Review

The effect of diet on risk of cancer

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Diet-related factors are thought to account for about 30% of cancers in developed countries. Obesity increases the risk of cancers in the oesophagus, colorectum, breast, endometrium, and kidney. Alcohol causes cancers of the oral cavity, pharynx, larynx, oesophagus, and liver, and causes a small increase in the risk of breast cancer. Adequate intakes of fruit and vegetables probably lower the risk for several types of cancer, especially cancers of the gastrointestinal tract. The importance of other factors, including meat, fibre, and vitamins, is not yet clear. Prudent advice is to eat a varied diet including plenty of fruit, vegetables, and cereals; to maintain a healthy bodyweight with the help of regular physical activity; and to restrict consumption of alcohol.

Dietary factors are thought to account for about 30% of cancers in western countries,[1] and thus, diet is second only to tobacco as a potentially preventable cause of cancer. The contribution of diet to risk of cancer in developing countries is lower, perhaps around 20%.[2] Research about the effects of diet on risk of cancer has uncovered few definite effects and left much uncertainty. Here, we summarise our view of the present state of knowledge, concentrating on recent reports and promising topics of research.

Evidence for diet as a risk factor for cancer

International comparisons, migrants, and time trends

Many of the prominent hypotheses for the effects of diet on risk of cancer have been derived from investigation of the associations between dietary patterns and cancer rates in various populations. It was noted in the 1970s that people in many western countries had diets high in animal products, fat, and sugar, and high rates of cancers of the colorectum, breast, prostate, endometrium, and lung; by contrast, individuals in developing countries usually had diets that were based on one or two starchy staple foods, with low intakes of animal products, fat, and sugar, and low rates of these cancers.[3] These observations suggest that the diets of different populations might partly determine their rates of cancer, and the basis for this hypothesis was strengthened by results of studies showing that people who migrate from one country to another generally acquire the cancer rates of the new host country,[1] suggesting that environmental rather than genetic factors are the key determinants of the international variation in cancer rates. Figure 1 shows estimated incidence rates for the most common cancers worldwide in 2000. In both developed and developing countries, breast cancer was the most common cancer in women and lung cancer was the most common in men; developed countries have much higher incidence rates of cancers of the breast, colorectum, and prostate than do developing countries.

In many countries, peoples' diet changed substantially in the second half of the twentieth century, generally with increases in consumption of meat, dairy products, vegetable oils, fruit juice, and alcoholic beverages, and decreases in consumption of starchy staple foods such as bread, potatoes, rice, and maize flour. Other aspects of lifestyle also changed, notably, large reductions in physical activity and large increases in the prevalence of obesity. Some of the most striking, rapid, and well-documented changes in diet were seen in Japan, where consumption of meat and dairy products increased ten-fold between the 1950s and the 1990s.[5] Figure 2 shows trends in cereal and meat consumption, and in colorectal cancer, in the UK and Japan since 1960.[5–13] 40 years ago, consumption of cereals was much higher in Japan than in the UK, whereas consumption of meat was high in the UK, but very low in Japan; since then, consumption of cereals has fallen in both countries, whereas consumption of meat has increased seven-fold in Japan and remained fairly constant in the UK. Incidence of colorectal cancer has risen by 35% in men in the UK and by almost five-fold in Japan, and the incidence is now as high in Japanese men as in men in the UK.[13]

