Commentary

Does Vitamin E Prevent or Promote Cancer?

Chung S. Yang1, Nanjoo Suh1, and Ah-Ng Tony Kong2

Abstract

The cancer preventive activity of vitamin E has been suggested by many epidemiologic studies. However, several recent large-scale human trials with α-tocopherol, the most commonly recognized and used form of vitamin E, failed to show 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 shown 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. On the basis of 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. Cancer Prev Res; 5(5); 701–5. ©2012 AACR.

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-, β-, γ-, and δ-T). Their structures are shown in Fig. 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 physiologic antioxidant mechanism to protect the integrity of biologic membranes (1). All the tocopherols are antioxidants; however, γ-T and δ-T, due to the unmethylated carbons at the 5-position at the chromanol ring, are more effective than α-T in trapping reactive nitrogen species (reviewed in ref. 2). Tocopherols are widely occurring in dietary oils such as corn, soybean, sesame, and cottonseed oils as well as nuts. In these oils, γ-T is 3 to 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 ingestion these tocopherols are transported to the liver via the lymphatic system. In the 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 issues; 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 α-oxidation/β-oxidation pathway (1). Whereas the biologic 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 3 isoprenoids and contains 3 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.

Epidemiologic Studies on Vitamin E and Cancer

The relationship between vitamin E nutrition and cancer risk has been investigated in many epidemiologic 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 3 reported cohort studies on lung cancer, 2 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 4 case–control studies on lung cancer, 3 studies found lower serum α-T levels in patients with lung cancer than in matched controls (2). For example, a case–control...
study in Europe found that the ORs of lung cancer for increasing quartiles of dietary \( \alpha \)-T intake were 1.0, 0.63, 0.58, and 0.39, respectively (\( P_{\text{trend}} < 0.0001; \) ref. 3). The authors concluded that \( \alpha \)-T accounted for 34% to 53% reduction in lung cancer risk (3). Because the intake of \( \gamma \)-T was also increased in proportion to \( \alpha \)-T in the diet, and at higher quantities, the beneficial effect could also be due to \( \gamma \)-T or the combined effects of all the forms of tocopherols. Of the 14 case–control studies on prostate cancer reviewed, 7 showed an inverse association between dietary or blood levels of tocopherols and risk of prostate cancer (2). In 2 nested case–control studies (CLUE I and CLUE II), serum levels of \( \gamma \)-T, but not \( \alpha \)-T, were inversely associated with prostate cancer risk (4, 5).

**Intervention Trials with \( \alpha \)-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 \( \alpha \)-T was the most commonly used form in vitamin E supplementation. The results from several large-scale intervention studies with \( \alpha \)-T have been disappointing (7–10). For example, in the Women’s Health Study with 39,876 healthy U.S. women aged 45 years or older, the administration of 600 IU of \( \alpha \)-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 \( \alpha \)-T every other day) or vitamin C (500 mg synthetic ascorbic acid) to physicians for 8 years did not reduce the risk of prostate cancer or any 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-\( \alpha \)-tocopherol acetate and 20 mg of \( \beta \)-carotene in a two-by-two design (11). Supplementation with \( \alpha \)-T or \( \beta \)-carotene, or both, for 5 to 8 years did not produce a preventive effect on the incidence of lung cancer (11). However, \( \alpha \)-T supplementation was found to be significantly associated with lower incidence of prostate cancer (as a secondary endpoint), and higher serum \( \alpha \)-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 4 groups and took 400 IU all-rac-\( \alpha \)-tocopherol acetate or 200 \( \mu \)g selenium from \( \gamma \)-selenomethionine daily, in a two-by-two design, for an average of 5.5 years. However, the result showed that the supplements did not prevent prostate or other cancers (9). It was noted that the \( \alpha \)-T supplementation caused a 50% decrease in the median plasma \( \gamma \)-T levels (9). In the recently published results of the follow-up (for 7–12 years) of this study, subjects receiving the \( \alpha \)-T supplementation had an HR 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 \( \alpha \)-T have obtained inconsistent results (2). On the other hand, our recent studies have shown an inhibitory effect of a naturally occurring, \( \gamma \)-T–rich mixture of tocopherols (\( \gamma \)-TmT) against lung, colon, mammary gland, and prostate cancers (14–23). \( \gamma \)-TmT is a by-product in the distillation of vegetable oil and usually contains (per g) 130 mg \( \alpha \)-T, 15 mg \( \beta \)-T, 568 mg \( \gamma \)-T, and 243 mg \( \delta \)-T. This ratio of tocopherols approximates the ratio of tocopherols in the U.S. diet.

