

CANCER

With research continuing to show the link between diet and a range of serious diseases, a major new Anglo-American report has now been published that provides overwhelming global evidence that diets high in fruit and vegetables can protect against most types of cancer and that cancer is a largely preventable disease.

The food-cancer link

THE IDEA that nutrition is an important factor in the risk of cancer is not new. Yong-He Yan, living in the Song Dynasty, (960-1279 AD) thought that poor nutrition was a cause of the condition we would now know as cancer of the oesophagus. Wiseman (1676) suggested that cancer might arise from 'an error in Diet, a great acrimony in the meats and drinks meeting with a fault in the Concoction' (digestion), and he advised abstention from 'salt, sharp and gross meats'.

Howard (1811) proposed that constipation was an important factor in cancer, basing his judgement on 40 years of clinical practice. Lambe (1815), a Fellow of the Royal College of Physicians of London, warned in his treatise on diet, cancer and other chronic diseases, against the danger of excess consumption of food in general and meat in particular. Bennett (1849), author of medical textbooks, wrote that 'the circumstances which diminish obesity, and a tendency to the formation of fat, would seem, *a priori*, to be opposed to the cancerous tendency'.

By the early twentieth century, similar views were commonplace. Shaw (1907) advocated a prudent regime designed to reduce the risk of cancers, with more foods of vegetable origin, less foods of animal origin, and less alcohol, tea and tobacco. Roger Williams in *The Natural History of Cancer* (1908), concluded that 'probably no single factor is more potent in determining the outbreak of cancer in the predisposed, than excessive feeding' and proposed that 'many indications point to the gluttonous consumption of proteins - especially meat - which is such a characteristic feature of the age, as likely to be specially harmful in this respect'. He also

identified 'deficient exercise, and probably lack of sufficient vegetable food'.

During the first half of the twentieth century, two influential hypotheses on the environmental causes of cancer were developed. The first focused on occupational causes, notably exposure of workers to carcinogenic agents (Hueper, 1942). The second general theory focused on diet. The medical statistician and epidemiologist, Frederick Hoffman, a founder of the American Cancer Society (ACS) and the US National Cancer Surveys (which eventually led to the national network of cancer repositories - SEER), undertook a systematic review of the then current literature on diet and cancer (Hoffman 1937). He concluded that 'excessive nutrition if not the chief cause is at least a contributory factor of the first importance'. He identified fatty, sugary foods, white bread and meat as possible specific factors.

Hoffman also undertook a systematic study of smoking and cancer, for the ACS and for insurance companies. He concluded (1931) that 'the inhalation of cigarette smoke..... unquestionably increases the danger of cancer development'.

Early research proposing that cancer had nutritional and other environmental causes did not always rely merely on individual clinical observations. Walshe (1846) and Williams (1908) noted the effects of migration on cancer risk, as did Hoffman (1915) whose later work (Hoffman, 1937) also drew on his own multi-centre case-control study using 2,234 cancer cases and 1,149 controls, and referred to contemporary animal studies of the effects of different diets on transplanted tumour tissue.

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This article is extracted from the introduction to *Food, Nutrition and the Prevention of Cancer: a global perspective*, published by the World Cancer Research Fund and the American Institute for Cancer Research.

Main conclusions of the report
There is overwhelming evidence that diets high in a variety of vegetables and fruits protect against many, if not all cancers.

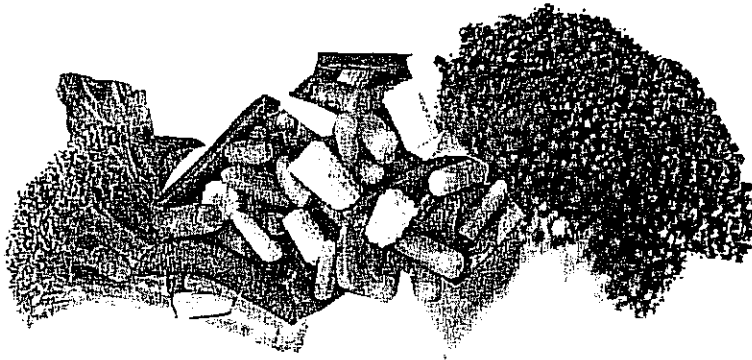
The reporting panel estimates that following the recommendation on vegetables and fruits alone, should, on a population basis, reduce cancer incidence by 20 per cent.

