Is cancer preventable? A literature review

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Abstract

Despite significant progress in tumour diagnosis and treatment over the last few years, cancer remains a major cause of death worldwide. Cancer prevention through diet and lifestyle changes is gaining importance, as our understanding of the potential of dietary patterns and single foods to avoid carcinogenesis is growing. This review article discusses available evidence for links between nutrition and cancer and summarizes some of the recent findings from observational and interventional studies on the potential of diet and specific nutritional components to reduce cancer risk.

Keywords: Cancer, Risk, Prevention, Diet, Nutrition, Chemopreventive

Substantial progress has been made in the field of oncology over the last few years. Widespread population screening programmes have significantly improved early detection of specific types of cancer (breast, prostate, cervical, and colorectal cancers) and enhanced survival rates. Nevertheless, cancer continues to be a major cause of death worldwide and killed almost 8 million people (13% of all human deaths) in 2008.[1]

Despite the enormous amount of research invested in the last decade, cancer remains a challenge in modern medicine. It is difficult to treat, if not impossible to cure, has a dramatic impact on patient's quality of life, and is lethal, particularly when not diagnosed at an early stage or aggravated by comorbidities. Treatment options (whether surgical removal of the tumours, chemotherapy, or radiation therapy) are limited, expensive, and coupled with adverse effects (e.g. chemotherapy-induced nausea and vomiting, immuno- and myelosuppression, cardio-, hepato-, or nephrotoxicity).

Cancer: a lifestyle disease

Cancer is a complex, multifactorial disease. Only a small percentage of cancer cases, approximately 5–10%, are thought to be entirely hereditary. The remaining proportion results from an interaction between biological or environmental insults and genetic predisposition. Common environmental factors that contribute to cancer death include diet and obesity (30–35%), smoking (25–30%), infections (15–20%), radiation (both ionizing and non-ionizing, up to 10%), stress, lack of physical activity, and environmental pollutants.[2] Hence, most forms of cancer have their roots in the environment and lifestyle and, as such, are preventable. And because cancer is difficult to manage, its prevention is the first and best strategy.

The correlation between lifestyle and cancer is evidenced by the large variation in rates of specific cancers in different countries and by the changes observed in incidence rates when people migrate to other countries.[2,3] Immigrants develop the cancer risk of their new country, often within one generation. Further evidence comes from studies in monozygotic twins, which showed that inherited genetic factors make only a minor contribution to susceptibility to most types of neoplasms.[4] These findings indicate that lifestyle and environmental factors have the principal role in causing sporadic cancer.[5,6]

A comprehensive report compiled by the World Cancer Research Fund and the American Institute for Cancer Research in 2007 presents a clear correlation between lifestyle and cancer risk.[7–9] The 670-page report was concerned with food, nutrition, physical activity, body composition, and the prevention of cancer worldwide. An expert panel composed of over 100 scientists from 30 different countries summarized a 5-year research of all evidence-based sources into eight general and two

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special recommendations. In summary, these are: keeping body weight within the normal range, being physically active, eating mostly foods of plant origin, limiting consumption of energy-dense foods, red meat, processed meat, salt, alcohol, and sugary drinks, and aiming to meet nutritional needs through diet alone rather than using dietary supplements. This sounds easy, does it not? But perhaps for most of us, there are too many items on the list to be followed.

Food-derived carcinogens

The pioneer work pointing to a link between diet and cancer was published 30 years ago by Doll and Peto,[10] in which they estimated that approximately 30–35% of cancer deaths in the USA were linked to diet. 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. In contrast, individuals in developing countries usually had diets that were based on one or two starchy staple foods, with low intake of animal products, fat, and sugar, and low rates of these cancers.[11] Diets that are high in processed or red meats and low in fruits, vegetables, and whole grains have been linked to a number of cancers.[12]

In theory, the link between diet and cancer is simple:

