Prospects for chemoprevention of cancer


The recent progress in molecular biology and pharmacology has increased the likelihood that cancer prevention will rely increasingly on interventions collectively termed ‘chemoprevention’. Cancer chemoprevention is the use of agents to inhibit, delay or reverse carcinogenesis. A number of potential targets for chemoprevention have recently been identified. Many classes of agents including antioestrogens, anti-inflammatories, antioxidants and other diet-derived agents have shown a great deal of promise. In this review, we will begin by describing the general classes of chemopreventive agents and the mechanisms by which these agents act. We will then describe the opportunities that presently exist for chemoprevention of specific cancers.

Keywords: anti-inflammatories, antioestrogens, antioxidants, cancer, chemoprevention, diet-derived agents.

Introduction

Cancer, currently the second leading cause of death in the western world, may outrank cardiovascular diseases in the US and other developed countries in a few decades [1–3]. The recent progress in molecular biology and pharmacology has increased the likelihood that cancer prevention, either primary or secondary, will rely increasingly on interventions collectively termed ‘chemoprevention’.

Cancer chemoprevention is the use of agents to inhibit, delay or reverse carcinogenesis. The progression towards invasive cancer is characterized by accumulation of mutations and increased proliferation. Because carcinogenesis is a multistage process and often has a latency of many years or decades, there is considerable opportunity for intervention. Molecular advances have led to the identification of genetic lesions and other cellular components, which may be involved in the initiation and progression of malignancies, and constitute potential targets for chemoprevention. As most cancers are likely to be associated with mutagens and/or mitogens, focusing on compounds that may inhibit or reverse either of the related processes may be crucial in the search for chemotherapeutic agents.

Chemoprevention has obvious common elements with chemotherapy, but also distinct differences. Thus, chemoprevention focuses on reduction of incidence and is related to classical epidemiology, whereas chemotherapy focuses on prognosis and is related to clinical epidemiology. Chemotherapy can
be either systemic or, in certain cases, localized, whereas chemoprevention is almost always systemic. In chemotherapy the outcome is generally a high frequency event (like death or metastasis), whereas in chemoprevention it is usually of low frequency (incident cancer cases); this is reflected in the required sample size in the corresponding studies. Last, chemotherapy is applied to seriously ill patients, for whom side-effects, even serious ones, may be acceptable, whereas chemoprevention is generally administered to healthy people for whom serious side-effects are unacceptable.

Several models have been developed to outline the pathways through which carcinogenesis may occur. These include the Vogelstein model for colon cancer [4], as well as models for cancer of the head and neck [5, 6], brain [7], bladder [8, 9] and lung [5, 10]. Valid models of cancer progression facilitate the identification of intermediate biomarkers. By serving as surrogate end-points, such markers are pivotal in identifying chemopreventive agents. The use of early markers of carcinogenesis allows chemopreventive studies to focus on stage arrest or reversion following treatment [11].

Many classes of agents have shown promise as chemopreventive agents. These include antioestrogens, anti-inflammatories and antioxidants, and other diet derived agents. In this review, we will begin by describing the general classes of chemopreventive agents and the mechanisms by which these agents act. We will then describe the opportunities that presently exist for chemoprevention of specific cancers.

Chemopreventive agents

Antioestrogens and antiandrogens

Sex steroid hormones have been implicated in the aetiology of a number of cancers including breast, endometrium, prostate, testis, ovary, thyroid and others [12]. These hormones are growth factors favouring cell proliferation, thus increasing the potential for mutations. Interruption of the hormonal stimulus is believed to slow the proliferation of cells and the progression of hormone-related cancer. Therefore, antioestrogens, aromatase inhibitors and 5-α reductase inhibitors are obvious candidates for chemoprevention of steroid-related cancers.

Tamoxifen and raloxifene are both selective oestrogen receptor modulators (SERMs). These compounds have different effects in different tissue types. In the breast, both of them act as oestrogen antagonists, by inhibiting the proliferative effects of oestrogens [13]. SERMs, however, can also act as oestrogen agonists in specific tissues by enhancing the growth promoting effects of oestrogens [13]; thus, raloxifene is considered beneficial against osteoporosis.

