Original article

Preventing cancer: dietary lifestyle or clinical intervention?

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In Australia, colorectal, prostate and breast cancers are the most frequently occurring cancers in our society, a pattern that is quite different from that of underdeveloped countries. While diet is largely responsible for these differences, technological advances mean that the solutions can be viewed as systematic, financial, lifestyle or technological. They range from those that require self-discipline and care for personal well-being through to those that are seemingly a quick technological fix that will work in spite of an unhealthy lifestyle. There are three main approaches available for prevention of these cancers: dietary lifestyle, chemoprevention and screening. It has been estimated that the potential for prevention by a healthy dietary lifestyle is excellent and might reduce the burden of breast, prostate and colorectal cancer by 33–55%, 10–20% and 66–75%, respectively. This should be safe and inexpensive and have collateral benefit such as reduced cardiovascular disease and osteoporosis. But, population compliance with more plant-based, less calorie dense foods is uncertain, the most healthy are likely to be the most compliant and evidence for effectiveness when interventional programs are undertaken is disappointing. It is not clear how dependable the dietary approach would be where inherited genetic factors determine risk for one of these cancers. Chemoprevention, the administration of natural or synthetic agents that delay, slow down or inhibit the process of tumorigenesis, are still under development and study. Hormone receptor modulators for breast and derivatives of non-steroidal anti-inflammatory drugs for colorectal cancers seem to have most promise and may reduce tumour incidence or death by as much as 50%. These agents are simpler to comply with than changing dietary lifestyle and they are more potent, hence they may be of particular value in high-risk settings. But they are likely to be more costly and run the risk of adverse effects with few collateral benefits. Screening, or the testing of an individual for a disease when that individual does not have any symptoms or signs suggesting that the disease is present, aims to prevent or delay the development of the cancer. Screening impacts on mortality more so than on incidence, reducing colorectal cancer mortality in the range 15–60% and breast cancer mortality by 23–37%. Screening has the advantage of being effective in high-risk as well as average-risk groups and is an ‘easy’ solution for the person who elects not to follow a healthy dietary lifestyle. Nonetheless, it is expensive, demanding on resources, provides no collateral benefits and does not have the same potential to reduce incidence of disease as does the dietary approach. With these Western cancers, we are fortunate that there are options for prevention. At least choices are available and some will suite certain circumstances and personalities more than others.

Key words: Breast cancer, cancer prevention, chemoprevention, colorectal cancer, dietary lifestyle, screening.

Cancer in our society

Cancer incidence and mortality have been steadily rising throughout the last century in most areas of the world.1 One in every three men and one in every four women will be directly affected by cancer before the age of 75. Cancer occurs more commonly in males than females and the risk of cancer increases with age.

The types of cancer vary between Westernized and underdeveloped countries. In the Africa/Latin America/Asia regions, the predominant diet is bulky and monotonous and comprises a large portion of cereal/starchy foods. Oesophageal, stomach and liver cancers predominate. In the Europe/North America/Australasia regions, the diet is much more varied, energy-dense and contains more fats/oils, animal foods, and refined sugars. Cancers of the breast, prostate, and colon and rectum predominate. These differences emphasize the importance of diet, which is further confirmed by the changing types and incidence of cancers in migrants to Western countries and in countries that are Westernising their dietary life-style.1

In Australia, colorectal, prostate and breast cancers are the most frequently occurring cancers in our society (Fig. 1). In males within Australia, cancer of the prostate followed by colorectal are the most commonly diagnosed cancers. In females, breast cancer is the most commonly diagnosed cancer followed closely by colorectal cancer. They are also a substantial cause of death.2 In both sexes, the second commonest cause of death from cancer is colorectal cancer (Table 1).

Strategies for prevention

The choices available for dealing with these cancers, are very different from each other and reflect the very nature of modern society. The solutions can be viewed as systematic,

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financial, lifestyle or technological. They range from those that require self-discipline and care for personal well-being through to those that are seemingly a quick technological fix that will work in spite of an unhealthy lifestyle.

There are three main approaches for prevention of cancer: dietary lifestyle, chemoprevention and screening. These three cancers, colorectal, prostate and breast, have been subject to not only many studies exploring the impact of the Western dietary lifestyle, but also to large scale studies addressing the value of screening and in some instances, chemopreventive agents. Before discussing the relative values of each, it is important to consider the key aspects of each approach to screening: the prime targets of each, how they work and what their impact might be. These are summarized in Table 2. It is apparent that there are major differences in each strategy. For instance, screening only reduces the incidence of cancer if it can detect precancer lesions, while we would anticipate that a healthy diet might prevent formation of even the precancer lesions.

From the following discussion, it will also be apparent that there are key differences in operational characteristics between the different approaches. The effects of each will differ for cancer incidence, for cancer death, for ease of population compliance with the intervention, for collateral benefits (i.e., those in addition to preventing the cancer in question) and for adverse effects. These will be compared later in the paper.

### Dietary relationships with cancer

Environmental factors, and particularly the diet, play a major role in cancer aetiology. Populations that migrate from countries with low rates of cancer to areas with high rates, or the reverse, commonly acquire the rates, characteristic of their new location. This may become apparent within the generation that migrate but becomes more pronounced after only one or two generations. \(^1\) Doll and Peto\(^3\) have estimated that between 10% and 70% of all cancer deaths might be attributable to dietary factors but this is a generalization and it is more valuable to consider each cancer in turn.

Tables 3 to 5 summarize the known dietary associations with the three main ‘Western’ cancers. There is strong and fairly consistent evidence that vegetables protect, with less strength of evidence and perhaps lesser benefit coming from fruits and whole grains, dietary fibre, certain micronutrients and physical activity. In the other direction, some fatty acids (especially animal fats), obesity, alcohol, meat in high amounts (certainly greater than 140 g/day) and food preparation methods may increase risk.

