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Review

Cancer Chemoprevention: A Summary of the Current Evidence

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Abstract. *Cancer chemoprevention is defined as the use of natural, synthetic, or biological chemical agents to reverse, suppress, or prevent either the initial phase of carcinogenesis or the progression of neoplastic cells to cancer. At present, the circle of agents with an established chemopreventive effect is restricted to tamoxifen and raloxifene in breast cancer, finasteride in prostate cancer, and celecoxib in colon polyp prevention. However, in recent years, there has been an exponential increase in the study of agents that have a chemopreventive potential against cancer. In this review, the current evidence regarding cancer chemoprevention in major target organs is summarised, discussing the epidemiological as well as the experimental data.*

Every year, more than 11 million people are diagnosed with cancer, while 6.7 million die from cancer worldwide (1). The most common new cancer diagnoses are lung (1.35 million), breast (1.15 million) and colorectal (1 million) cancer, while the most common causes of cancer death are lung (1.18 million), stomach (700,000) and liver (600,000) malignancies (2). The magnitude of the cancer problem, and the failure of advanced disease chemotherapy to effect major reductions in the mortality rates for the common types of malignancy, indicate that new approaches to the control of cancer are necessary. In this context, it is essential to adopt a more intensive approach to the prevention of this disease.

Chemoprevention is an area of cancer research that focuses on cancer prevention through pharmacological, biological, and nutritional interventions (3). Cancer chemoprevention, as first defined by Sporn in 1976, uses natural, synthetic, or biological chemical agents to reverse, suppress, or prevent either the initial phase of carcinogenesis or the progression of neoplastic cells to cancer (4). There are three strategies for cancer chemoprevention: (i) Primary chemoprevention involves interventions designed to help healthy individuals prevent the development of a certain cancer. These individuals may have high-risk features (*e.g.* genetic mutations) predisposing them to cancer development. (ii) Secondary chemoprevention is designed to provide treatment of premalignant lesions (*e.g.* colon adenomas) with the aim to prevent progression to cancer. (iii) Tertiary chemoprevention aims to help patients with a history of treated cancer to prevent the development of a second primary cancer.

We need to develop safe, tolerable, and clinically efficient agents for cancer chemoprevention. Meyskens and Szabo suggested several levels of evidence that should be evaluated prior to moving a potential chemopreventive agent into a randomized trial (5). In the ideal scenario, agents should have evidence of activity based on data from experimental (mechanistic, *in vitro*, animal), epidemiological (case–control, cohort, ecological, secondary analyses), and clinical (phase I, II) studies.

Below, we summarize the current evidence regarding cancer chemoprevention in major target organs, discussing the epidemiological and experimental data.

Bladder Cancer

COX inhibitors block the conversion of arachidonic acid to prostaglandins. They have shown antitumor activity. Indomethacin was evaluated for its ability to prevent bladder cancer formation in mice administered the carcinogen *N*-butyl-*N*-(4-hydroxybutyl)nitrosamine with promising results (6). The COX-2 inhibitor celecoxib similarly demonstrated protection against bladder cancer in rodents by decreasing tumor progression, incidence and number (7). Furthermore, some epidemiological studies have shown a significant decrease in bladder cancer risk among users of NSAIDs (non-steroidal anti-inflammatory drugs) (8, 9).

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Vitamin A, and vitamin A analogues (retinoids) stimulate cellular differentiation, regulate growth and facilitate apoptosis (10). *In vivo* studies showed that 13-cis-retinoic acid reduced the number and severity of bladder cancers in rats (11). However, epidemiological studies of retinoids for bladder cancer chemoprevention are conflicting (12-15). Vitamin B_6 has been suggested to decrease bladder cancer risk. However, the findings from randomized studies are also conflicting (16, 17). Similarly, epidemiological studies of vitamin C provide inconsistent results (12, 14, 18, 19). Vitamin E is a potent antioxidant that neutralizes free oxygen radicals and inhibits carcinogenic nitrosamine formation. Epidemiological evidence suggests that vitamin E may be protective against bladder cancer (19, 20).

Lycopenes are unsaturated, non-provitamin A carotenoids. They are found in tomatoes, watermelon and pink grapefruit, giving these fruits their red color. They are powerful antioxidants and have been suggested to decrease bladder cancer risk. A study in rats demonstrated a decrease in tumor number with no effect on incidence (21). Selenium is an essential trace mineral, for which an almost linear inverse association between serum levels and bladder cancer risk was shown (22).