Studies of prostate biology have identified androgenic stimulation as a permissive factor for the development of both benign prostate hyperplasia and cancer. Thus, factors involved in the production, activation and transport of androgens have been considered potential targets for chemoprevention. Dihydrotestosterone (DHT) is considered the principal androgen. This has led to the hypothesis that suppressing DHT synthesis may inhibit prostate enlargement and possibly carcinogenesis. 5-α-reductase is the enzyme, which converts testosterone to DHT. Hence, inhibitors of this enzyme, such as finasteride and turosteride, have a potential as chemopreventive agents.

Anti-inflammatories

It has long been suspected that inflammation is intimately linked to carcinogenesis. Thus, agents with anti-inflammatory properties, such as nonsteroidal anti-inflammatory drugs (NSAIDs), including aspirin, piroxicam and indomethacin are likely to exert chemopreventive action [14, 15]. A number of human observational studies have supported the hypothesis that regular aspirin use reduces the risk of colorectal cancer by about 50% [16, 17]. Both in vitro and in vivo models suggest that NSAIDs inhibit colon tumours through induction of apoptosis, i.e. programmed cell death [18].

Cyclooxygenases (COX-1 and 2) have been identified as important enzymes necessary for the synthesis of inflammatory prostaglandins from arachidonic acid. Overexpression of COX-2 is believed to be an early event in colon carcinogenesis and the development of other epithelial tumours [19]. NSAIDs are known to inhibit these enzymes. Moreover, selective inhibitors of COX-2 have been developed and these may play a beneficial role in modulating carcinogenic processes.
Table 1 Summary of study design and results of major randomized cancer chemoprevention trials

<table>
<thead>
<tr>
<th>Intervention Study</th>
<th>Supplementation</th>
<th>Design</th>
<th>Summary of Results</th>
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<tbody>
<tr>
<td>Nutritional Prevention of Cancer study group [48, 142]</td>
<td>Oral administration of 200 µg of selenium per day versus placebo</td>
<td>Multicentre double blind randomized control trial. 1312 patients treated for a mean of 4.5 years</td>
<td>Selenium did not protect against carcinoma of the skin. In the treatment group, there was a significant 63, 46, 58 and 37% reduction in prostate, lung, colorectal and total cancer incidence, respectively.</td>
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<tr>
<td>Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study (ATBC) [40, 122]</td>
<td>50 mg day(^{-1}) a-tocopherol alone, 20 mg day(^{-1}) (\beta)-carotene alone, both, or placebo</td>
<td>Large, randomized, double blind studies 29 133 male smokers</td>
<td>A statistically significant 18% increase in lung cancer amongst men receiving (\beta)-carotene compared with those who did not. Fewer cases of prostate cancer were detected amongst men receiving a-tocopherol.</td>
</tr>
<tr>
<td>The Carotene and Retinol Efficacy Trial (CARET) [28, 29]</td>
<td>30 mg day(^{-1}) (\beta)-carotene and 25 000 IU retinyl palmitate versus placebo</td>
<td>Large, randomized, double blind studies 18 314 men and women smokers, former smokers, men exposed to asbestos</td>
<td>A statistically significant 36% increase in lung cancer incidence amongst men receiving treatment compared with those on placebo.</td>
</tr>
<tr>
<td>Linxian, China Trials [108, 119, 120]</td>
<td>Retinol and zinc; riboflavin and niacin; vitamin C and molybdenum; (\beta)-carotene, vitamin E and selenium. Doses ranged to 1–2 times the US FIA</td>
<td>Randomized 29 584 adults in Linxian County, China</td>
<td>(\beta)-Carotene, vitamin E and selenium were associated with a statistically significant 21% reduction in gastric cancer incidence.</td>
</tr>
<tr>
<td>Physicians Health Study [160]</td>
<td>(\beta)-Carotene, aspirin, versus placebo</td>
<td>Randomized more than 22 000 US male physicians</td>
<td>Failed to detect a significant difference in colon cancer incidence.</td>
</tr>
<tr>
<td>Polyp Prevention Study [167]</td>
<td>1200 mg of elemental calcium versus placebo</td>
<td>930 subjects randomized with recent adenomas</td>
<td>A statistically significant 19% reduction in incidence of colon adenomas.</td>
</tr>
<tr>
<td>Phoenix Colon Cancer Prevention Physicians' Network [155]</td>
<td>High fibre (13.5 g day(^{-1}) of wheat-bran fibre) or low fibre (2 g day(^{-1}) of wheat-bran fibre) diet</td>
<td>Randomized 1429 men and women, who had one more adenoma removed within 3 months prior to recruitment</td>
<td>No statistically significant difference in adenoma recurrence rates between the two groups.</td>
</tr>
<tr>
<td>Breast Cancer Prevention Trial (part of the National Surgical Adjuvant Breast and Bowel project) [99]</td>
<td>20 mg tamoxifen versus placebo</td>
<td>Double blind randomized control trial. 13 388 high risk women</td>
<td>A statistically significant 49% reduction in breast cancer incidence. A significant 69% reduction in oestrogen receptor positive tumours. No significant difference on BR-tumours.</td>
</tr>
<tr>
<td>MORE Raloxifene Trial [104]</td>
<td>60 mg raloxifene, or 120 mg raloxifene versus placebo</td>
<td>Randomized 7705 normal risk, osteoporotic postmenopausal women with normal breast cancer risk</td>
<td>A statistically significant 65% reduction in breast cancer incidence.</td>
</tr>
<tr>
<td>Italian Tamoxifen Trial [101]</td>
<td>20 mg tamoxifen versus placebo</td>
<td>5408 normal risk women with normal breast cancer risk and hysterectomy</td>
<td>No appreciable difference in breast cancer risk with treatment.</td>
</tr>
<tr>
<td>Royal Marsden Hospital Tamoxifen Trial [100]</td>
<td>20 mg tamoxifen versus placebo</td>
<td>2471 women with high breast cancer risk</td>
<td>No appreciable difference in breast cancer risk with treatment.</td>
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</table>
Diet-derived agents

