Clinical review

Fortnightly review Diet and the prevention of cancer

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Cancer is responsible for more deaths annually in the United Kingdom than is ischaemic heart disease. Around half of cancer deaths are due to tumours at four principal sites: lung, bowel, breast, and prostate. These cancers are virtually absent in many countries in the developing world but increase in incidence within one or two generations when migrants move from low to high risk areas.¹ Thus many cancers common in Western populations are due to environmental factors, and these cancers should be largely preventable.

Diet is one of the most important lifestyle factors and has been estimated to account for up to 80% of cancers of the large bowel, breast, and prostate.^{2 3} Even lung cancer may have a dietary component, although cigarette smoking is the overwhelming cause of this and contributes also to oropharyngeal, oesophageal, and bladder cancer. Physical activity, reproductive and sexual behaviour, infection with hepatitis B and C viruses, infection with helicobacter, and exposure to sunlight, ionising radiation, and environmental chemicals are also important at particular sites. Nevertheless, food and drink has a part to play in many if not all cancers, albeit to a variable extent.

Methods

This review has been prompted by the recent publication of two reports, one from the Chief Medical Officer's Committee on Medical Aspects of Food (COMA) and one commissioned by the World Cancer Research Fund.^{4 5} Much of the evidence used in these reports is derived from epidemiological studies. Although food intake varies greatly worldwide, crude methods are often used to assess diet and these methods incur large measurement errors which reduce estimates of relative risk.4 Furthermore, mechanisms are needed6 to take account of genetic polymorphisms that may moderate effects of a particular dietary factor in individuals. This interaction between environmental, genetic, and other factors, such as helicobacter infection in gastric cancer, has so far largely gone uninvestigated. It is presently being tested in the European Prospective Investigation of Cancer (EPIC), in which dietary information and blood is being collected from 400 000 individuals living in nine European countries,⁷ and in human experimental models, but both approaches need validated biomarkers of risk to be developed.8

Summary points

Up to 80% of bowel and breast cancer may be preventable by dietary change

Diet contributes to varying extents to the risk of many other cancers, including cancers of the lung, prostate, stomach, oesophagus, and pancreas

Generally, fruit, vegetables, and fibre have a protective effect, whereas red and processed meat increase the risk of developing cancer

Other lifestyle factors that increase risk include smoking, alcohol, and overweight

Risk is decreased by physical activity

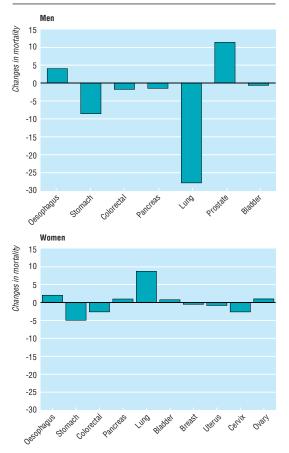
There is no evidence that vitamin supplements help to prevent cancer

Cancer incidence in Britain

Table 1 shows major cancers for men and women in the United Kingdom, and the figure shows the recent trends in mortality.^{4 9} Over the past 25 years, the incidence of registered cancers at all sites has increased by 8% in men and 17% in women, and cancer mortality has decreased by 5% in men and increased by 9% in women.¹⁰ The most striking change between 1981 and 1996 is the 9% increase in lung cancer mortality in women, whereas rates in men have declined by 28%.

Table 1	Deaths	from	cancer	in	England	and	Wales,	1996°	
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Site of cancer (ICD-9 number)	Men	Women	
Oesophagus (150)	3 567	2 268	
Stomach (151)	4 241	2 515	
Colorectum (153-4)	7 820	7 627	
Pancreas (157)	2 826	3 022	
Lung (162)	19 777	11 033	
Breast (174)	67	12 179	
Prostate (185)	8 742	_	
Uterus (179, 182)	_	1 303	
Cervix (180)	_	1 315	
Ovary (183)	—	4 060	
Bladder (188)	3 101	1 501	
All cancers (140-239)	72 464	66 995	



Changes in mortality per 100 000 population for major cancers between 1981-3 and 1994-6 in England and Wales. Age standardised to revised final mid-1991 population estimates

For the cancers in which diet has the greatest role, different trends are seen. The incidence of, but not mortality from, breast cancer in women has increased and both the incidence and mortality of prostate cancer in men, and oesophageal cancer in both men and women, have increased. Stomach cancer has shown a substantial decline in both incidence and mortality in both sexes.

