins A and C.
Dean *et al* (1979)	Correlation of beer and rectal cancer.
Jensen (1979)	No relation of beer and rectal cancer.
Phillips (1975)	Correlation with meat and fat and protective effect of vegetables.

More recent case-control studies have begun to yield results implicating fat and meat (Table 21.3). In particular Jain *et al* (1980) and Miller and Jain (1983) showed a strong dose-response correlation between colorectal cancer incidence and intake of fat and meat. Interestingly a number of recent European studies (*eg* Manousos *et al*, 1983; Macquart-Moulin *et al*, 1986; Tuyns *et al*, 1987; La Vecchia *et al*, 1988; Benito *et al*, 1991) have all continued to be unable to find a significant correlation with fat intake although meat was found to be correlated in 3 of the 5 studies cited. The most remarkable observation from the case-control studies have been the almost unanimous observation of a protective effect of vegetables, which has been confirmed in pooled analyses described in more detail in Chapter 17. The mechanism of this protection has been the subject of much interest. It could be due to the fibre content, but many of the studies included an investigation of fibre and found it to be more *weakly* correlated (Jain *et al*, 1980; Macquart-Moulin *et al*, 1986). It could be due to the antioxidant vitamin content, since the antioxidant vitamins are known to be scavengers of proximate carcinogens. However, in a number of studies the correlation with vitamin C was much weaker than that for vegetables (Jain *et al*, 1980; Tuyns *et al*, 1987; La Vecchia *et al*, 1988). It could be due to the array of anticarcinogens found in plant material and discussed in greater detail in Chapter 19, but there is an almost total lack of epidemiological information on this. Such data would be largely of academic interest but could reinforce the conclusions regarding the protective effect of vegetables.

Table 21.3—Case-control studies of diet and colorectal cancer

	Total fat/ Animal/ Sat. fat	Meat/ Protein	Fish	Fibre	Veg	Fruit	Vitamins		
							A	C	Ca
Jain *et al*, 1980	+	+	·	0	–	·		0	
Martinez *et al*, 1981	+	+	·	+	·	·			
Potter *et al*, 1982	+	+	·	+	·		0	–	

	Total fat/ Animal/ Sat. fat	Meat/ Protein	Fish	Fibre	Veg	Fruit	Vitamins		
							A	C	Ca
Manousos *et al*, 1983	·	+	·	·	–	0			
Bristol *et al*, 1985	+	0	·	0	·	·	0	0	
Macquart-Moulin *et al*, 1986	0	0	0	0	–	0	0	–	0
Tuyns *et al*, 1987	0	0	0	–	–	0	+	0	0
Kune *et al*, 1987	+	+	–	–	–	0	0	–	0
Lyon *et al*, 1987	+	+	·	–	·	·	·	·	
La Vecchia, 1988	0	+	–	·	–	·	0	0	
Young and Wolf, 1988	·	+	·	·	–	·	·	·	
Graham *et al*, 1988	+	0	+	0	·	·	0	0	0
Slattery *et al*, 1988	+	+	·	·	·	·	·	·	–
West *et al*, 1989	+	+	·	–	–	·	·	–	
Freudenheim *et al*, 1990	+	+	·	–	·	·	·	–	0
Benito *et al*, 1991	0	+	·	–	–	·	·	·	

21.4
COHORT STUDIES

The problems with case-control studies of colorectal cancer and diet are almost entirely related to the problems of dietary assessment at a pre-symptomatic time period (*ie* the problems of diet recall). In cohort studies these problems are avoided since the current diet is assessed in a group of healthy persons who are then followed until disease (or symptoms) develop. The results of such studies are therefore much more reliable than those from case-control studies. However, in order to get 100 incident cases of colorectal cancer it is necessary to assemble a cohort of 10,000 persons aged more than 50 years and to follow them for about 10 years. This is therefore extremely expensive both in financial terms (the cost of 10,000 diet assessments) and in time (10 years of follow-up), and in consequence relatively few such studies have been carried out. By far the biggest and best such study relating diet to cancer risk is that by Hirayama described in

Chapter 2 of this book. Table 21.4 describes the major cohort studies reported to date. Of these, two concerned diet in general and used reliable dietary assessment methods. That by Hirayama is described in detail in Chapter 2; the major observation was that in a low incidence population (Japan) the major dietary factor was the protective effect of green leafy vegetables; when this was controlled for, there was a positive correlation with intake of fat and meat. The study by Willett was of a cohort of American nurses and showed that (a) risk of the disease was related to intake of dietary fat and meat; (b) within the fat classification, the disease was much more strongly associated with animal than with vegetable fat, and more with saturated than with unsaturated or polyunsaturated fat; (c) within the meat classification the association was much stronger for beef and carcase meat than with poultry, whilst fish meat was protective; (d) fibre, particularly cereal fibre, was protective. The study by Garland *et al* (1985) was concentrated on the role of vitamin D and calcium (intake of the two being interdependent) and found that they were associated with decreased risk of colorectal cancer. The study by Pollack *et al* (1984) was of alcohol and cancer and showed, in particular, a strong association of beer intake with rectal cancer.

Table 21.4—Cohort studies of diet and colorectal cancer

Reference	Country	Observation
Hirayama (1985)	Japan	Protective effect of green/yellow vegetables; correlation with meat.
Willett *et al* (1990)	US	Correlation with fat and meat; protection by fibre.
Garland *et al* (1985)	US	Protective effect of vitamin D and calcium.
Pollack *et al* (1984)	US	Correlation of beer and rectal cancer.

21.5
ANIMAL AND EXPERIMENTAL STUDIES

The value of animal models of human disease is that they permit the isolation of particular factors for study with the rest being controlled. For example, in the study of diet and cancer, specific defined diets can be given to rodents every day for life, or for specific time periods; interactions with hormonal factors can be studied by comparing male and female animals, or comparing complete with neutered animals. The effect of diet on sensitivity to carcinogens can be studied by varying the diet in the weeks before administration of the carcinogen; its role in tumour promotion can be studied by varying the post-carcinogenesis diet. The role of genetic factors can be controlled by using animals from genetically pure strains; they can be kept under environmentally controlled conditions etc. In fact, all variables can, in theory, be closely controlled enabling the study of the effect of single isolated variables. For the experiments to be valid, however, it is

necessary for the animal disease to behave as similarly as possible to that in humans.