Agents derived from dietary sources have an inherent appeal for chemoprevention aimed at healthy populations, as they can be taken for long periods of time with simple dietary modification and no apparent health risk. Many diet-derived agents are currently being evaluated for potential chemopreventive activity. These agents, several with antioxidant properties, will now be reviewed.
Antioxidants

Antioxidants are compounds used by aerobic organisms for protection against oxidative stress, induced by free radicals and active oxygen species. They exert their protective action either by suppressing the formation of free radicals or by scavenging free radicals [20]. A wide range of biological effects, established experimentally, may inhibit carcinogenesis. These include effects on tumour initiation, promotion and progression, cell proliferation and differentiation, as well as DNA repair, cell membrane stability and immune function [20, 21]. Diet derived antioxidants such as carotenoids, vitamins C and E and selenium have received much attention as potential cancer chemopreventive agents.

Carotenoids. Carotenoids are fat-soluble compounds classifiable as xanthophylls, carotenes or lycopene. Over 600 carotenoids occur in nature and, amongst them, the most commonly available in human diet is β-carotene. Carotenoids, found in large quantities in green and yellow leafy vegetables, have in addition to antioxidant, other beneficial properties [21]. Moreover, these compounds are relatively nontoxic. Observational epidemiologic studies are fairly consistent in indicating a protective effect of carotene-rich vegetables, β-carotene, or in a few instances one or more other carotenoids, on cancers of the lung, oesophagus, stomach, colorectum, cervix, oropharynx and prostate [22–25]. Yet, it is unclear how much of this effect could be attributed to replenishment of these vitamins in deficient populations [26, 27] or to confounding by other compounds with cancer chemopreventive potential.

Hopes that carotenoids could become a valuable weapon against cancer, however, were dealt a blow from the results of two major randomized trials that failed to demonstrate preventive effectiveness of these compounds against lung cancer amongst high-risk individuals, like elderly smokers [28, 29]. These trials and other major chemoprevention trials are summarized in Table 1.

