

Antioxidants and the prevention of cancer

By Dr Luke Bereznicki

Learning objectives

After reading this article you should be able to:

- Discuss the role of diet in the prevention of cancer
- Compare and contrast the evidence relating to diet and antioxidant supplements and the prevention of cancer
- Discuss the implications of this research with your patients.

Competencies addressed: 6.2.4, 6.2.5, 6.3.2

Introduction

It has been estimated that Australians spend approximately \$4 billion annually on complementary and alternative medicine (CAM; includes purchases of products and visits to practitioners), just under half of which is spent on CAM products.¹ Spending on CAM products equates to roughly half of all non-subsidised health care products in Australia.^{1,2} The most frequently purchased CAM product type in Australian representative surveys is clinical nutrition, accounting for 50% to 60% of CAM product usage.^{1,3} CAM is most often used to improve general health, in the belief that dietary supplementation is useful to prevent chronic disease. Following the release of results from observation trials suggesting that a high dietary intake of fruits and vegetables is associated with reduced cancer incidence and mortality,⁴⁻⁶ there has been a strong awareness that intakes of some nutrients beyond the recommended daily intake may have a role in the prevention of many diseases. Diet is thought to play a significant role in the development of many diseases, including cardiovascular disease, stroke, macular degeneration, dementia and cancer. This article will briefly review the recent evidence surrounding the use of diet and dietary supplements to prevent cancer.

Antioxidant nutrients

Reactive oxygen species are produced normally as the by-products of cellular metabolic processes that utilise oxygen, and also as a component of the immune defence system.⁷ These reactive oxygen species include free radicals and other molecules which may act as oxidising agents, or may be converted to free radicals. The oxidant by-products of metabolism cause extensive damage to DNA, proteins and



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lipids, which is thought to contribute to the pathophysiology of age-related degenerative diseases such as cancer, cardiovascular disease, immune-system decline, brain dysfunction and macular degeneration.

It has been estimated that 88–90% of human cancers are environmentally induced, approximately 35% by diet.⁸ Experimental evidence indicates that free radicals have a role in the initiation and promotion of cancer, which involves changes in DNA, possibly by direct DNA damage.⁹ Oxidative damage to lipids and proteins (such as DNA repair enzymes) could also lead to mutations.¹⁰ The production of reactive oxygen species and free radicals is compensated for by a complex endogenous antioxidant system. However, a

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Table 1. Antioxidant components in food (from Wahlqvist et al. 1999⁴¹)

Components	Compounds	Food sources
Vitamins	Vitamin C	Citrus fruit, berries, papaya
	Vitamin E	Seed-like cereal grains, nuts and oils derived from plants
	Beta carotene and other carotenoids	Orange-pigmented and green leafy vegetables
Elements	Copper (as part of superoxide dismutases)	Cocoa, wheat bran, yeast
	Selenium (as part of glutathione peroxidase)	Grains, meats
Macronutrient-derived	Peptides, e.g. glutathione	Whey protein
Phytochemicals (food components of plant origin)	Isoflavones, e.g. genistein and daidzein	Soy
	Flavonols, e.g. quercetin and kaempferol	Tea, red wine, onions, apples
	Polyphenols, e.g. rosmarinic acid	Herbs – oregano, thyme
	Catechins, e.g. epigallocatechin gallate	Green tea
Zoochemicals (food components of animal origin)	Glutathione	Meats
	Ubiquinone (coenzyme Q10)	Meats, especially meat organs, fish

number of factors are thought to increase oxidative stress, such as hypertension, hyperlipidaemia, smoking, excessive alcohol intake, excessive sun exposure and exposure to air pollutants. Antioxidants are agents that reduce oxidation. There are a variety of compounds that possess antioxidant properties, many of which can be obtained from the diet (see Table 1). Beta-carotene, vitamin A, vitamin C, vitamin E and selenium all have antioxidant potential. Many other compounds found in food (phytochemicals) are powerful antioxidants and may also possess health benefits. In the case of cancer, high levels of antioxidants in fruits and vegetables are believed to contribute to cancer prevention, possibly by reducing oxidative stress.^{11–13}