Statins have also been suggested to decrease tumor growth and progression. For example, atorvastatin caused cytotoxicity, apoptosis and reduced cellular proliferation in bladder cancer lines (23). However, *in vivo* studies of statins are necessary before clinical trials can be carried out.

Breast Cancer

Selective estrogen receptor modulators (SERMS) comprise a class of agents that block the effects of estrogen on breast tissue. One SERM, tamoxifen, is approved for decreasing breast cancer risk in high-risk women. A large study (24) found that women who received tamoxifen for 5 years lowered their breast cancer risk by 50% . Raloxifene blocks the effects of estrogen similar to tamoxifen. The STAR trial (25), which compared tamoxifen and raloxifene in post-menopausal high-risk women, concluded that raloxifene was as effective as tamoxifen in reducing invasive breast cancer risk.

Aromatase inhibitors (anastrozole, letrozole, and exemestane) are used as adjuvant therapy for preventing breast cancer recurrence in women with cancers that are estrogen- or hormone receptor-positive. The ATAC trial (26) evaluated anastrozole as an adjuvant treatment for women with breast cancer, and detected a reduction in the risk of developing a new cancer in the other breast by 58% .

Several studies have also attempted to determine whether aspirin and other NSAIDs reduce breast cancer risk. The Women's Health Initiative (27) studied the use of NSAIDs by women over the age of 50. Those who used aspirin on a regular basis had a 21% decreased risk of developing breast cancer compared to women who were not regular users. Regular use of ibuprofen was associated with a 49% risk reduction in breast cancer risk.

A recent study on women diagnosed with breast cancer demonstrated that those who received fenretinide for 5 years decreased their risk for a second breast cancer (28). Fenretinide appeared to work best on premenopausal women, with women under the age of 40 having a 50% reduction in risk for a second cancer. The protective effect of fenretinide continued even after women stopped the medication.

Lately, a growing body of literature suggests that statins may have chemopreventive effect against breast cancer. Laboratory studies have demonstrated that statins induce apoptosis and reduce cell invasiveness in various cell lines, including breast carcinoma cells (29-32). However, the clinical relevance of these data remains unclear. Several randomized and observational studies have examined statins in relation to breast cancer risk. The findings from these studies are inconsistent. Some reported that the use of these drugs is inversely related to the risk of breast cancer, while others found no or positive associations, while a meta-analysis of these studies failed to find a beneficial effect. This neutral result was evident for both lipophilic and lipophobic statins (33-36).

Cervical Cancer

Several phase II and III clinical trials have evaluated beta-carotene and folic acid in women with cervical intraepithelial neoplasia (37-42). None of these trials had a statistically significant result.

Cervical cancer is caused by types of the human papilomavirus (HPV). Vaccines now exist for two types of HPV, HPV 16 and HPV 18, and initial results show 100% efficacy against persistent type-specific HPV infection for up to 4 years (43, 44).

There was also an interest in the use of iniquimod (immune modulator) as a topical agent in the treatment of cervical intraepithelial neoplasia. It appeared to be an effective agent. However, it caused severe irritation and burning to the cervix, and trials of its use in treating cervical intraepithelial neoplasia were abandoned (45).

Colorectal Cancer

Antioxidant vitamins (especially beta-carotene, vitamins E and C, and alpha-tocopherol) are ideal candidates for chemoprevention, given their minimal toxicity and their link with reduced colorectal cancer risk in studies examining serum levels or dietary intake (46-48). However, clinical trials have failed to show any benefit (49).

Calcium has the ability to bind and precipitate soluble fatty acids in the bowel lumen, inhibiting their carcinogenic

effects (50). Two clinical trials of calcium supplementation have demonstrated a risk reduction. In the Calcium Polyp Prevention Study, calcium supplementation resulted in a statistically significant 19% reduction in adenoma risk (51). The benefit was 35% when the endpoint was advanced adenomas (52).

Animal and observational studies have also shown that vitamin D protects against colorectal neoplasia (50). A study that used data from the Calcium Polyp Prevention Study (53) demonstrated that, among individuals with high serum vitamin D levels, calcium supplementation conferred a reduction in adenoma risk of almost 30% , but had no such effect among those with lower serum levels.

