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Does Vitamin E Prevent or Promote Cancer?

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Abstract

The cancer preventive activity of vitamin E has been suggested by many epidemiological studies. However, several recent large-scale human trials with α -tocopherol, the most commonly recognized and used form of vitamin E, failed to demonstrate a cancer preventive effect. The recently finished follow-up of the Selenium and Vitamin E Cancer Prevention Trial (SELECT) even showed higher prostate cancer incidence in subjects who took α -tocopherol supplementation. The scientific community and the general public are faced with a question “Does vitamin E prevent or promote cancer?” Our recent results in animal models have demonstrated the cancer preventive activity of γ - and δ -tocopherols as well as a naturally occurring mixture of tocopherols, and the lack of cancer preventive activity by α -tocopherol. Based on these results as well as information from the literature, we suggest that vitamin E, as ingested in the diet or in supplements that are rich in γ - and δ -tocopherols, is cancer preventive; whereas supplementation with high doses of α -tocopherol is not.

Vitamin E Consists of Different Forms of Tocopherols and Tocotrienols

Vitamin E is a group of fat-soluble antioxidant nutrients consisting of tocopherols and tocotrienols. Tocopherols are the major source of vitamin E in the U.S. diet. Each tocopherol contains a chromanol ring system and a phytyl chain containing 16 carbons. Depending upon the number and position of methyl groups on the chromanol ring, they exist as α -, β -, γ -, or δ -tocopherols (α -T, β -T, γ -T, and δ -T). Their structures are shown in Figure 1. α -T is trimethylated at the 5-, 7- and 8-positions of the chromanol ring, whereas γ -T is dimethylated at the 7- and 8-positions and δ -T is methylated at the 8-position. The phenolic group in the chromanol moiety effectively quenches lipid free radicals by one electron reduction. This is probably the most important physiological antioxidant mechanism to protect the integrity of biological membranes (1). All the tocopherols are antioxidants; however, γ -T and δ -T, due to the unmethylated carbons at the 5- and 7-positions at the chromanol ring, are more effective than α -T in trapping reactive nitrogen species (reviewed in (2)). Tocopherols are widely occurring in dietary oils such as those from corn, soybean, sesame and cottonseed oils as well as nuts. In these oils, γ -T is 3-5 times more abundant than α -T, and δ -T is as abundant in some oils; whereas β -T exists in only minute amounts. Upon ingestions these tocopherols are transported to the liver via the lymphatic system. In the

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liver, the α -T transfer protein preferentially transfers α -T to very low-density proteins, which carry tocopherols to the blood; γ -T is not effectively and δ -T is even less effectively transferred by this mechanism (1). Therefore, α -T is the most abundant form of vitamin E in the blood and nonhepatic tissues; γ -T levels are lower and δ -T levels are even lower. The γ -T and δ -T in the liver, however, are more actively metabolized through side-chain degradation by the ω -oxidation/ β -oxidation pathway (1). Whereas the biological activities of α -T have been extensively studied, the cancer preventive activities of γ - and δ -T are just beginning to be investigated.

α -, β -, γ - and δ -tocotrienols have the same chromanol ring structure as the corresponding tocopherols, but the side chain is made of three isoprenoids and contains three double bonds. Tocotrienols are found in palm oil and presented in low quantities in wheat and corn bran oils; they are not consumed in significant quantities in the United States, and will not be discussed herein.