Genetics of cancer

Cancer arises as the result of one, or more usually a series, of mutations in DNA which may be either germline (inherited) or somatic (acquired during life). In breast cancer the presence of germline mutations in BRCA1 and BRCA2 genes confer a greatly increased risk of breast and ovarian cancer, although they account for only 2-3% of these cancers overall.11 Most of the cancers that are common in Britain are sporadic, with mutations occurring at the tumour site rather than being inherited. In large bowel cancer, for which the genetics are best known, tumours are associated with the accumulation of mutations in several genes, including APC, p53, k ras, and MSH2.12 These genes are mainly concerned with cell growth (oncogenes and tumour suppressor genes) or DNA repair. Mutations may be inherited, as in adenomatous polyposis coli or hereditary non-polyposis colon cancer, but they are thought mostly to be acquired.

Role of diet

How could diet cause or prevent these mutations and their consequences? Experimental studies show that, for example, heterocyclic amines in cooked meat are carcinogens in the mammary gland and colon of rodents; that several dietary constituents induce apoptosis, which is one of the protective mechanisms against cancer; that antioxidants in food may suppress spontaneous mutations; and that dietary factors can influence cell proliferation and the methylation of DNA. Though there is currently no direct evidence relating diet to DNA damage relevant to current genetic models of cancer, this is the subject of an emerging research field.

Breast cancer

Some of the hormone related risk factors for breast cancer are affected by diet (tables 2 and 3). High energy intakes and higher levels of body fatness hasten the onset of menarche, but high intakes of non-starch polysaccharides (fibre) may delay it. In postmenopausal women, increased risk of cancer is associated with higher serum concentrations of oestrogen. Oestrogen is synthesised from the precursor hormone androstendione in adipose tissue, and after the menopause this becomes the major source; thus, in women who lose weight, serum concentrations of oestrogen fall. Postmenopausal, overweight women have up to a twofold greater risk of breast cancer, but the effect of weight in premenopausal women is not consistent. The role of dietary fat as a major risk factor for breast cancer has not been confirmed by recent prospective epidemiological studies. However, both meat and alcohol are associated with increased risk.13

The mechanisms supporting these associations are largely unknown. Heterocyclic amines are formed in meat when it is cooked and are known to be absorbed from the human gastrointestinal tract.14 Three have been shown to cause mammary cancer when given to laboratory rodents. Absorbed N-nitroso compounds formed endogenously in the human colon in response to eating meat may also be involved. Other dietary

Site of cancer	F	Probable	Possible		
	Increases risk	Decreases risk	Increases risk	Decreases risk	
Colorectum	Red meat Processed meat	Vegetables Non-starch polysaccharides (fibre)	Alcohol Fat	Folate	
Breast	Alcohol Red meat Fried meat	Vegetables		Fruit Phyto-oestrogens	
Lung			Alcohol Meat	Fruit and vegetables	
Stomach	Salt Pickled and preserved food	Fruit and vegetables Vitamin C		Carotenoids	
Prostate		Vitamin E	(Red) meat Fat	Vegetables	
Cervix		Fruit and vegetables Vitamin C		Folate Vitamin A	
Oesophagus	Alcohol	Fruit and vegetables			
Pancreas			Red meat	Fruit and vegetables Vitamin C Non-starch polysaccharides (fibre)	
Bladder		Fruit and vegetables			
Liver	Alcohol				

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Table 3 Lifestyle and other factors that affect cancer risk^{4 5}