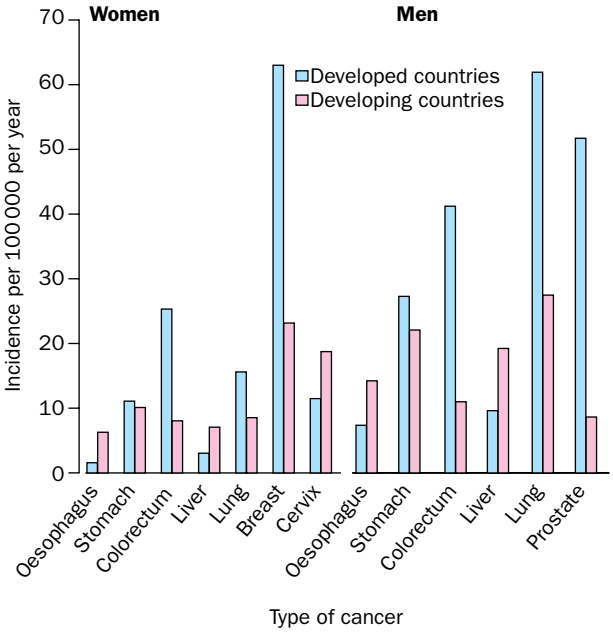

Figure 1: **Age-adjusted incidence rates of the most common cancers**[4]

Some of the main hypotheses derived from these observations in whole populations have not been

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consistently supported by the results of detailed studies of the diets of individuals.[14] However, the international variations in diet and cancer rates continue to suggest that diet is an important risk factor for many common cancers, and therefore that cancer could be partly preventable by dietary changes.

Analytical epidemiological studies

In the past 30 years, many studies have been published about the association between the diets of individuals and their risk of developing cancer. The earlier studies mostly used a case-control design, in which people who already had cancer were asked what they ate, and their diets were compared with those reported by people without cancer (controls). Such studies are useful to search for possible dietary effects, but cannot be relied on to detect smaller dietary associations because they are susceptible to recall and selection biases: people with cancer may recall their diet differently from healthy people, and healthy controls are rarely representative of the population and may report a healthy diet.[15] In this overview, therefore, we have focused on the results from prospective studies in which dietary intakes are measured at recruitment and people are followed-up for cancer incidence.

Intervention trials

The results of observational studies of diet and cancer, however well designed and implemented, must be interpreted with caution because of the potential for confounding—eg, dietary factors such as a high intake of fruit and vegetables are usually associated with other factors that affect development of cancer such as smoking and physical activity. Intervention trials, in which participants are randomly allocated to a dietary change or supplement, eliminate confounding and can therefore provide much stronger evidence of causality than observational studies. For diet and cancer, however, intervention trials cannot easily test hypotheses because they need to be very large and are therefore expensive, and because they can only test a small number of interventions during a short period. The design of intervention trials is straightforward for assessment of the effect of supplements such as vitamin pills, but much more difficult for investigation of changes in macronutrient or food intake (when it is not usually possible to blind participants to the intervention). Up to now, few intervention trials of diet and cancer have been published, but the results of those that have been published have been important in suggesting that some previous observations were misleading.[16]

Assessment of diet

Investigations of diet and cancer have included assessment of food intake and intake of specific nutrients; nutrient intakes can be estimated from food intakes and food composition tables, and the concentrations of nutrients in plasma or other tissues can be measured. Foods and nutrients are difficult to investigate because estimates of intake are not very accurate and because different factors often have strong correlations, making it difficult to attribute associations with risk to specific factors. Body-mass index and alcohol are special cases. Body-mass index is partly determined by the balance of energy intake and energy expenditure, and is therefore an indicator of chronic energy balance. In epidemiological studies, investigators can measure body-mass index much more accurately than either energy intake or energy expenditure. Alcohol is not always included under the term diet, but alcoholic drinks contribute a substantial supply of energy (through ethanol and sugar) and some nutrients in many populations. Although estimates of usual alcohol intake are commonly under-reported, they rank individuals much more accurately than do estimates of intakes of other foods and nutrients, mainly because of the very large variations in drinking habits within populations and because for many drinkers, alcohol consumption is a regular daily habit.

