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CANCER CHEMOPREVENTION (R AGARWAL, SECTION EDITOR)

Cancer Chemoprevention: What Have we Learned?

Chung S. Yang[1] · **Hong Wang**[1] · **Vi Dan**[1] · **Savanna San Filippo**[1]

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Abstract Cancer is a major disease worldwide and different approaches are needed to reduce its risk. Previous laboratory studies suggested that cancer can be prevented by many naturally occurring and synthetic chemicals. In human cancer prevention studies, however, most of the successful examples are the repurposing of existing drugs, such as tamoxifen and aspirin. Epidemiological studies have established associations between certain dietary patterns or nutrient insufficiencies with elevated cancer risk. Laboratory research has also shown impressive results on the cancer preventive activities of constituents from food and beverages. However, such cancer preventive activities have not been demonstrated in many human intervention trials. This article reviews the advances in this field and discusses the reasons for the discrepancies between laboratory studies and human trials. Lessons learned for cancer prevention research in the past decades will be illustrated using studies with β-carotene, vitamin E, green tea polyphenols, tamoxifen, and aspirin as examples. In future studies, more interdisciplinary collaboration in the integration of laboratory and human studies are needed to advance the field of cancer chemoprevention.

Keywords Cancer chemoprevention · Nutrients · Tocopherols · Polyphenols · Tamoxifen · Aspirin

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✉ Chung S. Yang
csyang@pharmacy.rutgers.edu

[1] Department of Chemical Biology, Ernest Mario School of Pharmacy, Rutgers, The State University of New Jersey, 164 Frelinghuysen Road, Piscataway, NJ 08854-8020, USA

Abbreviations

α-, γ- or δ-T	α-, γ- or δ-tocopherol
ATBC	α-Tocopherol and β-Carotene study
CARET	Carotene and Retinol Efficacy Trial
CVDs	cardiovascular diseases
EGCG	(−)-epigallocatechin-3-gallate
ESCC	esophageal squamous cell carcinoma
GCA	gastric cardia adenoma
LNIT	Linxian Nutritional Intervention Trial
NPC	Nutritional Prevention of Cancer study
PIN	prostate intraepithelial neoplasia
RCT	randomized controlled trial
ROS	reactive oxygen species
SELECT	Selenium and Vitamin E Cancer Prevention Trial

Introduction

The association between certain dietary patterns and cancer risks first gained recognition in the 1960s, and Dr. Lee Wattenberg proposed the concept of chemoprophylaxis of carcinogenesis by dietary chemicals and the possible mechanisms involved [124, 125]. Dr. Michael Sporn later coined the term "chemoprevention" to advocate cancer prevention by using chemicals, including those of dietary origin [109]. Since then, this term has been widely used. Subsequently, numerous laboratory studies on the cancer prevention activities of synthetic and naturally occurring compounds have been conducted [8, 33, 100, 125, 129]. In spite of the interesting results from many laboratory studies, very few agents have been shown to be effective cancer preventive agents in human trials. In this article, studies on nutrients such as vitamin E, β-carotene, and selenium; non-nutritive dietary compounds such as tea polyphenols; and chemopreventive drugs such as

tamoxifen and aspirin, are used to illustrate some of the progresses and challenges in this area of research. Reasons for the discrepancies among results from epidemiological observations, laboratory studies, and human trials, as well as possible ways to improve future cancer chemoprevention research, are discussed.

Early Cancer Prevention Studies on Antioxidant Nutrients

Early epidemiology studies established an association between certain micronutrient insufficiencies and risks for many types of epithelial cancer. Esophageal cancer, for example, was prevalent in populations with a monotonous diet, such as those in certain areas of northern China, central Asia, and northern Iran. In these populations, people survived on a diet with staples such as corn, wheat, or millet with a low intake of vegetables, fruits, and animal products, leading to insufficiency in micronutrients, such as vitamins A, B_2, and C, selenium, zinc, magnesium, and calcium [127]. Similarly, laboratory studies have demonstrated that diets with insufficiency in micronutrients enhance *N*-nitrosomethylbenzylamine-induced esophageal carcinogenesis in rats, which may be attenuated by supplementation with zinc, molybdenum, vitamin A, and riboflavin (reviewed in [129]).