Type or site of cancer	Increased risk	Decreased risk	
Colorectal	Adenomatous polyps, inflammatory bowel disease, obesity (men)	Physical activity	
Breast	Early menarche, late menopause, older age at first pregnancy, height, obesity (after menopause)	Physical activity	
Lung	Smoking, occupation	Physical activity	
Stomach	Helicobacter pylori infection		
Prostate			
Cervix	Human papillomavirus, smoking		
Endometrium	Exposure to unopposed oestrogen, obesity		
Oesophagus	Smoking, Barrett's oesophagus (gastro-oesophageal reflux disease)		
Pancreas	Smoking		
Bladder	Smoking, occupation, schistosoma infection		
Liver	Hepatitis B and C infection		
Ovary		Extended use of ora contraceptives	

factors that are implicated in breast cancer are low intakes of vegetable and non-starch polysaccharides, and low intakes of phyto-oestrogens, which act as weakly antioestrogenic compounds.¹⁵

Lung cancer

Smoking is the single most important cause of lung cancer.⁴ Patients who develop lung cancer report eating less fruit and vegetables than healthy controls but the effect is much less than the causative effect of smoking, with a relative risk of about 1.2 for individuals classified as low fruit consumers, a 16-fold difference compared with smoking.

The active chemopreventive agent in vegetables was thought to be β carotene, acting as an antioxidant.¹⁶ However, of the several trials of β carotene supplementation that have recently been completed to test this, none has confirmed the protective effect.¹⁷⁻¹⁹ The carcinogenic effects of smoking can not be ameliorated by supplements of antioxidant vitamins or minerals.

Colorectal cancer

Colorectal cancer is the cancer for which a genetic model of its causation is the best documented and one for which the evidence that diet is involved is probably strongest.

Non-starch polysaccharides (fibre) and vegetables are established factors that reduce risk, largely owing to the effect of non-starch polysaccharides in regulating bowel function. Stool weight is low in countries where the incidence of colorectal cancer is high,²⁰ and constipation is known from case-control studies to be a risk factor.4 5 Non-starch polysaccharides are fermented in the large bowel and the resultant short chain fatty acids, especially butyrate, may protect against colorectal cancer through the ability to arrest cell growth, promote differentiation, and select cells with damaged DNA for apoptosis.^{21 22} Fermentation also makes the contents of the large bowel more acid, which may affect concentrations of secondary bile acids. Current recommendations are therefore to increase consumption of non-starch polysaccharides by 50%, to 18 g a day, in order to increase stool weight and reduce constipation and thus reduce the risk of bowel cancer.

People who report eating greater amounts of "red" and processed meat are at higher risk of colorectal cancer. "Red" meat is taken to mean beef, pork and lamb in main dishes, and processed meat includes sausages; hamburgers; smoked, cured, and salted meat (including ham and bacon); and canned meat. This increase in risk due to red meat was shown in two large studies of health professionals carried out in the United States. The highest relative risk was about 1.8 for consumption of about 130 g a day, which is equivalent to about two portions of red meat a day. The lowest average consumption, with the least risk for an American population, was two portions a week.

Meat is likely to increase risk of bowel cancer in various ways. Heterocyclic amines are formed on the surface of meat when it is cooked by grilling, roasting, frying, and barbecuing. Humans have different enzymes involved in the metabolism of these compounds and individuals who have the "fast" acetylator phenotype are at increased risk of developing polyps and large bowel cancer.²³ Meat also increases the amount of and type of residue entering the large bowel,²⁴ thus affecting the byproducts formed by the colonic flora. *N*-nitroso compounds are formed in a dose dependent fashion, and with high meat diets the amounts found in the colon are greater than those in cigarette smoke.²⁵

Many other factors are implicated in colon cancer, including obesity, iron, calcium, and some compounds found in vegetables, such as folate, phyto-oestrogens, sulphur containing compounds, and antioxidants, including flavonoids and carotenoids with a similar structure to β carotene, such as lycopene in tomatoes and lutein in green vegetables.