It is clear from animal model studies that diet has a profound effect on the promotion phase of colorectal carcinogenesis; this was demonstrated several decades ago by Tannenbaum and Silverstone (1953) who demonstrated the effect of total calorie intake and total fat intake on the rate of development of spontaneous tumours in rats and mice. However, animal models have been less useful in demonstrating what the effect of specific dietary changes will be on colorectal cancer risk. Rodents do not normally develop colorectal cancers except at extremely low incidence rates. In consequence they must be given cancer initiators in order to *give* them colorectal cancer. Table 21.5 shows the effect of the nature of the initiator on tumour incidence; it shows that, for example, pectin might promote, or inhibit or have no effect on colon carcinogenesis depending on the initiator chosen, similarly, cellulose might protect against colon cancer or have no effect depending on the initiator used. The effect of a dietary manipulation might also vary with the route of administration of the carcinogen, or on the sex of the rodent.

Table 21.5—The effect of non-dietary parameters on the effect of dietary manipulation on colorectal carcinogenesis (for details see Hill, 1989)

Dietary supplement	Carcinogen	Route	Sex of rats	Effect on colorectal cancer
Nature of carcinogen				
Cellulose	AOM	Sc	M	No effect
	DMH	Sc	M	Protection
Pectin	MNU	IR	F	No effect
	AOM	Sc	F	Protection
	DMH	Sc	M	Promotion
Route of administration of carcinogen				
Cellulose	DMH	Sc	M	Protection
		Oral	M	No effect
Hemicellulose	DMH	Sc	M	No effect
		Oral	M	Protection
Bran	DMH	Oral	M	Protection
		Sc	M	Promotion
Sex of rats				
Bran	DMH	Oral	M	Protection
			F	No effect

Since we do not know what the initiation of human colorectal cancers is caused by, or the route by which it enters the human body, we have no idea of how to interpret the data in Table 21.5. In consequence, although from Table 21.5 it is

clear that diet has a profound effect on the rate of colorectal tumour formation it tells us nothing of the dietary factors of importance in human cancer.

21.6
HISTOGENESIS OF COLORECTAL CANCER

Colorectal carcinogenesis is not a single-step process but occurs as the result of a number of discrete steps that have been characterized by the histopathologists. The first step is the formation of a small area of dysplasia usually manifest as a raised lump—an adenoma. The second stage is adenoma growth; the third is the increase in the severity of epithelial dysplasia within the adenoma. The final stage is when the dysplastic lesion crosses the *muscularis mucosae*; this is important because it then has access to the vascular and lymph drainage systems for metastatic spread of the lesion. The background to this formulation of the adenoma-carcinoma sequence has been discussed in detail elsewhere (Hill, 1978, 1986, 1991).

The epidemiology of small adenomas difffers greatly from that of large adenomas and carcinomas and so they clearly have different epidemiologies and aetiologies. Although size is associated with severity of dysplasia in adenomas, many large adenomas remain only mildly dysplastic and so growth does not automatically result in increased severity of dysplasia; the latter must be caused. Table 21.6 summarizes what we know about the various steps in colorectal carcinogenesis.

Table 21.6—Factors implicated inthe stages of the adenoma-carinoma sequence

Adenoma formation	Cigarette smoking
	Rare in Africans but commin in black Americans
	Vegetables protective
Adenoma growth	*Western* diet and lifestyle
	Familial factors
	Alcohol
Severity of dysplasia	Colonic bile acids

21.6.1
Adenoma formation

Correa (1978) reviewed the epidemiology of adenomas. Although in general they have a high prevalence in areas with a high incidence of colorectal cancer, there are some major discrepancies, and areas exist with similar incidences of colon cancer and very different prevalence of colorectal adenomas; the converse is also true (Hill, 1986). Further, whereas at autopsy adenomas are evenly distributed along the colon, carcinomas tend to be concentrated in the sigmoid and rectum or the caecum. The distribution of adenomas geographically suggests the

importance of some aspect of western life style; their distribution along the colon suggests that they are caused by some factor delivered via the vascular system rather than the gut lumen (where any moiety would show a concentration gradient the slope of which would depend on its rate of formation and its rate of absorption from the colon). Adenomas are very rare in Africans but not in black Americans, suggesting that the protective factor is in the African diet and not in the African genes.

Cigarette smoking has been associated with adenoma formation in a number of studies (Hoff *et al*, 1986; Boutron *et al*, 1991; Faivre, 1992). If this is important then we should begin soon to see the effect of the massive decrease in tobacco usage amongst professional persons in the northern countries of Europe, which started in the 1970s.

In the study by Macquart-Moulin *et al* (1989), vegetable consumption was found to be protective. However, in that study adenomas were not graded by size and so it is impossible to know whether vegetables were protective against adenoma formation, or growth, or both of these.

In the study by Hill *et al* (1986) there was no relation between faecal bile acid concentration and adenoma formation. For reasons that will be discussed in the next section, this suggests that the factors associated with western life style and implicated in colorectal adenoma formation are not the high fat/high meat/low fibre diet usually characterized as western. Since this diet pattern would be expected to affect mainly the luminal contents, which are unlikely to be responsible for adenoma formation, this is not necessarily surprising.

21.6.2
Adenoma growth

The epidemiology of large adenomas differs from that of adenomas *per se*. Geographically, the prevalence of large adenomas is higher in western populations than in countries with a low incidence of colorectal cancer. Within the colorectum large adenomas are not evenly distributed but are predominantly in the sigmoid colon and rectum. Whereas only a tiny proportion of small adenomas contains a malignant component more than 40% of large adenomas do so. Similarly, the risk of severe dysplasia is very much higher in large than in small adenomas. The epidemiology of large and small adenomas is described in Table 21.7.