Experimental research

In addition to studies of cancer rates in human populations, much research has been done on the effects of diet on development of cancer in animals and the mechanisms by which dietary factors might affect development of cancer. Detailed review of these fields is beyond the scope of this article, but the most striking finding from studies on diet and cancer in animals is that energy restriction can substantially reduce incidence of cancer.[17] The implications of this observation for human populations are not yet clear, but understanding the mechanisms of this protective effect is important, and recent research suggests that a reduction in concentrations of insulin-like growth factor (IGF)-I might play a part.[17,18]

The role of diet in the cause of common cancers

Panel 1 summarises the established or probable associations of diet and diet-related factors with risk of common cancers. The best-defined effects are those of obesity, which increases risk of cancers of the oesophagus (adenocarcinoma), colorectum, breast, endometrium, and kidney, and of alcohol, which increases the risk of cancers

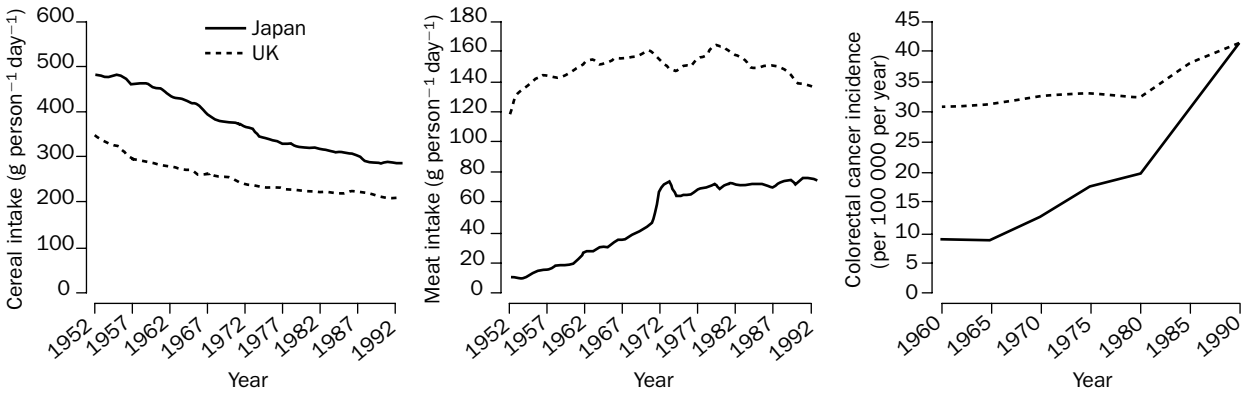

Figure 2: **Indicators of dietary change and trends in colorectal cancer (men) in the UK and Japan[5–13]**
Data are changes in consumption of cereals (left) and meat (middle), and incidence of colorectal cancer (right).

Panel 1: **Dietary risk factors, dietary protective factors, and other major risk factors for the common cancers**

Cancer	Dietary and diet-related risk factors	Dietary protective factors	Other major risk factors
Oral cavity, pharynx, and oesophagus	Alcohol Very hot drinks Obesity (adenocarcinoma of the oesophagus) Chinese-style salted fish (nasopharyngeal cancer)	Probably fruit and vegetables	Smoking
Stomach	Probably high intake of salt-preserved foods and salt	Probably fruit and vegetables	Infection by *Helicobacter pylori*
Colorectum	Obesity Possibly red and processed meat	Probably fruit, vegetables, and other plant foods rich in fibre	Sedentary lifestyle
Liver	High alcohol intake Foods contaminated with aflatoxins	None established	Hepatitis viruses
Pancreas	None established	None established	Smoking
Larynx	Alcohol	None established	Smoking
Lung	None established	Possibly fruit and vegetables	Smoking
Breast	Obesity after menopause Alcohol	None established	Reproductive and hormonal factors
Endometrium	Obesity	None established	Low parity
Cervix	None established	None established	Human papillomavirus
Prostate	None established	None established	None established
Kidney	Obesity	None established	None established

of the oral cavity, pharynx, larynx, oesophagus, liver, and breast. The greatest uncertainties are the effects of some aspects of typical diets in developed countries on cancers of the colorectum, breast, and prostate.