Linxian Nutrition Intervention Trial

The hypothesis that supplementation with micronutrients can prevent esophageal cancer was tested in a large-scale US-China Cooperative Linxian Nutritional Intervention Trial (LNIT) started in the early 1980s. The rural population in Linxian (now named Linzhou City) had low intake of micronutrients, and insufficiencies in some nutrients that were indicated in blood nutrient analyses [128, 131]. Because many micronutrients had been suggested to be associated with esophageal cancer, a design with nutrient combination was adopted, in which nutrients were divided into four groups: (A) retinol, zinc; (B) riboflavin, niacin; (C) ascorbate, molybdenum; and (D) α-tocopherol, β-carotene, selenium. The nutrient groups were combined in a factorial design with eight groups: placebo, AB, AC, BC, AD, BD, CD, and ABCD. Each nutrient was given at 1–3 times the levels of the US Recommended Daily Allowance (RDA). The study involved 29,584 adults (aged 40 to 69), who were randomized into eight groups and given supplementations as daily pills for 63 months (1985 to 1991). There were 2127 deaths during the trial period; 32% were due to esophageal and gastric cancer. The so-called *esophageal cancer* in Linxian actually consisted of 60% esophageal squamous cell carcinoma (ESCC) and 40% gastric cardia adenoma (GCA). The latter was therefore classified as gastric cancer in this trial. The study showed that supplementation with a combination of α-tocopheryl acetate (50 mg), β-carotene (15 mg), and selenium (50 μg) to the general population (aged 40 to 69) for 63 months decreased mortality due to gastric cancer (mainly GCA) by 20% and total cancer mortality by 13% [7], suggesting the involvement of these nutrients in this cancer. Nested case-control studies also showed that the blood levels of α-tocopherol and selenium were inversely associated with gastroesophageal cancer risk [78, 115]. Other nutrient combinations, however, did not show any effect on the endpoints measured [7]. Results from a 10-year follow-up found that the protective effect of α-tocopherol/β-carotene/selenium on GCA was sustained. In addition, this nutrient combination also protected against ESCC in subjects enrolled in the trial at age 55 years or younger (but not in those older than 55 years) [92].

It is possible that the intervention was ineffective in older subjects because they already had more advanced precancerous lesions than the younger subjects. This is consistent with the result of a parallel trial in Linxian on subjects with esophageal dysplasia, which showed a lack of beneficial effect by supplementation with multiple micronutrients [66]. These results are supported by studies in a rat model demonstrating that insufficiencies in vitamin E and selenium enhanced *N*-methylbenzylnitrosamine-induced esophageal carcinogenesis, and that the preventive effect was more pronounced when these nutrients were administered at the early stage of carcinogenesis [134]. The concept that chemoprevention is more effective in patients with less severe precancerous lesions was also demonstrated in a randomized placebo-controlled trial (RCT) in Linxian in the 2000s, which showed that supplementation with selenomethionine for 10 months improved squamous histology in 115 patients with mild esophageal dysplasia, but not in the 125 patients with severe dysplasia [70]. Celecoxib was also used in this trial, but had no effect on the squamous histology.

Trials with β-Carotene

In the 1980s, β-carotene was lauded as a very promising chemopreventive antioxidant [89]. This viewpoint was mainly based on epidemiological studies showing that decreased cancer risk was associated with vegetable and fruit consumption. The hypothesis that β-carotene can prevent lung cancer was tested in male Finnish smokers in the α-Tocopherol and β-Carotene (ATBC) study started in 1985 [34]. This was a randomized, double-blind, placebo-controlled primary-prevention trial with a total of 29,133 male smokers, 50 to 69 years of age, from southwestern Finland using α-tocopheryl acetate (50 mg per day) and β-carotene (20 mg per day) in a 2 × 2 factorial design for an average of 4.5 years, with follow-up continued for 5 to 8 years. Unexpectedly, among the 876 new cases of lung cancer diagnosed during the trial, increased lung cancer incidence (by 18%) was observed in the β-carotene

group. No effect in incidence was observed among the men who received α-tocopherol. However, supplementation with α-tocopherol was found to reduce the incidence of prostate cancer (by 45%) and other cancers in a secondary endpoint analysis [38].

In another large study involving β-carotene, the β-Carotene and Retinol Efficacy Trial (CARET), a primary-prevention trial involving a total of 18,314 smokers, former smokers, and workers exposed to asbestos in the USA, the relative risk of lung cancer was increased (~ 28%) in the group treated daily with a combination of 30 mg of β-carotene and 25,000 IU of vitamin A [84]. The CARET also indicated that the combination of β-carotene and vitamin A may increase the risk of deaths from lung cancer, cardiovascular disease, and other causes in smokers and workers exposed to asbestos.

These studies essentially ended further research on β-carotene as a preventive agent. The reasons for the β-carotene-enhanced lung cancer rate are not fully understood. It is possible that in an environment of excessive oxidative stress in the lung of individuals exposed to cigarette or asbestos, the redox active compound β-carotene may further enhance oxidative stress and promote lung tumorigenesis.

Trials with Selenium

Selenium is another "antioxidant" that has been studied extensively as a chemopreventive agent [18, 45, 57, 93]. A multicenter, double-blind, randomized, placebo-controlled cancer prevention trial, known as the Nutritional Prevention of Cancer Study (NPC), was conducted in the Eastern United States from 1983 through 1991 [16]. A total of 1312 patients with a history of basal cell or squamous cell carcinomas of the skin were randomized to take 200 μg of selenium per day as selenium-enriched yeast or non-enriched yeast as placebo orally for a mean of 4.5 years, and had a total follow-up of 6.4 years. After a total follow-up of 8271 person-years, selenium treatment did not significantly affect the incidence of basal cell or squamous cell skin cancer. However, secondary endpoint analysis yielded very interesting results showing that, compared to controls, patients treated with selenium had significant reduction in total cancer mortality, total cancer incidence, and incidences of prostate, lung and colorectal cancers. However, the Vitamins And Lifestyle (VITAL) prospective cohort study, which contained detailed questionnaires about vitamin E and selenium supplement intake from 35,242 men recruited between 2000 and 2002 in western Washington State, showed that a 10-year average intake of selenium at > 50 μg/day was not associated with a reduced prostate cancer risk. Nevertheless, risk of advanced prostate cancer (regionally invasive or distant metastatic) was significantly decreased with greater intake of supplemental vitamin E [88].