Epidemiological Studies on Vitamin E and Cancer

The relationship between vitamin E nutrition and cancer risk has been investigated in many epidemiological studies and this topic has been recently reviewed by us (2). Although the results are inconsistent, many studies strongly suggest a protective effect of vitamin E (2). For example, of the three reported cohort studies on lung cancer, two studies found a significant inverse association between dietary intake of vitamin E and risk of lung cancer; the cancer preventive effects were found in current smokers, suggesting a protective effect of vitamin E against insults from cigarette smoking. In four case-control studies on lung cancer, three studies found lower serum α -T levels in lung cancer patients than in matched controls (2). For example, a case-control study in Europe found that the odds ratios of lung cancer for increasing quartiles of dietary α -T intake were 1.0, 0.63, 0.58, and 0.39, respectively (P for trend < 0.0001) (3). The authors concluded that α -T accounted for 34-53% reduction in lung cancer risk (3). Since the intake of γ -T was also increased in proportion to α -T in the diet, and at higher quantities, the beneficial effect could also be due to γ -T or the combined effects of all the forms of tocopherols. Of the 14 case-control studies on prostate cancer reviewed, seven showed an inverse association between dietary or blood levels of tocopherols and risk of prostate cancer (2). In two nested case-control studies (CLUE I and CLUE II), serum levels of γ -T, but not α -T, were inversely associated with prostate cancer risk (4, 5).

Intervention Trials with α -Tocopherol

Vitamin supplementation is used by many people for the prevention of diseases, including cancer, but the effectiveness of this practice is doubtful. For example, a recent meta-analysis of 14 articles on randomized controlled trials, cohort studies and case-control studies indicated that "there is no convincing evidence that the use of supplemental multivitamins or any specific vitamin affects the occurrence or severity of prostate cancer" (6). These studies, of course, include vitamin E, and α -T was the most commonly used form in vitamin E supplementation. The results from several large-scale intervention studies with α -T have been disappointing (7-10). For example, in the Women's Health Study with 39,876 healthy US women aged 45 years or older, the administration of 600 IU of α -T on alternate days did not significantly affect the incidence of colon, lung or total cancers (7). In the Physicians' Health Study II Randomized Control Trial, supplementation with vitamin E (400 IU of α -T every other day) or vitamin C (500 mg synthetic ascorbic acid) to physicians for eight years did not reduce the risk of prostate cancer or all other cancers (8).

The Alpha-Tocopherol Beta-Carotene (ATBC) Cancer Prevention Study was initially designed to investigate the prevention of lung cancer in male smokers with a daily

supplement of 50 IU of all-rac- α -tocopheryl acetate and 20 mg of β -carotene in a two-by-two design (11). Supplementation with α -T or β -carotene, or both, for 5–8 years did not produce a preventive effect on the incidence of lung cancer (11). However, α -T supplementation was found to be significantly associated with lower incidence of prostate cancer (as a secondary endpoint), and higher serum α -T was associated with a reduced risk of prostate cancer (12, 13). These results encouraged the launching of the Selenium and Vitamin E Cancer Prevention Trial (SELECT), in which 35,533 men (blacks > 50 years old; others > 55 years old) were randomized into four groups and took 400 IU all-rac- α -tocopheryl acetate or 200 μ g selenium from L-selenomethionine daily, in a two-by-two design, for an average of 5.5 years. However, the result showed that the supplementations did not prevent prostate or other cancers (9). It was noted that the α -T supplementation caused a 50% decrease in the median plasma γ -T levels (9). In the recently published results of the follow-up (for 7-12 years) of this study, subjects receiving the α -T supplementation had a hazard ratio of 1.17 for developing prostate cancer (10). The conclusion “Dietary supplementation with vitamin E significantly increased the risk of prostate cancer among healthy men” is alarming (10).

Inhibition of Tumorigenesis by Mixtures and Single Forms of Tocopherols in Animal Models

Previous cancer prevention studies in different animal models with α -T have obtained inconsistent results (2). On the other hand, our recent studies have demonstrated an inhibitory effect of a naturally occurring, γ -T-rich mixture of tocopherols (γ -TmT) against lung, colon, mammary gland, and prostate cancers (14-23). γ -TmT is a by-product in the distillation of vegetable oil and usually contains (per g) 130 mg α -T, 15 mg β -T, 568 mg γ -T, and 243 mg δ -T. This ratio of tocopherols approximates the ratio of tocopherols in the U.S. diet.

