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ANALYSIS

Diet, nutrition, and cancer risk: what do we know and what is the way forward?

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Timothy J Key and colleagues describe the evidence linking diet and nutrition to cancer risk, concluding that obesity and alcohol are the most important factors

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Scientists have suspected for decades that nutrition has an important influence on the risk of developing cancer. Epidemiological studies as early as the 1960s showed that cancer rates varied widely between populations and that cancer rates in migrants moving from low to high risk countries could rise to equal or sometimes exceed the rates in the host population.[1 2] These observations implied the existence of important environmental causes of cancer, and other studies showed strong correlations between many types of cancer and dietary factors; for example, countries with high intakes of meat had high rates of colorectal cancer.[3] Furthermore, experiments in animals showed that cancer rates could be altered by manipulating diet, with compelling evidence that restricting energy intake causes a general reduction in cancer development.[4 5]

Cancer is predicted to be the leading cause of death in every country of the world by the end of this century.[6] Although dietary factors are thought to be important in determining the risk of developing cancer, establishing the exact effects of diet on cancer risk has proved challenging. Here we describe the relatively few dietary factors that clearly influence risk of cancers along the digestive tract (from top to bottom) and of other common types of cancer,[7 8] as well as challenges for future research.

Cancers of the oral cavity and pharynx

Nasopharyngeal cancer is common in a few populations around the globe, such as the Cantonese population in southern China and some indigenous populations of South East Asia, the Arctic, north Africa, and the Middle East.[9] Consumption of foods preserved with salt has been linked with this cancer, and the mechanism might be through nitrosamine formation or reactivation of the Epstein-Barr virus.[10] Based on case-control studies, Chinese style salted fish has been classified as a carcinogen by the International Agency for Research on Cancer (IARC), part of the World Health Organization.[10]

For oral and pharyngeal cancers overall, eating more fruits, vegetables, and related micronutrients such as vitamin C and folate is associated with lower cancer risk (boxes 1 and 2). These associations, however, might be influenced by residual confounding by smoking (a major non-dietary risk factor[7 14]) and alcohol consumption, so the evidence is only suggestive of a protective effect.[8 14]

Box 1: Are fruit and vegetables important determinants of cancer risk—and what about vegetarians?

Early case-control studies indicated that higher intakes of fruit and vegetables were associated with a lower risk of several types of cancer.[11] But subsequent prospective studies, which are not affected by recall or selection bias, produced much weaker findings. In the 2018 World Cancer Research Fund report neither fruits nor vegetables were considered to be convincingly or probably associated with the risk of any cancer.[8] There was suggestive evidence for protection of some cancers, and risk might increase at very low intakes. Specific components of certain fruits and vegetables might have a protective action.

Vegetarians eat no meat or fish and usually eat more fruit and vegetables than comparable non-vegetarians. The risk of all cancer sites combined might be slightly lower in vegetarians and vegans than in non-vegetarians, but findings for individual cancers are inconclusive. [12]

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Box 2: Do vitamins and minerals reduce cancer risk?

By definition, deficiencies of vitamins and essential minerals cause ill health; this might include increased susceptibility to some types of cancer, but establishing the details of any such effects has proved difficult. High dose vitamin or mineral supplements have not reduced cancer risk in well nourished populations and might increase risk; for example, high dose β carotene might increase the risk of lung cancer.[13] Vitamin and mineral supplements should not be used for cancer prevention, although they can be important for other aspects of health, such as folic acid supplements for women before conception.

Oesophageal cancer

There are two types of oesophageal cancer: squamous cell carcinoma and adenocarcinoma. The squamous form predominates in most of the world, whereas adenocarcinoma is relatively common only in Western countries, where rates have recently increased. Obesity is an established risk factor for adenocarcinoma, probably partly owing to reflux of stomach contents into the oesophagus.[15 16] Alcohol increases the risk of squamous cell carcinoma but not of adenocarcinoma.[17] Smoking increases the risk of both types, with a larger effect for squamous cell carcinoma.[17]

Oesophageal cancer incidence rates are very high in parts of eastern and southern Africa, Linzhou (China), and Golestan (Iran).[6 17] People in high risk populations have often consumed a restricted diet, low in fruit, vegetables, and animal products, so deficiencies of micronutrients have been postulated to explain the high risk (boxes 1 and 2). Despite several observational studies and some randomised trials, however, the relative roles of various micronutrients are not yet clear.[17-20] In Western countries early case-control studies indicated a protective role for fruit and vegetables,[21 22] but more recently published prospective studies show weaker associations, which might be due to residual confounding from smoking and alcohol consumption.[16]