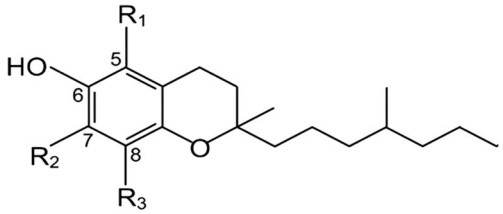
Recent Studies on Cancer Prevention by Tocopherols

Tocopherols, the major forms of vitamin E, contain a chromanol ring system and a phytyl chain of 16 carbons (Fig. 1). Depending on the number and position of methyl groups on the ring, they exist as α-, β-, γ-, or δ-tocopherol (α-, β-, γ-, and δ-T) [117]. The possible cancer preventive activities by tocopherols have been studied extensively (reviewed in [46, 51, 130]). Of interest is the result of a nested case-control study (CLUE II), showing that the prostate cancer risk was inversely associated with serum levels of γ-T (but not α-T) [43]. A recent report by Weinstein et al. on the Prostate, Lung, Colorectal, and Ovarian Cancer (PLCO) Screening Trial and some previous reports indicated that higher serum levels of α-T were associated with decreased risk of prostate cancer, particularly among smokers ([126] and references cited).

Disappointing Results from Recent Intervention Studies with α-Tocopherol

Because α-T is the most abundant form of tocopherols in blood and tissues, and has the highest activity in the classical fertility-restoration assay, α-tocopheryl acetate is the vitamin E used in many studies. The results from several large-scale intervention studies with α-T, however, have been disappointing [32, 56, 64, 71]. For example, in the Women's Health Study, supplementation with α-tocopheryl acetate (600 mg every other day) for 10 years failed to protect against cancer or cardiovascular diseases (CVDs) [64]. Similarly, in the Physicians' Health Study II RCT, supplementation with α-tocopheryl acetate (400 mg every other day) alone or in combination with vitamin C for 10 years did not prevent prostate or total cancer [32].

The Selenium and Vitamin E Cancer Prevention Trial (SELECT) was designed with great optimism based on the encouraging results from the ATBC and VITAL studies, as well as the NPC Nutritional trial. However, daily supplementation with 400 mg of α-tocopheryl acetate and 200 μg selenium (from L-selenomethionine) in a 2 × 2 design, for an average of 5.5 years, did not prevent prostate or other cancers [71]. In the 7–12 year follow-up of this study, subjects receiving α-T had a hazard ratio of 1.17 for developing prostate cancer [56]. It was noted that, in the SELECT, α-T supplementation caused a 50% decrease in median plasma γ-T levels [71]. The mean baseline median plasma level of α-T in subjects of the SELECT was at an adequate level of 12.5 μg/mL [71]. A possible interpretation for the lack of a cancer preventive effect of α-T is that the supplementation of a nutrient to a population that is already adequate in this nutrient may not produce any beneficial effect. Since γ-T has been suggested to have strong anti-inflammatory and cancer preventive activities [10, 39, 47, 51], the decrease in blood and tissue levels of γ-T,



α-Tocopherol (R_1, R_2, R_3 = CH_3)
β-Tocopherol (R_1, R_3 = CH_3, R_2 = H)
γ-Tocopherol (R_2, R_3 = CH_3, R_1 = H)
δ-Tocopherol (R_1, R_2 = H, R_3 = CH_3)

Fig. 1 The structures of tocopherols

caused by high doses of α-T, may have decreased the prostate cancer prevention potential [56, 71]. Another possibility is that some of these subjects already had preneoplastic lesions when entering the trial, and the supplementation with high doses of α-T promoted prostate cancer development. The exact reasons for these negative results from the SELECT and other trials are still not known. Nevertheless, the disappointing outcome of these large-scale trials reflects our inadequate understanding of the biological activities of tocopherols and points to the need for systematic studies of the disease preventive activities of the different forms of tocopherols.

New Insights from Recent Laboratory Studies of Specific Forms of Tocopherols

Previous cancer prevention studies in different animal models, mainly with α-T, have obtained inconsistent results [51]. However, the cancer preventive activity of γ-T has recently received much attention [10, 39, 47, 51, 86, 130]. Recent studies from our research team at Rutgers University have demonstrated the inhibition of cancer formation and growth in the lung, colon, mammary gland, and prostate by γ-T, δ-T, and a tocopherol mixture that is rich in γ-T (named γ-TmT) [14, 15, 23, 49, 62, 63, 74, 130]. γ-TmT, a product derived from vegetable oil usually containing (per g) 130 mg α-T, 15 mg β-T, 568 mg γ-T, and 243 mg δ-T, was shown to significantly inhibit the formation of colon adenoma in a mouse carcinogenesis model induced by azoxymethane and dextran sodium sulfate. We also demonstrated that δ-T was more active than (or had similar activity as) γ-T in inhibiting cancer cell growth in culture, human lung cancer H1299 cell tumorigenesis in a xenograft model, colon carcinogenesis induced by azoxymethane in rats, colon carcinogenesis by 2-amino-1-methyl-6-phenylimidazo(4,5-b)pyridine (PhIP) in CYP1A-humanized mice, and prostate carcinogenesis induced by PhIP, whereas α-T was not effective in these models [15, 35, 65]. Takahashi et al. also demonstrated that γ-T (0.005 or 0.01% in the diet), but not α-T, decreased the number of adenocarcinomas in the ventral lobe in the "Transgenic rat for adenocarcinoma of prostate" model [113]. In these studies, the possible mechanisms of inhibitory actions of δ-T and γ-T are the quenching of reactive oxygen and nitrogen species, the lowering of prostaglandin E2 and leukotriene B4 levels, inhibition of PI3K/AKT pathway, activation of PPARγ, and the enhancement of cancer cell apoptosis [14, 15, 23, 35, 65, 108, 123].

