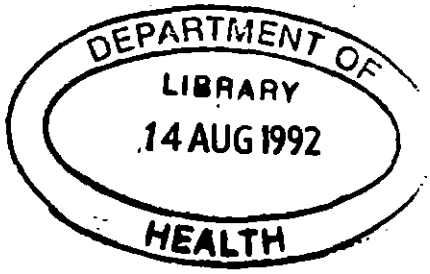
FOOD SAFETY ADVISORY COMMITTEE

DIET AND CANCER



Report to the
Minister for Health
and the Minister for Agriculture
and Food

REPORT NO.13
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FOOD SAFETY ADVISORY COMMITTEE

The Food Safety Advisory Committee was established by the Minister for Health and the Minister of Agriculture and Food in July, 1989.

Terms of Reference

1. To advise the Minister for Health and the Minister for Agriculture and Food on matters relating to food and zoonotic diseases referred to it and to make recommendations to the Ministers.

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DIET AND CANCER

I INTRODUCTION

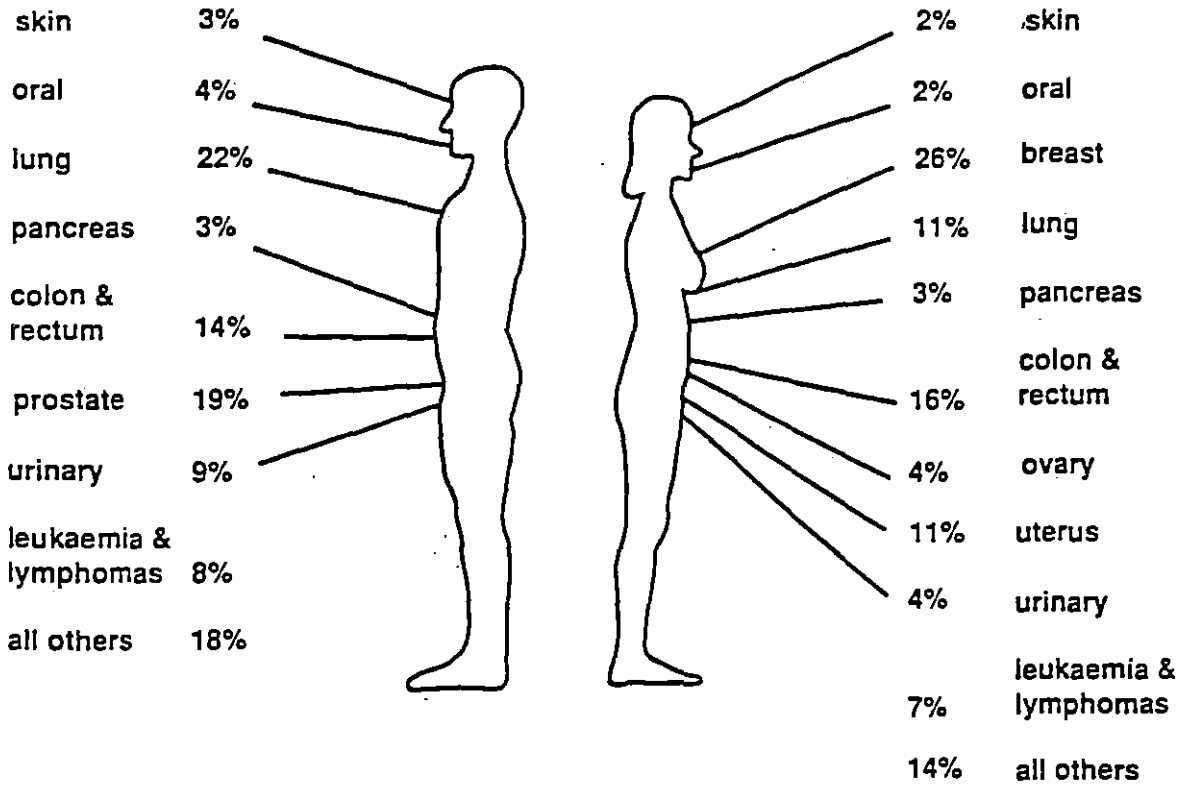
The relationship between diet and cancer is complex and our knowledge in this field is poor. One of the main reasons for this weakness lies in the lack of a biological intermediary between diet and cancer. Consider the contrasting pattern of diet and coronary heart disease (CHD). Elevated low-density lipoprotein (LDL) cholesterol is positively associated with increased risk of coronary heart disease while elevated high-density lipoprotein (HDL) cholesterol is negatively associated with the risk of this disease. Both these facts are repeatedly demonstrated in epidemiological investigations. Nutritionists conduct studies to show how the direction of LDL- and HDL- cholesterol moves in response to various changes in diet. Epidemiologists study how HDL- and LDL- cholesterol is linked to heart disease in different age and sex groups. The combination of these two sets of data give a good picture of the diet-risk factor link and the risk factor-disease link.