Consumption of drinks such as tea and mate when scalding hot is associated with an increased risk of oesophageal cancer,[23-25] and drinking beverages above 65°C is classified by IARC as probably carcinogenic to humans.[26]

Stomach cancer

Stomach cancer is the fifth most common cancer worldwide, with the highest rates in eastern Asia.[6] Eating large amounts of salted foods, such as salt preserved fish, is associated with an increased risk[27]; this might be caused by the salt itself or by carcinogens derived from the nitrites in many preserved foods. Salted food might increase the risk of *Helicobacter pylori* infection (an established cause of stomach cancer)[28] and act synergistically to promote development of the disease.[29] Some evidence indicates that eating large amounts of pickled vegetables increases the risk of stomach cancer because of the production of N-nitroso compounds by mould or fungi, which are sometimes present in these foods.[30 31]

The risk of stomach cancer might be decreased by diets high in fruit and vegetables and for people with high plasma concentrations of vitamin C (boxes 1 and 2).[32] A trial in Linzhou, China, showed that supplementation with β carotene, selenium, and α tocopherol resulted in a significant reduction in stomach cancer mortality,[18] and other trials have indicated enhanced regression of precancerous lesions with the use of supplements of vitamin C, β carotene, or both.[33 34] Prospective studies in Japan have also shown an inverse association between stomach cancer risk and green tea consumption in women (the majority of whom are non-smokers), perhaps related to polyphenols.[35] These studies indicate a protective role of antioxidant micronutrients or other antioxidant compounds, but these associations need clarification.

Colorectal cancer

Colorectal cancer is the third most common cancer in the world.[6] Overweight and obesity increase risk,[8 36 37] as do alcohol and smoking.[7]

Ecological analyses show striking positive correlations between eating meat and colorectal cancer rates.[3 38] In 2015 IARC classified processed meat as carcinogenic to humans and unprocessed red meat as probably carcinogenic,[39 40] partly based on a meta-analysis reporting an increase in risk of 17% for each daily 50 g increment in consumption of processed meat and 18% for each 100 g increment in consumption of red meat.[41] More recent systematic reviews have reported smaller increases in risk for unprocessed red meat.[8 42]

The chemicals used to preserve processed meat, such as nitrates and nitrites, might increase exposure of the gut to mutagenic N-nitroso compounds.[40] Both processed and unprocessed red meat also contain haem iron, which might have a cytotoxic effect in the gut and increase formation of N-nitroso compounds. Cooking meat at high temperatures can generate mutagenic heterocyclic amines and polycyclic aromatic hydrocarbons.[40] Whether any of these putative mechanisms explain the association between eating red and processed meat and risk for colorectal cancer is unclear.[39 40]

Higher consumptions of milk and calcium are associated with a moderate reduction in risk of colorectal cancer.[8 43-45] Calcium might be protective by forming complexes with secondary bile acids and haem in the intestinal lumen. Higher circulating concentrations of vitamin D are associated with a lower risk,[46] but this might be confounded by other factors such as physical activity. Mendelian randomisation studies of genetically determined vitamin D have not supported a causal relation.[47 48]

In the 1970s Burkitt suggested that the low rates of colorectal cancer in parts of Africa were caused by the high consumption of dietary fibre.[49] Prospective studies have shown that consuming 10 g more total dietary fibre a day is associated with an average 10% reduction in risk of colorectal cancer; further analyses suggest that cereal fibre and wholegrain cereals are protective, but not fibre from fruit or vegetables.[50 51]

High dietary folate intake has been associated with reduced risk of colorectal cancer, and adequate folate status maintains genomic stability,[8] but high folate status might promote the growth of colorectal tumours.[52] Whether folate or folic acid have any material impact on the risk of colorectal cancer is uncertain. Most randomised trials of folic acid supplementation have found no effect,[53 54] and although studies of the gene for methylenetetrahydrofolate reductase have indicated that lower circulating folate is associated with a slightly lower risk, the interpretation of these genetic data is not straightforward. [55]

Liver cancer

Alcohol is the main diet related risk factor for liver cancer, probably through the development of cirrhosis and alcoholic hepatitis.[7] Overweight and obesity also increase risk.[8] Aflatoxin, a mutagenic compound produced by the fungus *Aspergillus* in foods such as grains, nuts, and dried fruit when stored in hot and humid conditions, is classified as a carcinogen by IARC and is an important risk factor in some low income countries (for people with active hepatitis virus infection).[56] The major non-dietary risk factor is chronic infection with hepatitis B or C viruses.