#### Table 1. The most frequent cancers in Australia by number of new cases and number of deaths in 1997\(^2\)

<table>
<thead>
<tr>
<th>Cancer site</th>
<th>No. of new cases</th>
<th>No. of deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colorectal</td>
<td>11245</td>
<td>4678</td>
</tr>
<tr>
<td>Prostate</td>
<td>10166</td>
<td>2449</td>
</tr>
<tr>
<td>Breast</td>
<td>9725</td>
<td>2612</td>
</tr>
<tr>
<td>Melanoma</td>
<td>8366</td>
<td>910</td>
</tr>
<tr>
<td>Lung</td>
<td>7819</td>
<td>6683</td>
</tr>
<tr>
<td>Unknown site</td>
<td>3169</td>
<td>2255</td>
</tr>
<tr>
<td>Non-Hodgkin’s Lymphoma</td>
<td>3137</td>
<td>1540</td>
</tr>
<tr>
<td>Bladder</td>
<td>2681</td>
<td>807</td>
</tr>
<tr>
<td>Kidney</td>
<td>2047</td>
<td>796</td>
</tr>
<tr>
<td>Stomach</td>
<td>1919</td>
<td>1244</td>
</tr>
</tbody>
</table>

#### Table 2. Major differences in key aspects of strategy, mechanism and impact of the three main approaches available for prevention of Western cancers. Items in parentheses are of lesser relevance than the other items in the box

<table>
<thead>
<tr>
<th></th>
<th>Dietary Lifestyle</th>
<th>Chemoprevention</th>
<th>Screening</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prime target</td>
<td>Precancer stages</td>
<td>Precancer stages</td>
<td>Identifies and so facilitates</td>
</tr>
<tr>
<td>Mechanism of effect during tumorigenesis</td>
<td>Regulates cell biology; reduces initial mutations or retards steps in progression</td>
<td>Regulates cell biology; retards steps in progression</td>
<td>removal of lesion when curable</td>
</tr>
<tr>
<td>Totality of effect</td>
<td>Partial; unlikely to be complete</td>
<td>Partial; unlikely to be complete</td>
<td>Complete if removal is successful</td>
</tr>
<tr>
<td>Time-frame</td>
<td>Ongoing; lifelong</td>
<td>Ongoing; but probably only needed when disease is likely</td>
<td>Discrete events that may be once-off but usually repeated</td>
</tr>
<tr>
<td>Benefit</td>
<td>Delayed</td>
<td>Short-medium term.</td>
<td>Immediate or short-medium term</td>
</tr>
</tbody>
</table>
of free fatty acids. Epidemiological studies have generally supported the idea that high fat intakes and red meat consumption are strongly correlated with national per capita intake of fat and meat. Diets high in fat may elevate risk for colorectal cancer. In comparisons among countries, rates of colorectal cancer are strongly correlated with national per capita intake of fat and meat. Diets high in fat may elevate risk for colorectal cancer.

Table 3. Nutritional prevention of colorectal cancer

<table>
<thead>
<tr>
<th>Decreases risk</th>
<th>Increase risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vegetables</td>
<td>Red meat (&gt; 100–140 g/day)</td>
</tr>
<tr>
<td>Physical activity</td>
<td>Alcohol (&gt; 60 g/day)</td>
</tr>
<tr>
<td>NSP/fibre</td>
<td>Total fat/animal fat</td>
</tr>
<tr>
<td>Carotenoids</td>
<td>Sugar</td>
</tr>
<tr>
<td>Cereals</td>
<td>Energy intake/BMI</td>
</tr>
</tbody>
</table>

Summary derived from WCRF report. Note that the level of evidence varies between those factors listed. Also the level of risk often relates to the amount consumed and not just the fact of consumption.

Table 4. Nutritional prevention of prostate cancer.

<table>
<thead>
<tr>
<th>Decrease risk</th>
<th>Increase risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vegetables</td>
<td>Total fat</td>
</tr>
<tr>
<td></td>
<td>Animal fat</td>
</tr>
<tr>
<td></td>
<td>Red meat</td>
</tr>
<tr>
<td></td>
<td>Milk and dairy products</td>
</tr>
</tbody>
</table>

Summary derived from WCRF report. Note that the level of evidence varies between those factors listed. Also the level of risk often relates to the amount consumed and not just the fact of consumption.

Table 5. Nutritional prevention of breast cancer

<table>
<thead>
<tr>
<th>Decrease risk</th>
<th>Increase risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vegetables and fruits</td>
<td>Alcohol</td>
</tr>
<tr>
<td>Physical activity</td>
<td>Total fat</td>
</tr>
<tr>
<td>NSP/fibre</td>
<td>Animal fat</td>
</tr>
<tr>
<td>Carotenoids</td>
<td>Meat</td>
</tr>
</tbody>
</table>

Summary derived from WCRF report. Note that the level of evidence varies between those factors listed. Also the level of risk often relates to the amount consumed and not just the fact of consumption.

The following discussion provides more detail on each of the three cancers.

Colorectal cancer: epidemiological evidence

Consumption of large amounts in the diet of red meat, animal and saturated fat, refined carbohydrates, and alcohol, as well as total energy intake, are generally considered to increase the risk of developing colorectal cancer. Conversely, significant intakes of dietary starch and fibre, vegetables, fruits, cereals, antioxidant vitamins and calcium are believed to be negatively associated with the risk of developing colorectal cancer (Table 3).

Dietary fat and meat

Fat intake has long been regarded as the most important nutritional influence on colorectal cancer. In comparisons among countries, rates of colorectal cancer are strongly correlated with national per capita intake of animal fat and meat. Diets high in fat may elevate risk by elevating bile acid production and lumenal concentration of free fatty acids. Epidemiological studies have generally shown an association between risk of colorectal cancer and intake of fat and red meat.

There are three associations with red meat that complicate the issue and create controversy: fat content, burning during cooking, and processing. Epidemiological data tend to support a direct association between colorectal cancer incidence and the consumption of red meat. The Colon Cancer Panel of the World Health Organization Consensus Conference on Nutrition in Prevention and Therapy on Cancer have stated that consumption of red meat and processed meat was probably associated with increased risk for colorectal cancer and recommended that the consumption of fish and poultry should be preferred to red meat. However, risk due to red meat intake alone, independent of fat, burning and processing, only becomes consistently apparent when consumption exceeds 140 g/day.