In cancer, there are no widely acceptable biological intermediaries such as LDL- or HDL-cholesterol and so it is necessary to examine directly, the association of diet and cancer. The problems thereby generated are considerable. The development of cancer is not acutely associated with a given type of diet. Therefore it is necessary to unravel the type of diet which prevailed when the cancer was initiated. Tumor growth rates are such that 10 - 15 years may elapse between the initiation of the cancer and the subsequent clinical manifestation of the disease. Trying to retrospectively determine diet is fraught with error as will be discussed. Given that, an alternative approach to looking back in time is to look forward by accurately recording diet and other aspects of lifestyle in a large group of people at base-line and then monitoring them for 5, 10 or 15 years. The problem here is that the % of the population who will develop a cancer is low, in some cases extremely so, and thus the numbers required at the outset must be high. The attendant costs and logistical implications are evident.

Therefore, the study of diet and cancer is inherently difficult and totally unlike that for heart disease. One other difference between the two diseases is that heart disease is a disease of the coronary artery tree. Cancer can effect all organs and tissues and as can be seen from Figure 1, the cancers with the highest incidence are not always the cancers with the highest mortality (eg breast v lung respectively). The age-standardised mortality for several cancers in the EC is given in Figure 2a and 2d (WHO 1985).

Figure 1. Estimates of the incidence of cancer and mortality from cancer based on data from the National Cancer Institute's Surveillance Epidemiology and End Results (SEER) Programme. (1977 - 1981).

1986 ESTIMATED CANCER INCIDENCE BY SITE AND SEX



1986 ESTIMATED CANCER DEATHS BY SITE AND SEX

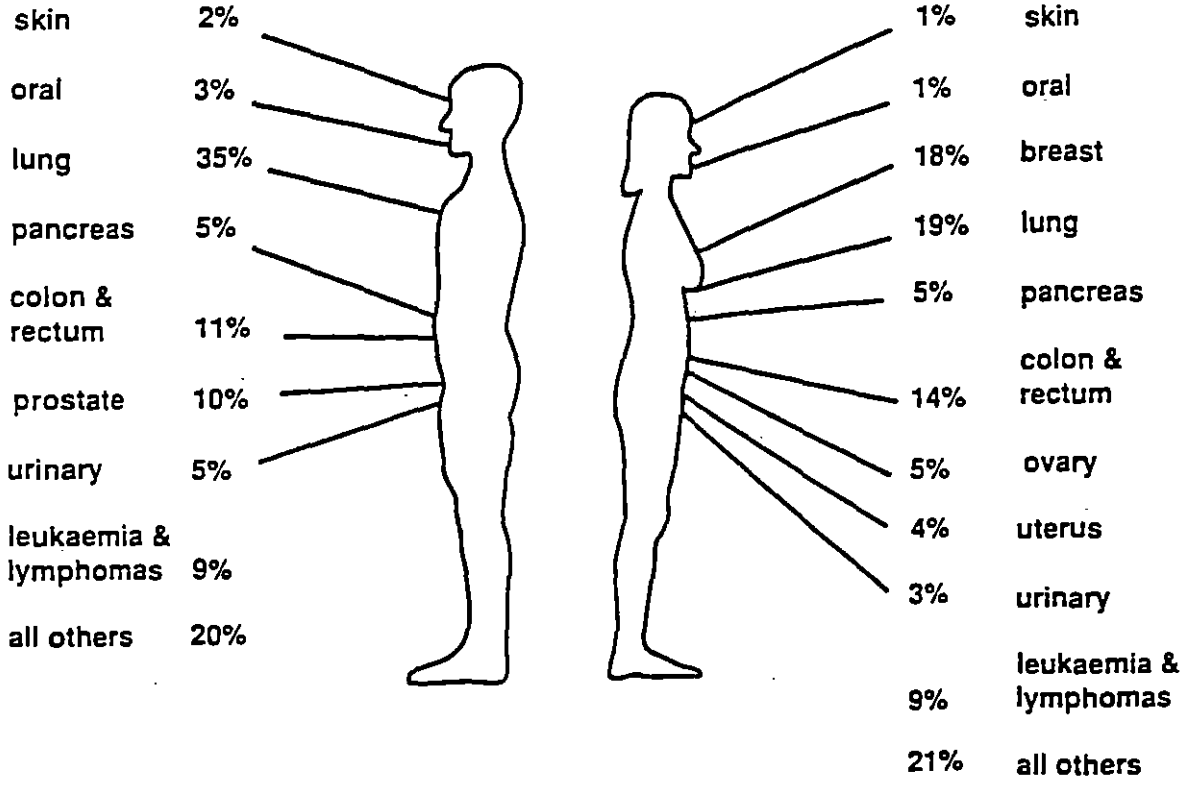
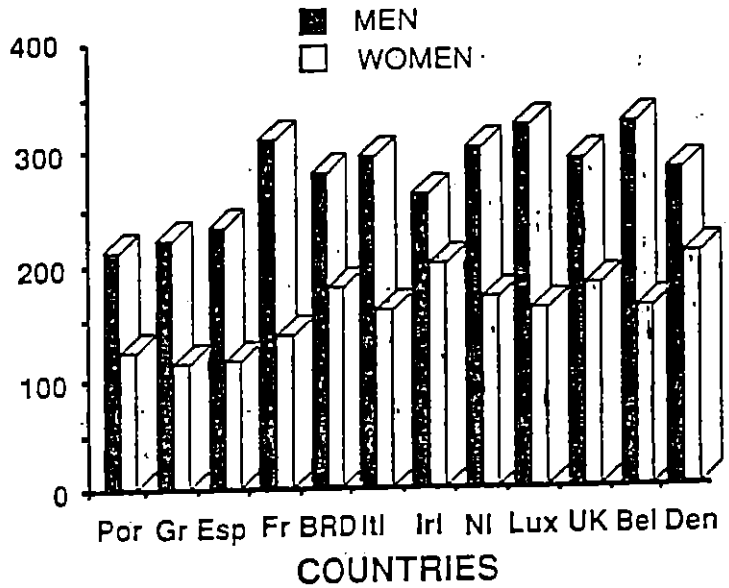