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Some studies indicate an inverse association between coffee drinking and risk of liver cancer.[8] Coffee might have a true protective effect because it contains many bioactive compounds,[57 58] but the association might be influenced by residual confounding, as well as by reverse causation if subclinical liver disease reduces appetite for coffee.

Pancreatic cancer

Obesity increases risk of pancreatic cancer by about 20%.[8] Diabetes is also associated with increased risk, and a mendelian randomisation analysis indicates that this is due to raised insulin rather than diabetes itself.[59] Studies of dietary components and risk have been inconclusive.[8]

Lung cancer

Lung cancer is the most common cancer in the world, and heavy smoking increases risk around 40-fold.[6 7] Prospective studies have indicated that diets higher in fruits and vegetables are associated with a slightly lower risk of lung cancer in smokers, but not in never smokers.[60 61] The weak inverse association of fruit and vegetables with lung cancer risk in smokers might perhaps indicate some true protective effect, but it might simply be due to residual confounding by smoking (box 1). Trials that tested supplements of β carotene (and retinol in one trial) to prevent lung cancer showed an unexpected higher risk of lung cancer in participants in the intervention group.[13 62]

Breast cancer

Breast cancer is the second most common cancer in the world.[6] Reproductive and hormonal factors are key determinants of risk.[63] Obesity increases breast cancer risk in postmenopausal women, probably by increasing circulating oestrogens, which are produced by aromatase in adipose tissue.[64] Most studies have shown that obesity in premenopausal women is associated with a reduction in risk, perhaps due to lower hormone levels related to an increased frequency of anovulation. [65] Alcohol increases risk by about 10% for each drink consumed daily[8 66]; the mechanism might involve increased oestrogens.

Much controversy has surrounded the hypothesis that a high fat intake in adulthood increases breast cancer risk. Early case-control studies supported this hypothesis, but prospective observational studies have overall been null,[8] and two randomised controlled trials of a reduced fat diet were also null.[67 68]

Studies of other dietary factors including meat, dairy products, and fruit are generally inconclusive.[8] Some recent studies have indicated an inverse association between vegetable intake and risk of oestrogen receptor negative breast cancer[8 69 70] and between dietary fibre and overall risk.[8 71] Isoflavones, largely from soya, have been associated with a lower risk of breast cancer in Asian populations.[72] These associations are potentially important and should be investigated for causality.

Prostate cancer

Prostate cancer is the fourth most common cancer in the world.[6] The only well established risk factors are age, family history, black ethnicity, and genetic factors.[73] Obesity probably increases the risk for more aggressive forms of prostate cancer.[8]

Lycopene, primarily from tomatoes, has been associated with a reduced risk, but the data are not conclusive.[8] Some studies have indicated that risk might be reduced with higher levels of other micronutrients including β carotene, vitamin D, vitamin E, and selenium, but the findings from trials and mendelian randomisation analyses are overall null or inconclusive.[47 74-76]

Isoflavones, largely from soya foods, have been associated with a reduced risk for prostate cancer in Asian men,[77] and plasma concentrations of the isoflavone equol might be inversely associated with prostate cancer risk in men in Japan.[78]

Substantial evidence shows that prostate cancer risk is increased by high levels of the hormone insulin-like growth factor 1, which stimulates cell division, and further research is needed to determine whether dietary factors, such as animal protein, might influence prostate cancer risk by affecting production of this hormone.[79]

Evaluations by expert groups

Given the huge variation in diets around the world and the large number of cancers that diets can influence, how do we know which foods or diets should be avoided and which should be recommended? The World Cancer Research Fund (WCRF) and IARC have reviewed the carcinogenic risk of foods and nutrients using systematic reviews of the evidence and evaluation by expert panels. As with much nutritional research the topic is complex, but the WCRF and IARC have identified nutritional factors with convincing evidence or probable evidence of cancer risk.

WCRF and IARC concluded that obesity and alcohol cause cancer at several sites (fig 1). For overweight and obesity, increases in risk for every 5 kg/m^2 rise in body mass index (BMI) vary from 5% for colorectal cancer to 50% for cancer of the endometrium (IARC also considered the evidence to be sufficient for meningioma, thyroid cancer, and multiple myeloma).[80] For alcohol, risk increases for each 10 g rise in consumption a day vary from 4% for liver cancer to 25% for squamous cell carcinoma of the oesophagus.