Small adenomas are very common and only a tiny proportion will progress to malignancy; in contrast large adenomas are much less common but carry a very high malignant potential. Clearly, therefore, the rate limiting step in colorectal carcinogenesis is adenoma growth and the epidemiology of colorectal cancer overall will be dominated by that of the rate limiting step—adenoma growth. Thus, the role of high fat/meat, low fibre, low fresh fruit and vegetables in colorectal cancer is likely to be at the adenoma growth stage. In addition, adenoma growth has been associated with high alcohol intake (Faivre, 1992).

Table 21.7—Epidemiology of small and large adenomas

	Small adenomas	Large adenomas
Distribution along the colon	Even	Concentrated in left colon
Malignant potential	Low	High
Proportion with dysplasia	Low	High
Proportion of all adenomas		
in Japan	High	Low
in USA	High	Higher than in Japan
Relation to smoking	Correlation	No correlation
Relation to alcohol	Weak relation	Good correlation

The importance of fat and meat at the adenoma growth stage is supported by the observation that the rate of adenoma size is correlated with the faecal bile acid concentration (Hill, 1986), the major determinants of which are fat intake and (inversely) cereal fibre.

21.6.3
Dysplasia

The severity of dysplasia in an adenoma correlates with its size (Morson *et al*, 1983), but not all severely dysplastic adenomas are large and not all large adenomas will become severely dysplastic. Severity of dysplasia therefore has a cause. However, the correlation between adenoma size and severity of dysplasia is similar in Japan, UK and Sweden, suggesting that the responsible factors are ubiquitous. We know little of the role of diet in this process, except that dietary calcium ameliorates the dysplastic activity of bile acids (Wargovich *et al*, 1983; Rafter *et al*, 1991).

21.7
CONCLUSIONS

Clearly, diet is important in the causation of colorectal cancer, but in order to understand its role we need to know more of the role of different dietary factors in the different stages of colorectal carcinogenesis. Within Europe there is a wide range of diet patterns and this provides an ideal setting for the study of the causation of colorectal adenomas—the first step in carcinogenesis. It is very apparent how great the contribution of the cancer registries has been to our understanding of cancer overall. What we need now is registries of precancerous lesions, preferably with details of size, severity of dysplasia, location, appearance at follow-up etc. We need also to know more of the natural history of adenomas, but such a study would present insurmountable ethical problems.

REFERENCES

Armstrong BD, Doll R (1975). Environmental factors and cancer incidence in different countries, with special reference to dietary practices. *Int J Cancer* **15:** 617–31.

Benito E, Stiggelbout A, Bosch FX *et al* (1991). Nutritional factors in colorectal cancer risk: a case-control study in Majorca. *Int J Cancer* **49:** 161–7.

Bjelke E (1974). Epidemiological studies of cancer of the stomach, colon and rectum; with special emphasis on the role of diet. *Scand J Gastroenterol* **9 (Suppl 31):** 1–235.

Boutron M-C, Wilpart M, Faivre J (1991). Diet and colorectal cancer. *Eur J Cancer Prev* **1 (Suppl 2):** 13–20.

Bristol JB, Emmett PM, Heaton KW, Williamson RCN (1985). Sugar, fat and risk of colorectal cancer. *BMJ* **291:** 1467–70.

Correa P (1978). Epidemiology of polyps and cancer. In *The Pathogenesis of Colorectal Cancer* (ed Morson BC); Saunders, Philadelphia, pp. 126–52.

Dean G, MacLennan R, McLoughlin H, Shelly E (1979). The causes of death of blue-collar workers at a Dublin brewery. *Br J Cancer* **40:** 581–89.

DeCosse JJ, Bayle JC (1985). Overview of epidemiology and risk factors associated with colorectal cancer. *Prog Clin Biol Res* **186:** 1–12.

Doll R, Muir C, Waterhouse J (1970). Cancer Incidence in Five Continents. Vol II. IUCC, Geneva.

Drasar BS, Irving D (1973). Environmental factors and cancer of the breast. *Br J Cancer* **27:** 168–72.

Enstrom JE (1977). Colorectal cancer and beer drinking. *Br J Cancer* **35:** 674–83.

Faivre J (1992). Diet and colorectal cancer. In *Public Education on Diet and Cancer* (eds Benito E, Giacosa A, Hill MJ); Kluwer, Lancaster, pp. 53–68.

Faivre J, Boutron M-C, Hillon P *et al* (1985). Epidemiology of colorectal cancer. In *Diet and Human Carcinogenesis* (eds Joossens J, Hill M, Geboers J); Excerpta Medica, Amsterdam, pp. 123–36.

Freudenheim JL, Graham S, Marshall JR, Haughey BP, Wilkinson G (1990). A case-control study of diet and rectal cancer in western New York. *Am J Epidemiol* **131:** 612–24.

Garland C, Shekelle RB, Barrett-Connor E, Criqui MH, Rossof AM, Paul O (1985). Dietary vitamin D and calcium and risk of colorectal cancer: a 19-year prospective study in men. *Lancet* **7:** 307–9.

Graham S, Marshall J, Haughey B *et al* (1988). Dietary epidemiology of cancer of the colon in western New York. *Am J Epidemiol* **128:** 490–503.

Gregor O, Toman R, Prusova F (1969). Gastrointestinal cancer and nutrition. *Gut* **10:** 1031–4.

Haenszel W, Berg JW, Kurihara M, Locke F (1973). Large bowel cancer in Hawaiian Japanese. *JNCI* **51:** 1765–99.

Haenszel W, Locke FB, Segi M (1980). A case control study of large bowel cancer in Japan. *JNCI* **64:** 17–22.

Higginson J (1966). Etiological factors in gastrointestinal cancer in man. *J Natl Cancer Inst* **37:** 527–45.

Hill MJ (1986). *Microbes and Human Carcinogenesis*. Edward Arnold, London.

Hill MJ (1989). Experimental studies of fat, fibre and calories in carcinogenesis. In *Diet and Aetiology of Cancer* (ed Miller AB); Springer-Verlag, Heidelberg, pp. 31–8.

Hill MJ (1991). Bile acids and colorectal cancer: a hypothesis. *Eur J Cancer Prev* **1 (Suppl 2):** 69–74.