- Sporadic cancer arises from mutations caused by carcinogens or free radicals.
- A major source of carcinogens is food; they come from either the food itself, food contaminants (e.g. aflatoxins, dioxins, pesticides), food additives (e.g. nitrates, nitrites), or from food preparation (frying, barbecueing) at high temperatures (e.g. nitrosamines, heterocyclic amines, polycyclic aromatic hydrocarbons).
- Several food carcinogens have been shown to activate inflammatory pathways such as those involving nuclear factor-kappa B (NF-κB).
- Some nutrients are able to minimize oxidative damage to DNA caused by free radicals. These are basically antioxidants found in fruits, vegetables, cereals, spices, and teas.
- Nutrients interact with other molecules, particularly proteins including enzymes and lipids, within cells; some of these are then able to regulate expression of genes (e.g. oncogenes, tumour suppressor genes) and activity of enzymes that are involved in the control of cell proliferation and differentiation, and programmed cell death.

The extent to which diet contributes to cancer varies greatly depending on the type and anatomical site of the cancer.[3] For instance, diet is thought to account for 70% of colorectal cancer cases. Consumption of red meat, fat, and alcohol is associated with an increased risk of colorectal cancer.[13–15] Heavy consumption of red meat or processed meat (sausages, bacon, and hot dogs) is a risk factor for several cancers, especially for those of the gastrointestinal tract, but also for prostate, bladder, and breast cancers.[2] Epidemiological association studies have linked consumption of grilled meat to an increased risk of oesophagus and stomach cancer,[16] colon cancer,[17] pancreatic cancer,[18] and breast cancer,[19] a phenomenon which could be due to the presence of carcinogens in foods cooked at high temperatures.[20]

Obesity and cancer

According to a prospective cohort study of 900 000 US Americans published in 2003, obesity correlates with increased mortality from various cancers.[21] In both men and women, body mass index (BMI) was significantly associated with higher rates of death due to cancer of the oesophagus, colon and rectum, liver, gallbladder, pancreas, kidney, non-Hodgkin's lymphoma, and multiple myeloma. Significant trends of increasing risk with higher BMI values were observed for death from cancers of the stomach and prostate in men, and for death from cancers of the breast, uterus, cervix, and ovary in women. On the other hand, caloric restriction has been shown to reduce cancer incidence in animals and humans.[2,22]

The correlation between obesity and cancer might have several causes. Obese people usually eat an unhealthy diet rich in processed food, saturated fatty acids, *trans* fatty acids, refined sugar, red meat, and processed meat products, which are a good source of carcinogens. They eat less fruits, vegetables, and grains, and are physically less active. In addition, they present comorbidities such as diabetes and cardiovascular diseases that may contribute to a bad health state, for instance, by activating inflammatory signalling cascades and increasing systemic chronic inflammation parameters.

Studies have shown that common denominators between obesity and cancer include neurochemicals, hormones (such as insulin-like growth factor 1, insulin, and leptin), sex steroids, inflammation, and insulin resistance.[23] Hyperglycaemia, for instance, has been shown to activate NF-κB.[24] Likewise, several cytokines produced by adipocytes, such as leptin, tumour necrosis factor, and

interleukin-1, are also known to activate NF-κB.[25] The mammalian target of rapamycin (mTOR), a protein kinase which is activated by high cellular nutrient and energy levels, is another possible link between obesity and cancer.[22] The mTOR protein regulates growth, proliferation, motility, and survival of cells. mTOR activity is enhanced in obese and overweight people, and this state is thought to increase the probability of carcinogenesis. The counteractor of mTOR, adenosine monophosphate-activated protein kinase (AMPK), is implicated in the prevention of metabolic disorders. Decreased AMPK activity has been associated with an increased risk of carcinogenesis, and treatment with the AMPK activator metformin reduces cancer incidence in type 2 diabetes patients.[26] AMPK is emerging as an interesting metabolic tumour suppressor and a promising target for cancer prevention and therapy.