Energy intake

Energy intake is often difficult in studies to distinguish between energy intake and intake of fat. Calories are known to play important roles in cell division and enhanced cell proliferation may enhance cancer risk. There have been significant associations observed between total energy intake and colorectal cancer; however, not all studies have found consistent results and therefore the data on energy intake and colorectal cancer is only suggestive.

Physical activity

Physical activity has consistently been associated with decreased risk of colorectal cancer. Most studies have concentrated on occupational activity, although studies examining leisure time and total activity, and participation in school athletics, also have shown a reduced risk for the more active. It is hypothesized that physical activity stimulates colon peristalsis, which in turn decreases the time that dietary factors, toxic and carcinogenic components reside in the colon. It might also improve insulin homeostasis and decrease proliferative drive for tumour cells.

Dietary fibre/non-starch polysaccharides (NSP)

A favourable role of dietary fibres on colorectal carcinogenesis was hypothesized by Burkitt who observed that colorectal cancer rates were low in Africa where fibre intake rates have been traditionally high. The protective effect may be attributed to increased stool bulk or rapid intestinal transit with resultant decrease in duration of exposure of the colonic mucosa to potential carcinogens and/or to fermentation of NSP by colonic microflora to short chain fatty acids, in particular butyrate, which has antineoplastic properties. Epidemiological studies generally support that foods high in fibre are protective. Cereals contribute a major amount of dietary fibre as well as associated phytochemicals. Protective observation has been observed for consumption of vegetables and fruit and colorectal cancer. Also, a consistent protective observation has been observed for consumption of vegetables and fruit and colorectal cancer. Vegetables and fruits are rich in fibre but also contain a large array of micronutrients such as carotenoids, folate, vitamin C and bioactive compounds such as phenolics, and flavonoids which have apparent anticarcinogenic properties.
The results from prospective studies which assess the diets of a large group of healthy individuals and include follow-up over time, during which a number of people will develop colorectal cancer have, however, been inconsistent. This may be because fibre is heterogeneous and intake not easy to measure, consumption in some studies has been low, or other aspects of dietary lifestyle have been particularly adverse and so counteracted the benefit.

The World Cancer Research Fund and American Institute of Cancer Research report have stated that diets high in dietary fibre possible decrease the risk of colorectal cancer.

### Carbohydrates

While Cassidy et al. showed protection by dietary starch intake when examined on a country by country basis, other epidemiological studies do not clearly show whether carbohydrates (starch, resistant starch or polysaccharides) protect against colorectal cancer. However refined sugars, particularly sucrose may increase colorectal cancer risk, maybe through greater colonic cell proliferation and stimulation of insulin.

### Vitamins and minerals

Plant foods such as vegetables, fruits and cereals, are good sources of vitamins and minerals. Some of these, such as vitamin E, vitamin C, β-carotene and selenium, have antioxidant potential and along with calcium, vitamin D and folate may protect against colorectal cancer. Many epidemiological studies have examined these micronutrients and many suggest protection with β-carotene, vitamin C, folate, calcium and vitamin D. While it is prudent to include these in a healthy diet, evidence remains insufficient to depend on just one or another of these factors.

### Alcohol intake

The majority of epidemiological studies have reported either an increased risk or no association between alcohol intake and colorectal cancer. The effects of alcohol and colorectal cancer risk may depend in part on methionine and folate intake. A large prospective study found that men who consumed more than 20 g alcohol per day were not at increased risk for colorectal cancer but only if they consumed high amounts of methionine and folate. The carcinogenic effect of alcohol may act through induction of microsomal enzymes that convert pro-carcinogens to more active forms and to inhibit DNA repair.

### Prostate cancer: epidemiological evidence

Prostate cancer is a 'hormonally' determined cancer but the evidence for an important role of diet in its genesis has increased over the last decade. It appears that diet is the most likely factor explaining the striking international variability in its incidence and mortality. The panel from the World Cancer Research Fund and American Institute for Cancer Research stated that currently there was no conclusive evidence that any particular food group, food item, macronutrient or micronutrient is associated with prostate cancer risk. However, the panel accepted that it was possible that vegetable intake is inversely associated with risk for prostate cancer and that consumption of meat, milk and dairy products, saturated fat of animal origin and total fat is positively associated with this risk (Table 4).

### Dietary fat

Dietary fat may influence prostate cancer via stimulation of androgenic hormones, which are thought to be important determinants of the risk for prostate cancer. There have been numerous epidemiological studies that have studied the relationship between fat and prostate cancer. The majority of studies have reported increased risk of prostate cancer with higher intakes. Animal fat consumption has also shown positive associations with prostate cancer.

### Dairy products

The consumption of dairy products appears to be positively correlated with prostate cancer risk. Countries with a high per capita consumption of dairy products have higher incidence rates of prostate cancer than do countries in which few dairy products are consumed. In a review of 12 of 14 epidemiological studies reported significant elevations in relative risk (1.5–2.5) comparing high with low dairy product intake. Dairy products, through their high calcium content, might influence prostate cancer development by down-regulating the production of 1,25-dihydroxy-vitamin D3, a hormone thought to protect against prostate cancer. Interestingly, calcium is probably preventive against colorectal cancer.

### Fruit and vegetables

The results for an effect of fruit and vegetable intake and decreased prostate cancer risk are certainly not as clear as that for colorectal cancer. However, there is some evidence that high vegetable consumption may decrease prostate cancer risk. The beneficial effects may be attributed to isoflavonoids, which have been shown to inhibit growth of prostate cancer cell lines and are inhibitors of several steroid metabolizing enzymes. Because of the dependence of prostate cancer on testosterone, it is intriguing to postulate a role for phyto-oestrogens but the evidence is indirect at this stage.