Based on the above epidemiological and laboratory studies, we propose that under conditions of vitamin E insufficiency, all forms of vitamin E contribute to cancer prevention. In vitamin E sufficient individuals, however, supra-nutritional levels of γ-T, δ-T, and γ-TmT prevent cancer, whereas α-T is not effective. The preventive activities of δ-T, γ-T, and γ-TmT warrant further investigation in preclinical and clinical studies.

Studies on Cancer Prevention by Non-nutritive Dietary Constituents

Numerous dietary phytochemicals have been studied for their cancer preventive activities. These include a variety of polyphenols, such as tea catechins, resveratrol, curcumin, genistein, chlorogenic acid, epigenin, delphinidin, luteolin, and silibinin; terpenoids such as carnosol and limonene; and organosulfur compounds such as sulforaphane, phenethylisothiocyanate, indole-3-carbinol, and diallyl sulfide. A great deal of interesting results from laboratory studies have accumulated [8, 33, 100]. However, convincing evidence on cancer preventive activities from human studies are lacking. We will use studies on green tea as examples to illustrate the challenges in extrapolating results from in vitro studies to animals, and from studies in animal models to human situations.

Studies on Tea in Animal Models

Green tea, made from the leaves of the plant *Camellia sinensis*, is a popular beverage worldwide. The abundance of data from investigations on green tea provides a unique opportunity for us to compare results obtained from laboratory and human studies. The characteristic tea polyphenols can be used as exposure biomarkers in epidemiological studies. The structures of the major green tea polyphenols known as catechins: (−)-epigallocatechin-3-gallate (EGCG), (−)-epigallocatechin (EGC), (−)-epicatechin-3-gallate (ECG), and (−)-epicatechin (EC) are shown in Fig. 2. Among the tea polyphenols, EGCG is the most abundant, most active, and most studied. The cancer preventive activities of green tea extracts, tea polyphenols, and EGCG have been demonstrated in many animal models (reviewed in [132, 133]). These include chemically induced and genetic models for lung, oral, esophageal, stomach, small intestinal, colorectal, and prostate cancers. The inhibitory activity against carcinogenesis in the lung and other organs has been observed when tea preparations are administered to mice during the initiation, promotion, or progression

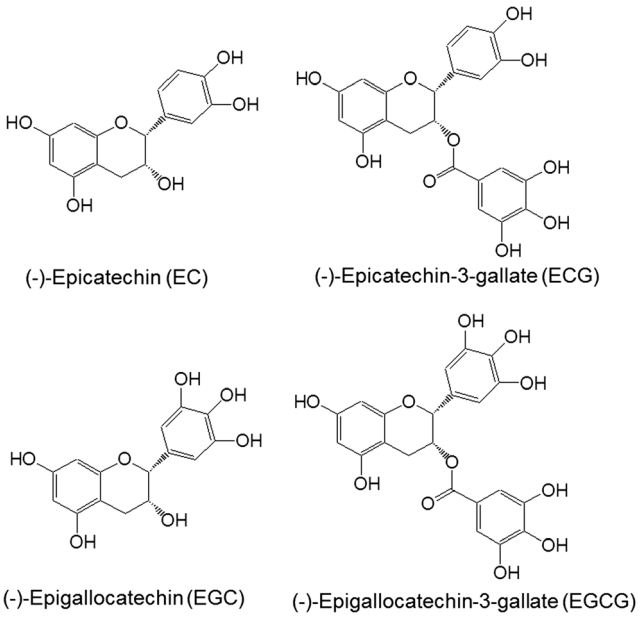


Fig. 2 The structures of tea catechins

stages. These results demonstrate the broad cancer preventive activities of tea catechins in animal models.

Studies on Tea In Vitro and Mechanistic Considerations

The biological activities of tea catechins, especially EGCG, have been studied extensively in vitro and in vivo (reviewed in [132, 133]). EGCG is known for its antioxidant action, but it can also produce reactive oxygen species (ROS), especially in vitro. The phenolic groups of EGCG are donors for hydrogen bonding, and EGCG binds strongly to many different proteins via multiple hydrogen bonds. Some of these proteins have been proposed as targets of EGCG for inhibitory actions against cancer cells [132, 133]. For example, EGCG has been proposed to bind to different molecular targets, inhibit the activities of many key enzymes, and inhibit several receptor-dependent signaling pathways [133]. Binding of EGCG to the 67-kDa laminin receptor with a dissociation constant (K_d) value of 0.04 μM was observed using a surface plasmon resonance assay, and this was proposed to be a mechanism for the anti-cancer actions of EGCG [59, 112]. Dong et al. identified vimentin, IGF-1R, GYN, GRP78, 2AP70, G3BP1, and Pin1 as high affinity EGCG binding or EGCG target proteins [28, 29, 37, 67, 104, 105, 121, 133]. In several studies, the binding of EGCG to proteins showed rather low (sub μM) K_d or K_i values; however, the concentrations required for inhibiting cell growth or inducing apoptosis are in the range of 10–30 μM EGCG [133]. This is most likely due to the non-specific binding of EGCG to other proteins and cellular materials.