In studying the lung cancer preventive activity of γ -TmT, we treated A/J mice with a tobacco carcinogen, 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK) or NNK plus benzo[a]pyrene (B[a]P), a ubiquitous environmental pollutant (14). In both models, treatment of the mice with 0.3% γ -TmT in the diet significantly inhibited tumor multiplicity and tumor burden (14). In a xenograft tumor model, when 0.3% γ -TmT was given to NCr nu/nu mice in the diet one day after implantation of human lung H1299 cells, an inhibition of xenograft tumor growth was observed (14). After 6 weeks, the tumor size and weight were significantly reduced by 56% and 47%, respectively, as compared to the control group. In a similar experiment, the effectiveness of different forms of pure tocopherols in inhibiting the initiation and growth of H1299 xenograft tumor was compared (15). δ -T was found to be most effective, showing dose-response inhibition when given at 0.17% and 0.3% in the diet, and pure γ -T and γ -TmT were less effective. Studies of H1299 cells in culture also showed that δ -T was more effective than γ -T and γ -TmT in inhibiting cell growth, whereas α -T was not effective (14). In another transplanted tumor study, dietary 0.1% and 0.3% γ -TmT were found to dose-dependently inhibit the growth of subcutaneous tumors (formed by injection of murine lung cancer CL13 cells) in A/J mice (16). The inhibitory activities of γ -TmT, γ -T and δ -T in these carcinogenesis and xenograft tumor models were associated with enhanced apoptosis as well as decreased levels of 8-oxo-2'-deoxyguanine (8-oxo-dG, a marker for oxidative DNA damage), phosphorylated-histone 2AX (γ -H2AX, a response to double-strand DNA breakage), nitrotyrosine (a product of protein nitration), prostaglandin E2 (PGE2), and angiogenesis (14, 15).

Previous studies concerning the effect of α -T on colon carcinogenesis have yielded mostly negative results (2). Recently, we studied the effect of γ -TmT in the colons of mice that had been treated with azoxymethane (AOM) and dextran sulfate sodium (DSS) (17). Dietary γ -

TmT treatment (0.3% in the diet) resulted in a significantly lowered colon inflammation index (to 52% of the control) on day 7, and reduced the number of colon adenomas (to 9% of the control) on Week 7. γ -TmT treatment also resulted in higher apoptotic indexes in adenomas; lower PGE2, leukotriene B4 (LTB4) and nitrotyrosine levels in the colon on Week 7. In a second experiment, with AOM/DSS-treated mice sacrificed on Week 21, dietary γ -TmT treatment significantly inhibited adenocarcinoma and adenoma formation in the colon (to 17-33% of the control). These studies demonstrated the anti-inflammatory and anti-carcinogenic activities of γ -TmT in the colon. In another study, the inhibitory activities of α -T, γ -T, δ -T and γ -TmT were compared in an AOM-induced colon carcinogenesis model in rats (18). δ -T was most effective in inhibiting the formation of aberrant crypt foci (ACF) and high grade dysplastic ACF. γ -TmT and γ -T had slightly lower activities, but α -T was ineffective (18). This is the first clear demonstration of the higher cancer preventive activity of δ -T than γ -T, and the ineffectiveness of α -T, in an animal carcinogenesis model.

In previous studies on mammary carcinogenesis, four studies showed a protective effect of α -T, but one study showed no effect (2). Recently, we demonstrated that dietary administration of γ -TmT significantly inhibited *N*-methyl-*N*-nitrosourea-induced mammary tumorigenesis in rats (19, 20). We found that mammary tumor growth and tumor multiplicity, as well as a proliferation marker, proliferating cell nuclear antigen (PCNA), were markedly decreased by administration of γ -TmT. Administration of 0.1%, 0.3% or 0.5% γ -TmT dose-dependently suppressed mammary tumor development and growth (20). The inhibition of mammary tumorigenesis was associated with increased expression of p21, p27, PPAR- γ and cleaved caspase-3; whereas Akt and the estrogen-dependent signaling pathways in mammary tumors were significantly decreased by γ -TmT treatment (19). Furthermore, in *N*-methyl-*N*-nitrosourea-treated rats, dietary γ -TmT, γ -T and δ -T decreased PCNA levels, and increased the level of cleaved-caspase 3 in mammary tumors; but α -T was not active (21).