Hill MJ, McLennan R, Newcombe J (1979). Diet and large bowel cancer in three socioeconomic groups in Hong Kong. *Lancet* **i:** 436.

Hill MJ, Morson BC, Bussey HJR (1978). Etiology of the adenoma-carcinoma sequence. *Lancet* **i:** 245–7.

Hirayama T (1985). Diet and cancer: feasibility and importance of prospective cohort study. In *Diet and Human Carcinogenesis* (eds Joosens JV, Hill MJ, Geboers J); Elsevier, Amsterdam, pp. 191–8.

Hoff G, Moen E, Trygg K *et al* (1986). Epidemiology of polyps in the rectum and sigmoid colon. Evaluation of nutritional factors. *Scand J Gastroenterol* **21:** 199– 204.

Jain M, Cook GM, Davis FG, Grace MG, Howe GR, Miller AB (1980). A case-control study of diet and colorectal cancer. *Int J Cancer* **26:** 757–68.

Jensen OM (1979). Cancer morbidity and causes of death among Danish brewery workers. *Int J Cancer* **23:** 454–63.

Jensen OM (1985). The role of diet in colorectal cancer. In *Diet and Human Carcinogenesis* (eds Joossens J, Hill M, Geboers J); Excerpta Medica, Amsterdam, pp. 137–47.

Kune S, Kune GA, Watson LF (1987). Case-control study of dietary etiological factors: the Melbourne colorectal cancer study. *Nutr Cancer* **7:** 21–42.

La Vecchia C, Negri E, Decarli A *et al* (1988). A case-control study of diet and colorectal cancer in northern Italy. *Int J Cancer* **41:** 492–8.

Liu K, Moss M, Persky V *et al* (1979). Dietary cholesterol, fat and fibre and colon cancer mortality. *Lancet* **ii:** 782–5.

Lyon JL, Mahoney AW, West DW (1987). Total food intake: a risk factor in colorectal cancer. *JNCI* **78:** 853–61.

MacKeon-Eyssen GE, Bright-See E (1984). Dietary factors in colon cancer: international relationships. *Nutr Cancer* **6:** 160–70.

Macquart-Moulin G, Riboli E, Cornee J, Charnay B, Berthezene P, Day N (1986). Case-control study on colorectal cancer and diet in Marseilles. *Int J Cancer* **38:** 183–91.

Manousos O, Day NE, Trichopoulos D, Gerovassilis F, Tzonou A, Polychronopoulou A (1983). Diet and colorectal cancer: a case control study in Greece. *Int J Cancer* **32:** 1–5.

Martinez I, Torres R, Frias Z, Colon JR, Fernandez N (1981). Factors associated with adenocarcinomas of the large bowel in Puerto Rico. *Rev Latinoam Oncol Clin* **13:** 13–20.

Miller AB, Howe GR, Jain M, Craib KJP, Harrison L (1983). Food items and food groups as risk factors in a case control study of diet and colo-rectal cancer. *Int J Cancer* **32:** 155–61.

Modan B, Barrel V, Lubin F, Modan M, Greenberg RA, Graham S (1975). Low fiber intake as an etiologic factor in cancer of the colon. *JNCI* **55:** 15–18.

Morson BC, Bussey HJR, Day DW, Hill MJ (1983). Adenomas of the large bowel. *Cancer Surveys* **2:** 451–78.

Muir C, Waterhouse J, Mack T *et al* (1987). Cancer Incidence in Five Continents. Vol V. IARC, Lyon.

Pernu J (1960). An epidemiological study of cancer of the digestive organs and respiratory system. *Ann Med Intern Fenn* **49:** 1–117.

Philips RL (1975). Role of life style and dietary habits in risk of cancer among Seventh Day Adventists. *Cancer Res* **35:** 3513–22.

Pollack ES, Nomura AMY, Heilbrun LK, Stemmermann GN, Green SB (1984). Prospective alcohol consumption and cancer. *New Engl J Med* **310:** 617–21.

Potter JD, MacMichael AJ, Hartshorne JM (1982). Alcohol and beer consumption in relation to cancers of the bowel and lung: an extended correlation analysis. *J Chronic Dis* **35:** 833–42.

Rafter JJ, Branting C (1991). Bile acids—interaction with the intestinal mucosa. *Eur J Cancer Prev* **1 (Supple 1):** 49–54.

Segi M (1984). *Age-adjusted death rates for cancer for selected sites*. Segi Inst of Cancer Epidemiol, Nagoya.

Slattery ML, Sorenson W, Ford MH (1988). Dietary calcium intake as a mitigating factor in colon cancer. *Am J Epidemiol* **128:** 504–14.

Tannenbaum A, Silverstone J (1953). Nutrition in relation to cancer. *Adv Cancer Res* **1:** 451–501.

Tuyns AJ, Haelterman M, Kaaks R (1987). Colorectal cancer and the intake of nutrients: oligosaccharides are a risk factor, fats are not. A case-control study in Belgium. *Nutr Cancer* **10:** 185–96.

Wargovich MJ, Eng VW, Newmark H, Brace WR (1983). Calcium ameliorates the toxic effect of deoxycholic acid on colonic epithelium. *Carcinogenesis* **4:** 1205–7.

Waterhouse J, Muir C, Correa P, Powell J (1976). Cancer Incidence in Five Continents. Vol III. IARC, Lyon.

Waterhouse J, Muir C, Shanmuguratnam K, Powell J (1982). Cancer Incidence in Five Continents. Vol IV. IARC, Lyon.

West DW, Slattery ML, Robinson LM *et al* (1989). Dietary intake and colon cancer: sex- and anatomic site-specific associations. *Am J Epidemiol* **130:** 883–94.

Willett WC, Stampfer MJ, Colditz GA, Rosner BA, Speizer FE (1990). Relation of meat, fat and fiber intake to the risk of colon cancer in a prospective study among women. *New Eng J Med* **323:** 1664–72.

Wynder EL, Shigematsu T (1967). Environmental factors of cancer of the colon and rectum. *Cancer* **20:** 1520–61.

Young TB, Wolf DA (1988). Case-control study of proximal and distal colon cancer and diet in Wisconsin. *Int J Cancer* **43:** 167–75.