In studying the lung cancer preventive activity of \( \gamma \)-TmT, we treated A/J mice with a tobacco carcinogen, 4-(methyl-nitrosamino)-1-(3-pyridyl)-1-butanone (NNK) or NNK plus benz[a]pyrene (B[a]P), a ubiquitous environmental pollutant (14). In both models, treatment of the mice with 0.3% \( \gamma \)-TmT in the diet significantly inhibited tumor multiplicity and tumor burden (14). In a xenograft tumor model, when 0.3% \( \gamma \)-TmT was given to NCr nu/nu mice in the diet 1 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 with 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). \( \delta \)-T was found to be most effective, showing dose–response inhibition when given at 0.17% and 0.3% in the diet, and pure \( \gamma \)-T and \( \gamma \)-TmT were less effective. Studies of H1299 cells in culture also showed that \( \delta \)-T was more.

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**Figure 1.** Structures of tocopherols.
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/I 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). 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. Because 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 previous studies on mammary carcinogenesis, 4 studies showed a protective effect of α-T, but one study showed no effect (2). Recently, we showed 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 multicentricity, 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, heme-oxygenase-1, and phase II detoxifying enzymes was observed, and γ-TmT treatment prevented the loss (22). Takahashi and colleagues showed 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 and colleagues showed that γ-T (administered intragastrically at 125 mg/kg body weight 3 times a week) decreased LNCaP xenograft tumor growth in nude mice by 35% (26). We recently showed 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).

Published OnlineFirst April 3, 2012; DOI: 10.1158/1940-6207.CAPR-12-0045

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suggest that the activation of PPARγ and the inhibition of 
ERα-dependent estrogen signaling are involved in the inhi-
bition 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 cas-
pases-3 and -9, the involvement of caspase-independent 
pathways, and interruption of de novo synthesis of spin-
golipids 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 supranutritional levels. We propose 
that, at the nutritional level, all forms of vitamin E are cancer 
preventive. This concept is consistent with many observa-
tions 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 oxida-
tive stress (2–5). At the supranutritional 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 μg/mL, 
indicating a sufficiency in vitamin E nutrition of the parti-
cipants. 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 shown. There may be other reasons for the 
enhanced prostate cancer risk by α-T supplementation and 
some have been discussed (28).

**Concluding Remarks**

On the basis of 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 supranutritional 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 biologic 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 (29), could also be used 
as biomarkers for the intake and metabolism of γ-T and 
δ-T.

4. More research on the biologic activities of the different 
forms and mixtures of tocopherols is needed. The 
possible adverse effects of high doses of tocopherols 
warrant further investigation.

**Disclosure of Potential Conflicts of Interest**

No potential conflicts of interest were disclosed.

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**Development of methodology:** C.S. Yang, N. Suh, A.-N.T. Kong

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izing data, constructing databases):** C.S. Yang

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**Acknowledgments**

The authors thank Drs. Allan H. Conney and Xi Zheng for helpful 
discussions; and Drs. Guangxun Li, Zhihong Yang, and Fei Guan for their 
contributions to the research on this topic.

**Grant Support**

This work was supported by U.S. NIH grants CA133021, CA141756, and 
CA152826 as well as the John L. Colaluzzo Chair Endowment Fund.

**Received January 27, 2012; revised March 2, 2012; accepted March 16, 
2012; published OnlineFirst April 3, 2012.**

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