### Overview of diet

It seems likely that dietary manipulation of prostate cancer tumorigenesis is less powerful than with colorectal cancer, perhaps reflecting the fact that hormonal factors are more important for prostate cancer.

### Breast Cancer: epidemiological evidence

Factors that affect the risk of breast cancer probably act early in life, there is evidence that rapid early growth and greater adult height increases breast cancer risk. Dietary factors (see Table 5), in particular dietary fat and alcohol, have been hypothesized to account for the large variation in breast cancer incidence around the world and the increases amongst migrants. Like prostate and unlike colorectal cancer, breast cancer is somewhat dependent on hormonal factors.

### Dietary fat and meat

Dietary fat may increase breast cancer risk via effects on hormone metabolism. The epidemiological data on dietary fat and breast cancer risk is somewhat weak. If the intake of dietary fat is more...
important early in life it may explain the inconsistencies observed in the epidemiological studies which have measured fat intake during adulthood.

The type of fat may be important in influencing breast cancer risk. Studies in Europe have demonstrated that monounsaturated fat sources such as ‘olive oil’ may decrease risk in comparison to animal/saturated fat sources. The same seems to apply to colorectal cancer.

Moderate increased risk for breast cancer with the consumption of large amounts of red meat have been reported. However, no significant associations have been reported in many studies.

Dietary Fibre/NSP, vegetables and fruit Dietary fibre may protect against breast cancer by reducing the intestinal reabsorption of oestrogen that is excreted via the biliary system. The results of many epidemiological studies on the effect of diets high in fibre suggest that fibre either has a weak protective effect or null effect on breast cancer risk. Fibre from fruit and vegetables has been reported to be protective overall more abundant and consistent protective associations are seen for vegetables, particularly green vegetables, than for fruits. Vegetables and fruit contain high levels of many vitamins (carotenoids, vitamin C, vitamin E) and it may be through their role as antioxidants that reductions in breast cancer risk are achieved.

Alcohol The association of alcohol consumption with increased risk for breast cancer has been a consistent finding in a majority of epidemiological studies over the last 20 years. The World cancer Research Fund and the American Institute for Cancer Research have stated that alcohol intake probably increases the risk of breast cancer. Alcohol’s impact on hormone status via increasing circulating oestrogens may be one such explanation for an aetiological relationship between alcohol and breast carcinogenesis. Another plausible mechanism may be through ethanol’s ability to induce enzymes (such as cytochrome-P450) responsible for carcinogen activation.

Physical activity Physical activity possibly decreases the risk of breast cancer, particularly in post menopausal breast cancer. Several studies have reported that moderate physical activity is associated with a lower risk of breast cancer. Obesity increases risk for postmenopausal but not premenopausal women.

The potential for dietary prevention of Western cancers It has been estimated that between 30 and 40% of cancer incidence worldwide is preventable by dietary means. This represents a figure of 3–4 million cases of cancer a year (Table 6). The degree of achievable protection varies between the key Western cancers; the impact of diet is stronger in those where hormonal influences are less strong. Not only has the dietary approach got great potential but it will be safe, inexpensive relative to other means, and likely to deliver collateral benefits for diseases outside cancer such as, osteoporosis and cardiovascular disease.

Feasibility of dietary prevention The case for dietary prevention of breast, prostate, and colorectal cancers is convincing. However, does the promise translate into effectiveness at a population level? Indeed, results from dietary intervention studies in these cancers raise significant doubts.

To date only a handful of randomized intervention trials in humans have been carried out examining dietary factors and cancer. The majority of these trials have focused on fibre and colorectal cancer, using adenomas as the primary endpoint (Table 7). From Table 7 it can be seen that the effect of fibre is not strong although it does seem more apparent when larger doses are used (> 20 g supplement per day).

Calcium may protect against the recurrence of colorectal adenomas and will have collateral benefits for instance with osteoporosis. Selenium supplementation may lead to a protective effect against colorectal cancer however, care must be taken when with this because in one intervention trial the primary endpoint was carcinoma of the skin and colorectal cancer results were from a secondary endpoint analysis. Also, selenium did not seem effective in another trial when combined with a range of dietary agents. Indeed, in Table 7 it can be seen that when attempts were made to intervene with a more wholistic healthy diet, no benefit was seen.

We are in the early stages of understanding exactly how to do studies such as these. In all, adenomas were used as a surrogate endpoint for cancer. Only about 10% are likely to progress to cancer; hence, a benefit might be diluted and adenomas are not as precise an end-point as might be imagined. Compliance varies between participants, is hard to measure and to maintain in such large groups (made necessary by the infrequency of the outcomes needed).

<table>
<thead>
<tr>
<th>Cancer</th>
<th>Protection attributed to a healthy diet</th>
<th>Importance of sex hormones</th>
<th>Cases preventable by healthy diet</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast</td>
<td>33–50%</td>
<td>Strong</td>
<td>300,000–455,000</td>
</tr>
<tr>
<td>Prostate</td>
<td>10–20%</td>
<td>Strong</td>
<td>40,000–80,000</td>
</tr>
<tr>
<td>Stomach</td>
<td>66–75%</td>
<td>Weak</td>
<td>670,000–760,000</td>
</tr>
<tr>
<td>Colorectal</td>
<td>66–75%</td>
<td>Weak</td>
<td>580,000–660,000</td>
</tr>
<tr>
<td>All cancers</td>
<td>30–40%</td>
<td>varies</td>
<td>3–4 million</td>
</tr>
</tbody>
</table>

Data derived from reference 2. Gastric cancer is included for comparison but its incidence falls in Western countries with good refrigeration.
Table 7 Summary of dietary intervention studies and colorectal cancer