Previous studies on the effects of α -T and its synthetic analogs on prostate carcinogenesis and xenograft cancer growth have not yielded consistent results (2). Our recent work showed that 0.1% γ -TmT in the diet inhibited prostate carcinogenesis in the TRAMP model (22). During the development of prostate cancer in the TRAMP mouse, loss of expression of Nrf2 and related chemoprotective enzymes, such as catalase, superoxide dismutase, glutathione peroxidase, hemeoxygenase-1 and phase II detoxifying enzymes was observed, and γ -TmT treatment prevented the loss (22). Takahashi *et al.* 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 (24) and the inhibitory action was associated with enhanced apoptosis (activation of caspases). γ -T at 0.02% in the diet, however, did not inhibit the growth of transplanted Dunning R3327-H rat prostate tumors in male Copenhagen rats (25). Jiang *et al.* demonstrated that γ -T (administered *i.g.* at 125 mg/kg b.w. three times a week) decreased LNCaP xenograft tumor growth in nude mice by 35% ($p = 0.07$) (26). We recently demonstrated the dose-dependent inhibition of LNCaP prostate cancer growth by γ -TmT (0.1%, 0.3% and 0.5% in the diet) in a xenograft tumor model in severe combined immunodeficiency (SCID) mice (23).

Possible Mechanisms of Action by Which γ -T and δ -T Inhibit Carcinogenesis

As reviewed previously (2), many mechanisms have been proposed for the actions of tocopherols. Since our recent results show that γ -T and δ -T effectively inhibit carcinogenesis and xenograft tumor growth, but α -T does not, an important mechanistic issue is how γ -T and δ -T act differently from α -T. All tocopherols are antioxidants. However, the unmethylated 5-position of the chromanol ring enables γ -T and δ -T to

effectively quench reactive nitrogen species. In our studies on lung and colon cancers, the inhibitory activities of γ -TmT, γ -T and δ -T were mostly associated with the quenching of reactive oxygen and nitrogen species as well as inhibition of arachidonic acid metabolism. In addition, γ -T and δ -T are more extensively metabolized via side-chain degradation by the ω -oxidation/ β -oxidation pathway. The resulting metabolites, retaining the intact chromanol ring structure, have been reported to have interesting biological activities (2). The long chain metabolites have been shown to inhibit cyclooxygenase-2 activity (27). In mice and rats receiving δ -T or γ -T supplementation, substantial amounts of short-chain metabolites, δ - or γ -carboxyethyl hydroxychroman (CEHC) and carboxymethylbutyl hydroxychroman (CMBHC) have been found in blood and tissues (15). These metabolites, without the hydrophobic side chain, may effectively trap reactive oxygen and nitrogen species in the cytosol.

It has been shown that PPAR γ was more effectively activated by γ -T and δ -T in comparison to α -T (20), and this may be a mechanism for cancer prevention. Our results suggest that the activation of PPAR γ and the inhibition of ER α -dependent estrogen signaling are involved in the inhibition of mammary carcinogenesis (20). γ -T and δ -T have also been shown to be more active than α -T in inhibiting the growth and inducing apoptosis of different cancer cell lines (2). Cell cycle arrest at the S phase and related decreases in cyclin D1, cyclin E, p27, p21 and p16 have been reported (2, 20). For the induction of apoptosis, activation of caspases-3 and -9, the involvement of caspase-independent pathways, and interruption of *de novo* synthesis of sphingolipids have been proposed (2). Other mechanisms for cancer prevention that contribute to the higher activity of δ -T and γ -T, in contrast to the lack of activity of α -T, still remain to be elucidated.

Does Vitamin E Prevent or Promote Cancer?