The anti-cancer diet

A presumable 'anti-cancer diet' has been extensively discussed in the last years. The topic crossed the boundary of the scientific environment and reached the lay community, fostered by the publication of several books. A few examples are *Foods that fight cancer* (by Richard Béliveau and Denis Gingras, and another one written by Patricia Hausman), *Beating cancer with nutrition* (Patrick and Noreen Quillen), *The cancer-fighting kitchen* (Rebecca Katz and Mat Edelson), *The everything cancer-fighting cookbook* (Carolyn Katzin), *Beyond the magic bullet – the anti-cancer cocktail* (Raymond Chang).

Diets rich in fruits, vegetables, whole grains, and spices have been linked to reduced risks of cancers of the colon, rectum, stomach, liver, oral cavity, pharynx, and other sites, including breast and prostate. A list of 100 fruits, vegetables, cereals, and spices with the potential to prevent cancer is provided in an expert review by Preetha Anand *et al.*[2] from the Cytokine Research Laboratory of the University of Texas, USA. According to this review, the protective role of fruits and vegetables against cancers that occur in various anatomical sites is now well supported, with more than 25 000 different phytochemicals identified that may have anti-cancer activity. They include beta-carotene, lycopene, resveratrol, quercetin, silymarin, indole-3-carbinol, and sulphoraphane from fruits and vegetables, as well as catechins, curcumin, diallyl disulphide, capsaicin, gingerol, anethol, and eugenol from spices and teas. Although most of the evidence of the chemopreventive efficacy of these compounds has come from cell and animal studies, they have advantages in comparison with synthetic drugs because they are regarded as safe and usually target multiple cell signalling pathways.[27]

For instance, catechins interact with more than 10 genes involved in the cellular response to oxidative stress.[28] They are 100 times more powerful than vitamin C and 25 times more powerful than vitamin E in their antioxidant/growth inhibitor potential.[29] Not only tea drinkers but also coffee lovers may enjoy the hot cup. Coffee has been reported to inversely correlate with liver cancer.[30]

Another important source of anti-carcinogens is whole grains. Besides being rich in dietary fibres, they contain chemopreventive antioxidants such as tocotrienols, phenolic acids, lignans, and phytic acid.[2] Whole-grain intake was found to reduce the risk of several cancers, including carcinomas from different sites, lymphomas, and leukaemias, by 30–70%.[31] The most evident correlation between dietary fibre intake and reduced cancer risk has been observed for colorectal cancer.[32,33] A meta-analysis involving 25 prospective cohort and case–control studies published in November 2011 confirmed the protective effect of dietary fibre on colorectal cancer incidence but also revealed that the risk reduction varies among different types of fibres, with the greatest benefits seen for legume fibre (relative risk/RR = 0.62) and cereal fibre (RR = 0.90).[34] Whole grains contain less antioxidants than some berries, but more than common fruits or vegetables.[35] However, the refining process used in most industrialized countries reduces their content of nutrients by removing the outer layers.[36]

Some isoflavones (genistein, daidzein, equol) have been linked to a lower incidence of breast cancer. However, there is also controversy on whether isoflavones, as phytoestrogens, might rather contribute to hormone-dependent cancers.[37] The effects of isoflavones on early breast cancer markers differ between pre- and post-menopausal women. Human and animal studies have yielded conflicting results with regard to the effect of soy isoflavones on breast cancer risk. As recently shown, this may be due to differences in isoflavone metabolism between humans and rodents.[38]

The most important class of phytoestrogens in the Western diet are lignans (found in flaxseeds, sesame seeds, rye bran). They are transformed by the intestinal microflora into enterodiol, and enterolactone. Lignans are capable of binding to oestrogen receptors and interfering with the cancer-promoting effects of oestrogen on breast tissue. In a meta-analysis, high lignan intake was shown to be associated

with a significantly reduced risk of breast cancer in post-menopausal women,[39] but this finding was not confirmed in an epidemiological study.[40] Among women (but not men), colorectal cancer risk was inversely associated with enterolactone and total enterolignans.[40] On the other hand, enterolignan intake positively correlated with prostate cancer risk, but this correlation was attenuated after adjustment for dairy intake.