Cancers of the oral cavity, pharynx and oesophagus

Incidence rates of cancers of the oral cavity, pharynx, and oesophagus vary widely between populations; for example, oesophageal cancer is over a hundred times more common in parts of central Asia, China, and southern Africa than in most parts of Europe, North America and West Africa.[4] The main risk factors in developed countries are alcohol and tobacco, and up to 75% of these cancers are attributable to these two lifestyle factors.[19] In some developing countries, however, alcohol and tobacco are less important risk factors, but chewing of betel quid is the major risk factor for oral cancer in the Indian subcontinent, and consumption of opium may be a risk factor in some regions.[19]

Results of epidemiological studies[14] have shown that high intakes of fruit and vegetables are associated with a reduction in risk of these cancers, although some caution is needed in interpretation of these data because they are mostly from case-control studies and because the results could have been biased by some residual confounding by smoking. In the parts of the world with very high rates of oesophageal cancer, traditional diets can be very restricted. Because such diets are low in fruit, vegetables, and animal products, they are therefore deficient in several nutrients such as riboflavin, folate, ascorbic acid, and zinc.[14] Results of trials in China[20,21] have suggested that supplementation of poor diets with micronutrients reduces risk of oesophageal cancer (panel 2), but the roles of specific micronutrients are not yet clear. Consumption of drinks, and presumably foods, at a very high temperature increases risk of these cancers.

Obesity is an established risk factor for adenocarcinoma (but not squamous cell carcinoma) of the oesophagus,[31,32] perhaps because it is associated with reflux of acid from the stomach into the oesophagus, which damages the oesophageal epithelium.[33] Nasopharyngeal cancer is very common in southeast Asia,[4] and has been consistently associated with a high intake of nitrosamine-rich foods, such as Chinese-style salted fish, especially during early childhood,[34] and with the Epstein-Barr virus.[35]

Stomach cancer

Until about 20 years ago, stomach cancer was the most common cancer in the world, but rates have been falling steeply in all western countries,[36] and stomach cancer is now much more common in Asia than in Europe or North America.[4] Infection with the bacterium *Helicobacter pylori* is an established risk factor associated with an approximately three-fold increase in risk of stomach cancer, and probably accounts for about two thirds of non-cardia stomach cancers.[37] The prevalence of infection with *H pylori* varies between populations, usually 20–90%, and is associated with low social class and poor housing conditions during childhood, probably accounting for the high prevalence of infection in developing countries (80–90%), and has decreased in successive generations in western countries.[38]

Diet also contributes to development of stomach cancer, and dietary changes have been implicated in the widespread declines in incidence of this disease.[39] Evidence suggests that risk is increased by high intakes of some traditionally preserved salted foods, especially meats and pickles, and with salt per se, and that risk is decreased by high intakes of fruit and vegetables,[39] perhaps because they have high concentrations of ascorbic acid. The introduction of refrigeration has also been associated with decreased risk, probably because it

Panel 2: **Chemoprevention with dietary supplements**

Vitamins and minerals

High intakes of vitamins and minerals—or micronutrients—might reduce risk of some cancers. Thus, supplements of these compounds could provide a cheap, safe, acceptable and effective means for prevention of cancer.

Diseases caused by deficiencies in micronutrients, such as xerophthalmia (vitamin A deficiency) and goitre (iodine deficiency), are associated with poverty and arise mostly in developing countries. Oesophageal cancer is very common in some regions where the diet has been extremely restricted, such as some regions in China and central Asia. The results of trials[20,21] in Linxian, China, aimed at reduction of oesophageal cancer rates with micronutrient supplements, have been promising but not conclusive.

In western countries, investigators have mostly concentrated on nutrients with antioxidant properties, with a focus on prevention of lung cancer. The results have been disappointing; neither b-carotene or vitamin E was shown to have a protective effect against lung cancer.[16,22–24] Post hoc analyses of two trials have suggested that vitamin E[25] and selenium[26] reduce risk of prostate cancer, but since these hypotheses were not prespecified, they need further investigation. The role of antioxidants in carcinogenesis is not well understood; oxidation is a crucial physiological process, and oxidative damage is not necessarily an important rate-limiting step in carcinogenesis, nor are concentrations of micronutrients necessarily the limiting factor among the many chemicals that determine the total antioxidant defence capacity of the tissues.