Observational studies of diet and cancer incidence

Many observational trials have shown a significant benefit associated with higher intakes of fruit and vegetables compared to lower intakes in the prevention of chronic diseases, including cancer.^{4–6} Epidemiological data suggest an overall cancer risk reduction of between 30% and 50% associated with high dietary intake of fruits and vegetables.⁸ Prospective cohort studies, where large groups of participants can provide information of interest and be followed for long periods of time, are useful for studying the impact of dietary risk factors for diseases. A review of 20 cohort studies that have examined the relationship between vegetable and fruit intake and different types of cancer found that 19 of the 20 studies reported a protective effect on cancer incidence for at least one category of vegetable and/or fruit (categories included vegetables, fruit, raw vegetables, cruciferous vegetables, legumes, allium vegetables, green vegetables, carrots, tomatoes and citrus fruits).⁶ Twelve studies showed a statistically significant association. The cohort study evidence is most consistent for lung cancer, but studies have involved all cancer sites.

Retrospective case-control studies identify people with a particular disease (usually through hospital records or disease registries) and ask them about their past history in order to identify risk factors for their disease state. Control subjects without the disease in question are also identified and are also asked about potential risk factors for the disease in question for comparison with the case-subjects. Case-control studies require fewer subjects than prospective cohort studies, and can be completed in a shorter time frame. Their most obvious limitations are that participants must recall information from their past, and their responses may be influenced by their beliefs regarding the disease process. Over 100 case-control studies have been conducted to investigate the relationship between diet and cancer. A review of 174 of these studies found statistically significant relationships between diets low in vegetables and/or fruits and increased cancer incidence in 80% of studies involving cancers of the stomach, oesophagus, lung, oral cavity, rectum, bladder, cervix, endometrium and larynx.⁶ The case-control study evidence strongly suggests that vegetables and fruit are protective against a range of cancers, including cancers of the lung, stomach and oesophagus. The evidence for other sites is either less abundant or less consistent, but is suggestive of a protective effect against cancers of the oral cavity and pharynx, colon, breast, pancreas and bladder.

A high dietary intake of vegetables in general, and raw vegetables in particular, is consistently associated with positive outcomes in observational studies. Observational

Table 2. Possible anticarcinogenic mechanisms of substances in vegetables and fruit (from Steinmetz et al. 1996⁶)

Antioxidant effects
Effects on cell differentiation
Increased activity of enzymes that detoxify carcinogens
Blocked formation of nitrosamines
Altered oestrogen metabolism
Altered colonic milieu (including bacterial flora, bile acid composition, pH, faecal bulk)
Preserved integrity of intracellular matrixes
Effects on DNA methylation
Maintenance of normal DNA repair
Increased apoptosis of cancer cells
Decreased cell proliferation

studies however, do not clearly show which specific dietary constituents of fruit and vegetables might be beneficial. Additionally, causal inferences are difficult to establish from observational studies. The protective effects of a diet high in vegetables and fruits on cancer incidence are probably due to combinations of nutrients and also to the presence of non-nutrient substances found in these foods. Additionally, diets high in fruits and vegetables might also be protective because they result in a lower intake of fat and a higher intake of fibre, both of which may also be protective. A myriad of substances in fruit and vegetables have been shown to possess anticarcinogenic properties. Some possible biological mechanisms by which these substances might help prevent cancer are shown in Table 2. It is possible that the protective substances in foods act in integrated systems or cascades, and they may require co-ingestion of other substances.