<table>
<thead>
<tr>
<th>Study</th>
<th>Case diagnosis</th>
<th>Intervention</th>
<th>Duration</th>
<th>Primary endpoint</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>De Cosse et al. (1989) [86]</td>
<td>FAP, total colectomy, &amp; ileorectal anastomosis</td>
<td>Low-fibre supplement (2.2 g/day) + Vit. C (4 g/day) + Vit. E (400 mg/day) vs. High fibre supplement (22.5 g/day) + Vit. C (4 g/day) + Vit. E (400 mg/day) vs. Placebo</td>
<td>4 year</td>
<td>FAP Adenoma regression/occurrence</td>
<td>High-fibre protective only if &gt; 11 g/day Vitamins C, E; trend toward protection</td>
</tr>
<tr>
<td>Toronto Polyp Prevention Group (McKeown-Eyssen et al. 1994) [37]</td>
<td>Previous colorectal adenomas</td>
<td>Placebo</td>
<td>2 year</td>
<td>Sporadic Adenoma recurrence</td>
<td>Intention to treat, no effect Non-significant 50% reduction in women and 90% increase in men with high fibre diet</td>
</tr>
<tr>
<td>Australian Polyp Prevention Project (MacLennan et al. 1995) [38]</td>
<td>Previous colorectal adenomas</td>
<td>Placebo</td>
<td>4 year</td>
<td>Sporadic Adenoma recurrence</td>
<td>Low fat, high fibre decreased recurrence of adenomas &gt; 10 mm (P = 0.03)</td>
</tr>
<tr>
<td>Hofstad et al. (1998) [39]</td>
<td>Previous colorectal adenomas</td>
<td>β-Carotene (15 mg/day) + Vit. C (150 mg/day) + Vit. E (75 mg/day) + Selenium (101 µg/day) + Calcium (1.6 g/day) vs. Placebo</td>
<td>3 year</td>
<td>Sporadic Adenoma recurrence</td>
<td>No effect on polyp growth</td>
</tr>
<tr>
<td>Baron et al. (1999) [40]</td>
<td>Previous colorectal adenomas</td>
<td>3 g/day calcium carbonate vs. Placebo</td>
<td>4 year</td>
<td>Sporadic Adenoma recurrence</td>
<td>Calcium supplementation significantly lowered risk of recurrent adenomas</td>
</tr>
<tr>
<td>European Cancer Prevention Organization Study Group (Bonithon-Kopp et al. 2000) [41]</td>
<td>Previous colorectal adenomas</td>
<td>Calcium 2 g/day + Fibre 3.5 g/day (psyllium) vs. Placebo</td>
<td>3 year</td>
<td>Sporadic Adenoma recurrence</td>
<td>Calcium supplementation was associated with a modest-non-significant reduction in the risk of adenoma recurrence</td>
</tr>
<tr>
<td>Phoenix Colon Cancer Prevention Physicians’ Network (Alberts et al. 2000) [42]</td>
<td>Previous colorectal adenomas</td>
<td>13.5 g/day wheat bran fibre vs. 2 g/day wheat bran fibre</td>
<td>3 year</td>
<td>Sporadic Adenoma recurrence</td>
<td>No effect on adenoma recurrence</td>
</tr>
<tr>
<td>Polyp Prevention Trial (Schatzkin et al. 2000) [43]</td>
<td>Previous colorectal adenomas</td>
<td>Diet low in fat (20% of total calories), + high in fibre (18 g per 1000kcal) + high in fruits and vegetables (3.5 servings per 1000 kcal) vs. Control diet (standard usual diet)</td>
<td>4 year</td>
<td>Sporadic Adenoma recurrence</td>
<td>No effect of diet low in fat and high in fibre, fruits, and vegetables of recurrence of colorectal adenomas</td>
</tr>
</tbody>
</table>
Chemoprevention of cancer

Chemoprevention of cancer can be defined as administration of natural or synthetic agents that delay, slow down or inhibit the process of tumorigenesis. The goals are to reduce incidence and/or decrease mortality of a particular cancer.

There are certain potential advantages when compared with dietary prevention. Bioavailability of the agent can be clearly defined and monitored in similar fashion to a drug. Compliance may be easier as consumption of the agent does not require a change in dietary lifestyle (although it would be desirable to do so). A more potent effect might be possible, making it especially useful for those at increased risk for a particular cancer due to say a family history.

There are, however, several disadvantages. Side-effects might occur, especially as high doses can be easily consumed. Chemopreventive agents might also carry quite unpredictable risks. An example is the possible procoagulant effect of the cyclooxygenase (COX)-2 inhibitor drug (which has been shown to be protective against colorectal cancer). Therefore, safety requires at least equal and probably stronger consideration than efficacy. Chemopreventive agents might be rendered ineffective in the context of an otherwise unhealthy dietary lifestyle and seem unlikely to carry the collateral benefits that a healthy diet brings in that the benefit is much more limited. They are generally more expensive than implementing a healthy diet, even when simply consuming a dietary component such as folate.

Sources and action of chemopreventive agents

In practice, a chemopreventive agent may be a drug (e.g., a non-steroidal anti-inflammatory drug (NSAID), or an antioestrogen drug), a micronutrient (e.g., folate supplement), a macronutrient (such as fish oil) or a component of a food (e.g., a phytochemical), when taken specifically for the purpose. A list of possible chemopreventive agents is shown in Table 8.

These agents have widely varying modes of action and a description is beyond the scope of this review. In simple terms, they may act to reduce the frequency of the mutation events that give rise to the biological changes that initiate tumorigenesis or they may act to retard or normalize the consequential biological events such as increased proliferative activity or disordered apoptosis (programmed cell death).

Chemoprevention and breast cancer

Hormone receptor modulators and breast cancer

The best studied example is the use of the oestrogen receptor modulator tamoxifen for the prevention of breast cancer.

The possibility that breast cancer might be prevented by using antioestrogenic agents has been strongly supported by epidemiological, experimental, and clinical data. Three trials involving over 20,000 women, using tamoxifen 20 mg/day or placebo in healthy women, have so far been reported. One, the American National Surgical Adjuvant Breast Project randomised over 13,000 women to take tamoxifen or placebo and showed a 49% reduction in the early incidence of breast cancer. However, there was an increased risk of antioestrogenic side-effects such as hot flushes, menstrual abnormalities, endometrial cancer, cataract and thromboembolic phenomena. Thus, it is not yet clear if the benefit outweighs the risks. Situations where the benefit of breast cancer risk reduction might outweigh risk of serious side-effects include women with prior oestrogen receptor-positive cancer, women aged over 50 years who have been hysterectomized or perhaps those premenopausal women with a very strong familial risk. It is not yet clear whether tamoxifen can reduce breast cancer incidence in women who have inherited BRCA1 and BRCA2 mutations (and hence are at very high risk). The other two studies, the Royal Marsden and Italian national tamoxifen trials, are not yet completed.