NSAIDs have been shown to have substantial and consistent effects against colorectal neoplasia, in more than 90 out of over 100 rodent studies published to date. Several epidemiological studies have also demonstrated a chemopreventive effect, suggesting that the colorectal cancer risk can be reduced by about 50% among individuals who regularly use aspirin or other NSAIDs (54). Although the activity of NSAIDs in the prevention of colorectal cancer has been promising, several points still need to be considered. The majority of evidence supporting the anticancer effect of NSAIDs is based on retrospective studies. Thus, large randomized studies are still required before NSAIDs could be recommended for colorectal cancer chemoprevention. Similarly, the dosage and duration of treatment have to be determined. Recently, several studies have suggested that treatment with selective COX-2 inhibitors, especially rofecoxib, is associated with an increased risk for cardiovascular events including stroke and myocardial infarction, leading to the withdrawal of rofecoxib from the market. Despite these findings, NSAIDs are still largely promising drugs for cancer chemoprevention and it is essential to continue research on the use of NSAIDs, with the aim of reducing detrimental side-effects while maintaining their beneficial effects (55).

Treatment with ursodeoxycholic acid has also been shown to prevent colon carcinogenesis (56). Epidemiological studies have indicated an inverse relation between this particular treatment and colorectal neoplasia among patients with ulcerative colitis, primary sclerosing cholangitis, and primary biliary cirrhosis (57-59). Two trials have confirmed these findings. In the first trial, the risk of colorectal cancer decreased by more than 70% in patients with ulcerative colitis treated with ursodeoxycholic acid, while the second trial found a risk reduction of almost 40% for recurrence of highly dysplastic adenomas (56).

Hormone replacement therapy was evaluated for colorectal cancer chemoprevention in two meta-analyses of observational studies (60, 61) and was found to be protective. The Women's Health Initiative trial (62) also demonstrated a 37% reduction in risk of colorectal cancer in the treatment group (combined estrogen and progestin). However, the underlying mechanisms remain unclear.

Lately, a growing body of literature suggests that statin use may prevent colorectal cancer. Statins have been shown to inhibit colorectal carcinogenesis in rodents (63-65). However, the clinical relevance of these data is unclear. Several epidemiological studies have examined the relation between statins and colorectal cancer. It was the publication by Poynter *et al*. (66) that captured the most attention in the literature, with a 47% reduction in the risk of colorectal cancer. An accompanying editorial stated that it is perhaps time for a paradigm shift in chemoprevention to "beyond the one drug, one disease model" (67). However, in contrast to results from this study, other epidemiological studies, as well as a recent meta-analysis do not support an association between statin use and colorectal cancer risk (68).

Esophageal and Gastric Cancer

Use of NSAIDs has been associated with a reduction in risk of esophageal cancer in observational studies. A meta-analysis has also supported this inverse association (69). On the other hand, two randomized trials in China have explored the association between esophageal cancer and the use of different mixtures of vitamins and minerals, including beta-carotene, alpha-tocopherol, ascorbic acid and selenium (70, 71). None of the combinations of these agents was found effective.

Regarding chemoprevention of gastric cancer, NSAIDs appear to exert preventive effects, but trials have not explored this association (72). On the other hand, two clinical trials conducted in China focused on cancer of the gastric cardia, and demonstrated a reduction of 21% in the risk of cancer among individuals randomized to beta-carotene, alpha-tocopherol and selenium (71).

Haematological Malignancies

Several recent mechanistic, *in vivo* and observational studies have suggested that statins may have chemopreventive potential in haematopoietic and lymphatic tissue (73-75). However, a meta-analysis of randomized and observational studies failed to find a beneficial effect (76).

Liver Cancer

Hepatitis B virus infection accounts for 80% of all hepatocellular cancers. Several studies have demonstrated the value of immunization for the primary chemoprevention of this cancer. A nationwide hepatitis B vaccination program in newborns eradicated liver cancer in children, in Taiwan (77). Another risk factor for hepatocellular cancer, in areas with high prevalence of hepatitis B virus infection, is the dietary

consumption of aflatoxins that are produced by two fungi, *Aspergillus flavus* and *Aspergillus parasiticus*. The synergism between hepatitis B virus and aflatoxins in causing hepatocellular cancer has been well documented in the literature (78). Two potential chemopreventive agents have been tested with satisfactory results; oltipraz (which induces the detoxifying enzymes in the liver) and chlorophyllin (which binds aflatoxins and impairs their absorption) (78).