Processed meat was judged to be a convincing cause of cancer by both WCRF and IARC; in the most recent WCRF report the relative risk for colorectal cancer was 1.16 (1.08 to 1.26) for each 50 g/day increment.[8] IARC judged Chinese-style salted fish to be a carcinogen (with a relative risk of nasopharyngeal cancer of 1.31 (1.16 to 1.47) for each additional serving per week), [8 10] as well as foods contaminated with aflatoxin.[56] Neither expert body judged any dietary factor to be convincingly protective against cancer.

Uncertainty remains

WCRF and IARC judged some associations between nutritional factors and cancer risk to be "probably" causal or protective (table 1). Some researchers might think that the criteria for "probable" are not stringent enough. Further evidence might change the conclusions, and this should be kept in mind when using the reports to estimate the likely effects of diet or to make dietary recommendations. Notably, WCRF also categorised adult and young adulthood body fatness as probably protective for premenopausal breast cancer; with new evidence[65] we consider this convincing, so the association is shown in figure 1 rather than table 1.

Obesity probably increases the risk of cancers of the oral cavity and pharynx and of aggressive prostate cancer. Alcohol probably increases the risk of stomach cancer but is inversely associated with the risk of kidney cancer, which might indicate a true biological effect or reflect residual confounding or bias.[81] Very hot drinks probably increase the risk of cancer of the oesophagus, foods preserved by salting probably increase the risk of stomach cancer, and several dietary factors probably

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reduce the risk of colorectal cancer. The expert panels also concluded that the risk of endometrial cancer is probably increased by a diet with a high glycaemic load. Coffee was judged to probably be protective for liver and endometrial cancer, but some of the current authors think that this conclusion is too strong and that the data on coffee and endometrial cancer might be affected by selective publication of only part of the evidence.[82]

Independently from overweight and obesity, greater adult height is associated with the risk of several cancers (box 3).

Box 3: Why do taller people have a higher risk of cancer?

The risk for most types of cancer increases with height. A WCRF systematic review showed that increases in risk for each 5 cm increment in height ranged from 4% for prostate cancer to 12% for malignant melanoma.[83] The mechanism is uncertain but might be related to taller people having more stem cells at risk of cancer or a factor such as insulin-like growth factor 1 having effects on both height and cancer risk.[84] Undernutrition causes restricted growth, and some aspects of adequate nutrition during childhood and adolescence, such as an ample intake of energy and protein, might lead to relatively greater height and a higher overall cancer risk.[83] It is not clear, however, whether better understanding of this pathway could lead to strategies for reducing cancer risk.

Acrylamide, a chemical produced during high temperature cooking and in the manufacture of many types of carbohydrate-rich foods (such as potato chips, cereal crispbreads, and coffee), is classified by IARC as probably carcinogenic to humans.[85] This conclusion was based largely on studies in experimental animals; epidemiological studies have been mostly null or inconclusive[86] but are limited by the difficulty of estimating long term exposure and by confounding owing to smoking. Recent research on possible mutational signatures of this chemical indicate that it might contribute to risk.[87]

How important is diet as a preventable cause of cancer?

Figure 2 shows recent estimates of the proportions of cancer cases in the UK attributable to modifiable risk factors, including dietary factors classified by WCRF or IARC as convincing causes of cancer. [88] Overweight and obesity is the second largest attributable cause, responsible for 6.3% of cancers in the UK, and is the largest cause in non-smokers. Alcohol (3.3%), dietary fibre (3.3%), and processed meat (1.5%) are also among the top 10 causes (although dietary fibre is currently classed by WCRF as only "probable"). Analyses from some other countries have produced broadly similar estimates; recent estimates for Brazil were 4.9% for overweight and obesity, 3.8% for alcohol, 0.8% for dietary fibre, and 0.6% for processed meat. [89] In Japan, however, where the prevalence of obesity is lower, estimates were 1.1% for overweight and obesity and 6.3% for alcohol (and 1.6% for salt). [90]