There are several important principles to be drawn from these trials. Achievable reductions in risk using a single agent are significant – here they are close to a 50% reduction. But there is a real likelihood of a cost in terms of side-effects that may derive directly from the very action that suppresses the cancer. Thus very large studies are needed to be sure of the risk:benefit ratio. It will be necessary to carefully identify those subgroups in which the benefit outweighs the risk. Those who have a higher risk than the general population may stand to benefit most and might be best in whom to target a chemopreventive approach.

It is difficult to compare such benefit to those that might be achieved by dietary means. One might expect a dietary

<table>
<thead>
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<th>Table 8. Examples of potential chemopreventive agents</th>
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<td>Hormone receptor modulators(^5)</td>
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<tr>
<td>Phytochemicals(^1)</td>
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<tr>
<td>Micronutrients(^1)</td>
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<tr>
<td>Others(^5)</td>
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Chemoprevention in prostate cancer
Androgenic stimulation over a period of time has been suggested to be a cause of prostate cancer. The corollary to this is that lowering androgenic stimulation over time, i.e., androgen deprivation therapy, will prevent prostate cancer. Decreasing androgenic stimulation of the prostate with 5-alpha-reductase inhibitors such as finasteride has been shown to decrease prostate size. A large, long-term clinical trial is now underway using finasteride to determine if it can prevent prostate cancer, with results expected in 2004. Of particular concerns for this type of prevention are anti-androgenic side-effects and the emergence in a tumour of androgen resistance.

A randomized double-blind trial designed to determine whether selenium and vitamin E decrease the risk of prostate cancer in healthy men is currently underway in view of the epidemiological evidence. Similar evidence suggests that increased intake of phyto-oestrogens and vitamin D as well as vitamin E and selenium could be protective and some of these appear to have an antitumour action even in the presence of androgen resistance.

Chemoprevention of colorectal cancer
A very broad range of agents, especially food-derived, have been considered as candidates for chemoprevention of colorectal cancer (many of those listed in Table 8). To date, formal interventional studies have been limited to just a few with NSAIDs, folate, selenium, β-carotene and vitamin C being amongst the most studied (see Table 7).

Folate and chemoprevention
Folate shows considerable promise. Epidemiological studies consistently show an inverse association between folate intake (and/or levels) and the frequency of colorectal neoplasms. The greatest benefit comes from long-term use of supplements of folate over and above dietary intake. Initial studies using surrogate endpoints are underway but it will be some years before we have a clear idea of its value. Folate perhaps has collateral benefits with protection against other cancers.

NSAIDs and protection against colorectal cancer
Of 32 epidemiological studies, 30 show a relationship between an apparent protective effect and NSAID usage, for both adenomas and cancers.101 With aspirin, most studies suggest that at least 600 mg/day is required to be effective. NSAIDs restore apoptosis to normal in human colorectal neoplasms and in various cancer cell lines where adenomatous polyposis coli (APC) gene function has been lost.102 The NSAIDs represent an example of molecular-targeted chemoprevention, as cyclooxygenase is active in tumours, it increases prostaglandin levels and inhibits apoptosis, or programmed cell death, an important mechanism for removing genetically damaged cells.

Most interventional studies to date have been carried out in patients with a propensity to develop adenomas due to an inherited mutation of the APC gene. These patients, who have familial adenomatous polyposis or FAP, develop colorectal cancer in almost 100% at average age 35 years. Randomised studies have shown that the NSAID sulindac103–105 and the selective COX-2 inhibitor celecoxib, induce regression in adenomatous polyps in FAP patients. Perhaps surprisingly, in the most recent study sulindac does not prevent development of new adenomas in these patients. Furthermore, those on sulindac long-term are known to develop resistant adenomas.106 Celecoxib has been evaluated in a randomised study of 77 patients with FAP. At the high dose of 400 mg/day, there was a significant reduction in the number of polyps.107 COX-2 inhibitors are safer in terms of less gastric ulceration and GI bleeding but there is slight concern about a possible prothrombotic potential.94

APC mutations also occur commonly (50–80%) in sporo-
dadic (i.e., not inherited) colorectal cancer. Whether there are lessons about NSAID usage in preventing progression of sporadic colorectal adenomas to cancers is yet to be deter-
mined but trials are underway. The evolution from adenom-
atous polyp to invasive cancer takes 4–11 years.108 Hence, for them to be effective, chemopreventive agents may need to be taken for prolonged periods and must be devoid of side-
effects. Even rare, but serious, toxicity can offset the benefit of treatment, when the drug is administered to healthy people with a low annual risk of developing colorectal cancer.102

There are a range of well known adverse events in those taking NSAIDs, the most important of which are GI ulceration and bleeding.101 There is a three-fold increased risk of GI bleeding in those on just 150–300 mg aspirin/d and the chance of haemorrhagic stroke is increased. At this stage, NSAIDs as chemopreventive agents for colorectal cancer cannot be recommended at present for average-risk individ-
uals or for those with sporadic colorectal neoplasia. Use of COX-2 inhibitors in high-risk groups and especially FAP is justified, however.

Screening and the prevention of cancer
Screening is defined as the testing of an individual for a disease when that individual does not have any symptoms or signs suggesting that the disease is present. The goal is to prevent or delay the development of the cancer, or to alleviate the consequences of it. It is generally agreed that the most important measure of this goal is a reduction in mortality from the cancer in question. From an operational perspective, as shown in Table 2, the target is detection and removal of precancer lesions or curable cancer.