The possible roles of supplementary calcium and folic acid in inhibition of adenoma growth and carcinogenesis in the colon are also being investigated.

Non-nutrient anticarcinogens

Many chemicals that are naturally present in plants, but are not nutrients, have been shown in the laboratory to have potentially anticarcinogenic properties.[27] Classes of compounds under investigation include: carotenoids and flavonoids, which can act as antioxidants; isothiocyanates, which can increase the activity of phase 2 detoxification enzymes; sulphur-containing compounds, which might inhibit synthesis of nitrites by bacteria in the stomach;[28] isoflavones, which could have antioestrogenic effects;[29] and phytosterols, which could affect signal transduction pathways and apoptosis.[30] Such research is promising, but few epidemiological data support the possible protective effects of these chemicals.

leads to reduced intakes of salted foods and facilitates availability of fruit and vegetables throughout the year.[14]

The results of micronutrient supplementation trials[20,21] in developing countries have been encouraging, but not conclusive (panel 2). In Linxian, China, combined supplementation with β-carotene, selenium, and α-tocopherol significantly reduced deaths from stomach cancer, but no significant benefit was recorded with ascorbic acid.[20] A trial in Colombia[40] showed regression of precancerous gastric dysplasia both in participants given β-carotene and in those given ascorbic acid.

Further prospective data are needed, in particular to examine whether some dietary associations are partly confounded by *H pylori* infection and whether dietary factors modify the association of *H pylori* with risk.

Colorectal cancer

Colorectal cancer is the third most common cancer in the world.[4] Incidence rates vary 20-fold between countries, with the highest rates in North America, Europe, and Australasia and the lowest rates in Africa and Asia. Diet-related factors could contribute up to 80% of the differences between countries,[41] yet to date, the only clearly established dietary-related risk factor is obesity.[32] Tall adult height, which is partly determined by the adequacy of nutrition in childhood and adolescence, is weakly associated with increased risk, and physical activity has been consistently associated with reduced risk.[32,42] These factors together, however, do not account for the large variation between populations, suggesting that some aspects of a western diet, such as a higher intake of meat or fat, and lower intake of fibre, fruit, and vegetables, are major determinants of risk.

Meat—Results of international correlation studies[3] have shown a strong association between consumption of meat per capita and deaths from colorectal cancer. Findings in individuals have varied, but in a meta-analysis,[43] investigators concluded that, overall, risk increases with increasing intake of red meat and processed meat, but is not associated with total meat intake. However, results of cohort studies[44] of vegetarians in developed countries have not shown low death rates from colorectal cancer, suggesting that meat is not the key factor leading to high rates of this cancer in developed countries. Many mechanisms have been proposed to explain how meat consumption might increase risk of colorectal cancer: mutagenic heterocyclic amines and polycyclic aromatic hydrocarbons can be formed when meat is cooked at high temperatures;[45,46] nitrites and related compounds in smoked, salted, and some processed meats are converted to carcinogenic N-nitroso compounds in the colon;[47] and high concentrations of iron in the colon could increase formation of mutagenic free radicals.[48] So far, however, none of these potential mechanisms has been established to affect development of colorectal cancer.