22
Diet and gastric cancer
M J Hill

22.1
INTRODUCTION

The environment in a rich source of carcinogens, mutagens and modulators of carcinogenesis. The diet contains a wide range of naturally occurring carcinogens, together with a wide array of carcinogens produced during cooking (NRC, 1982), particularly by the pyrolysis of nitrogen components (Table 22.1). The first resting place of such compounds in the body is the stomach. In addition the food contains a wide array of substrates for the bacterial production of carcinogens (Table 22.2); this is of relevance since in much of the world a significant proportion of populations is hypoacidic and harbours a rich gastric bacterial flora (Hill, 1986).

The atmosphere contains an array of carcinogens, principally industrial effluents and the pyrolysis products in motor exhaust fumes. When inhaled such compounds dissolve in nasal and throat secretions, which are then swallowed and rest in the stomach. Drinking water contains carcinogens such as halothanes which also reach the stomach.

In consequence, the stomach is exposed to a massive and varied carcinogen load; in general this is well resisted but there can be little doubt that gastric cancer has a multifactorial aetiology, with different carcinogens being of primary importance under different circumstances. Although it is very likely that diet is of primary importance in the causation of gastric cancer it is extremely unlikely that the relationship is a simple one.

However, the position is further complicated by two factors with regard to gastric carcinogenesis itself. The first of these is that there are two histological types of gastric cancer—the so-called intestinal and diffuse types (Lauren, 1965) which have clearly distinct aetiologies and epidemiologies (Table 22.3). In particular the diffuse type is strongly associated with familial factors (Lehtola, 1978) whilst the intestinal type is caused by environmental factors such as diet and is responsible for most of the geographical variation in gastric cancer incidence (Correa, 1988; Hirayama, 1988; Munoz and Asvall, 1971). Most cancer statistics do not distinguish between the two forms, and so in studies of diet and

gastric cancer the diffuse type cancers (unrelated to diet) confuse any correlations with the intestinal type cancers.

Table 22.1—Carcinogens/mutagens in food

Compound	Comments
Aflatoxins and other mycotoxins	Fungal contamination of stored foods.
N-nitroso compounds	Foods preserved with nitrate or nitrite; alcoholic beverages.
Hydrazines	Naturally present in mushrooms.
Polycyclic aromatic hydrocarbons	In all smoked foods.
Bracken fern toxin	In bracken ferns.
Pyrrolizidine alkaloids	In alkaloid-containing plants.
Methylxanthines	In tea and coffee.
Cycasin	In cycad nuts and cycad flour.
Thioureas	In certain fungi.
Tannins	Widely distributed in plants; coffee and tea; used as a food additive.
Ethyl carbamate	Fermentation products in wines, yogurts etc.
Harman, nor-harman etc	Pyrolysis products formed during cooking meat and protein.

Table 22.2—Substrates for bacterial production of carcinogens or tumour promoters

Substrate	Product	Action
Nitrate and nitrite	N-nitroso compounds	Carcinogen
Secondary amines	N-nitroso compounds	Carcinogen
Tryptophan	Various metabolites	Promoter
Tyrosine	Phenols	Promoter
Methionine	Ethionine	Carcinogen
Nitrogen compounds	Ammonia	Promoter

Table 22.3—The differences in the epidemiology and characteristics of diffuse and intestinal type gastric cancer

	Histological type	
	Diffuse	Intestinal
Sex ratio M/F	Approx 1	Greater than 1
Relative age of onset	Younger	Older
Location	Often cardia	Usually antrum
Relative risk in close relations	7-fold	No excess
Association with environment	None	Strong
Gross morphology	Ulcerous	Polypoid

	Histological type	
	Diffuse	Intestinal
Prognosis	Poor	Better
Predisposing lesions	Hyperplasia	Gastric atrophy
		Intestinal metaplasia

In addition, gastric cancer of the intestinal type is a multistage process (Correa *et al*, 1975) with the first stage being atrophic gastritis (AG) followed by intestinal metaplasia (IM), increasingly severe epithelial dysplasia (ED) and finally cancer. There are good reasons for suspecting that the early stages are associated with poor living standards whilst the later stages are not (for example, Caygill *et al*, 1990) and so studies of the role of diet in gastric carcinogenesis are further complicated.

Historically, gastric cancer has been the commonest cancer in all countries of the world. For example, in European countries and North America cases of gastric cancer greatly outnumbered lung cancers as late as 1940 in all countries and 1950 in some; it is still the commonest site of cancer mortality in Portugal. On the global scale, gastric cancer was the leading cause of cancer mortality as late as 1988 and has only just been overtaken by lung cancer. There is still, therefore, considerable interest in the role of diet in this very important cancer.

22.2
EPIDEMIOLOGY OF GASTRIC CANCER

The epidemiology of gastric cancer has been reviewed in detail elsewhere (Hill, 1986, 1991). The incidence of gastric cancer has a world distribution which is the reverse of that of colorectal cancer. The incidence is very high in eastern Asia and in the Andean countries of South America and is relatively low in North America, Australasia and northern and western Europe (Table 22.4). Within Europe it is more common in southern and eastern Europe than in the northern and western countries (see Chapter 4). The incidence is decreasing worldwide—a process that began in the 1930s and 1940s in countries which now have relatively low incidences and later in higher incidence countries. The incidence is higher in males than in females, usually by a factor of between 1.5 and 2.5. It is also inversely related to socioeconomic status in all countries.