Vitamin C. Vitamin C, a water-soluble vitamin, is an important free radical scavenger in plasma and acts to regenerate active vitamin E in lipid membranes. Vegetables, citrus fruits and tubers are good sources of vitamin C. Although several different factors in fruits and vegetables probably act jointly, the epidemiologic and biochemical evidence indicate an important role for vitamin C [30]. The evidence for a protective effect of vitamin C is strong for cancer of the stomach, and upper aerodigestive track and weaker for other forms of cancer [20, 21].

Vitamin E. Vitamin E, a fat-soluble vitamin, is the major lipid-soluble antioxidant of the cell membrane. It acts as a free-radical scavenger and inhibits peroxidation [31]. It has been reported to block the in vivo formation of N-nitroso compounds [32] and suppress chemically induced tumours in experimental animals [33]. α-Tocopherol is the most active amongst the tocopherols and tocotrienols with vitamin E activity. Vegetable oils, whole-wheat products and nuts are amongst the best sources of vitamin E.

Overall, observational epidemiological studies suggest a protective effect of vitamin E against cancers of the lung [34, 35], colorectum [36] and the cervix [37–39]. In the context of the α-Tocopherol, β-Carotene Cancer Prevention Study (ATBC) randomized intervention study [40], an inverse association between vitamin E intake and cancers of the lung, colorectum and prostate was also reported.

Selenium. Selenium is a trace element and an essential cofactor for the major antioxidant enzyme glutathione peroxidase, which catalyses the oxidation of hydroperoxides [41]. Selenium is also involved in cell signalling and immune response processes [42], which may contribute to its cancer chemopreventive potential. Selenium and vitamin E may mutually compensate deficiency of each other and act synergistically to inhibit carcinogenesis [43, 44]. The amount of selenium that appears in our diet is determined by the selenium content of the soil in which fruits and vegetables are grown. Seafood, liver and meat are also good sources of selenium.

In animal models, selenium has been shown to be antitumourigenic when administered at high doses [45]. Ecological studies originally indicated that there may be an inverse association between selenium levels and cancer overall, as well as cancer of the breast, pancreas, ovary, colon, lung and cervix and pancreas [46]. Results from analytical epidemiological studies remain inconclusive, with observational studies supportive of a protective role of selenium against cancers of the lung, liver and...
stomach, and one randomized controlled trial indicating an inverse association of selenium with cancers of the lung, colon and prostate [47, 48].

**Flavonoids.** Flavonoids are phenolic compounds with anticarcinogenic [49, 50], tyrosine kinase [51, 52] and aromatase-inhibiting [53, 54] properties. Tea polyphenols, in particular, are strong scavengers of superoxide, hydrogen peroxide, hydroxy radicals and nitrogen oxides [55] and may enhance the levels of antioxidant enzymes such as catalase [56]. Flavonoids are found in fruits, vegetables and tea leaves.

A number of animal studies have demonstrated that catechins, the main flavonoids found in tea leaves, prevent induction of cancers of the lung [57], the colon [58], the oesophagus [59, 60], the pancreas [61, 62], the liver [63, 64] and the mammary gland [65, 66]. Observational studies in humans have generated conflicting results, and long-term population studies are now being considered [67–69].

**Isoflavones.** Isoflavones, found mainly in soy products, are structural isomers of flavonoids and share biological properties with them. They have antioestrogenic effects [70], and thus could act as chemopreventive agents in hormone dependent cancers. Genistein, a prominent isoflavone in soy products has also been shown to induce apoptosis *in vivo* [71]. Epidemiologic studies suggest that women and men in Asian countries consuming high amounts of soy products may be at lower risk for breast cancer and prostate cancer, respectively [72].

**Curcumin.** Curcumin is a plant phenol widely used as a spice (curry) and food-colouring agent. *In vivo* and *in vitro* studies have demonstrated that it may prevent initiation of DNA damage and is involved in antipromotion mechanisms such as apoptosis [73, 74]. A number of animal studies have shown that curcumin is effective in inhibiting carcinogenesis in the skin [75, 76], colon [77, 78], oral cavity [79], stomach [77, 80] and mammary gland [81, 82]. Results from human trials have not been reported.