The way forward

Research into the effects of nutrition on health is difficult. [91] We have summarised here the relatively few well established clear links between nutrition and cancer, but future research might show further important risk factors—perhaps for specific food components or for broader dietary patterns, such as so called plant based diets. To move forward, the new generation of studies needs to improve estimates of long term exposure with, for example, repeated dietary records, which are now feasible using web based questionnaires.[92] Biomarkers of dietary intake and nutritional status can be used more extensively, and new biomarkers might be found through metabolomics, for example, but they will need to be validated and interpreted in the light of possible confounding and reverse causation. For some exposures, both for intake and nutritional status, mendelian randomisation will help to clarify causality,[93] and randomised trials will be needed to test specific hypotheses. It will also be important to attempt to coordinate systematic analyses of all the data available worldwide, to reduce the risk of publication bias.[94] For public health and policy, the top priority should be tackling the known major diet related risk factors for cancer, particularly obesity and alcohol.

Key messages

- Obesity and alcohol increase the risk of several types of cancer; these are the most important nutritional factors contributing to the total burden of cancer worldwide
- For colorectal cancer, processed meat increases risk and red meat probably increases risk; dietary fibre, dairy products, and calcium probably reduce risk
- Foods containing mutagens can cause cancer; certain types of salted fish cause nasopharyngeal cancer, and foods contaminated with aflatoxin cause liver cancer
- Fruits and vegetables are not clearly linked to cancer risk, although very low intakes might increase the risk for aerodigestive and some other cancers
- Other nutritional factors might contribute to the risk of cancer, but the evidence is currently not strong enough to be sure

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Table

Table 1 | Still uncertain: dietary and nutritional factors that expert groups have classified as "probable" causal or protective factors for cancer

Cancer	Probably increase risk	Probably decrease risk
Oral cavity and pharynx	Obesity	
Oesophagus	Drinking very hot beverages Mate (for squamous cell carcinoma)	
Stomach	Food preserved by salting Alcohol	
Colorectum	Red meat	Foods containing dietary fibre Wholegrains Dairy products Calcium supplements
Liver		Coffee*
Prostate, aggressive disease	Obesity	
Endometrium	Glycaemic load	Coffee*
Kidney		Alcohol

Categorisations are from WCRF[8] except hot beverages from IARC.[26] *Some of the current authors think that this conclusion is too strong.

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Figures

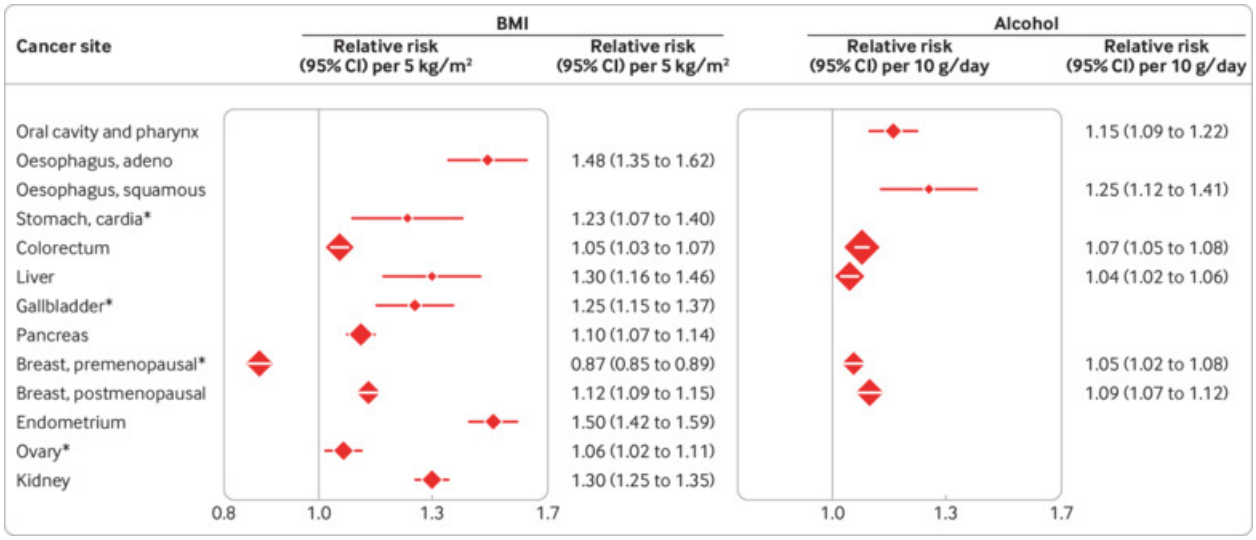

Fig 1 Body mass index (BMI), alcohol, and cancer risk. Convincing associations according to the World Cancer Research Fund[8] or the International Agency for Research on Cancer (marked by asterisks), or both,[10 80] with relative risks from meta-analyses.[8] We also consider the association between BMI and risk of breast cancer in premenopausal women to be convincing.[65] RR, relative risk (plotted with squares proportional to amount of statistical information); CI, confidence interval