For a cancer to be considered as possibly appropriate for screening, it should meet certain criteria defined by WHO that can be summarized as follows:109
1. It is a serious problem in the target community and is not rare.
2. It is curable especially when detected early.
3. The preclinical phase (when curable) is detectable.
4. Treatment in the preclinical phase gives better outcomes than when treated later.

In a Western-style country such as Australia, breast, prostate, and colorectal cancer meet these criteria. Hence, the most pertinent issues to be addressed are whether there is evidence that screening reduces mortality, the feasibility of screening and its cost-effectiveness. These issues will be addressed in turn for each of the three main Western cancers.

The process of screening has the following steps:110
1. Approach those in the population perceived to be at sufficient risk.
2. Invite participation in the screening test.
3. Perform the screening test, which is normally simple and inexpensive.
4. Use result of the screening test to identify those who should undertake the diagnostic procedure.
5. Ensure that appropriate diagnostic follow-up is complied with.
6. Ensure adequate subsequent treatment for what ever condition is identified.
7. Re-offer the screening test at an appropriate future interval.

Screening is thus expensive and resource intensive for any cancer. It also requires public education and exposure to increase awareness so that the majority participate, but with the risk that people might over-estimate its value and importance. Beyond politics and public opinion, it therefore requires the highest standard of proof, even more than for the treatment of disease, since the target population perceive themselves as healthy. Proving benefit requires us to establish that health is improved rather than that disease is alleviated!

**Screening for colorectal cancer**

There are various tools that can be used.111 Those to be discussed briefly here include faecal occult blood tests (FOBT) and colonoscopy. Faecal occult blood tests work by detecting microscopic (‘occult’) blood in faeces; cancers especially but some adenomas (the benign precancer lesion that may take the shape of a polyp in the colon or rectum) show occult bleeding in the preclinical, and curable, phases. Colonoscopy acts to directly visualize either cancer or adenomatous polyps and so allow their biopsy for diagnosis or removal (in the case of most polyps). Both thus direct us to the relevant targets (Table 2).

**Screening for colorectal cancer by FOBT** All three finalized, randomised controlled trials of screening by FOBT have shown that it is effective in reducing mortality at the population level on an intention-to-screen basis.112–114 Depending on the type of FOBT and frequency of use (annual or biennial), mortality is reduced on an intention-to-screen basis by 15–38%. In those who actually do the test, mortality is reduced by at least 40%.113

When a positive test result occurs (i.e. it shows the presence of microscopic blood in the stools), it is essential that a full diagnostic evaluation of the large bowel is undertaken, usually, and best, done by colonoscopy.111 Thus, access to good clinical facilities are necessary and FOBT should not be undertaken if these are not available. FOBT acts to select out those in the general population who are more likely to have a curable cancer.110 However, they may miss cancers, perhaps 10–50%, depending on the exact test used.110–114 But even with this problem, they do reduce mortality at the population level. Furthermore, because they are simple and easily done at home, people will do them and participation rates up to 70–80% are achievable.112–115 National screening programs are run in Germany and Japan, reimbursement is available in many countries and pilot national programs are underway in Australia and the UK.110

With the older guaiac-based FOBT, which were the basis of the randomised controlled trials, there were problems with interference by diet and drugs, although these can now be overcome by using the new immunochemical tests.111,115 FOBT, while reasonably good at detecting curable cancer, are less effective at detecting adenomas.111 Clearly if we could effectively detect and hence remove adenomas, we would reduce not just the mortality from colorectal cancer but also the incidence of the disease.

**Screening for colorectal cancer by colonoscopy** Colonoscopy adds the dimension of more reliable detection of adenomas in addition to better sensitivity for cancer.116 However, it is invasive and expensive, and is often reserved as the first test for those who are at increased risk for colorectal cancer.117 The commonest causes of increased risk are family history and/or personal history of cancer or adenomas. While there is no evidence from randomised controlled trials that colonoscopic screening works (and hence the true magnitude of complications in this setting and the degree to which they negate the value are not clear), there is less direct evidence that it is of value. This includes case-control studies in high risk groups118 and cohort studies of the value of polypectomy.119

From the perspective of a population approach, its cost is high and acceptance is likely to be low. For the individual, it is invasive and inconvenient. While the risk is small, about 1–2 major complications per 1000 procedures112 these are not inconsequential if colonoscopy is applied to large numbers of people.

**Cost-effectives of screening for colorectal cancer** The best way to test this is by calculation of cost-per-life-year-saved (CPLYS). FOBT screening is clearly cost-effective in Australia, at about $20 000–40 000 CPLYS, and comparable to screening for breast cancer.120 Indeed, despite the up-front expense of colonoscopy, it also seems cost-effective.121

**Screening recommendations for colorectal cancer** While recommendations differ a little around the world, it is considered justifiable to commence screening of the general population at age 50 years and at least by annual or biennial FOBT.117 High risk groups may justifiably be offered colonoscopy and there is an increasing view that colonoscopic screening of the average risk population may be justified.
Breast cancer

Mammography is the main method for screening although manual breast examination (by self or a professional) does add value. Mammography acts by radiological identification of cancer or premalignant lesions termed ‘DCIS’ (ductal carcinoma in situ). About half the cancers found are DCIS and a significant proportion of the rest are of limited extent. A mammographically identified lesion requires biopsy confirmation before surgical excision although these may often be done in sequence at the one session.

Breast cancer screening by mammography

There have been seven reported randomised controlled trials of screening mammography with mortality as the outcome measured on an intention-to-screen basis. Benefit, when shown, was confined to women aged 50–70 years although the studies were not large enough individually to reach a conclusion about those in the younger age groups.

Two of the seven studies showed significant protection with mortality reductions of 31% and 35% in 50–70 years olds. Four of the seven showed a non-significant trend. Two different meta-analyses of all the data from all the trials shows a significant reduction in mortality of 23% and 24%.