Fibre, fruit, and vegetables—Burkitt[49] suggested in the 1970s that the low rates of colorectal cancer in Africa were due to high consumption of dietary fibre; several mechanisms have been suggested for a protective effect. Fibre increases the bulk of stools and speeds up transit of food through the colon, thereby diluting the gut contents and perhaps reducing absorption of carcinogens by the colonic mucosa. Fermentation of fibre (and resistant starch, which escapes digestion by enzymes) in the large intestine produces short-chain fatty acids such as butyrate, which might protect against colorectal cancer through their ability to promote differentiation, induce apoptosis, and inhibit production of secondary bile acids by reduction of pH in the lumen.[50,51] Results of many case-control studies[27,52] of colorectal cancer have shown lower risk in association with high consumption of dietary fibre, fruits, and vegetables, than with low consumption, but the findings of large prospective studies[53–56] have been inconsistent. Furthermore, results from randomised controlled trials[57–59] have shown no relation between supplemental fibre or a diet low in fat and high in fibre, fruit, and vegetables and recurrence of colorectal adenomas.

Folate—Investigators from several prospective studies[60–62] have reported that risk of colorectal cancer is increased by low intake of folate, low intake of methionine, and by high intake of alcohol—factors that impair the function of folate. Folate plays an important part in DNA metabolism, and deficiency in folate could increase the risk of cancer through several mechanisms, including reduced methylation of DNA and incorporation of uracil instead of thymine into DNA.[60]

Calcium and vitamin D—High intakes of calcium, vitamin D, or both might also reduce risk of colorectal

cancer,[14,63,64] and supplemental calcium could have a modest protective effect on recurrence of colorectal adenomas.[58,65]

Liver cancer

Rates of liver cancer vary more than 20-fold between countries, and are much higher in sub-Saharan Africa and southeast Asia than in Europe and North America.[4] The major risk factor for hepatocellular carcinoma, the main type of liver cancer, is chronic infection with hepatitis B, and to a lesser extent, hepatitis C virus.[66] Ingestion of foods contaminated with the mycotoxin aflatoxin[67] is an important risk factor in developing countries. Excessive consumption of alcohol is the main dietary-related risk factor for liver cancer in developed countries, probably through development of cirrhosis and alcoholic hepatitis.[14,19]

Pancreatic cancer

Pancreatic cancer is more common in developed than in developing countries,[4] and incidence is increasing in most parts of the world, although some of this increase could be because of improvements in diagnostic methods.[19] The only established risk factor is smoking.[19] Obesity possibly increases risk,[14,68] and results of some studies[14] have suggested that risk is increased by high intakes of meat, and reduced by high intakes of vegetables, but these data are not consistent and are mostly from case-control studies.

Laryngeal cancer

Cancer of the larynx is caused by tobacco and alcohol.[19] Results of some studies[14] have shown that high intakes of fruit and vegetables are associated with a reduction in the risk for this cancer, but these data are mostly from case-control studies and therefore might have been affected by residual confounding by smoking.

Lung cancer

Lung cancer is the most common cancer in the world.[4] Heavy smoking increases the risk of this disease by around 30-fold, and smoking causes over 80% of lung cancers in developed countries.[19] The possibility that diet might also have an effect on risk of lung cancer was raised in the 1970s after the observation that, after allowing for smoking, a low dietary intake of vitamin A was associated with an increased risk of this disease.[69] Since then, investigators from many observational studies have shown that patients with lung cancer generally report a lower intake of fruits, vegetables, and related nutrients (such as β-carotene) than controls.[14,63] The only one of these factors to have been tested in controlled trials, β-carotene, has had no benefit when given as a supplement at high doses for up to 12 years (panel 2).[16,22–24]

The possible effect of diet on lung cancer risk remains controversial. Although fruits and vegetables have been associated with reduced risk, the results of some prospective studies[70] have shown no such association and the apparent relation in many studies might have resulted from residual confounding by smoking, since smokers generally eat less fruit and vegetables than non-smokers.[71] In public health terms, the over-riding priority for prevention of lung cancer is to reduce prevalence of smoking.