The consistency of the evidence between cancer sites and between cancer and other diseases was such that the panel was able to make its recommendations in the confident knowledge that these will also help reduce the risk of other diseases and therefore prolong healthy life in general.

Among the earliest formal epidemiological studies of diet and cancer were those by Orr (1933), who undertook an ecological study of oral cancer in India, and the other by Stocks (1933), who conducted a case-control study of cancer in England and Wales; each identified distortions of dietary patterns (especially low intakes of vegetables and fruit) as risk factors.

In the second half of the twentieth century, theories of the dietary origin of cancer tended to be increasingly discounted, in favour of alternative theories that cancer is either the result of random genetic error, exposure to viruses or exposure to specific chemical carcinogens. Laboratory research began to concentrate on the investigation of

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cellular, and ultimately, molecular carcinogens, as well as on the effectiveness of surgery, radiotherapy and chemotherapy, as cancer treatments. The index of the fifth edition of the standard textbook *Human Nutrition and Dietetics* (Davidson et al, 1972) included no reference to diet and cancer, and its text included only cursory reference to evidence that cancers of some sites may have some relationship with diet.

However, rates of incidence and death from various cancers continued to rise in industrialised countries (compare, for instance Park, 1899 and Parkin et al, 1987) and epidemiological investigation indicated that this trend was not just a function of ageing. Further, studies of variations in cancer incidence from country to country, and in successive generations of people who migrated from one part of the world to another, strongly suggested that cancers were largely environmental in origin. In the second half of the twentieth century, a new body of experimental and epidemiological work (Tannenbaum and Silverstone, 1957; Doll, 1967) began to indicate that diet was indeed a major environmental factor affecting the incidence of cancers of a number of sites.

1950 to 1980

In recent decades, increasing attention has been paid to various foods and nutrients as modifiers of cancer risk, and current thinking on diet and cancer is a synthesis of findings from epidemiological and experimental research.

Much early research on cancer was based on the idea that disease is caused by over-exposure to specific discrete pathogenic factors. This concept, originating from the late nineteenth century discoveries of microbial agents of infectious diseases, has some application to chronic diseases (Stewart, 1968). Thus, excess intake of alcohol has been studied, initially with reference to upper aerodigestive cancers. Diets high in fat have been thought to be important factors in increased risk of some cancers more common in economically developed countries.

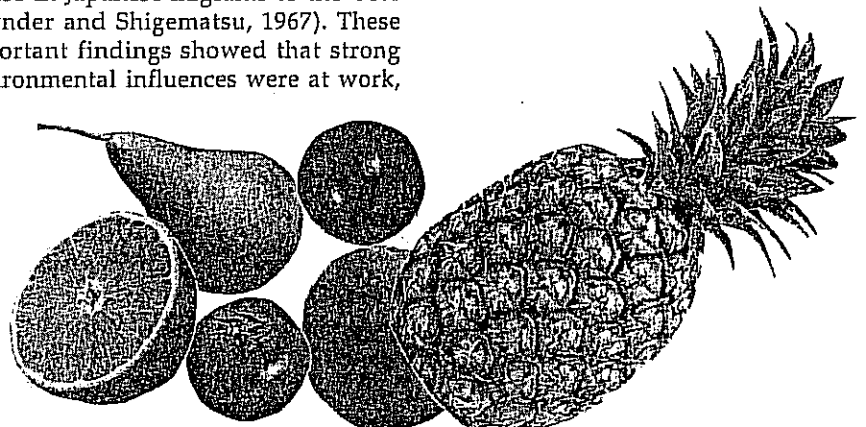
In the 1960s, the search for specific

dietary causes of human cancer gained momentum as the experimental model of laboratory carcinogenesis became widely used. There was a corresponding expectation that various specific chemical carcinogens would be identified in the human diet, as had been done in occupational cancer epidemiology, for example, with specific dyes, asbestos and benzene.