Potential hazards of breast cancer screening

Compared with FOBT screening for colorectal cancer, mammography is a ‘better’ test as its miss rate on the first screen is about 7–17% depending on age. False-positives occur at a rate of about 6–10%; most of those with a ‘positive’ mammogram do not have a cancer and the positive predictive value is in the range 4–18%. False-positives lead to anxiety, unnecessary biopsies and perhaps surgery, and additional costs. There is also the potential for radiation exposure actually giving rise to breast cancer; while the risk is small, it must be considered if screening is started before age 50.

Feasibility and cost-effectiveness of breast cancer screening

In the true population studies, compliance was 60–80% and this level is often achieved now in Australian populations. Hence, it is feasible. It is also cost-effective when judged by CPLYS calculations with estimates around $22 000.

Natural history of breast cancer

It is generally felt that the early stage of disease where dysplastic cells are confined to glands without invasion (‘DCIS’ – ductal carcinoma in situ), progresses to malignancy over 5–10 years. It remains controversial as to the ‘natural’ history of DCIS and there is a view that perhaps only 30% will progress to malignancy.

Recommendations for screening for breast cancer

In many countries, and while the detail may vary, recommendations are that women aged 50–70 or 75 years be screened at least on a biennial basis. Screening in older women is acceptable if life expectancy is good and there are no other major health problems. For screening in younger women (aged 40–50 years), the concerns are cost-effectiveness and drop out with time, but it seems reasonable especially in those with a family history.

Screening for prostate cancer

Prostate cancer is common in men, especially as they age and it presents a significant burden to health services. The purpose of screening for prostate cancer is to identify cancers that are potentially curable. To ensure that a program satisfies the requirement that it should do more good than harm, especially in terms of mortality and quality of life, several conditions need to be met.

First, we need to know more of the natural history. Prostate neoplasms range from small, slowly growing lesions to rapidly advancing tumours but with regard to the early lesions, there is controversy about which screen-detected lesions will become clinically significant and hence justify the efforts of detection and removal.

Second, the test should have adequate sensitivity and specificity. Measurement of serum prostate specific antigen (PSA), followed by transrectal ultrasound and biopsy, is the usual approach but concerns remain about adequacy of specificity and sensitivity.

Third, it is not clear if early treatment of early lesions is any better than just observing them. Of the two treatment options for localized disease: radical prostatectomy or radical radiotherapy, there is no randomised controlled trial evidence to suggest a survival advantage of these treatments above simple observation and treatment if progression becomes evident. Each treatment has risks and cost:benefit ratio is unclear.

When a man requests prostate screening, it is recommended that they be assisted by providing a balanced presentation of the known risks and potential but unproven benefits of detection and treatment options.

Overview of the effectiveness of screening

Table 9 summarizes the state of the evidence about key features of screening for each of these three cancers. It can be readily seen that population screening for breast or colorectal cancer is justifiable. While the evidence is less compelling for prostate cancer, it is fairly widely practised around the world.

Comparing chemoprevention with screening

A comparison of the main features of each is summarized in Table 2. There are various approaches to the means by which operational outcomes can be compared head-to-head. The ideal would be formal study in randomised or cohort populations where each approach were compared side-by-side. Unfortunately, such studies would involve large numbers, take a long time and be very expensive. Policy-makers will need to make decisions using less robust information of which unfortunately, there is little. However, in the case of colorectal cancer prevention, there has been a specific
attempt to compare cost-effectiveness of aspirin usage and colonoscopic screening. Suleiman et al.\textsuperscript{132} used a Markov process to compare four strategies: (a) no intervention; (b) colonoscopy once per 10 years and every 3 years in subjects with adenomas; and (c) chemoprevention with 325 mg of daily aspirin. Comparison was performed by calculating incremental cost-effectiveness ratios (ICER). In cohorts of 100,000 subjects, colonoscopy prevented 4400 cancers and saved 8000 life-years at an ICER of $11,000 per life-year saved compared with no intervention. Aspirin prevented 3000 cancers and saved 5300 life-years at an ICER of $50,000 per life-year saved compared with no intervention. They concluded that the high complication cost and the lower efficacy of aspirin made screening colonoscopy a more cost-effective strategy to prevent colorectal cancer.\textsuperscript{132}

Overall conclusions

More extensive comparisons on a formal basis, such as comparing dietary intervention with screening, will be very difficult. The prime targets tend to be different. Diet is likely to reduce incidence and hence reduce mortality with a long lead-time, perhaps as much as 20–30 years. Screening may reduce mortality in a lesser time-frame, say 5–15 years, with reductions in incidence only coming later.

A consideration of the key differences summarized in Table 2, plus the unlikelihood of ever being able to do head-to-head studies with mortality as the end-point, mean that one has to think strategically when developing policy.

Prevention of Western cancers by dietary lifestyle should be safe and inexpensive. Its potential is excellent and it is likely that there is collateral benefit such as reduced cardiovascular disease and osteoporosis. But, population compliance with plant-more based, less calorie dense foods is uncertain, the most healthy are likely to be the most compliant and evidence for effectiveness when applied to cancer-related end-points is deficient. In addition, it is not clear how dependable the dietary approach would be in high risk settings such as a family history of breast or colorectal cancer. The biggest challenge is to demonstrate that populations will do what they should do.

Chemopreventive approaches are still under development and study. These agents may be simpler to comply with and they may be more potent and hence of particular value in high-risk settings. But they are likely to be more costly and run the risk of adverse effects with perhaps few collateral benefits. It is justified though to pursue such options.

Screening for colorectal and breast cancers is proven to be effective and feasible at the population level. Screening has the advantage of being effective in high-risk as well as average-risk groups and is an ‘easy’ solution for the person who elects not to follow a healthy dietary lifestyle. Nonetheless, it is expensive, demanding on resources, provides no collateral benefits and does not have the same potential to reduce incidence of disease as does the dietary approach. Perhaps it is fortunate though for the human nature that screening is available.

With these Western cancers, we are fortunate that there are options for prevention. At least choices are available and some will suit certain circumstances and personalities more than others.

References


Preventing cancer: diet or screening? S631