Fruits and vegetables: the value of a good reputation

The few examples given above stress how complex the influence of diet and specific nutrients on the risk of various cancers is. Despite the currently available body of evidence from *in vitro*, animal and human studies for the chemopreventive effect of a healthy diet, some observational studies have found that consuming lots of fruits and vegetables has little or no effect on preventing cancer. The European Prospective Investigation into Cancer and Nutrition (EPIC) study, for instance, only detected a very small inverse association between the intake of total fruits and vegetables and cancer risk (hazard ratio/HR = 0.97 for 200 g/day increased intake of fruits and vegetables combined).[41] The reduced risk of cancer associated with high vegetable intake was restricted to women (HR = 0.98). Stratification by alcohol intake suggested a stronger risk reduction in heavy drinkers and was confined to cancers caused by smoking and alcohol. Similar results were published in another report from the EPIC study, which showed that a high intake of fruits and vegetables was associated with a decreased risk of lung cancer in current smokers.[33] A Mediterranean dietary pattern exerted similar protective effects against smoking-related cancers in the EPIC cohort.[42]

Lifestyle issues are powerful confounding factors when investigating the effect of fruits, vegetables, and dietary fibre on health.[22] For instance, smoking and alcohol are usually associated with low intake of fruits and vegetables, whereas people who consume large amounts of fruits and vegetables are less likely to smoke or drink alcohol.[43]

The polemic findings of the EPIC study are discussed by Walter Willett from the Harvard School of Public Health in an editorial of the *Journal of the National Cancer Institute*.[44] He argued that the evidence for a large preventive effect of fruits and vegetables against cancer has come primarily from case–control studies, which can be biased by differences in recall of past diets. Even more problematic is a selective participation (as control subjects) of more health-conscious people who have a healthier diet and lifestyle compared with those who do not participate. These biases are avoided in prospective cohort studies, and this type of study has shown that the results of case–control studies were overly optimistic and that any association of intake of fruits and vegetables with risk of cancer is weak at best. Nevertheless, Willett remarked that a very weak or undetectable association between total fruits and vegetables and risk of cancer does not exclude the possibility that one or a small group of fruits or vegetables, or a specific substance in some of these foods has an important protective effect.

Not only case–control and cohort studies have yielded conflicting results, but also and most notably epidemiological studies and randomized clinical trials (RCTs). This topic is discussed by Todd Gibson *et al.*[45] from the National Cancer Institute, USA. The authors listed several sources of discrepancy, including differences in study populations, dose and timing of the exposure, compliance, length of follow-up, and the primary endpoint. They agree with Willett in that null findings in RCTs do not necessarily indicate a lack of effect of the tested compound, as RCTs can only test a specific intervention in a certain population over a relatively short period of time. They believe that some nutrients may have chemopreventive effects if given to the right subjects at the right time and in the right dose. Furthermore, they postulate that dietary benefits against cancer arise from a combination of factors rather than single components acting in isolation. Two limitations inherent to RCTs are (1) the difficulty in testing combinations of nutrients and other bioactive food components in their natural context and (2) the need to intervene in older subjects to achieve sufficient statistical power. Both aspects are crucial when analysing the impact of diet on cancer risk.