Figure 2a - 2d. Age standardized mortality rates per 100,000 in 1985 in the European Community (WHO 1985).

(a) Total Cancer Mortality



(b) Lung Cancer Mortality

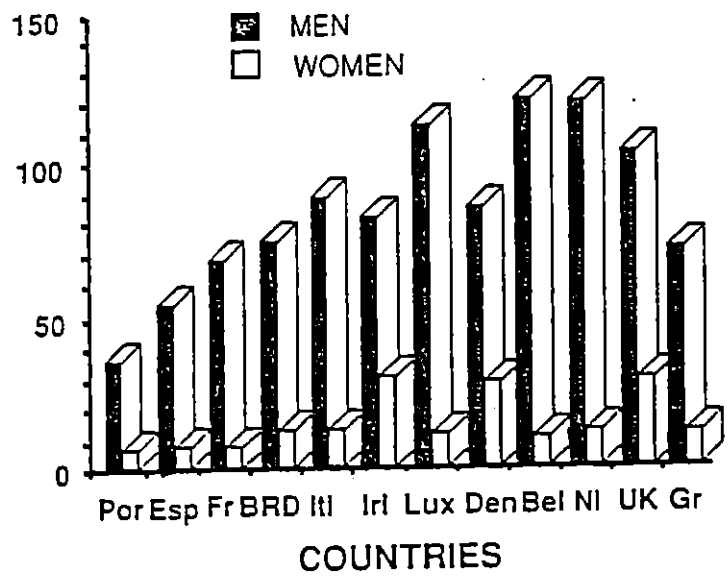
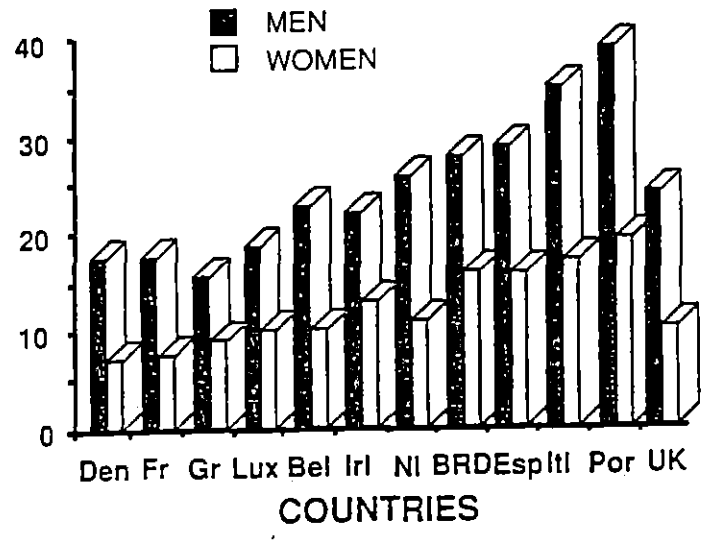
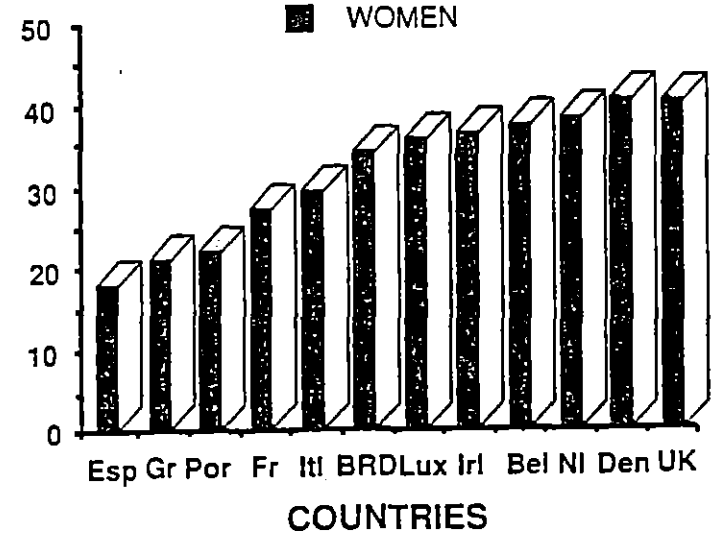


Figure 2a - 2d. Age standardized mortality rates per 100,000 in 1985 in the European Community (WHO 1985).