Trials involving antioxidant supplementation to prevent cancer

Given the epidemiological evidence suggests that diets high in fruits and vegetables may prevent cancer, it is not surprising that many people take antioxidant supplements in the belief that additional supplementation is beneficial. In Australia, nutritional supplements are the most widely used CAM, accounting for around 50–60% of CAM usage.^{1,3} The situation is similar in other Western countries.^{14–17} These supplements are most often taken to improve general health or to boost immunity, rather than to treat specific disease processes. It is currently unclear as to whether these supplements play any role in the prevention of cancer, or whether, in fact, they might be harmful.^{18–21} It is possible, as with any medication or supplement, that too much might

be harmful; antioxidant supplementation in high doses may therefore act as a double-edged sword. The evidence on whether antioxidant supplements are effective in decreasing the incidence of cancer, particularly gastrointestinal cancer, is contradictory.^{22–24} A series of systematic reviews have recently been conducted to better inform the use of antioxidant supplements for a range of clinical situations, including cancer prevention.^{21,25–31}

A systematic review and meta-analysis aimed at establishing whether antioxidant supplements reduced the incidence of gastrointestinal cancer and mortality was published in 2004 and updated in 2008.^{21,30} The original meta-analysis included 17 randomised controlled trials (RCTs) and 170,525 patients.²¹ In this analysis beta-carotene, vitamins A, C, E and selenium (alone or in combination) were compared to placebo on oesophageal, gastric, colorectal, pancreatic and liver cancer incidences. The meta-analysis did not show any benefit associated with antioxidant supplementation on mortality. Certain combinations of antioxidants were actually associated with increased mortality (beta-carotene with vitamin A or vitamin E), while beta-carotene supplementation given alone displayed a tendency to increase mortality. Selenium supplementation however, showed significant beneficial effects on the incidence of gastrointestinal cancer. The updated meta-analysis included an additional three RCTs and around 40,000 additional patients.³⁰ Antioxidant supplementation was again not found to significantly reduce the risk of gastrointestinal cancers, or the risk of mortality. Again, beta-carotene in combination with vitamin A or E was found to significantly increase mortality risk and selenium was found to significantly reduce the risk of gastrointestinal cancers.

Another meta-analysis investigated the dose-response relationship between vitamin E supplementation, used for the prevention of cardiovascular disease or cancer, and mortality.²⁵ This study involved 19 RCTs and almost 140,000 patients. The key finding was that high-dose vitamin E supplementation (> 400 IU per day) appeared to significantly increase the risk of death compared to placebo. A dose-response analysis showed a statistically significant relationship between vitamin E dosage and all-cause mortality, with increased risk at doses exceeding 150 IU per day (bear in mind that the recommended daily intake of vitamin E [as alpha-tocopherol equivalents] in Australia for adults is currently 15 IU per day for men and 10.5 IU per day for women).³²

The risks associated with beta-carotene, vitamin A and vitamin E supplementation were further demonstrated in another recent meta-analysis.^{26,31} This analysis included all RCTs of antioxidant supplementation in which mortality was an endpoint, and included trials involving either primary or secondary prevention of disease. A total of 68 RCTs and 232,000 patients were included. Overall, there

was no significant effect of antioxidant supplements on mortality. In well-controlled trials with a low risk of bias, antioxidant supplementation increased the risk of mortality. Beta-carotene, vitamin A and vitamin E, singly or in combination, increased the risk of mortality, while selenium and vitamin C had no significant effect. The use of supplemental vitamin C and E was not found to prevent or treat cancer in two other reviews.^{27,28}

Finally, a review focussed solely on the effect of antioxidant supplementation on primary cancer incidence and mortality reported similar findings.²⁹ Antioxidant supplementation did not reduce the overall risk of cancer, mortality or any site-specific cancer incidence. Beta-carotene was shown to increase the risk of cancer among smokers, a finding largely based on the results of two large RCTs,^{33,34} and was also associated with a trend towards increased cancer mortality. Selenium supplementation was associated with a reduced cancer incidence in men, but not in women, and with reduced cancer mortality. Vitamin E supplementation had no effect on overall cancer incidence or cancer mortality.