Breast cancer

Breast cancer is the second most common cancer in the world and the most common cancer in women. Incidence rates are about five times higher in western countries than in developing countries and Japan.[4] Much of this international variation is due to differences in established reproductive risk factors such as age at menarche, parity and age at birth, and breastfeeding,[72,73] but differences in dietary habits and physical activity might also contribute. In fact, age at menarche is partly determined by dietary factors, since restricted dietary intake during childhood and adolescence leads to delayed menarche. Tall adult height is also weakly positively associated with risk, and is partly determined by dietary factors during childhood and adolescence.[73]

Obesity increases risk of breast cancer in postmenopausal women by around 50%, probably by increasing serum concentrations of free oestradiol.[73] Obesity does not increase risk in premenopausal women, but is associated with a moderate reduction in breast cancer risk in premenopausal women in developed countries. This probable small reduction in risk in premenopausal women who are obese cannot be fully explained in terms of delayed diagnosis in women who are obese,[73,74] and might be partly due to a reduction in hormone exposure because obesity frequently leads to anovular menstrual cycles. However, obesity in premenopausal women probably leads to obesity throughout life, and most breast cancers develop in postmenopausal women, therefore obesity is an important risk factor for this disease.

The only other established dietary risk factor for breast cancer is alcohol. Results from a pooled analysis[75] have shown small increases in risk with increasing consumption of alcohol, with about a 7% increase in risk for an average of one alcoholic drink every day. The mechanism for this association is not known, but could involve increases in oestrogen concentrations.[76]

Much research and controversy has surrounded the hypothesis that a high intake of fat increases risk of breast cancer. The best data available, however, do not support this hypothesis,[77] and dietary fat has not been shown to change circulating concentrations of oestrogen.[78] The results of studies[14,63,79,80] of other dietary factors including meat, dairy products, fruit and vegetables, fibre and phyto-oestrogens are inconsistent. Oestradiol and perhaps other hormones have a key role in the cause of breast cancer, and any dietary effects on risk are probably mediated by hormonal mechanisms (panel 3).

Endometrial cancer

Risk of endometrial cancer is about three-fold higher in women who are obese than in those who are not.[32] As with breast cancer, the effect of obesity in post-menopausal women on risk of endometrial cancer is probably due to the increase in serum concentrations of oestradiol and the reduction in serum concentrations of sex hormone-binding globulin. Obesity also increases the risk of endometrial cancer in premenopausal women (by contrast with breast cancer), and the mechanism probably involves the increase in anovulation and consequent increased exposure to oestradiol unopposed by progesterone.[82] Results of some case-control studies[14] have suggested that diets high in fruit and vegetables could reduce risk and that diets high in saturated or total fat could increase risk, but the data for such effects are few.

Cervical cancer

The major cause of cervical cancer is infection with some subtypes of human papillomavirus.[93] Fruits, vegetables, and related nutrients such as carotenoids and folate tend to be inversely related to risk,[14,63] but these associations could be due to confounding by papillomavirus

Panel 3: **Relation between diet, hormones, and cancer**

Sex hormones

Sex hormones contribute to development of several hormone-dependent cancers, including cancer of the breast[81] and endometrium[82] in women, and probably cancer of the prostate in men.[83,84] The relation between obesity and risk of breast and endometrial cancer is probably mediated by oestradiol; obese women with more adipose tissue have more aromatase, which catalyses conversion of androgens to oestrogens and is the main source of endogenous oestradiol in postmenopausal women.[85] Dietary components such as total fat, dietary fibre, or isoflavones might also affect concentrations of sex hormones in the blood and tissues, but results of studies to date have not established such effects.[78,86]

Insulin-like growth factor-I (IGF-I)

Results of prospective studies[18] have suggested that high circulating concentrations of IGF-I are associated with increased risk of cancers of the colorectum, breast (pre-menopausal), and prostate. Circulating concentrations of IGF-I are sensitive to nutritional changes such as severe energy and protein restriction, and IGF-I is positively associated with consumption of animal protein, even without energy restriction.[87–89] Whether plant-based diets reduce risk of the typical Western cancers by reducing concentrations of IGF-I needs to be investigated.