At the same time, descriptive and ecological epidemiology showed that the



incidence rates of various cancers, including those of the oesophagus, pancreas, stomach, colon and rectum, varied greatly between countries. Rates also varied over time as people migrated from one country to another. For example, colon and breast cancer rates were noted to rise in Japanese migrants to the USA (Wynder and Shigematsu, 1967). These important findings showed that strong environmental influences were at work,



and epidemiologists reasoned that these were likely to include diet.

The first reliable data for cancer incidence worldwide were collected by cancer registries set up for the purpose. The data was published initially by the International Union Against Cancer (UICC, 1965, 1970), and later by the International Agency for Research on Cancer. An early analysis of these data by Higgison and Muir (1973) noted that the incidence of most, if not all, cancers varied greatly in different countries and regions, and concluded, that '80 to 90 per cent of cancers are due to external factors and are thus theoretically preventable'.

A wide range of specific hypotheses about diet and cancer emerged during the 1970s. The investigation of these hypotheses was helped by the development of various biochemical and metabolic assays, most helpful in ecological and prospective studies. Particular attention began to be paid to dietary fat, in light of its strong population-level association with cancer rates, and of the experimental evidence that fat induced cancer.

The distinguished Irish surgeon, Denis Burkitt, who identified the lymphoma that bears his name, developed the hypothesis that a lack of dietary fibre in the 'western' diet accounted for the rise of various chronic diseases, including colon cancer (Burkitt, 1969). But how could low-fibre, high fat diets increase exposure to chemical carcinogens? To answer this question epidemiologists and laboratory scientists, working in collaboration, proposed that the key biological events may involve bile acid metabolism, gut microbial ecology, chemical concentration and mucosal contact time (see, for example, Stephen and Cummings, 1980, for a synthesis of these ideas).

Meanwhile laboratory scientists proposed that salt-pickled and other abrasive foods and drinks, in combination with low vitamin C intake, made the gastric mucosa vulnerable to dysplastic change, and the gastric contents to carcinogenic nitrosamine production.

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Insights into the multistage nature of carcinogenesis were derived from animal experiments early in the century and extended by increasingly sophisticated mathematical models of cancer risks. These set epidemiologists to thinking about types of dietary influences that did not entail direct damage to DNA. For example, the association of breast cancer with reproductive factors and sex hormone profile, the changes in risks with migration, the sex hormone difference between meat eaters and vegetarians, and animal experimental evidence showing modulation of carcinogen-induced mammary cancer by dietary fat, together suggested that diet may act directly on breast cancer by influencing hormonal and other metabolic processes. Other models followed.

Alcohol (that is, ethanol) was suspected of aiding the trans-membrane movement of chemical carcinogens (particularly those in tobacco smoke) in the mucosal cells of the upper aerodigestive tract, or else of impeding intracellular defences. Various micronutrients were proposed as reinforcing antioxidant defences, or switching metabolic pathways that deactivated carcinogens.

An emerging consensus

Interest in nutritional causes of cancer began to revive in the 1970s, at first in the USA. This was partly because overall cancer rates remained obstinately high while costs of treatment accelerated; partly because of the new evidence on diet and cancer; and partly because 'winning the war against cancer' was perceived as a national goal equivalent in importance to the earlier achievement of putting a man on the moon (Proctor, 1995).

The USA's National Cancer Act of 1971 required the National Cancer Institute (NCI), as a government agency, to investigate the relationship between nutrition and cancer. Following the revised Act of 1974, the NCI, jointly with the privately-funded American Cancer Society (ACS), organised a symposium on 'Nutrition in the Causation of Cancer'

(AACR, 1975). In his summary, Professor Mark Hegsted of the Harvard School of Public Health commended a prudent diet with 'less fat, less meat, less cholesterol and less food and more fruits, vegetables and cereals, especially crude cereals'.



A further review by Wynder and Gori (1977) proposed that, for both men and women, the 'preventative potential' for all cancers was 80-90 per cent and that diet accounted for 40 per cent of all male cancers and 60 per cent of all female cancers. It was suggested that key dietary causes of cancer, in general, included overeating, fat and meat. The fact that incidence of stomach cancer varies inversely with the incidence of breast and of colon cancer was interpreted as suggesting that high-fat, low-carbohydrate diets might protect against stomach cancer.