Summary and conclusions

The available evidence from RCTs appears to contradict the data from observational trials linking antioxidants with a reduced risk of cancer. There are many possible explanations for this. Firstly, fruits and vegetables provide a cocktail of micro- and macronutrients, including antioxidant compounds, which may interact in ways of which we are currently unaware to reduce the risk of cancer. The observational studies do not clearly show which specific dietary constituents of fruits and vegetables might be beneficial. It seems that high doses (well above the recommended daily intake in most trials) of individual antioxidant compounds do not provide a reduction in cancer incidence, with the possible exception of selenium. There are many other antioxidant compounds in foods that might be at least partially responsible for the benefits seen in observational studies. Secondly, there may be a combination of reasons why people who favour a diet high in fruits and vegetables have a lower risk of cancer. Randomisation in RCTs might account for these variables to some degree. Additionally, it may be unrealistic to expect large doses of antioxidant supplements to reduce the incidence of diseases such as cancer, with a long latency period, over a period of only a few years in middle-aged subjects. It is perhaps more plausible that a diet containing a wide variety of foods containing physiological doses of a wide range of nutrients over a lifetime might be beneficial.

High-dose antioxidant supplements, particularly beta-carotene and vitamins A and E, seem to increase the risk of mortality, rather than reduce it. Large quantities of antioxidants may in fact be pro-oxidant and induce oxidative stress.^{35,36} This effect has been demonstrated

with beta-carotene, where it has been shown to increase the risk of cancer in smokers.

Selenium supplementation appears to be the most likely supplement to provide beneficial effects on cancer incidence, particularly for gastrointestinal cancers and in men. A recent study found an association between serum selenium levels and all-cause and cancer mortality in a representative sample of the US population.³⁷ However, the investigators also found that overly elevated serum levels may be associated with increased mortality. The SELECT study recently found that selenium supplementation alone, or a combination of selenium and vitamin E supplementation, did not prevent prostate cancer in the population studied, while another trial found that supplementation was beneficial.^{38,39} Most of the trials involving selenium have been conducted in areas where residents were likely to be selenium deficient; it is possible that selenium supplementation is only effective in those who are nutritionally deficient. Men appear to benefit more from selenium supplementation than women, which may be due to differences in tissue response to selenium, selenium metabolism, hormones and tumour biology between men and women.⁴⁰

In summary, a high dietary intake of fruits and vegetables appears to be beneficial in reducing the incidence of cancer, while high doses of individual supplements do not. Selenium is a possible exception, particularly in those who may be deficient. Clearly, individual supplements do not compensate for poor nutritional intakes. The available data suggests that the ideal diet to prevent cancer is one that is high in a variety of fruits and vegetables and includes a range of cereals. The available data do not support the use of high-dose antioxidant supplements to prevent cancer or to reduce mortality – these supplements may instead result in harm.

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Questions

(A score of 4 out of 5 attracts 1 credit point.)

1. which of the most common reason for the use of complementary and alternative medicines in Australia?
 - a) To improve general health.
 - b) To prevent cancer.
 - c) To treat musculoskeletal complaints.
 - d) To improve the circulation.
2. Approximately what proportion of human cancers are thought to be linked to dietary problems?
 - a) 15%.
 - b) 25%.
 - c) 35%.
 - d) 45%.
3. Diets high in fruits and vegetables may protect against cancer because:
 - a) They contain antioxidant vitamins.
 - b) A diet high in fruits and vegetables is likely to contain less saturated fat.
 - c) They contain a variety of micro- and macronutrients.
 - d) All of the above.
4. Which one of the following supplements is the most likely to be beneficial in preventing gastrointestinal cancers?
 - a) Vitamin A.
 - b) Beta-carotene.
 - c) Vitamin E.
 - d) Selenium.
5. Which one of the following statements is false?
 - a) Observational studies do not clearly show which specific dietary constituents of fruit and vegetables might be beneficial in preventing cancer.
 - b) High-dose antioxidant supplements, particularly beta-carotene and vitamins A and E, seem to increase the risk of mortality, rather than reduce it.
 - c) High dose beta-carotene has been shown to decrease the risk of cancer in smokers.
 - d) Large quantities of antioxidants may be pro-oxidant and induce oxidative stress.