Prostate

The incidence of and mortality from prostate cancer has increased considerably in recent years. High consumption of meat, especially red meat, and of fat are associated with modest increases in risk. Vegetables, especially salads and tomatoes, are associated with lower risk. There are conflicting reports of the importance of other environmental factors in prostate cancer.²⁶ Several genetic abnormalities have been reported, including mutations in ras, KAI 1, C-erbB-Z, E-caderin, and p53. Up to 10% of men with prostate cancer have a family history of the disease.²⁶ In a recent intervention trial, vitamin E supplements significantly reduced risk.²⁷

Stomach

Gastric cancer is in decline world wide, possibly because of a reduction in salt intake and the replacement by refrigeration of more traditional methods of food preservation such as pickling and salting. The relatively recent discovery that Helicobacter pylori infection of the stomach is the major cause of chronic gastritis, a precursor of gastric cancer, has made all previous studies difficult to interpret. H pylori infection results in a chronic inflammatory response, greater production of oxidative free radicals, and DNA damage leading to carcinoma; it increases the risk for stomach cancer sixfold.²⁸ Vegetables are sources of many antioxidants, such as β carotene and vitamin E, which would be important in preventing the damaging effects of free radicals. Concentrations of vitamin C have been shown to be lower in gastric juice of individuals infected with Helicobacter pylori, and they return to normal when the infection is eradicated by antibiotics.²⁹ Individuals eating 5-20 servings of fruits and 5-20 servings of vegetables each week have about half the risk of stomach cancer.

Oesophagus

In Western countries, alcohol and smoking are important risk factors for cancer of the oesophagus. There is a threefold to eightfold increase in risk in individuals who consume 40-100g alcohol a day, and there are multiplicative effects with smoking.¹³ These two factors account for the great majority of cases of squamous cell carcinoma, the commonest type of cancer of the oesophagus in Western countries. Adenocarcinoma is less common, although its incidence is increasing and seems to be associated with obesity as well as alcohol and smoking.

In well nourished populations, case-control studies suggest that fruit and vegetables may be protective because low intakes confer on average a twofold increase in risk compared with high intakes. Equally, in less well nourished populations, a diet restricted in fruit and vegetables also confers increased risk. Other causative factors that have been suggested include contamination of poorly stored corn by toxins from the fungus *Fusarium* and *N*-nitroso compounds in some smoked foods.

Pancreas

Although pancreatic cancer accounts for only 2% of all cancer deaths world wide, its incidence is rising and the outlook remains poor. The dietary factors which are associated with increased risk are meat, red meat in particular, and energy. Protection is provided by fruit and vegetables, which is probably the most consistent finding overall, and vitamin C and non-starch polysaccharides (fibre). The evidence regarding coffee is inconsistent, and alcohol, despite being a major factor in chronic pancreatitis, is not a cause. The mechanism of pancreatic cancer development is very poorly worked out. A multifactorial model has been proposed³⁰ in which endocrine, metabolic, dietary, and other factors combine to produce pancreatic hyperplasia and eventually malignant change. Animal models suggest that chronic overstimulation with cholecystokinin may be important. Smoking is the principal non-dietary risk factor.

Uterus (cervix and endometrium)

Limited information shows that the risk of cancer of the cervix is lower for women who consume greater amounts of vegetables, antioxidant vitamins, and folic acid. Few studies have taken non-dietary factors, such as numbers of sexual partners, parity, cigarette smoking, and infection with human papillomavirus, into account.

Cancer of the endometrium is more common in developed countries, with a pattern of hormonal risk factors similar to breast cancer. Unopposed oestrogens increase risk, as does body weight. In those weighing 40% or more than the average, relative risks are 5.4 compared with relative risks of less than 2 for breast cancer in this same group of women.³¹

Other cancers

The major known risk factors for other sites are non-dietary, for example infection with hepatitis B virus and alcohol consumption in liver cancer, smoking in bladder and kidney cancer, and sunlight exposure in skin cancer.² Late menopause, infertility, and possession of the BRCA1 and BRCA2 genes explain some of the risks in ovarian cancer, and a low

Dietary advice to reduce cancer risk

• Eat plenty of fruit and vegetables (at least five portions a day)

• Eat plenty of cereal foods, mainly in an unprocessed form (as a source of non-starch polysaccharides)

- Maintain ideal body weight (body mass index 20-25); avoid fatty foods
- + Eat red meat and processed meat in moderation (no more than $140~{\rm g/day})$
- Avoid high doses of vitamin supplements
- Alcohol in moderation (a maximum of two units a day for women and three units a day for men)
- Avoid highly salted and mouldy foods

intake of vegetables and high intake of fat, milk products, and meat increase risk.