Many of these proposed mechanisms are quite interesting; however, it is uncertain whether many of these proposed mechanisms are relevant to cancer prevention in animals. EGCG can be autoxidized under the conditions of many cell culture studies. For example, at 50 μM, most EGCG is generally autoxidized within 2 h (mediated by superoxide in a chain reaction) to dimers, which are unstable and converted to unidentified products [41]. The dimers of EGCG may have even higher affinities for protein binding. It is unclear whether many of the in vitro binding studies are affected by the formation of dimers or other derivatives and whether some of the reported cell-killing effects of EGCG are mediated by its autoxidation products, superoxide and hydrogen peroxide, generated outside of the cells.

Mechanisms derived from cancer prevention studies in animal models are likely to be more relevant than those from studies in vitro. These include the induction of apoptosis in different animal models, inhibition of phosphorylation of c-JUN and ERK1/2 in lung tumorigenesis models, suppression of nuclear β-catenin and phospho-AKT levels in colon cancer models, inhibition of the IGF/IGF-1R axis in colon and prostate cancer models, and suppression of VEGF-dependent angiogenesis in lung and prostate cancer models [1, 12, 50, 73, 106, 133]. It is still unclear whether these molecules are direct targets for EGCG or from downstream events of the primary action. In theory, the high affinity binding proteins mentioned above could serve as initial targets, but this point remains to be substantiated in vivo. From the limited human studies available, the action of tea constituents in reducing oxidative stress and enhancing the elimination of carcinogens could also be important mechanisms for the cancer preventive activity of tea [36, 99, 114].

Possible Cancer Prevention by Tea in Humans

In spite of the strong evidence for the cancer preventive activity of tea constituents in animal models, results on such activities in humans from epidemiological studies have not been consistent (reviewed in [132, 133, 137]). A large cohort study in Japan suggested that tea consumption decreased deaths due to CVDs, but not cancer [60]. In the Chinese Prospective Smoking Study of 165,000 adult men in China, tea consumption was associated with a significant reduction of deaths from cancer, as well as CVDs, in men who never smoked. In smokers, protective effects against risk of cancer death was only observed in those who consumed high quantities of tea (> 10 g/day) [72]. However, another large cohort study in Shanghai did not show an association between tea consumption and deaths from cancer, even though a decreased risk for CVDs was observed [138].

A comprehensive review by Yuan et al. [137] concluded that the consumption of green tea was frequently associated with a reduced risk of upper-gastrointestinal tract cancer, after adjusting for confounding factors, and limited data supported

its protective effect of lung and hepatocellular carcinogenesis. However, intake of black tea was not associated with a lower risk of cancer [137]. Some recent studies are consistent with this conclusion. For example, a meta-analysis of perspective cohort studies in Asian populations (nine studies involving 465,274 participants and 3694 cases of liver cancer) found that protective effects of green tea for liver cancer was only observed in women (RR, 0.78), but not in men [44]. A population-based cohort study in Japan also suggested that green tea consumption lowered the risk of biliary tract cancer [75]. In a recent systematic review and meta-analysis for endometrial cancer, a protective effect was found with green tea, but not black tea consumption [139].

Smoking and probably alcohol drinking are strong interfering factors. In a case-control study on esophageal cancer in Shanghai by Gao et al. [31], a protective effect of tea consumption was only observed in non-smokers and non-drinkers, who were mostly women. Similarly, a systematic review of cohort studies in Japan showed an inverse association between green tea consumption and gastric cancer only in non-smoking, non-drinking women [97]. The relationship between tea consumption and cancer risk may become clearer if the interfering factors are corrected for. Nevertheless, the above results suggested the cancer preventive effect of tea in humans is only mild.

The results of human intervention studies with green tea polyphenols, mostly small randomized clinical trials (RCT), have been inconsistent. It is disappointing that some of the exciting results from earlier studies have not been fully reproduced in recent studies. For example, an earlier RCT on oral cancer prevention in China, with a mixed tea product (3 g/day administered orally or topically) in patients with oral mucosa leukoplakia for 6 months, showed significant decrease in the number and total volume of proliferation index and silver-stained nucleoli organizer regions [68]. However, a later phase II RCT in the USA with green tea extract (500, 750, or 1000 mg/m^2 2 times daily) for 12 weeks, to patients with oral pre-malignant lesions, showed possible beneficial effects in the suppression of oral pre-malignant lesions, but it was not statistically significant [118]. In an impressive prostate cancer prevention study in Italy, 30 men with high-grade prostate intraepithelial neoplasia (PIN) were given 600 mg of green tea catechins daily for 12 months [5]. Only one patient developed prostate cancer, whereas 9 of the 30 patients with high-grade PIN in the placebo group developed prostate cancer. The difference was highly significant. However, a recent trial in Florida with a similar design using Polyphenon E (proprietary mixture of green tea catechins containing 400 mg of EGCG) in 97 men with high-grade PIN and/or atypical small acinar proliferation showed no differences in the number of observed prostate cancer cases between the treatment group ($n = 49$) and the placebo group ($n = 48$) [58]. Yet, some beneficial effects and a decrease in serum prostate-specific antigen were observed in the supplemented group. Some recent intervention studies on breast cancer and esophageal adenocarcinoma were only able to obtain results on bioavailability and some biomarkers [48, 96]. At present, the earlier optimistic expectation of cancer preventive activity by tea polyphenols has not materialized in RCTs.