**Other diet-derived agents**

**Retinoids.** The best known retinoid is vitamin A or retinol, found in foods of animal origin, such as liver, milk and dairy products, egg yolk and fish liver oils, but there are also several synthetic compounds [21]. Retinoids are required for the maintenance of normal cell growth and differentiation. In contrast to carotenoids, they act primarily in the postinitiation phases of promotion and progression [20]. Retinoids do have known limitations, in that they may be toxic at therapeutic levels and would require lifetime use for protection [83, 84].

Various retinoids have been shown to suppress or reverse epithelial carcinogenesis at several sites in many animal systems. Several chemoprevention trials have been undertaken or are ongoing. The most promising results have been reported for oral carcinogenesis [85, 86].

**Vitamin D.** 1,25-Dihydroxyvitamin D3 (1,25-D3) is the active form of the fat-soluble vitamin D. Major dietary sources of vitamin D include liver, fatty saltwater fish and eggs. Vitamin D inhibits proliferation and DNA synthesis, alters expression of several oncogenes, reduces lipid peroxidation and angiogenesis and induces differentiation [87].

Epidemiologic studies support an inverse association between vitamin D intake and colorectal cancer risk [21] and have also shown that vitamin D3 deficiency [88], and low plasma levels of 1,25-D3 [89, 90] increase the risk for prostate cancer. The overall evidence, however, remains insufficient.

**Folic acid.** Folic acid is abundant in many of the fruits and vegetables that are rich in carotenoids. Together with vitamin B12, methionine and choline, it is involved in methyl group metabolism. Much of the basic cancer research has focused on DNA methylation, and hypomethylation has been associated with DNA abnormalities [91]. An inverse association between dietary folate intake and adenomatous polyps or colorectal cancer has been reported in both case–control [92] and cohort studies [93].

**Chemoprevention at specific cancer sites**

**Oral cavity and other head and neck tumours**

Head and neck cancers account for 2–3% of all cancers worldwide [94, 95]. Most head and neck cancers are found in the oral cavity and more than two-thirds of oral cancer cases can be attributed to tobacco, either alone or in concert with alcohol [3].
Cancers of the head and neck are almost always preceded by precursor lesions, such as leukoplakia, which can easily be visualized with examination of the oral cavity. Precancerous lesions have been useful surrogate markers for the effect of chemopreventive agents.

Early studies looking at retinoids and β-carotene indicated that these agents have considerable potential for chemoprevention of oral cancer [83, 85, 96]. Enthusiasm, however, has been curtailed by a number of factors, such as variability in the reported efficacy of the evaluated agents, inability to distinguish between replenishment effects in deficient populations and monotonic exposure response across various dose levels [27], and difficulty to accommodate the required long-term administration of the compounds, particularly in view of their limited but established toxicity [83, 84]. Currently, a number of synthetic retinoic acid derivatives, vitamin E and NSAIDs are being studied to determine efficacy and safety.

Breast

Epidemiologic studies have identified a number of component causes of breast cancer, most of which are either difficult to modify (reproductive variables), or require drastic to ethically questionable interventions (preventive mastectomy in breast cancer gene carriers). For this reason, scientific interest has shifted to chemoprevention as a means of primary prevention of breast cancer.

After observing a reduction in risk of contralateral breast cancer amongst women with tamoxifen treatment, it was suggested that tamoxifen may have the potential to prevent breast cancer [97, 98]. Results concerning the efficacy of tamoxifen as a chemopreventive agent for breast cancer have been reported from three randomized trials (summarized in Table 1) [99–101]. Cuzick et al. conducted a meta-analyses of the available data and found that the results are compatible with a 42% reduction in incidence of breast cancer, which is restricted to oestrogen receptor positive cases [102]. An increased risk for endometrial cancer, stroke and deep vein thrombosis are listed amongst the potential side-effects of tamoxifen [99, 103].

Raloxifene, a newer SERM intended for prevention of osteoporosis may be at least as effective as tamoxifen in preventing breast cancer and, unlike tamoxifen, does not appear to increase the risk for endometrial cancer. Yet it appears to share with tamoxifen the side-effect of thromboembolic events [102, 104]. Finretidine, a vitamin A analogue, has also been examined as a chemopreventive agent for breast cancer. A recent randomized control trial detected no difference between treated and untreated women, although data suggest a possible benefit in premenopausal women [105].