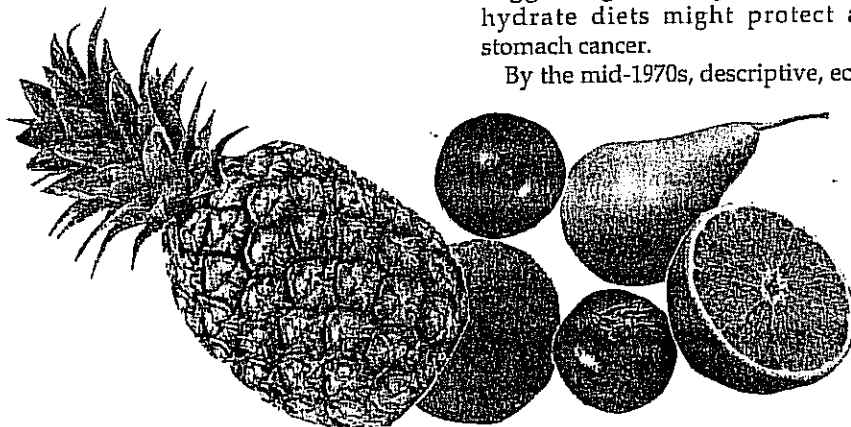
By the mid-1970s, descriptive, ecological

and analytical epidemiological studies were proving a growing daily body of evidence of links between diet and cancer. The British epidemiologists Richard Doll and Richard Peto were commissioned by the US Congress to estimate to what extent cancer is avoidable. Their review, *The Causes of Cancer* (Doll and Peto, 1981), is still frequently cited. Formally, their conclusions apply only to the USA, but their references were from the world literature and, in the view of this and other expert panels, their interpretations have wide application.

Doll and Peto's review, which helped to reset the agenda for thinking on food, nutrition and cancer, included estimates of the extent to which cancer in general, and specific cancers, can be avoided by changes in diet.

Doll and Peto agreed that alcohol, in all forms, increases the risk of cancers of the upper aerodigestive tract and that this risk is exacerbated when drinkers smoke. They attributed approximately three per cent of all cancer deaths to alcohol, while also stating that most of these deaths would be avoided if drinkers did not smoke. They concluded that environmental carcinogens, other than those in tobacco and diet, are relatively unimportant causes of cancer. This conclusion was based partly on ecological data which showed no coherent pattern (across various countries and regions) between cancer trends and the degree of external pollution.

The report of Doll and Peto anticipated that results of further research 'may well be' as follows: 'Diet will be shown to be a factor in determining the occurrence of a high proportion of all cancers of the stomach and large bowel as well as the body of the uterus (endometrium), gall bladder and (in tropical countries) of the liver.' Diet may also prove to have a material effect on the incidence of cancers of the breast and pancreas and, perhaps through the anti-carcinogenic effects of various micronutrients, on the incidence of cancers in many other tissues. 'If this is so, it may be possible to reduce US cancer death rates by practicable dietary means by as much as 35 per cent (for specific sites their estimates were: stomach and large bowel, 90 per cent; endometrium, gall



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bladder, pancreas and breast, 50 per cent; lung, larynx, bladder, cervix, mouth, pharynx and oesophagus, 20 per cent; other types of cancer 10 per cent.'

This estimate of 35 per cent Doll and Peto judged as 'plausible', while stressing the imprecision of the figures for individual cancers, and suggested that anything between 10 and 70 per cent of all deaths from cancer may be caused by diets such as those consumed in the USA.

Aspects of diet mentioned in Doll and Peto's report as possibly protective against cancer included antioxidant vitamins, vegetables, such as carrots and leafy greens that are rich in these compounds, and bioactive microconstituents such as indoles and protease inhibitors. Fibre, or rather foods that make faeces bulky, were also cited as important. Aspects of diet mentioned as possible causes of cancer were over-consumption (cancers of the uterus and gallbladder in women), fat (cancers of the breast, colon and rectum) and meat (cancers of the colon and rectum). Those considered to be relatively unimportant causes of cancer were food additives (including colours and sweeteners), contaminants (apart from aflatoxin in relation to liver cancer), and methods of food preparation and storage that create carcinogens.