In developed countries, chronic infection with hepatitis C virus is a major risk factor for hepatocellular cancer (79). Some observational studies have reported an inverse association between interferon therapy and hepatocellular cancer in patients with hepatitis C virus. However, only one randomized study has confirmed this finding (80).

Lung Cancer

Currently, there are no chemoprevention agents that have demonstrated a clear benefit in lung cancer. The alpha-tocopherol/beta-carotene (ATBC) trial, the beta-carotene and retinol efficacy trial (CARET), and the Physicians health study (PHS), all demonstrated no benefit from beta-carotene, either alone or in combination (81-85). The two more informative trials –ATBC and CARET– demonstrated significant increases in lung cancer risk, along with higher risks of cardiovascular and total mortality (86).

A recent large case–control study (87) indicated a beneficial effect of statins in relation to lung cancer risk. However, this finding has not been supported in a meta-analysis of large randomized controlled trials (88).

Melanoma

Despite efforts to promote sun protection behaviors, melanoma incidence continues to increase. NSAIDs have been proposed for melanoma chemoprevention. They inhibit COX enzymes, preventing synthesis of prostaglandins and other pro-inflammatory molecules that may play a role in skin carcinogenesis (89, 90). NSAID use was associated with decreased melanoma risk in a case–control study (91), while a retrospective cohort study of melanoma patients showed that those prescribed a COX inhibitor had a lower risk of new melanoma, recurrence and metastasis (92). However, convincing evidence for a chemopreventive effect of NSAIDs is lacking. Furthermore, the recent data on cardiovascular toxicity has posed some limitations regarding long-term use of COX-2 specific inhibitors in the general population (93).

Statins have also been proposed for melanoma chemoprevention. They inhibit proliferation and invasion through inhibition of isoprenoid protein modification required by signaling proteins such as Ras, Rac and Rho, induce melanoma cell apoptosis through a geranylation-specific mechanism, inhibit activation of proteins important for cell cycle regulation through increased expression of cyclin-dependent kinase-inhibitors and inhibit nuclear factor-κB, key in cell migration and inflammation (94-96). However, a meta-analysis of randomized controlled trials of cardiovascular outcomes failed to find an association between statin use and melanoma risk (97).

A number of nutrients have also been studied for melanoma chemoprevention, such as vitamins D and E, beta carotene, lycopene, flavonoids, epigallocetechin 3-gallate, resveratrol, selenium, ginseng and perillyl alcohol (98-102). Many of these compounds may function as antioxidants, which counter the free radicals that cause DNA damage and promote tumorigenesis. Retinoids may also play a role in inhibiting melanoma formation by inducing cellular differentiation, growth arrest, apoptosis, and inhibition of angiogenesis (103).

Non-melanoma Skin Cancer

At present, retinol and the retinoids are the only agents that have proven to be chemopreventive (104-108). In addition, lycopene (100), celecoxib (89, 109), green tea (110, 111) and silymarin (112) have been shown to be effective in mice.

Ovarian Cancer

Oral contraceptives (OCs) have been shown to reduce ovarian cancer risk in several epidemiological studies (113-118). This beneficial effect has been attributed to reduction in the number of ovulatory events associated with regular use of OCs. Several studies have also suggested that the degree of protection is associated with the duration of use (116-119). The length of protection also appears to be correlated with the duration of use. Prolonged risk reduction has been reported when OCs are used for longer than four years, while minimal benefit has been detected if utilization is restricted to a period up to two years (116, 117, 119). Furthermore, the protective effect of OCs weakens with time and returns to baseline approximately 15 years after the last regular use of OCs (116-118).