Table 22.4—Age-standardized incidence rates of gastric cancer and life time risk (data from Munoz, 1988)

	Incidence		Life time			Incidence		Life time	
	M	M	M	F		M	F	M	F
Asia					*Europe*				

	Incidence		Life time			Incidence		Life time	
	M	M	M	F		M	F	M	F
Japan-Miyagi	79.6	36.0	9.7	4.2	Italy-Parma	44.0	19.9	4.5	2.1
China-Shanghai	58.3	24.6	7.4	3.0	Poland-Warsaw	23.2	8.9	2.8	1.0
Singapore-Chinese	37.3	15.4	4.6	1.8	Yugoslavia	34.9	15.1	4.4	1.7
Hong Kong	19.2	9.6	2.5	1.1	Hungary	32.4	12.8	4.1	1.5
India-Madras	13.7	6.7	1.6	0.7	Spain-Navarra	31.6	13.5	3.8	1.4
Philippines	9.4	6.7	1.1	0.7	Finland	24.6	12.9	2.8	1.4
					England/Wales	18.5	7.8	2.2	0.9
S America									
Colombia	49.6	26.3	5.2	2.7	Denmark	14.3	6.7	1.6	0.7
Brazil-Sao Paulo	53.6	25.1							
Costa Rica	58.8	25.2	7.0	3.0	*Australasia*				
					New Zealand	13.7	6.0	1.6	0.6
N America					Australia	13.1	5.7	1.5	0.6
USA-Los Angeles									
White	8.6	4.0	1.0	0.4	*Middle-East*				
Black	15.6	6.4	1.8	0.8	Israel	16.2	9.3	1.8	1.1
Connecticut					Kuwait	3.7	1.6	0.3	0.2
White	10.8	4.3	1.3	0.5					
Black	19.4	9.1	2.2	1.1	*Africa*				
					Nigeria	7.1	4.0	-	-
Canada					Senegal	3.7	2.0	-	-
Alberta	11.8	4.8	1.4	0.5	Swaziland	1.8	0.2	-	-
Newfoundland	25.3	10.7	3.0	1.3					

Incidence rates are age-standardized per 100,000 per annum. Life time risks are expressed as percentage risk.

When migrants travel from a high incidence country (*eg* Japan, Korea) to a low incidence one (*eg* United States) they retain the high risk associated with their homeland unless they migrated as children. In the latter case their risk of gastric cancer is closer to that of their new homeland than of their birthplace. Children of migrants born in the new homeland have the risk associated with their new homeland. This indicates that the disease risk is not determined by racial/genetic factors but by environmental factors acting in early life. These risk factors have a high prevalence in eastern Asia and South America and a very low prevalence in Africa, the middle east and in North America.

Gastric cancer risk is associated with certain industries, particularly those involving dusty work such as coal mining or other mining, potteries, foundry workers, railway footplatemen etc. Such occupations are also associated with gastritis.

There are disease states that predispose to gastric cancer (Hill, 1988) including pernicious anaemia, hypogammaglobulinemia, gastric atrophy, intestinal metaplasia and gastric epithelial dysplasia, gastric polyps and gastric surgery (Table 22.5). In addition, a number of diseases are associated with increased risk of gastric cancer such as typhoid infection (Caygill *et al*, 1993), gallbladder cancer (Caygill *et al*, 1992), relatives of colon cancer cases (Lovett, 1976).

Table 22.5—Associated and predisposing diseases and gastric cancer

Disease	Magnitude of excess risk*
Predisposing disease	
Gastric atrophy	2–3 fold
Chronic atrophic gastritis	4–6 fold
Intestinal metaplasia	4–6 fold
Severe dysplasia	Very high
Gastric polyps	Very high
Hypogammaglobulinemia	50 fold
Bilroth surgery	4–6 fold
Vagotomy and drainage	10-fold
Associated disease	
Biliary infection	Increased
Colon cancer relatives	Increased

*Data collected from various sources; see Hill (1986).

22.3
DIET AND GASTRIC CANCER

The earliest studies of diet and digestive tract cancer were by Stocks in the 1930s, but unfortunately these did not distinguish between gastric and colorectal cancers. In addition, all early studies gave very weak associations with diet

because (a) they included an unknown proportion of diffuse type cancers that are not diet-related, and (b) they usually used the case-control technique and therefore necessarily used diet recall methods which are innately very unreliable. Table 22.6 summarizes the results of early diet studies; these tended to show an association with consumption of root vegetables and cereals (*eg* Hakama and Saxen, 1967; Modan *et al*, 1974; Risch *et al*, 1985). In retrospect, the implicated foods may simply have been markers of poor nutrition. An early study by Bjelke (1974) showed a protective effect of vitamin A and vitamin C but a positive correlation with smoked foods; these latter were also incriminated in gastric cancer in Iceland (Dungal, 1961) and in Japan (Hitchcock and Scheiner, 1965). Later studies have appeared to reach some degree of consensus on the protective effect of fresh raw vegetables (*eg* salad foods) and fresh fruits, and this is summarized in Table 22.7. Much more detail on this can be found in Chapter 17.

Table 22.6—Dietary risk factors in gastric cancer from early epidemiology studies (data from Hill, 1986)

Population studied	Dietary item
Finland	Grain products
Iceland	Smoked foods
Norway	Smoked foods
	Grain products
Holland	Fried foods
Slovenia	Potatoes
Wales	Fried foods
Japan	Rice and starchy food
	Smoked food
China	Root vegetables
Colombia	Cereal products
	Root vegetables
	Fava beans
United States	Starchy foods
	Root vegetables
Israel	Starchy foods
Canada	Starchy foods

22.4 HISTOPATHOGENESIS

There is a histopathological sequence in the genesis of gastric cancer, a crucial stage of which is the loss of gastric acidity either (a) as a result of natural ageing via gastric atrophy and chronic atrophic gastritis (CAG); or (b) surgery involving vagotomy (which immediately interrupts stimulated acid secretion and rapidly

progresses to atrophy of the gastric mucosa); or (c) genetic defects in acid secretion as in pernicious anaemia and hypogrammoglobulinemia. In each of these there is a high risk of progression to intestinal metaplasia (IM). This can be incomplete IM (type III), or complete (type I) or intermediate (type II); it is the type III lesion that carries a high risk of progression through increasingly severe epithelial dysplasia (ED) and cancer (GC), and the type I lesion carries much less risk of such progression (Filipe, 1988).