This question can be better answered by examining the cancer preventive activities of specific forms of tocopherols at the nutritional and supra-nutritional levels. We propose that, at the nutritional level, all forms of vitamin E are cancer preventive. This concept is consistent with many observations that the dietary intake or plasma levels of α -T and other tocopherols was inversely associated with cancer risk, especially among smokers, who are under stronger oxidative stress (2-5). At the supra-nutritional level, however, α -T is not cancer preventive, which has been shown in several recent cancer prevention trials (7-10). In the SELECT, the mean baseline median plasma level of α -T was 12.5 μ g/mL, indicating a sufficiency in vitamin E nutrition of the participants. These results are consistent with many studies in animal models, by others and us, showing the lack of cancer preventive activity of α -T supplementation (2, 15, 18). Recent results further showed that δ -T, γ -T and γ -TmT are cancer preventive in animal models (2, 14-23), and we propose that γ -T and δ -T are also cancer preventive in humans. This concept may help to interpret the enhanced prostate cancer risk in subjects who took daily supplementation of 400 IU of α -T in the SELECT (10). This supplementation caused a 50% decrease in the median plasma γ -T level (9), and this may decrease the cancer preventive effect of γ -T. High concentrations of α -T may also decrease the cancer preventive activity of γ -T or δ -T by competing for its binding to proteins that are important for cancer prevention, but this possibility remains to be demonstrated. There may be other reasons for the enhanced prostate cancer risk by α -T supplementation and some have been discussed (28).

Concluding Remarks

Based upon the above discussions, we would like to make the following remarks:

1. Although α -T is the major form of vitamin E found in blood and tissues, α -T is not equivalent to vitamin E. For cancer prevention, we need to consider γ -T and δ -T;

γ -T is the most abundant form of dietary vitamin E and δ -T is also abundant in some dietary sources.

2. “We propose that, at the nutritional level, all tocopherols are cancer preventive, and either α -T or tocopherol mixtures can be used for cancer prevention. At the supra-nutritional levels, however, γ -T and δ -T are cancer preventive, but α -T is not effective. Future human cancer prevention trials with pure δ -T or γ -T could be very interesting. However, high doses of γ -T could lower blood and tissue levels of α -T (15). The biological effects of δ -T have not been studied sufficiently. From the lesson learned in the SELECT and a public health point of view, we suggest the use of the readily available, naturally occurring mixture γ -TmT or similar tocopherol mixtures for the first trial. Whether there are optimal ratios for these tocopherols for cancer prevention remains to be determined.”
3. In future clinical trials with tocopherols, it is important to have baseline blood levels of α -T, γ -T and δ -T before the trials begin. We propose that α -T would be cancer preventive when the blood levels of α -T are low. It is also important to measure the blood levels of different tocopherols at different time points during the intervention trial to understand how different subjects respond to the tocopherol supplements. The levels of side-chain degradation metabolites such as γ - and δ -CEHC, which exist in urine samples (2929), could also be used as biomarkers for the intake and metabolism of γ -T and δ -T.
4. More research on the biological activities of the different forms and mixtures of tocopherols is needed. The possible adverse effects of high doses of tocopherols warrant further investigation.

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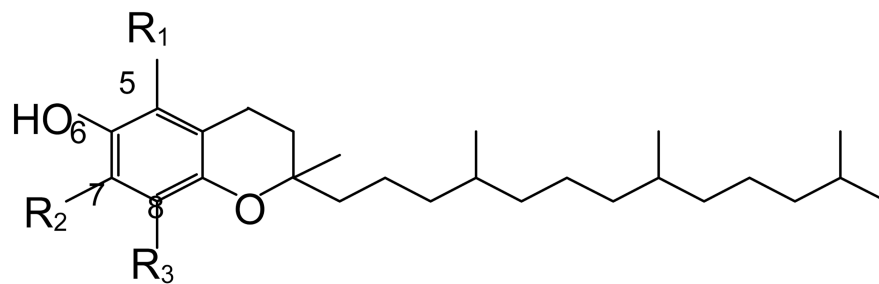
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α -Tocopherol

$R_1=R_2=R_3=CH_3$

β -Tocopherol

$R_1=R_3=CH_3, R_2=H$

γ -Tocopherol

$R_2=R_3=CH_3, R_1=H$

δ -Tocopherol

$R_1=R_2=H, R_3=CH_3$

Figure 1. Structures of tocopherols