(c) Stomach Cancer Mortality



(d) Breast Cancer Mortality



This review will examine the methodological approaches to diet and cancer, re-iterating and elaborating on the difficulties of these methodologies. Having done so it will consider the proposed role of all environmental factors in cancer followed by the role of the food supply in general and end with the role of specific nutrients.

II METHODOLOGICAL APPROACHES TO THE STUDY OF DIET AND CANCER.

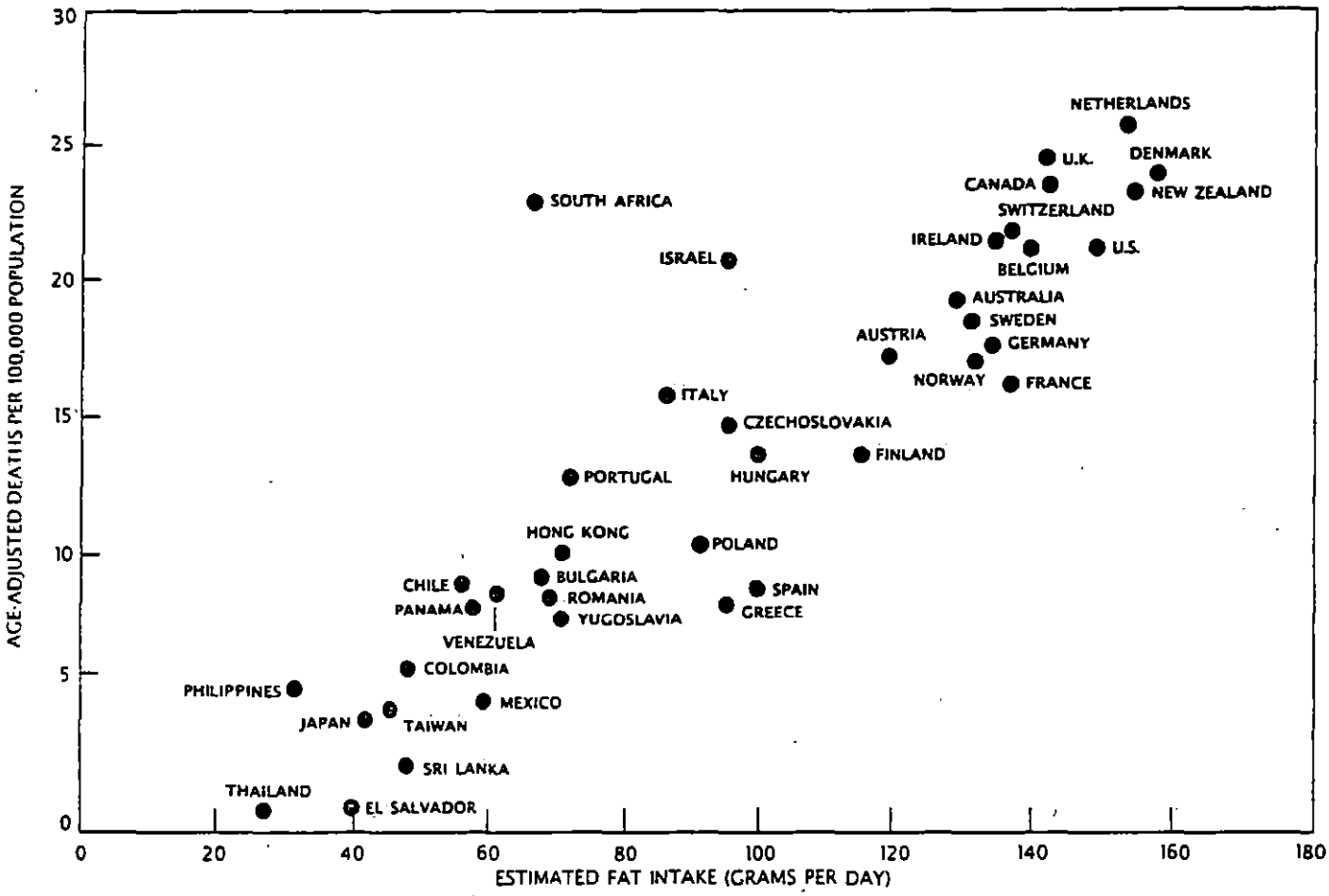
(a) Ecological studies using Food Balance Sheets

For decades now the Food and Agricultural Organisation (FAO) of the United Nations has published food balance sheets (FBS) for over 50 countries. These provide data on the "disappearance" of foods and give an extremely crude estimate of nutrient intake. FBS are based on the sum of imports and production, minus exports, divided by the population. In developed countries they lead to marked overestimates of consumption, as is evident from this comparison with direct national diet surveys .

	Energy intake (kcal/d)	
	National Dietary Surveys	Food Balance Sheets
Ireland	2381	3446
UK	2040	3343
Denmark	2714	3419
Netherlands	2478	3372

The overestimate is due to the failure of FBS to account for the huge wastage which occurs in the developed countries at the distributive, retail, catering and domestic levels. The FBS data are useful only for time-trend analyses where, in effect, it is acceptable to make the same error year after year. These time-trend analyses are useful for strategic purposes in predicting necessary changes in agricultural practices or food trading policies in less developed countries. They are utterly useless for single time-point analyses across countries. Notwithstanding this, FBS are repeatedly misused to show relationships between, for example fat consumption (g/d) and cancer incidence (Cohen 1987; See Fig 3). Their poor value can be seen in the comparison of the resultant correlation coefficient of colon cancer and fat intake of + 0.80, with that of colon cancer and road vehicles per head of + 0.75. To make these simple comparisons between cancer and the intake of nutrients in different countries, using FBS or other data, is to ignore other factors which one might consider important in this area such as age at

Figure 3. Data frequently quoted from Food Balance Sheets linking dietary fat intake and breast cancer.