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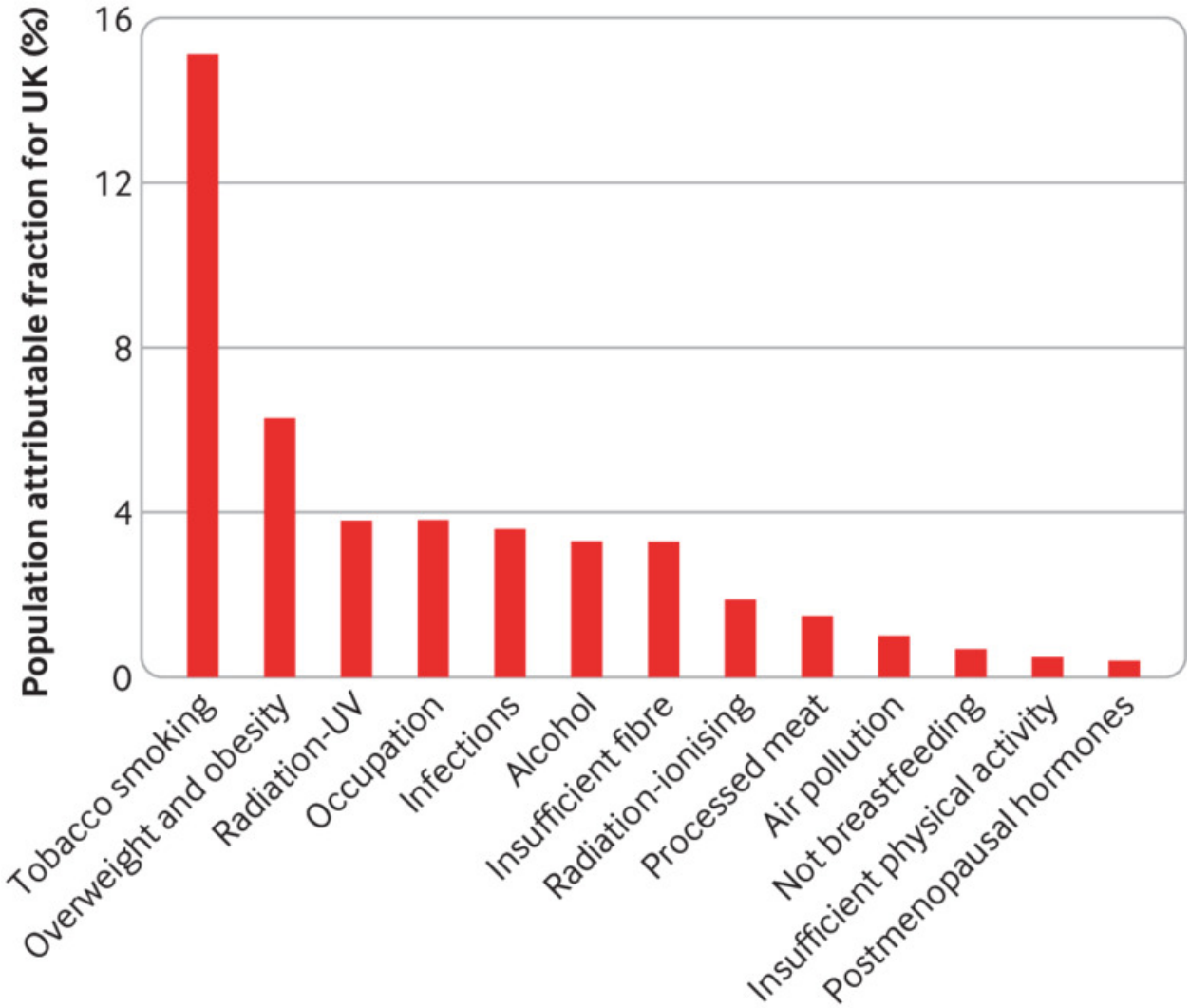

Fig 2 Percentages of cancer cases in the UK attributable to different exposures.[88]

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