Successful Examples of Chemopreventive Agents for High-Risk Populations

The scientific basis for chemoprevention is that the development of most epithelial cancers involves a series of genetic and epigenetic alterations over a rather long period of time, from 10 to 40 years [120]. If effective and safe drugs can be used to arrest or reverse these carcinogenic effects, cancer can be prevented.

Selective Estrogen Receptor Modulators (SERMs)

Among the most well-studied drugs are the SERMs, such as tamoxifen and raloxifene, for the prevention of breast cancer in high-risk populations [21, 22, 24, 76]. These compounds, which are effective for the prevention of estrogen receptor (ER)-positive breast cancer, have been approved in the USA for breast cancer prevention. The efficacy of tamoxifen in the treatment and prevention of ER-positive breast cancer has long been known. In 1986, the Royal Marsden Tamoxifen Breast Cancer Prevention Trial began, involving treatment with either tamoxifen or placebo for a period of 8 years. In 2006, the study was unblinded. The hazard ratio (HR) of the treatment was 0.77. After a follow-up for 5 and 10 years, the HR decreased to 0.48, suggesting a greater preventive effect post treatment [24]. These findings are promising in that this may lead to reduced side effects if administration time is shortened because of a long post-treatment activity. In addition, this study further confirmed that the incidence of only ER-positive, not ER-negative, breast cancer is reduced [24]. According to a recent review, tamoxifen reduces breast cancer by almost 50% in high-risk populations and by 62% in patients with BRCA mutations [76].

Raloxifene, another SERM, has shown similar effectiveness to tamoxifen, but it has fewer side effects including less uterine cancer, cataract development, pulmonary embolisms, deep-vein thromboses, and vasomotor symptoms [21, 76]. The most common side effects with raloxifene are thromboembolism and vasomotor symptoms [20, 76]. In addition to its SERM effects, raloxifene has anti-inflammatory activities involving upregulation of transcription factors: Nrf-2 and heat shock factor-1 [103]. Decreased intracellular levels of ATP and the activated AMPK/ULK1 pathway by raloxifene have been proposed to enhance autophagy-dependent cell death and contribute to the chemopreventive activity

[54]. An added advantage of raloxifene is its reduction of bone fracture incidence and prevention of osteoporosis in postmenopausal women [80]. A recent study showed that raloxifene increased bone-mineral density in the femoral neck and lumbar spine by 1.4% after 1 year of therapy and by 2.1% after 2 years of therapy [135].

To reduce the side effects, clinical trials have been conducted to use lower doses, less frequent dosing, hydroalcoholic gel for topical application, and low-dose tamoxifen in combination with fenretinide. An approach to co-target ER and NF-κB pathways has been proposed, and the concept has been demonstrated by a hybrid drug raloxifene-fumarate [52]. In a human trial, the addition of diindolylmethane, a metabolite of indole-3-carbinol—a constituent in cruciferous vegetables, to tamoxifen therapy increased serum sex-hormone binding globulin and reduced tamoxifen metabolites compared to tamoxifen treatment alone, but did not change in breast density [116]. A recent study in rats showed that combination with n-3 fatty acids enabled the use of a lower dose of raloxifene and increased the chemopreventive effect against ER-negative breast cancer [77]. More research is needed to find better combinations of SERMs with drugs or dietary chemicals to enhance chemoprevention at doses that minimize adverse side effects.

The use of SERMs, even by women at high risk for breast cancer, has been limited by their side effects, including cardiovascular events and infertility, as well as by risk perception [69, 83, 94]. Women may be reluctant to initiate tamoxifen because studies have not shown an increase in overall survival rate or quality of life. In a 2016 survey of 622 women, it was shown that women see cancer prevention and maintenance of fertility as the two top concerns and they do not feel that current drugs meet their needs [69]. Risk perception is one of the main reasons for low uptake of tamoxifen as well as other chemopreventive drugs. Despite research that correlates early menopause to lowered breast cancer risk, women who have an early onset of menopause have a higher worry over breast cancer and a lower likelihood to initiate tamoxifen therapy [94]. Emotional counseling in high-risk women may lead to an increase in initiation and maintenance of therapy, but this needs to be verified.