Note that the data are really not "intake" but "food disappearance data", failing to account for the massive wastage in developed countries and low wastage in poorer countries. The data is confounded by variation in energy intake and intakes of other nutrients such as fibre and antioxidant vitamins. Finally, no account is taken for differences in reproductive habits, age at menarche, height, weight, alcohol, tobacco and so forth. Armstrong & Doll (1975) have shown that the relationship between Gross National Product and breast cancer is better than that for dietary fat and breast cancer.

menarche, reproductive and sexual patterns, height, weight, smoking, other illnesses, alcohol intakes and so on. All in all, these cross-cultural studies, particularly using food balance sheets are utterly unacceptable in determining cause and effect relationship between diet and cancer.

(b) Case-control studies

These are a very popular choice when it comes to studying diet and cancer. Patients with a newly diagnosed cancer are matched for age and sex with controls. Exclusion criteria can help select a fairly homogenous group of patients. The cases and controls are interviewed with regard to many aspects of lifestyle and the manner in which these may have changed over the several years. The big problem for case-control studies is trying to retrospectively determine dietary patterns or trying to determine changes which have occurred in food selection over time. The problems of retrospective dietary analysis have been studied by Bazzare & Myers (1978), Byers et al (1987), Marshal et al (1980), Byers et al (1983) and Rohan & Potter (1984). In general, these dates show that whereas point estimates of nutrient intake can not be accurately determined, crude classifications of the levels of ingestion of nutrients between cases and controls can be determined. Therefore the data has to be treated cautiously. One other problem in case-control studies has been the occasional use of surrogate interviewees where randomly selected patients have been too ill to participate. In lung cancer, for example, the median survival after the diagnosis is only 5 months (Axtell et al 1976). Such studies frequently require surrogate data, requiring cautious interpretation of the results.

(c) Prospective or cohort studies.

These studies overcome much of the difficulties outlined for case-control studies, particularly in relation to collecting accurate dietary data. However, the scale of investment is orders of magnitude higher. For example, the Nurses Cohort involved a detailed dietary and lifestyle analysis of 89,588 women at base line and, over a 5 - year period, yielded 601 cases of breast cancer. The costs of collecting, storing, tracking and retrieving data on this scale is obvious. It is however the most favoured route to the study of diet and cancer. It does become a problem when cancers with a relatively low incidence are being studied. For example, 26,000 adults, tracked for 10 years yielded only 42 cases of cancer of the pancreas. Willet (1990) in reviewing future directions of diet-cancer studies has highlighted the growth in prospective studies eg California Seventh Day Adventists (40,000), Nurses Health Study (95,000), New

York State Cohort (80,000), Canadian cancer study (56,000), Dutch cancer study (130,000) and so on. A major pan-European prespective study is now under way involving almost 300,000 people.

(d) Intervention studies.

Both case-control studies and prospective or cohort studies provide data from which hypotheses may be generated. These require testing in intervention studies. A number of such are underway and should become available in the literature in the next few years. These will be crucial in elucidating the diet-cancer association (Holm 1990; Heinderson 1992).

(e) Animal studies

While a number of animal models exist for coronary heart disease, such as the Wattanabe rabbit, no reliable animal model exists for the study of diet and cancer. Most of the studies involve the use of known carcinogens administered to animals fed different diets. These carcinogens include polycyclic aromatic hydrocarbons, n-nitrosomethylurea etc. Whilst these studies are valuable in the basic questions of tumour development, it is unwise to extrapolate these findings to human cancers.

III ENVIRONMENTAL FACTORS AND CANCER

A number of environmental factors have been associated with cancer including tobacco, alcohol, pollutants, radiation, industrial processes, medicines, sexual habits, geophysical factors, and food (Doll & Peto, 1981). The relative importance of each one varies with different cancers. Smoking may be strongly related to lung cancer but geophysical factors may be more pertinent in skin cancer. All of the environmental factors must interact with a genetic predisposition towards cancer. Unless the effect under investigation is strong, the study of the environment and cancer may mean that the real effect is undetectable against a background of "noise" from other sources.

(1) Food and cancer.

There are several ways in which food may contribute to cancer either in promoting or inhibiting its development.

* Natural endogenenous plant chemicals may be carcinogenic
* Contaminants and residues may play a role
* There are the known carcinogenic effect of several mycotoxins
* Carcinogens may develop during processing or storage
* Carcinogens may develop during cooking
* Nutrients themselves may play a role.