Table 22.7—The protective effect of fresh green vegetables, fruit, vitamins and micronutrients on gastric carcinogenesis

Study	Country	Observation
Bjelke (1974)	Norway/ USA	Protective effect of vitamins A and C, and of lettuce and salad vegetables
Graham *et al*, 1972	USA	Protective effect of fresh vegetables
Risch *et al*, 1972	Canada	Protective effect of fresh vegetables
Trichopoulos *et al*, 1985	Greece	Protective effect of fresh vegetables
La Vecchia *et al*, 1987	Italy	Protective effect of fresh vegetables
Hu *et al*, 1988	China	Protective effect of fresh vegetables
Hirayama, 1988	Japan	Protective effect of green leafy vegetables
Gey *et al*, 1987	Switzerland	Protective effect of antioxidant vitamins
Haenszel *et al*, 1976	Colombia	Protective effect of green leafy vegetables

This progression was formulated by Correa *et al* (1975) based on a copious amount of data form Finland, Iceland, Japan and Colombia (*eg* Jarvi, 1962; Correa *et al*, 1970; Jarvi and Lauren, 1951). Some of the strongest support for it has come from a study by Correa in Colombia of 1,649 persons followed for up to 21 years. During the years of follow-up 765 persons developed gastric atrophy, 429 intestinal metaplasia and 94 dysplasia. All of the 94 ED cases arose in precursor IM and none arose except via this route. Similarly all of the IM cases arose in precursor atrophic gastritis. In general, atrophic gastritis developed within precursor hyperplasia; 19 did not, but none of these progressed further to IM.

Although there is this clear progression in the histopathology, the lesions can regress as well as progress. At present there is no information on the rate of progression/regression of gastric lesions although this is currently being studied by the Gastric Group of ECP (Reed, 1993).

22.5
DIET AND THE HISTOLOGICAL STAGES

There is only limited evidence on the role of diet in the individual stages of gastric cancer, but some information has emerged from the ECP study of diet and

intestinal metaplasia. The mechanism of the histological pathway has been discussed in more detail by Hill (1986, 1993).

22.5.1 Gastric atrophy

There is evidence that gastric atrophy (which can be the result of natural ageing) progresses abnormally rapidly in persons with a poor diet as eaten by lower socioeconomic groups in Brazil, Colombia, Peru, Venezuela, South India, Southern Iran. Further, gastric atrophy was much more prevalent in Iceland and Finland before the war than in more recent decades as the nutritional status has improved. Gracey *et al* (1977) demonstrated that gastric acid secretion was lower in malnourished children than in well nourished infants; Thomason *et al* (1981) demonstrated that gastric achlorhydria could be experimentally induced in rats through protein malnutrition. In many studies CAG is associated with infection with *Helicobacter pylori*, but in gastric surgery the CAG is more associated with bile reflux and not with *H. pylori* infection.

In the ECP-IM study data were available from a small group of CAG patients and these had normal levels of serum vitamins.

22.5.2 Intestinal metaplasia

In the ECP-IM study data were obtained on diet, serum vitamins, gastric juice analyses and urinary nitrate, sodium and potassium. The data are summarized in Table 22.8. The IM cases were similar to controls in serum selenium, vitamin A and E and ß-carotene and in urinary nitrate and sodium. The IM cases were characterized by low serum vitamin C and low urinary potassium, relatively elevated gastric juice pH, nitrite and bacteria and high carriage of *H. pylori*.

H. pylori does not colonize intestinalized tissue but is presumably colonizing the CAG tissue in which the IM arose and so these results would be expected. Similarly the lack of association with nitrate was expected since there are no hypotheses for a role for nitrate in the early stages of gastric carcinogenesis. The gastric juice analyses demonstrate that even at this early stage there was an increased prevalence of detectable bacteria and nitrite; this would be expected on the basis of hypotheses for the role of N-nitroso compounds in the later stages of gastric carcinogenesis.

The results of serum vitamin C, urinary sodium and urinary potassium were unexpected. We have no good hypothesis for a role for potassium, but sodium has been claimed to be of importance in causing gastric atrophy through osmotic stress (Joossens and Kesteloot, 1988). In the ECP study it clearly played no part in causing this early stage. The strong evidence of a protective effect of vitamin C has already been described in section 22.3 but it has been suggested that its role is as a scavenger of nitrite and nitroso compounds at the later stages. From

this study, however, it clearly appears to be protecting against the development of IM in gastric atrophy.

Table 22.8—Summarized results from the ECP-IM study

Parameter	Observation
Dietary questionnaire	Intake of fresh fruit (particularly citrus fruits) and vegetables higher in IM cases than in controls.
Serum vitamins	Levels of vitamin C highly significantly lower in IM than in control persons. ß-carotene non-significantly lower in IM.
Serology	Carriage of *H.pylori* (as measured by serology) in more than 80% of IM cases but less than 20% of controls.
Gastric juice analyses	In IM cases, compared with controls, there was a higher proportion of persons with pH greater than 4, and of persons with a resident gastric bacterial flora, and of nitrite (produced by bacterial reduction of nitrate).
Urinary analyses	There was no difference between IM cases and controls in total intake of salt and of nitrate, but IM cases had significantly lower intakes of potassium.

22.5.3 Dysplasia

Most of the work on dysplasia has been carried out in gastric surgery and, in these patients, there is strong evidence that dysplasia is caused by refluxed bile and by N-nitroso compounds locally produced by bacterial action. The ECP-IM study showed that even in early IM cases the conditions were being established to enable N-nitrosation to occur (*ie* presence of bacteria and nitrite). There have been many studies showing a correlation between bacterial colonization and nitrite (and N-nitroso compounds) and dysplasia of the gastric epithelium (Hill, 1988, 1991).

The diet is a rich source of nitrate (the substrate for gastric juice nitrite formation); it is present in root vegetables, in particular, as well as in salad vegetables, drinking water and cured meat products. A major difference between root vegetables (rich in nitrate and associated with a high risk of gastric cancer) and salad vegetables (high in nitrate but associated with a low risk of gastric cancer) is that the latter are eaten raw and so retain their high levels of antioxidant vitamins. It has been demonstrated (Reed *et al*, 1983) that vitamin supplements decrease gastric juice nitrite, nitroso compounds and mutagen levels, and numerous similar studies have been carried out in experimental animals with the same results. Clearly then, ascorbic acid should protect against the latter stages of gastric cancer and it has been hypothesized that this is the mechanism by which salad vegetables and fresh fruit protect against gastric cancer.