Nonsteroidal Anti-inflammatory Drugs (NSAIDs)

Inflammation is known to promote cancer development, especially colorectal cancer (CRC) [26]. CRC prevention by NSAIDs has been extensively studied [4, 11, 119]. The major mechanism by which NSAIDs prevent CRC is the inhibition of cyclooxygenase enzymes and suppression of the NF-kB pathway, which decreases inflammation and increases apoptosis [119]. Aspirin is an inhibitor of both cyclooxygenase (COX)-1 and -2. The strong evidence of colon cancer prevention by aspirin, as well as its side effects in causing gastrointestinal bleeding in some individuals, have been studied extensively [2, 13, 19, 30, 42, 95]. Early epidemiological studies have suggested that aspirin intake is associated with a lower incidence of CRC. In five RCTs in more than 3000 subjects with a prior history of adenoma or CRC, intake of aspirin (doses ranged of 81–325 mg daily) showed significantly reduced risk for the recurrence of colon adenoma. In two large cohort studies: the Nurses' Health Study and the Health Professional Follow-Up Study, starting in 1980 and 1986, respectively, information on diet aspirin use, tobacco use, BMI, and other information were taken. In these studies, regular aspirin use for more than 10 years was found to reduce the risk of CRC by more than 30%. Further studies also indicated that aspirin use in this cohort also significantly reduced CRC-specific mortality. However, aspirin use was found to have a dose-dependent increase in gastrointestinal bleeding, showing a relative risk of 1.59 in groups using 6–14 standard tablets of aspirin per week [42]. Because of this concern, the US Preventive Service Task Force recommended against routine use of aspirin or NSAIDs to prevent CRC in average risk individuals in 2007. However, the Task Force recently reversed its position and recommended the use of aspirin for the prevention of CRC, because recent studies revealed more beneficial effects of aspirin use [6]. For example, a study suggests that aspirin intake not only reduces the risk of CRC but also other cancers [2, 95]. In the two large cohort studies mentioned above, aspirin was found to be more effective in individuals with low expression of 15-hydroxyprostaglandin dehydrogenase [30]. Regular aspirin use was found to reduce the risk and mortality in patients with tumors overexpressing COX-2 and reduced CRC-induced mortality within patients with tumors expressing mutant PIK3CA. The use of aspirin for the treatment of cancer has also been explored. After a systematic review and meta-analyses of the published studies, the authors highlighted the need for randomized trials of aspiring treatment in a variety of cancers [27].

To avoid the side effects due to inhibition of COX-1, many selective COX-2-inhibitors have been developed for the treatment of pain-associated arthritis. Such drugs have also been studied for CRC prevention. For example, celecoxib (400 mg/day) was studied in individuals who have a history of adenomas in two trials, with treatment and follow-up for 3 years [3, 4]. Celecoxib treatment was shown to significantly reduce the relative risk of adenoma recurrence and advanced adenocarcinoma incidence. However, these two trials had to be terminated early because of cardiovascular events. Other related "-coxib" COX-2 inhibitors have also been shown to have similar cardiovascular toxicity to celecoxib, with a higher risk in patients with pre-existing cardiovascular risk factors. Because of this concern, two COX-2 inhibitors, rofecoxib and valdecoxib, were withdrawn from the market. A risk and benefit analysis indicated that the risk of celecoxib for

inducing cardiovascular events outweighs its beneficial effect for the prevention of CRC [91]. Some researchers believe that drugs, such as celecoxib, can still be used to prevent colon cancer by individuals who are at high risk for this cancer but at low risk for CVDs. A microbead formulation being studied has the potential to decrease the cardiovascular side effects [122]. Another approach is to use these NSAIDs at low doses in combination with another class of drugs. A successful example is the use of sulindac in combination with a low dose of difluoromethylornithine in a trial for preventing the progression of adenomas [82].

In the development of chemopreventive drugs, repurposing existing drugs appears to be an effective approach, because the safety profile of the drug is already known. The successful stories are tamoxifen and aspirin. Since tamoxifen is already a therapeutic drug for breast cancer, its application illustrates the concept of "early treatment." In the study of "-coxib" drugs for CRC prevention, after much effort and earlier excitement, the risk for cardiovascular events destroyed a good story.

Lessons Learned

Leads from epidemiological studies have generated interesting hypotheses on cancer prevention by dietary constituents, but few human trials have yielded convincing data to support the hypotheses tested [79]. A great number of laboratory studies suggested the potential cancer preventive activities of many naturally occurring and synthetic compounds, but results of these agents in human studies have been disappointing. In this section, we will discuss why many of the human trials failed to generate the expected results. The lessons learned in cancer chemoprevention research are discussed below.

Importance of Nutritional Status of the Population

As discussed above, epidemiological studies have shown associations between lower intake of certain micronutrients and increased cancer risk. In most situations, supplementation of a nutrient is only effective in preventing cancer in subjects with insufficiency in that nutrient. This concept is consistent with the result from the LNIT in studying a population with general micronutrient insufficiency. The NPC trial also showed that a beneficial effect of selenium supplementation was observed only in individuals with low baseline serum levels of selenium [16, 25]. Thus, trials would probably not work in subjects with sufficient levels of the intervening nutrients. This may be the case with the SELECT [71]. The mean baseline median plasma level of α-T and serum level of selenium was 12.5 μg/mL and 135 ng/mL, respectively, indicating the sufficiency of these nutrients. Many efforts have been made to develop metabolites or derivatives of nutrients as chemopreventive agents. For example, retinoic acid derivatives [110] have shown promise in the prevention of head and neck cancers in early studies [40], but later studies demonstrated lower beneficial to risk ratio [53, 85]. There are yet good examples to show that nutrients or their derivatives can be used as pharmaceutical agents for cancer prevention.