Within these categories, the effects may be either beneficial or detrimental. Cooking, for example may induce the formation of mutagens but it may also destroy mutagens naturally occurring in food. Equally storage may create or destroy mutagens. When the role of food in cancer is therefore being considered, there are a number of positive and negative aspects to be considered at all levels and while attempts have been made to quantify these effects, such efforts are often meaningless. What can be said is that when nutrition and cancer is considered in isolation, it may only be a small fraction of the total role which food plays. Thus Hargraves (1987) in a review of mutagens in cooked foods, indicates that the mutagenic load from this process may be equivalent to the smoking of 5 cigarettes per day. The data do not allow an estimation of how many mutagens are destroyed on cooking but the work of Ames and his colleagues allow us some insight into the significance of naturally occurring mutagens or carcinogens. Of the synthetic chemicals investigated in the maximally-tolerated-dose rat model, 50% are found to be carcinogenic. So too with natural plant chemicals, However, the human load of the latter is several orders of magnitude greater than for synthetic chemicals. Thus, Ames & Gold (1990) estimate that we ingest 0.09mg/d of synthetic pesticides as residues and 1500 mg/d of natural pesticides. Of the 52 natural pesticides tested for carcinogenicicity in rodents, 27 (ca 50%) have been found to be carcinogenic. The potential role of natural mutagens / carcinogens must not be understated. Neither, of course, must it be overstated.

(2) Nutrition and cancer

The balance of nutrients in our diet influences a great many aspects of our metabolism and it is reasonable to assume that some of the as yet unknown metabolic factors which initiate, promote or suppress cancers, will also be influenced by diet. Among the nutrients implicated in cancer are fat, fibre, calcium and vitamins E and C and ß-carotene. Other nutrients have been implicated at the hypothetical level but these six have been the most extensively studied. For a variety of reasons, it is wise to consider the role of energy intake before considering these nutrients.

Many of the earlier studies of diet and cancer and regrettably, some of the more recent ones, have used estimates of nutrient intake without providing data on energy intake. The reason for this omission is due to the use of poorly designed food-frequency questionnaires (FFQ). This approach to estimating nutrient intake is attractive because it is quick and cheap. Its best use is not in estimating *absolute intakes* but in classifying people into non-consumers v consumers of specific foods or into *low* and *high* consumers of specific nutrients. For example, most of our carotene intake comes form carrots, tomatoes and green vegetables. It is therefore possible to rank people with respect to carotene intake based on fairly simple questions on the intakes of these foods. If average servings are assumed, it is even possible to quantify carotene intake. However, there are two reasons why carotene may be low (or high). An individual may have a normal energy intake but for reasons of personal taste, have a low intake of carotene rich foods. Another individual may have a low energy intake and consequently have a low intake of all foods including carotene rich foods. The first such individual has a low-carotene diet, the other has a diet low in <u>all</u> nutrients including carotene. If data on energy intakes are not collected, this distinction cannot be made and people may be classified as being low carotene consumers when in fact they are also low in other nutrients of importance to the question at hand. The significance of this can be illustrated as follows: Bingham et al (1985) showed that intake of non-starch polysaccharides (dietary fibre) was negatively correlated to age-truncated (35 - 64) average annual colon cancer death rates in nine regions of Great Britain. The correlation coefficient was + 0.72. When energy intake was adjusted for, the correlation coefficient dropped to + 0.45. Thus the main dietary differences between the regions were due to differences in energy intake. The differences in fibre intake were largely secondary to this.

Further caution needs to be exercised in interpreting data relating intakes of *foods* to cancer as opposed to *nutrients* and cancer. Fox example, the Irish National Nutrition Survey shows that only 70% of adults aged 18 - 25 consume carrots. If, in a comparison of cases and controls, cases are found to have a lower overall intake of carrots, one can legitimately ask the question : is the intake lower because fewer people eat carrots or because the % consuming carrots is normal but cases simply eat less. Such confounding factors may seem nit-pickish but they are profoundly important in interpreting this confusing and conflicting literature. Against this cautious background, the role of diet in cancer will be briefly reviewed.

IV DIETARY FIBRE AND CANCER

Fibre may play a protective role in cancer through several mechanisms including the dilution of carcinogens, decreased transit time in the large intestine, reduction in faecal pH, chemical sequestration and altered colonic microflora. In addition, the volatile fatty acids produced by anaerobic fermentation, in particular butyric acid, may play an important role in the normal differentiation of colonic mucosa. These mechanisms remain hypothetical at present.

In a recent review, Shankar and Lanza (1991) have cited 15 observational epidemiological studies of the association between dietary fibre and colon cancer. Thirteen showed a protective effect while one showed no effect and another a negative effect. The US Surgeon Generals report (DHHS 1988) cited 19 case-control studies of fibre and colon-rectal cancer. To-date there have not been any perspective studies of the role of fibre in colon cancer. Fibre has also been studied in relation to other cancers in case control studies, 7 in breast cancer, 1 in oesophageal cancer, 1 in pharangeal cancer, 2 in stomach cancer, 1 in rectum cancer, 1 in endometrum cancer and 2 in ovarian cancer. These have been considered in the review of Shankar and Lanza (1991). The great majority have shown a protective effect. On balance, however, most of the interest in dietary fibre and cancer has centered on colorectal cancer. In a recent review, Boutron et al (1991) concluded that the evidence linking vegetable intake with a protective effect on colorectal cancer was consistent. The authors, however, concluded : "Available data are not sufficient to serve as a basis for strong specific dietary advice and studies on large bowel cancer should be undertaken, particularly in the field of intervention studies".