The magic bullet

Although foods containing certain nutrients have been shown to be beneficial against cancer, intake of isolated nutrients has failed to confer the same benefits. Quite the contrary, harmful effects have been reported with supplementation of certain compounds. For instance, an *increased* risk of lung cancer among smokers who took beta-carotene supplements was reported in the Alpha Tocopherol, Beta-carotene Cancer Prevention (ATBC) trial[46] and in the Beta-Carotene and Retinol Efficiency Trial (CARET)[47] (20 and 30 mg of beta-carotene

supplementation, respectively). In the ATBC study, beta-carotene had little or no effect on the incidence of cancer other than lung cancer. However, total mortality was 8% higher among participants who received beta-carotene than among those who did not, primarily due to more deaths from lung cancer and ischaemic heart disease.[46] The effect is specific to the supplementation dose, as no lung damage was detected in those who were exposed to cigarette smoke and who ingested a physiological dose of beta-carotene (6 mg), in contrast to high pharmacological doses (20–30 mg).[48] The harmful effect also seems to be specific to smoke exposure.

The initial report of the Selenium and Vitamin E Cancer Prevention Trial (SELECT) found no reduction in the risk of prostate cancer with either selenium (200 μg/day from L-selenomethionine) or vitamin E (400 IU/day of all rac-alpha-tocopheryl acetate) supplements, but a statistically non-significant increase in prostate cancer risk with vitamin E.[49] Follow-up (7–12 years) data published in October 2011 provided further evidence that dietary supplementation with vitamin E significantly *increased* the risk (HR = 1.17, $P = 0.008$) of prostate cancer among healthy men.[50] The vitamin E dose used in SELECT was 12 times higher than the recommended intake, which is 33 IU daily.

For vitamin C supplementation, the scenario is even more unclear. Three RCTs performed at the Mayo Clinic using oral vitamin C for cancer patients were negative.[51] It has been controversially debated whether or not vitamin C has any clinically significant antitumour activity.

Conclusions

Many cases of sporadic cancer are preventable. Cancer prevention based on dietary and lifestyle changes remains a hot research topic because of the potential of an effective intervention to decrease cancer incidence at low cost and with a high positive impact on health economics globally. However, conflicting results obtained from epidemiological studies versus clinical trials underscore the need for improving study designs.

Effective cancer prevention involves smoking cessation; minimal consumption of fat, red meat, and processed meat; increased ingestion of fruits, vegetables, and whole grains; avoidance of alcohol; caloric restriction; physical activity; avoidance of prolonged exposure to sunlight; vaccinations; and regular check-ups.[2] Increased consumption of fat, red meat, and processed meat has been clearly associated with increased cancer risk. However, the key link between diet and cancer seems to be obesity, a condition fostered by diets based on high-fat meat products.

Inconsistent results from many studies have not been able to conclusively establish an inverse association between fruit and vegetable intake and overall cancer risk.[41] It has been claimed that fruits, vegetables, and dietary fibre *per se* have a very marginal, if any, effect on cancer incidence,[22] except for cancers caused by smoking and alcohol, and this effect might be due to residual confounding by these factors.[43] Nevertheless, negative results from RCTs of individual compounds do not preclude that single foods or whole dietary patterns have chemopreventive effects in settings different from those that can be investigated within RCTs.

A diet rich in fruits and vegetables helps avoid the risk of obesity, metabolic syndrome, and cardiovascular diseases.[52,53] In addition, it provides valuable sources of antioxidants and other phytochemicals with chemopreventive activity. Evidence is accumulating that active phytochemicals have synergetic effects that cannot be achieved with mono-supplementation of isolated compounds. The use of nutritional supplements in well-nourished individuals is not supported by current evidence. Not all substances present in fruits, vegetables, spices, and teas have been studied, and there are certainly many of them not yet identified. Taking this into account, future research should focus on whole dietary patterns and other lifestyle factors.

As pointed out by Gibson *et al.*,[45] future efforts need to recognize the integrative nature of dietary exposures and attempt to study nutrients in the larger context of the foods and diets in which they are consumed. Given the limitations of RCTs, we may need to rely more on observational evidence. Therefore, it is of paramount importance to improve the methodology for conducting high-quality, conclusive observational studies and, most importantly, to translate their results into meaningful benefits in cancer prevention.

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