In 1982, the US National Academy of Sciences (NAS) published *Diet, Nutrition and Cancer*, commissioned by the NCI in 1980 (NAS, 1982). The 478-page volume, with well over 2,000 citations, was the first report of a multidisciplinary expert panel specifically on diet and cancer, the first to derive its findings from a thorough survey of epidemiological and experimental data, and the first to derive dietary recommendations designed to reduce the risk of cancer.

The report drew conclusions that informed the agenda for international and national agencies, that influenced patterns of research funding, and that added considerable impetus to the change in direction initiated by Doll and Peto.

A key passage in the NAS report has come to be generally accepted (Trichopoulos et al, 1996; Willett et al, 1996) and is endorsed by the panel of this present report: 'It is abundantly clear that the incidence of all common cancers in humans is being determined by various potentially controllable external factors. This is surely the most comforting fact to come out of all cancer research, for it means that cancer is, in large part, a preventable disease.' Doll and Peto had concluded in related fashion: 'It is highly likely that the United States will eventually have the option of adopting a diet that reduces its incidence of cancer by approximately one-third and it is

could be prevented by abolishing smoking. These reductions would be roughly equivalent to the reduction in mortality from the infectious diseases brought about by improved hygiene and better health care delivery during the nineteenth century.'

The NAS report proposed six interim dietary guidelines 'both consistent with good nutritional practice and likely to reduce the risk of cancer'. These included recommendations to reduce intake of fat to 30 per cent of total calories, to include fruits, vegetables and wholegrain cereals in the daily diet, to minimise consumption of salted and smoked foods, and to drink alcohol in moderation, if at all. Concern was expressed about carcinogens and mutagens in food.

Since 1982, a large number of reports and statements on diet and cancer or on diet and chronic diseases more generally have been published.

The diet and cancer story is complex, if only because there are a large number of cancers of different types and sites. Further complexity has been created by the fact that different approaches to the study of cancer have been taken by scientists from separate disciplines. For example, much of the dietary causation of the cancers more common in economically developed countries tends to be seen in terms of metabolic and hormonal influences on carcinogenesis. By contrast, the dietary aetiology of cancers more common in developing countries tends to be seen in terms of chemical carcinogenesis; this involves dietary components and contaminants (for example, nitrosamines and mycotoxins) and deficiencies of specific microconstituents, as well as biological agents such as the human papillomaviruses, the hepatitis viruses and the bacterium *Helicobacter pylori*.

During the 1980s and 1990s, several previously identified relationships between aspects of diet and cancer have been confirmed. Other relationships have emerged: for example, alcohol consumption has recently been consistently associated with an increased risk of cancer of the colon, rectum and breast (Kearney et al, 1995; Longnecker 1988, 1994). The recent body of evidence has reduced the importance of specific nutrients, for example, fat, in favour of foods, for example, meat. These and other examples, including the relatively much clearer evidence of the protective effect of regular physical activity, are reviewed and assessed in this latest report.

Perhaps the most important finding that has emerged strongly in recent years (fully assessed in the latest report) is that diets high in vegetables and fruits (and therefore fibre, antioxidants and other

associated with reduced risk of most, if not all, epithelial (skin) cancers (Steinmetz and Potter, 1991, 1996).

Correspondingly, the list of specific cancers the incidence of which is related to diet and factors related to diet has tended to increase (Willett and Trichopoulos, 1996). These include cancers of the mouth and pharynx (Marshall and Boyle, 1996), larynx (Riboli et al, 1996), oesophagus (Cheng and Day, 1996), lung (Ziegler et al, 1996), pancreas (Howe and Burch, 1996), stomach (Kono and Hirohata, 1996), colon and rectum (Potter, 1996), breast (Hunter and Willett, 1996), endometrium (Hill and Austin, 1996), cervix (Potischman and Brinton, 1996), prostate (Kolonel, 1996), kidney (Wolk et al, 1996) and bladder (La Vecchia and Negri, 1996); these are all sites reviewed and assessed in the full report.