Stomach

Although the rates of stomach cancer have been decreasing, it remains the second most common cancer worldwide, after lung cancer. Asian countries have high incidence rates of gastric cancer [94]. Analytical epidemiological studies have highlighted several important risk factors including diets poor in fresh fruits and vegetables, and high in salt [106]. Infection with *Helicobacter pylori* is thought to play a key role in the majority of gastric cancer cases [107]. The multifactorial nature of gastric cancer provides diverse opportunities for intervention. In a number of studies, increased intakes or plasma levels of β-carotene and vitamin C were inversely associated with gastric cancer. The Linxian study (summarized in Table 1) in China is a randomized control trial to study the effect of supplementation with multiple micronutrients on the incidence of cancer. This study revealed a 21% decrease in gastric cancer mortality amongst participants receiving β-carotene, vitamin E and selenium [108]. As there are limited methods of screening for gastric cancer and eradication of *H. pylori* infection is currently unrealistic, chemoprevention, as well as salt reduction, may represent effective ways for controlling gastric cancer.

Liver

Most cases of primary liver cancer are hepatocellular carcinomas (HCC). The majority of cases of HCC in Africa and Asia are linked to chronic infection with hepatitis B (HBV) and/or hepatitis C (HCV) virus and perhaps to aflatoxin contamination of foods [109, 110]. In economically developed countries, however, alcohol drinking and tobacco smoking may be responsible for most cases, although in about 50% of them no obvious cause is epidemiologically identifiable [111, 112]. Evidence concerning antioxidants
in the diet and HCC is inconsistent [113, 114]. Although vaccination against HBV and public health measures to reduce infection by HCV are obvious priorities in Asian and African countries, the size of the problem in these countries creates room for chemopreventive interventions.

Oltipraz [5-(2-pyrazinyl)-4 methyl-1,2 dithiole-3-thione] is a single dose agent that affects the metabolism of aflatoxin and reduces the number of aflatoxin DNA adducts in animal models. A randomized trial of Oltipraz in Qidong, China, observed a reduction of adduct levels in subjects on the treatment arm, with minimal adverse effects [115]. There are also studies exploring the effect of supplementation with curcumin, green tea and herbs or selenium in the chemoprevention of liver cancer [116].

**Oesophagus**

Although oesophageal cancer is uncommon in most parts of the world, its fatality is very high. For both squamous cell carcinoma (SCC) and adenocarcinoma, alcohol and tobacco play an important aetiological role in developed countries, although additional important factors are likely to play an aetiological role in adenocarcinoma [117]. In developing countries, however, diet, and particularly dietary deficiencies are also implicated and there is considerable evidence that consumption of fruits and vegetables reduces the risk of oesophageal cancer of any type in most populations [118].

Randomized chemoprevention trials undertaken in areas of China with high incidence of oesophageal cancer have indicated that vitamin and mineral supplementation convey some protection against oesophageal cancer and related precancerous lesions [119, 120]. However, these results were not striking, and may not be generalizable because the study population groups were nutritionally deficient and did not allow the identification of the most important micronutrient, because multivitamin and mineral supplements were used. Candidate micronutrients for oesophageal cancer chemoprevention include β-carotene, vitamin C, retinol, riboflavin or zinc [119, 120].

**Lung**

Lung cancer is the leading cause of cancer related deaths globally and tobacco smoking is by far the most important risk factor [121]. The limited success of both screening and treatment of lung cancer made lung cancer an early target for chemoprevention trials. The original driving force to use β-carotene as a chemopreventive agent came largely from epidemiologic studies, which consistently suggested that people consuming diets rich in fruits and vegetables are at a reduced risk of developing many types of cancers, including lung cancer. Although there was little direct evidence to support the hypothesis that β-carotene was the critical agent in fruits and vegetables, there was nonetheless a great deal of optimism that β-carotene was going to be the ‘magic bullet’ against cancer.