Insulin

Westernisation leads to increased prevalence of insulin resistance and diabetes, probably because of a combination of excess energy intake, high consumption of foods with a high glycaemic index, and low physical activity. Hyperinsulinaemia might increase risk of breast and colorectal cancer due to the mitogenic actions of insulin (and other related metabolic effects).[90–92] However, few data lend support to such an hypothesis.

infections, smoking, and other factors. Further research is needed, especially on the possible role of folate deficiency.[14,63,94]

Prostate cancer

Incidence rates of prostate cancer are strongly affected by diagnostic practices and are therefore difficult to interpret, but death rates show that death from prostate cancer is about ten times more common in North America and Europe than in Asia.[4]

Little is known about the cause of prostate cancer, although results of ecological studies suggest that it is positively associated with a western-style diet. Data from prospective studies have not established causal or protective associations for specific nutrients or dietary factors.[14,63] Diets high in animal products have been implicated in development of prostate cancer in at least some studies, but the data are not consistent. Randomised controlled trials have provided substantial, consistent evidence that supplements of β-carotene do not change the risk for prostate cancer,[22,25] but have suggested that vitamin E[25] and selenium[26] might have a protective effect. Lycopene, mainly from tomatoes, has been associated with reduced risk in some studies.[95]

Hormones control the growth of the prostate, and many prostate tumours respond to androgen deprivation therapy. Therefore endogenous hormones probably play a part in the cause of the disease and diet might affect prostate cancer through its effects on hormones (panel 3).

Kidney cancer

Obesity is an established risk factor for cancer of the kidney, and could account for up to 30% of kidney cancers in both men and women.[96] Little is known about the role of diet in kidney cancer, but some investigators have recorded an increase in risk with high intakes of meat and dairy products and a reduced risk with high intakes of vegetables.[14]

The role of genes in an individual's response to dietary factors

Some common genotypes, such as those involved in metabolic activation, detoxification, DNA methylation, and vitamin metabolism could determine the effects of diet on cancer.[97] In theory, subdividing participants in a study by genotype could reveal substantial diet-related risks that are obscured when all participants are investigated together. Two examples of promising areas are genetic determinants of carcinogen activation and folate metabolism.[98,99]

Metabolic activation genes, heterocyclic amines, and colorectal cancer

The genes that code for enzymes involved in metabolic activation of heterocyclic amines are polymorphic. Results of some studies have suggested that individuals with the rapid variant of N-acetyltransferase 2, and who eat a lot of red meat, are much more likely to develop colorectal cancer than individuals with this genotype who don't eat much red meat, or those who eat a lot of red meat but have the slow variant of N-acetyltransferase 2.[98] More data are needed to clarify this association.

Folate metabolising gene, folate intake, and colorectal cancer

Methylenetetrahydrofolate reductase (MTHFR) regulates metabolism of folate and methionine, and a common polymorphism in the *MTHFR* gene (667C→T, *ala→val)* reduces the activity of this enzyme. Individuals homozygous for *val* have reduced conversion of 5,10-methylenetetrahydrofolate to 5-methyltetrahydrofolate, the form of folate that circulates in plasma.[60,99] In people with a low dietary intake of folate, this *val/val* genotype could confer an increased risk for colorectal cancer, perhaps because low concentrations of 5-methyltetrahydrofolate lower synthesis of methionine and thus cause hypomethylation of DNA and consequent abnormal gene expression.[60]

Recommendations

Despite extensive research during the last 30 years, few specific dietary determinants of cancer risk have been established, even for cancers such as colorectal cancer for which most researchers agree that diet probably has important effects. The main factors that have held back progress are the inaccuracy of methods for estimating food and nutrient intake and the biases in case-control studies. The results of existing large prospective studies and controlled trials should substantially advance our understanding of the role of diet in cancer during the next few years. At present, prudent advice is to maintain a healthy weight, restrict alcohol consumption, and select a conventionally balanced diet ensuring an adequate intake of fruit, vegetables, and cereals.

Contributors

All authors contributed to the writing of the report.

Conflict of interest statement

T J Key is a member of the Vegan Society.

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