Whilst the strength of evidence that high fibre intakes protect against many cancers appears good, the data requires careful consideration. Firstly, and as previously outlined, many of these studies did not take other nutrients into account. That is, it remains uncertain as to whether the effects were truly independent of energy intakes or of the intakes of other nutrients found in fibre-bearing foods. Secondly, dietary fibre is a very broad term and it is often difficult to dissociate the effects of cereal fibre, which is poorly fermented in the large intestine from the effects of fruit and vegetable fibre which is extensively fermented. Thirdly and most importantly, a high fibre diet, particularly a high-fibre diet based on fruit and vegetables, may also be a low-fat diet or more significantly, a high vitamin C, vitamin E and ß-carotene diet.

V ANTI-OXIDANT MICRONUTRIENTS AND CANCER

As indicated in the previous section, much of the work carried out in the past in relation to dietary fibre and cancer needs to be revised in light of it being possibly confounded by the protective effects of the anti-oxidant micronutrients. The anti-oxidant micronutrients include ß-carotene, vitamin C, vitamin E and selenium. They function by reducing oxidative-generated free radicals. The literature in this area of nutrition and cancer is growing rapidly and is producing the most consistent set of data. A recent review of the literature by Zeigler et al (1992) shows that increased intakes of vegetables, fruit and ß-carotene and elevated blood levels of ß-carotene are consistently associated with reduced risk of lung cancer in epidemiologic studies. The same research also suggests that carotenoids in general may reduce the risk of other cancers although the evidence is less extensive and consistent. A review by Dorgan and Schatzkin (1991) shows that high vitamin C intakes appears to exert some level of a protective effect against lung cancer and to a lesser effect against oral and oesophageal cancers. Block (1991) reviewed the epidemiological evidence on vitamin C and cancer and concluded that of the 90 such studies, the vast majority have found statistically significant protective effects. The results for vitamin E and cancer are less conclusive according to the review of Dorgan & Schatzkin (1991). However, the data of Knekt et al (1991) suggest a protective effect of vitamin E in gastrointestinal cancers. Overall, the evidence associating reduced risk of cancer with higher intakes of fruits and vegetables is the most impressive of the nutrient-cancer area. Perhaps more importantly, this coincides with increasing evidence that antioxidant vitamins also help protect against cardiovascular disease as evident from the data of Gey et al (1991) on vitamin E and of Enstrom et al (1992) on vitamin C.

VI DIETARY FAT AND CANCER

The most extensively studied nutrient-cancer association is that between dietary fat and breast cancer. Willett et al (1987) reported on 601 cases of breast cancer which developed in the Nurses Cohort Study of 80,303 pre-menopausal women over a five year period and found no evidence of an association between dietary fat and breast cancer. Jones et al (1988) reporting on 5,485 pre-menopausal women from the NHANES I study found "no evidence of a positive relation between total or saturated fat, polyunsaturated fat or cholesterol and the risk of breast cancer". Knekt et al (1990) in the third of these prospective cohort trials, in this case involving 3,988 women over a 20 year follow-up period, found "no statistical association between fat intake and

breast cancer". A substantial case-control study of breast cancer in post-menopausal women recently reported by Graham et al (1991) found that "fat intake whether studied in terms of quantity or the proportion of total calories derived from fat, was not associated with risk of breast cancer". Byers (1988) in reviewing the data in the period 1983 - 1988, also concluded that with regard to types of dietary fat (saturated v unsaturated) that "there was no consistent pattern of effect for one type of fat as compared to the other". This author also found the data linking dietary fat to colon cancer in this period to be inconsistent.

VII NUTRITION AND CANCER : CONCLUSIONS

This review attempts to look critically at the problems of studying the links between diet and cancer and also to look at some of the major studies and reviews in this area. With regard to the latter, the literature is so vast that an exhaustive analysis of all studies has not been attempted, nor have all possible nutrient-cancer links been examined. On balance the evidence in general tends to be inconsistent which, given the problems inherent in this area of study, is not surprising. However, the evidence linking the antioxidant vitamins and cancer is developing a level of consistency that merits its translation into public health goals on diet, particularly since these vitamins have also been shown to have a potentially protective role in CHD. In practical terms this means an increased consumption of fruit and vegetables in Ireland. Mean consumption of fruits and vegetables in Ireland is one third that of Spain and half that of Italy as can be seen in Table 1.

Table 1. Comparison of intakes of fruits and vegetables in the European Communtiy based on national dietary survey data.

	Fruit (g/d)	Vegetable (g/d)	Fruit and Vegetables (g/d)
United Kingdom	62	102	164
Ireland	107	86	193
Denmark	78	129	207
Germany	103	118	221
Netherlands	128	163	291
Portugal	168	219	387
Italy	223	177	400
Spain	278	221	499

Source : Nutriscan EC Food and Nutrition Atlas

REFERENCES

Ames, B.N. & Gold, L.S. (1990). Too many rodent carcinogens : mitogenesis increases mutagenesis. Science, 249, 970 - 971.