The Carotene and Retinol Efficacy Trial (CARET) and the ATBC study are two large, randomized, double blind studies specifically designed to determine if β-carotene, other antioxidants or retinol would reduce the incidence of lung cancer in high risk populations (see Table 1) [28, 29, 40, 122]. The hopes were dashed, when both trials reported a slight increase – rather than a decrease – of lung cancer incidence in the β-carotene arms.

**Skin**

Skin cancer is by far the most common type of cancer, having a substantial impact on morbidity and health care resources [123], accounting for approximately 40% of all diagnosed cancers in the US [124]. The most promising preventative agents to date have been sunscreens.

In skin tumourigenesis models, ultraviolet radiation acts as a complete carcinogen [125]. Ultraviolet exposure of normal skin can cause DNA thymine dimers, or single strand breaks, which may result in permanent mutations maintained through DNA replication [126–128]. In this model, the promotion from initiated cells into a preneoplastic state may take 10 years or longer. Well-described signal transduction pathways during this long promotion phase, provide potential targets for chemoprevention.

In some epidemiologic studies, some forms of tea have been associated with a decreased risk of cancer [129]. Polyphenols in green tea have antimutagenic and antitumour activities [130, 131]. Furthermore, in animal studies, epigallocatechin gallate (EGCG), the most abundant polyphenol in green tea, reduced the incidence of ultraviolet light induced skin tumours [129, 132].
It has been suggested that oral vitamin A may have a role in skin cancer chemoprevention. One double blind randomized study of retinol found a 32% reduction in risk of developing SCCs compared with placebo, without significant toxicity [133]. There are a number of mechanisms by which retinoids are believed to act. In the skin, retinoids promote cellular differentiation, may increase epidermal thickness thereby decreasing ultraviolet transmission or through immunoregulatory functions [134, 135].

Prostate

Migration studies have shown that men who move from countries of low incidence to countries of high incidence have an increase in prostate cancer [136] and have, thus, implicated environmental factors in the role of stimulating progression of latent microfocal cancer to clinical disease.

There is epidemiologic evidence that nutritional factors, such as meat, dairy products, and saturated fat are associated with an increased risk, whilst fruits and vegetables, tomatoes, and foods high in selenium and vitamin E have been associated with reduced risk [21, 137].

Studies of prostate biology have identified long-term androgenic stimulation as a key component of prostate carcinogenesis. For this reason, genes involved in the production, activation and transport of androgens have been considered potential targets for chemoprevention. DHT has been implicated as the principal androgen responsible for hyperplastic growth of the prostate. This has led to the hypothesis that suppressing DHT synthesis may inhibit prostate carcinogenesis. 5-α-reductase is the enzyme, which converts testosterone to DHT. Hence, inhibitors of this enzyme, such as finasteride and turosteride, are plausible agents for chemoprevention.

Animal studies using 5-α-reductase inhibitors have been promising, demonstrating that these agents are capable of preventing or slowing the growth of prostate cancer, as well as, preventing prostate pathology [138, 139]. Finasteride has been approved for the treatment of benign prostatic hyperplasia by many regulatory agencies. Overall, it is considered to have an acceptable safety profile, but impotence and loss of libido are reasons for concern [140].

There is evidence from randomized trials that selenium and vitamin E intake may convey some protection against prostate cancer. Subjects in the ATBC study randomized to vitamin E supplements showed a 33% reduction of prostate cancer incidence [122, 141]. The serendipitous findings of this study and the selenium studies [48, 142] have prompted the US National Cancer Institute to design a trial entitled ‘SELECT’. The recently initiated trial will randomize men to selenium, vitamin E, both selenium and vitamin E, or placebo and will look at prostate, lung and colorectal cancers as its primary outcomes [143].

Data from epidemiologic and animal studies suggest that vitamin D may also be chemopreventive in prostate cancer. Newly developed nontoxic vitamin D3 analogues, showing antiproliferative effects on prostate cells [144], are currently being considered.