During its four years of work, the panel responsible for the report came to the view that the most appropriate approach to the prevention of cancer by dietary means is to emphasise foods and drinks in the contexts of whole diets, within existing cuisines and cultures. For example, the traditional Mediterranean diet is, as a whole, a low-risk cancer diet relative to others in Europe, North America and other economically developed countries (Ferro-Luzzi, 1994), and it is defined by its food, regional climate and culture.

The panel also endorsed the view of others (Franceschi, 1994) that dietary diversity itself is probably a key factor in protection against cancer, especially in certain parts of the world and among impoverished populations. Diversity maximises the likelihood of more balanced as well as more adequate diets. Diets in poor rural populations around the world are often monotonous and marginal or even deficient in various microconstituents that may protect against some cancers (as well as the longer standing scourges of iodine, iron, and retinol/carotenoid deficiencies); cancers therefore, at least in part, can be seen as diseases of deficiency.

It is possible to construct four general patterns of the environmental causes of cancer (Potter, 1996b). Cancers generally more common in the past in the developed world, and which persist in the economically less developed world, can be seen as largely caused by either dietary deficiency, of which the root cause is insecure, or inadequate food supplies. Alternatively, they are caused by infection or infestation, also a manifestation of poverty. Cancers generally now more common in the economically developed world, and in urban areas elsewhere in the world, can be seen as largely caused by exposure to carcinogenic agents either

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consequence of industrialisation but always a consequence of the ubiquitous use of tobacco. The other general pattern is that of an excess of energy-dense foods in the context of physical inactivity, a situation that follows urbanisation. The first and the fourth patterns may be obverse sides of the same risk; an excess of fat and sugar-rich foods may produce a deficiency of protective dietary constituents almost as readily as a monotonous high-starch diet.

The diet and cancer relationship can be considered as part of a still larger picture, within an evolutionary framework (McMichael, 1994). Oxygen, released by photosynthesis, has accumulated in the lower atmosphere during the second half of the Earth's existence. For aerobic organisms, including *Homo sapiens*, this oxygen is a double edged sword: it enables efficient aerobic metabolism, but it also causes reactive damage to macromolecules. Terrestrial plants have evolved antioxidant defences against oxidative assault. These defences depend on certain elements (for example, selenium) and on the synthesis of complex molecules (for example, carotenoids and polyphenols).

Not surprisingly, many of these micronutrients have also become, through

co-evolution, the antioxidant defences of the animals that eat those plants. Leaves and ripening fruits, the metabolically active parts of the plant, contain high levels of antioxidant vitamins. In contrast, seeds comprise dormant genetic material and energy stores and they have lower antioxidant concentrations. Because the evolutionary formative primate/hominid diet that shaped human biology was very high in antioxidant-rich leafy vegetables and fruit (Milton, 1993), human metabolism should therefore function best with diets high in foods rich in antioxidants. However, in most modern human populations, who have a relatively low intake of fresh vegetables and fruits, the daily oxidative assault from our oxygenated environment may be less well countered, thus facilitating carcinogenesis.

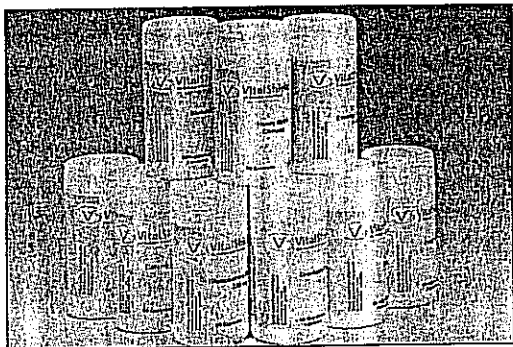
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By its nature, in common with other subjects of research, the diet and cancer story remains incomplete. Data will continue to accumulate, and results of observational studies, metabolic studies and some large controlled trials are awaited. Recommendations based on an evolving science of food, nutrition and cancer will themselves evolve.

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