Problems in Interpreting Results from Laboratory Studies

At high enough concentrations, most phytochemicals are likely to inhibit growth or induce death of cancer cells in culture, and a large number of associated molecular changes can be observed. Based on these results, numerous mechanisms for the action of these agents have been proposed. Because of the large differences between situations in vitro and in vivo, it is possible that most of these proposed mechanisms are just the effects observed under the experimental conditions, but may not be related to cancer prevention. Even when an agent can be demonstrated to prevent cancer in rodent models, such activity in humans cannot be predicted because of the biological differences between rodents and humans. The dose-response relationship is also an important issue.

Bioavailabilities of Chemopreventive Agents and Dose-Response Relationship

Bioavailability is a major issue in correlating results from studies in cell lines, animals, and humans. An agent is only effective if sufficient concentrations can reach the target organs. Without considering the poor bioavailability of certain compounds (such as EGCG and curcumin), cell line studies could be misleading. A human trial may yield negative results because the dose of an agent may be too low or too high. For most agents, the doses required to demonstrate a cancer preventive effect in laboratory animals are usually higher than the levels of human consumption. However, a recent study of Apc^{Min} mice on a high-fat diet showed a nonlinear dose-response of resveratrol: the lowest dose of resveratrol (0.00007% in the diet) suppressed intestinal adenoma development better than a higher dose (0.0143% in diet) did [9]. The dose of 0.00007% in the diet (corresponding to 0.35 mg for a person taking 500 g of food in dry weight per day) is extremely low. The results are intriguing. This demonstrates more studies on dose-response relationships are needed.

Side Effects and Toxicity

With pharmacological agents, there are often side effects. The cardiovascular risk of some "-coxib" NSAIDS outweighs the benefits in CRC prevention, and their use in cancer prevention is not recommended. On the other hand, the CRC preventive activity of aspirin outweighs

the gastrointestinal bleeding issues (in some individuals) and the US Prevention Task Force recently endorsed the use of aspirin for the prevention of CRC [6]. For developing new drugs, toxicity is always a concern. The concept that natural products have very low or no toxicity may not be correct. For example, liver toxicity, due to intake of green tea extract-based supplement in large bolus doses for weight reduction, is well documented [61, 98]. The concept that naturally occurring compounds are nontoxic is based on observations from the intake of moderate doses or from agents with low bioavailabilities. When the bioavailability is significantly increased, for example, by the use of nanoparticles, toxicity should be an important concern.

Limitations of Current Chemoprevention Trials

Some dietary constituents may exert their protective effects early in life or many years before the onset of pre-malignant lesions. Clinical intervention studies are not able to study the population at such an early stage or for a long period of time. Some intervention studies might have started too late, such as when individuals already had precancerous lesions, or ended too early. Therefore, post-intervention follow-up is very important. It has been reported that in rats, supplementation with folic acid at an early stage of carcinogenesis decreased colon carcinogenesis, whereas supplementation at the late stage enhanced colon carcinogenesis [55]. The latter phenomenon is also consistent with the results of a human trial on colon cancer [17]. Therefore, a negative result in a human trial does not imply a lack of cancer preventive effect of this agent in early life or under other settings. Research on cancer chemoprevention is a rather complicated field. It is possible that many of the inconsistent observations in human studies were due to the lack of power to detect a protective effect in some intervention trials or due to chances for false negative or false positive results when multiple endpoints were analyzed.

Concluding Remarks

Important advances have been made in the field of cancer chemoprevention in the past 30 years [101, 111]; however, there are also many inconsistent and disappointing results. There is even the notion that “Chemoprevention of cancer is an almost universal failure” [90]. We do not agree with this statement. Many trials yielded disappointing results because of problems in the hypothesis, agent and the dosage used, the trial population, and/or the short trial period as described above. Therefore, more basic and clinical studies are needed. After we understand why some of the previous human trials failed, we can design better studies in the future.

Development of new approaches and new agents is urgently needed for cancer chemoprevention. The importance of immune defense is well-recognized and rapid advancement in immunotherapy has been made (reviewed in [81, 102, 107]). Phytochemical approaches for developing cancer immunotherapy has also been discussed [136]. The development of agents that enhance immune functions, such as natural killer cells mobilization and redistribution—recently demonstrated in mice subjected to running wheel exercise [87]—may be a promising approach for cancer prevention.

Among the lessons that we have learned, we would like to emphasize the importance of the integration of laboratory and human studies. For laboratory researchers, it is important to have human relevance in mind when pursuing studies. It is also important for epidemiologists and human trial investigators to appreciate the value of laboratory studies and recognize the limitation in the power of their studies in testing a hypothesis. Cancer prevention is an important field of research aimed to reduce human suffering. More interactions between laboratory researchers and scientists in human studies will lead to fruitful collaborations to advance the field of cancer chemoprevention.

Compliance with Ethical Standards

Conflict of Interest On behalf of all authors, the corresponding author states that there is no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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