A diet to reduce cancer risk

What is remarkable about the diet-cancer story is the consistency with which certain foods emerge as important in reducing risk across the range of cancers. Vegetables and fruit are almost invariably protective for the major cancers. The evidence is best for a protective effect of vegetables in the large bowel and for fruits and vegetables in stomach cancer. Consumption of these foods in Britain is less than half that in Mediterranean populations where cancer rates are low. Average consumption of fruits and vegetables in Britain should at least double to five portions a day, and consumption of non-starch polysaccharides should increase from 12 g/day.

Similarly there is consistency for increased risk. High consumption of meat, especially red meat and processed meat, is linked with higher risk of bowel, breast, prostate, and pancreatic cancer. There is some evidence of an association with lung cancer, and of an association of barbecued meat and oesophageal cancer. Two recent major reports have recommended that consumption of red and processed meat should be reduced or not rise.⁴ The World Cancer Research Fund's report has recommended that "If eaten at all, red meat [should] provide less than 10% of total energy" on average. The advice to individuals was "limit intake of red meat to less than 80 g daily." The quantitative basis for the recommendation to restrict intake to 80g per day is not given.5 The Department of Health has advised that consumption of red and processed meat should not rise and that people who are consuming high levels-more than 14 portions a week (140 g cooked weight per day)-should consider a reduction. This amount represents one standard deviation of the mean above average intake of red and processed meat. Fifteen per cent of consumers, mainly men, eat more than this amount at present.

Obesity is associated with a considerably increased risk of endometrial cancer and with a greater risk of breast cancer in postmenopausal women and to some extent bowel cancer in men. Body weight should therefore remain in the healthy range of a body mass index of 20-25. Diets high in fat are not now convincingly linked to cancer, but because they contribute to obesity the current guidelines to lower total fat consumption to avoid heart disease are appropriate also for cancer.

Alcohol is a significant risk factor for upper gastrointestinal cancer, liver cancer, and breast cancer. Intake should be restricted to no more than 2 units a day for women and 3 units a day for men.

Advice on lifestyle factors to reduce cancer risk

- Do not smoke
- Take regular exercise
- Do not be sexually promiscuous
- · Avoid prolonged exposure to direct sunlight
- Avoid hepatitis B and C risks

There is no evidence that isolated supplements of vitamins help to prevent cancer, and some studies of smokers show that supplements of β carotene may be harmful. β Carotene supplements should therefore be avoided, and caution should be used with high doses of purified supplements of other vitamins and minerals.

Importance of diet in other diseases

Cancer is only one of the major killers in the world. Is the diet for cancer prevention going to prejudice public health programmes for the prevention of other diseases such as coronary heart disease, hypertension, obesity, and diabetes? The answer is no-in fact quite the reverse. A diet high in fruit, vegetables, and cereals and low in meat, fat, and salt, but containing adequate minerals and vitamins, is a good prophylactic for preventing many chronic diseases of lifestyle. Further, a plant based food economy is much more sustainable than one based on livestock. Providing that other lifestyle factors are also taken into account, the diet for cancer prevention can, on the basis of current knowledge, form the basis for a rational public health policy.

Competing interests: None declared.

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Correction

ABC of oxygen: diving and oxygen

An editorial error occurred in this article by Peter Wilmshurst (10 October, p 996-9). The table on decompression illness (p 997) was incorrectly interpreted. It should have appeared as below. In addition, on p 998 the legend to the diagram of the oxygen rebreather should state that nitrogen accumulation [not carbon dioxide] is a problem. The picture at the bottom of the page is of a professional surface supplied diver.

Types of decompression illness and their causes

	Type of illness					
Cause	Neurological	Cardiorespiratory	Skin	Joint		
Paradoxical gas embolism-intracardiac shunt	Frequently	Sometimes	Frequently	No association		
Arterial gas embolism after pulmonary barotrauma:						
Lung disease	Sometimes	Sometimes	No association	No association		
Rapid ascent	Sometimes	Sometimes	No association	No association		
Gas nucleation caused by unsafe decompression profile	Sometimes	Sometimes	Sometimes	Frequently		