Armstrong, B. & Doll, R. (1975). Environmental factors and cancer incidence and mortality in different countries, with special reference to dietary practices. International Journal of Cancer, 15, 617 - 631.

Axtell, L.M., Asire, A.J. & Myers, M.N. (1976). Cancer patient survival. Report number 5. US Department of Health, Education and Welfare; Bethesda: DHEW Puiblication no (NIH) 77 - 992.

Bazarre, T.L. & Myers, M.P. (1978). The collection of food intake data in cancer epidemiology studies. Nutrition & Cancer, 1, 22 - 45.

Bingham, S.A., Williams, D.R. & Cummings, J.H. (1985). Dietary fibre consumption in Britain : new estimates and their relation to large bowel cancer mortality. British Journal of Cancer, 52, 399 - 402.

Boutron, M., Wilpart, M. & Faivre, J. (1991). Diet and colorectal cancer. European Journal of Cancer Prevention 1, 13 - 20.

Byers, T.E., Rosenthal, R.I., Marshall, T.I. (1983). Dietary history from the recent past : A methodological study. Nutrition and Cancer 5, 69 - 77.

Byers, T.E., Marshall, J., Anthony, E., Fielder, R. & Zielezny, M. (1987). The reliability of dietary history from the distant past. American Journal of Epidemiology 125, 999 - 1011.

Byers, T. (1988). Diet and cancer. Any progress in the interim ? Cancer, 62, 1713 - 1724.

Cohen, L.A. (1987). Diet and Cancer. Scientific American 257, 42 - 48.

Dorgan, J.F. & Schatzkin (1991). Antioxidant micronutrients in cancer provention. Haematology-Oncology Clinics of North America 5, 43 - 68.

Enstrom, J.E., Kanim, L.E. & Klein, M. (1992). Vitamin C intake and mortality among a sample of the United States population. Epidemiology, 3, 194 - 202.

Gey, K.F., Puska, P., Jordan, P. & Moser, U.K. (1991). Inverse correlation between plasma vitamin E and mortality from ischaemic heart disease in cross-cultural epidemiology. American Journal of Clinical Nutrition, 53, 3265 - 3345.

Graham, S,, Hellman, R., Marshall, J., Freudenhein, J., Vena, J., Swanson, M., Zielezny, M., Nemoto, T., Stubbe, N. & Raimondo, T. (1991). Nutritional Epidemiology of post menopausal breast cancer in Western New York. American Journal of Epidemiology, 134, 552 - 566.

Hargreaves, W.A. (1987). Mutagens in cooked food. In "Nutritional Toxicology - Volume II" pp 157 - 172. J.N. Hathcock, editor. Academic Press : New York.

Henderson, M.M. (1992). Role of intervention trials in research on nutrition and cancer. Cancer Research, 52, 2030 - 2034.

Holm, L.E. (1990). Nutritional intervention studies in cancer prevention. Medical Oncology and Tumor Pharmacotherapy, 7, 209 - 215.

Jones, D.Y., Schatzkin, A. Green, S.B., Block, G., Brinton, L.A., Ziegler, R.G., Hoover, R. & Taylor, P. (1987). Dietary fat and breast cancer in the National Health and Nutrition Examination Survey I. Epidemiologic follow-up Study. Journal of the National Cancer Institute, 79, 465 - 471.

Knekt, P., Aromaa, A., Maatela, J., Aaran, R.K., Nikkari, T., Hakama, M., Hakulinen, T., Peto, R. and Teppo, L. (1991). Vitamin E and cancer prevention. American Journal of Clinical Nutrition 53, 2835 - 2865.

Knekt, P., Albanes, D., Seppanen, R., Aroman, A., Jarvinen, R., Hyvonem, L., Teppo, L. & Pukkals, E. (1990). Dietary fat and breast cancer. American Journal of Clinical Nutrition, 52, 903 - 908.

Marshall, J., Priore, R. & Haughey, B. (1980). Spouse-subject interviews and the reliability of diet studies. American Journal of Epidemiology, 112, 675 - 683.

Rohan, T.E. & Potter, J.D. (1984). Retrospective assessment of dietary intake. American Journal of Epidemiology 120, 876 - 887.

Shankar, S. & Lanza, E. (1991). Dietary fibre and cancer prevention. Haematology-Oncology Clinics of North America, 5, 25 - 42.

Willet, W.C., Stampler, M.J., Colditz, G.A., Rosner, B.A., Hennekens, C.H. & Speizer, F.E. (1987). Dietary fat and the risk of breast cancer. New England Journal of Medicine 316, 22 - 28.

Willett, W. (1990). Nutritional Epidemiology pp 380 - 386. Monographs in Epidemiology and Biostatistics, volume 15, Oxford University Press : Oxford.

WHO (1985)., World Health Statistics Annual; WHO : Geneva.

Zeigler, R., Subar, A.F., Craft, N.E., Ursin, G., Patterson, B.H. & Graubard. B.I. (1992). Does ß-carotene explain why reduced cancer risk is associated with vegetable and fruit intake. Cancer Research, 52, 2060 - 2066.