22.6 CONCLUSIONS

There is now a large body of evidence to suggest that a diet rich in antioxidant vitamins protects against gastric carcinogenesis. The worldwide decrease in gastric cancer incidence could easily be the result of improved nutrition, particularly with respect to the freshness of the vegetables.

REFERENCES

Bjelke E (1974). Epidemiological studies of cancer of the stomach, colon and rectum. *Scand J Gastro* Suppl 31.

Caygill CPJ, Hill MJ, Knowles RL *et al* (1990). Occupational and socioeconomic factors associated with peptic ulcer and with cancers following consequent gastric surgery. *Ann Occ Hyg* **34:** 19–27.

Caygill CPJ, Hill MJ (1992). Malignancy following surgery for benign peptic disease: a review. *Ital J Gastro* **24:** 218–24.

Caygill CPJ, Hill MJ, Braddick M *et al* (1993). Excess cancer mortality in chronic typhoid and paratyphoid carriers. *J Med Microbiol* (in the press).

Correa P (1988). Precancerous lesions of the stomach: phenotypic changes and controlling factors. IN *Gastric Carcinogenesis* (eds Reed PI, Hill MJ); Excerpta Medica, Amsterdam; pp. 127–36.

Correa P, Cuello C, Duque E (1970). Carcinoma and intestinal metaplasia of the stomach in Colombian migrants. *JNCI* **44:** 297–306.

Correa P, Haenszel W, Cuello C *et al* (1975). A model for gastric cancer epidemiology. *Lancet* **ii:** 58–60.

Dungal N (1961). The special problem of stomach cancer in Iceland with particular reference to dietary factors. *J Am Med Ass* **178:** 789–98.

Filipe I (1988). Intestinal metaplasia and the histogenesis of gastric cancer. In *Gastric Carcinogenesis* (eds Reed PI, Hill MJ); Excerpta Medica, Amsterdam, pp. 19–28.

Gey KF, Brubacher G, Stahelin HB (1987). Plasma levels of antioxidant vitamins in relation to ischemic heart disease and cancer. *Am J Clin Nutr* **45 (Suppl 5):** 1368– 77.

Gracey M, Cullity G, Suharjono M *et al* (1977). The stomach in malnutrition. *Arch Dis Childhood* **52:** 325–7.

Graham S, Schotz W, Martino P (1972). Alimentary factors in the epidemiology of gastric cancer. *Cancer* **30:** 927–38.

Haenszel W, Correa P, Cuello C *et al* (1976). Gastric cancer in Colombia. II. Case-control epidemiologic study of precursor lesions. *JNCI* **57:** 1021–6.

Hakama M, Saxen E (1967). Cereal consumption and gastric cancer. *Int J Cancer* **2:** 265–8.

Hill MJ (1986). *Microbes and Human Carcinogenesis*. Edward Arnold, London.

Hill MJ (1988). Gastric carcinogenesis: luminal factors. In *Gastric Carcinogenesis* (eds Reed PI, Hill MJ); Excerpta Medica, Amsterdam; pp. 187–200.

Hill MJ (1991). *Nitrate and Nitrite in Food and Water*. Ellis Horwood, London.

Hill MJ (1993). Mechanisms of gastric carcinogenesis. *Eur J Cancer Prev* **2 (Suppl 2):** in the press.

Hirayama T (1988). Actions suggested by gastric cancer epidemiological studies in Japan. In *Gastric Carcinogenesis* (eds Reed PI, Hill MJ); Excerpta Medica, Amsterdam; pp. 209–28.

Hitchcock DR, Scheiner SL (1965). The early diagnosis of gastric cancer. *Surg Gyn Obs* **113:** 665–72.

Hu J, Shang S, Jia E *et al* (1988). Diet and cancer of the stomach: a case-control study in China. *Int J Cancer* **41:** 331–5.

Jarvi O (1962). A review of the part played by gastrointestinal heterotopias in neoplasmogenesis. *Proc Finn Acad Sci* 151–87.

Jarvi O, Lauren P (1951). On the role of heterotopias of the intestinal epithelium in the pathogenesis of gastric cancer. *Acta Path Mic Scand* **29:** 26–44.

Joossens J, Kesteloot H (1988). Salt and stomach cancer. In *Gastric Carcinogenesis* (eds Reed PI, Hill MJ); Excerpta Medica, Amsterdam, pp. 105–26.

La Vecchia C, Negri E, Decarli A *et al* (1987). A case-control study of diet and gastric cancer in North Italy. *Int J Cancer* **40:** 484–9.

Lehtola J (1978). Family study of gastric carcinoma, with special reference to histological types. *Scand J Gastro* **13 (Suppl 50):** 1–54.

Lauren P (1965). The two histological main types of gastric carcinoma: diffuse and so-called intestinal type. *Acta Path Mic Scand* **64:** 31–49.

Lovett E (1976). Family studies in cancer of the colon and rectum. *Br J Surg* **63:** 13–18.

Modan BW, Lubin F, Barrell V *et al* (1974). The role of starches in the etiology of gastric cancer. *Cancer* **34:** 2087–92.

Munoz N, Asvall J (1971). Time trends of intestinal and diffuse types of gastric cancer. *Int J Cancer* **8:** 144–57.

National Research Council (1982). *Diet, Nutrition and Cancer*. National Academy Press, Washington.

Reed PI (1993). Primary prevention of gastric precancerous lesions. *Eur J Cancer Prev* **2 (Suppl 2):** in the press.

Reed PI, Summers K, Smith PLR *et al* (1983). Effect of ascorbic acid treatment on gastric juice nitrite and N-nitroso compounds in achlorhydric subjects. *Gut* **24:** 492–3.

Risch HA, Jain M, Choi NW *et al* (1985). Dietary factors and cancer of the stomach. *Am J Epidem* **122:** 947–57.

Thomason H, Burke V, Gracey M (1981). Impaired gastric function in experimental malnutrition. *Am J Clin Nutr* **34:** 1278–80.

Trichopoulos D, Ouranos G, Day NE *et al* (1985). Diet and cancer of stomach: a case-control study in Greece. *Int J Cancer* **36:** 291–7.

Author index

Index