NSAIDs and paracetamol have also been suggested as chemopreventive agents for ovarian carcinoma. NSAIDs have been shown to result in growth inhibition and increased apoptosis in ovarian cancer cell lines (120). However, a meta-analysis of observational studies failed to find a beneficial effect of NSAID use on ovarian cancer risk (121). On the other hand, interesting evidence for an antigonadotropic effect in animals exists for paracetamol. Paracetamol has a phenol ring, similar to estradiol, and an acetyl group similar to progesterone, indicating a potential sex steroid-antagonist property (122). Evidence of antigonadotropic activity was suggested by toxicology studies demonstrating ovarian, uterine and testicular atrophy

in rodents fed with paracetamol (123). In addition, a recent meta-analysis evaluating the relationship between paracetamol use and ovarian cancer has suggested a risk reduction of up to 30% associated with regular use (124).

Experimental evidence indicates that retinoids can inhibit growth and promote cellular differentiation in ovarian cancer cells (125). The ability of retinoids to prevent ovarian carcinoma is also supported by a phase III trial (126, 127). This trial of fenretinide for the prevention of second breast cancers demonstrated a significantly lower incidence of ovarian malignancy in the treatment group.

Pancreatic Cancer

Several experimental and epidemiological studies have examined various drugs as potential chemopreventive agents for pancreatic cancer. Somatostatin analogues, selective estrogen modulators and anti-androgen agents have demonstrated some chemopreventive potential in animal and *in vitro* studies (128). Aspirin, NSAIDs and selective COX-2 inhibitors have also been proposed (128). However, it will be very difficult to resolve these issues with clinical trials, given the rare occurrence of pancreatic cancer.

Prostate Cancer

Cancer of the prostate has long been recognized as an appropriate target for chemoprevention, given the high incidence of the disease and its significant mortality. The Prostate Cancer Prevention Trial (129) demonstrated a 25% reduction of prostate cancer incidence, as well as prostate volume, for men on finasteride compared with placebo. However, the increase in the number of high-grade tumors detected at biopsy in the finasteride group was an unexpected finding of the study.

Vitamin E (alpha-tocopherol) is an antioxidant with apoptotic and anti-androgen effects (130). The alpha-tocopherol beta-carotene trial, designed to assess their effects on lung cancer prophylaxis, demonstrated a 32% reduction in prostate cancer incidence and a 41% reduction in prostate cancer mortality at 6 years (131). However, doses of vitamin E higher than 400 IU/day are associated with increased rates of heart failure and all-cause mortality (132, 133). Doses are therefore recommended not to exceed 150 IU/day.

Animal studies have demonstrated inhibition of prostate cancer growth with NSAIDs (134, 135). Recently, a meta-analysis of the association between aspirin use and the risk of prostate cancer indicated an inverse association (136). Subsequent studies reported similar results (137, 138). It appears that men on long-term low-dose aspirin for cardiovascular preventative reasons might potentially get a secondary urological benefit.

Regarding lycopene, a meta-analysis indicated that men with high consumption of tomatoes (a product rich in lycopene) have a substantially lower risk of prostate cancer (139). However, at present, specific recommendations for lycopene with regard to prostate cancer are difficult to make.

Statins have shown certain mechanisms of action in prostate cancer chemoprevention. They may reduce activation of Ras and Rho proteins and interfere with cyclin-dependent kinases and epidermal growth factor signal transduction (140, 141). However, findings from a recent meta-analysis of randomized and observational studies (142) do not support the hypothesis that statins, when taken at low doses for managing hypercholesterolemia, reduce the risk of prostate cancer.

Conclusion

Chemoprevention is an innovative area of cancer research that focuses on cancer prevention through pharmacological, biological and nutritional interventions. The development of a chemopreventive agent from a basic biological observation to a clinically effective antitumor regimen is a difficult task. Firstly, chemoprevention must be safe. The agent must be tolerable during long-term administration to patients who are healthy and who may be elderly and exhibit comorbidities. Secondly, to assess benefit, chemoprevention trials must be lengthy and the patient cohorts must be of uniform, defined cancer risk. As a result of these challenges, few agents have yet demonstrated a clinical benefit in humans.

At present, the circle of agents with an established chemopreventive effect is restricted to tamoxifen and raloxifene in breast cancer, finasteride in prostate cancer and celecoxib in colon polyp prevention. However, there is reason to be optimistic that effective chemopreventive agents will be developed from current research and that strategies can be devised to use these drugs safely in appropriate populations. In recent years, there has been an exponential increase in the study and development of chemopreventive agents for several tumor types, yet many challenges are ahead. Continued commitment to cancer chemoprevention will significantly reduce the economic and medical burden of cancer.

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