Large bowel

Colorectal cancer is one of the most common malignancies in developed countries with a relatively high fatality that depends critically on the stage of disease at diagnosis [145]. The molecular changes involved in colorectal tumourigenesis have been well described by Vogelstein and others [146]. Prevention of colorectal cancer can potentially occur anywhere along this multistep process. There is convincing evidence that colon cancer arises from adenomas with specific factors involved in the development of adenomas and further progression to invasive cancer. A number of studies have focused not only on the primary prevention of, but also on the secondary prevention of adenoma recurrence and growth.

Epidemiologic studies have indicated that the consumption of fruits and vegetables prevents against colon cancer [21, 137]. Folate, a micronutrient highly abundant in fruits and vegetables, has gained a great deal of attention in the prevention of colorectal cancer [147, 148]. It appears that the benefit is greater amongst those who obtain their folate from supplements [149, 150]. In the Nurses’ Health Study, supplementation of folic acid, primarily from multivitamin use, was protective against colon cancer and became statistically significant after 15 years of use, suggesting that folate may act early in the carcinogenic process [150].

Diets high in red meat and animal fat consumption have been associated with an increased risk of colorectal cancer [21, 137]. Whilst the exact
mechanism is still unclear these foods may increase the production of secondary bile acids [151]. Calcium is hypothesized to prevent carcinogenesis in the colon by either binding bile acids and/or fatty acids in the lumen or by having a direct inhibitory effect on the proliferation of the epithelial cells in the colon. Animal models support this hypothesis and the majority of epidemiologic studies provide some modest support for an inverse relationship between the intake of calcium and colon adenomas as well as colorectal cancer [152–154]. Recently, a randomized control study assessed the efficacy of calcium supplementation on the risk of new colon adenoma formation amongst individuals with a history of adenomas [155]. Endoscopic examinations conducted after 1 and 4 years from the initiations of the study found that those on the treatment arm (3 g of calcium carbonate daily) compared with those on placebo had a reduced incidence of adenomas apparent after just 1 year of supplementation.

Nonsteroidal anti-inflammatory drugs have been widely studied because there are a number of mechanisms through which these agents might prevent colon cancer. Animal studies have provided strong evidence, showing a 90% reduction in the number of adenomas [156] and a 52% reduction in the total volume of colon tumours [78, 157]. These, as well as molecular and epidemiological studies support the idea that NSAIDs have their preventative function early in the carcinogenic process. Specifically, a number of case–control studies have found a 40–50% reduction in colon cancer incidence amongst patients taking aspirin regularly [158, 159]. In contrast, the Physicians’ Health Study, a randomized control trial, did not find any protective effect of low dose aspirin use on incidence of colorectal cancer [160].

Although the mortality rates from colorectal cancer have been decreasing during the past two decades, this decrease has been greater amongst women. One hypothesis to explain this is the increased use of hormone replacement therapy (HRT) amongst women. There are a number of proposed mechanisms by which oestrogens may prevent colorectal cancer. These include decreasing the production of secondary bile acids, and reducing the production of insulin growth factor I (IGF1) [161]. Both the Cancer Prevention Study and the Nurses’ Health Study also observed a significant protection from colon cancers amongst current users of HRT [162, 163]. The protective effect in the Nurses’ Study was limited to those currently using therapy and disappeared 5 years after stopping use, which is supported by case–control studies [164, 165]. This information, along with the proposed mechanism of action, supports the idea that oestrogens have a late effect in colorectal carcinogenesis.

Epidemiologic studies have provided modest support of a protective role of fibre against colon cancer [21, 137]. However, two large randomized control trials evaluating the effect of high fibre diets amongst individuals with history of adenomas failed to provide evidence of a protective effect [166, 167].

Conclusion

Chemoprevention is an attractive concept and may represent a priority area for the utilization and exploitation of our rapidly increasing understanding of the molecular processes involved in carcinogenesis. In this context, it is quite possible that genetic polymorphisms will be used to identify groups that would benefit most from chemopreventive interventions. There are, however, serious constraints in the identification and subsequent implementation of chemopreventive interventions. Most important amongst these is the fact that chemoprevention has a long latency, which makes it difficult to document effective interventions, as the later may have to depend on two or more cycles of randomized intervention trials.

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