Does Vitamin E Prevent or Promote Cancer?
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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 absent in some oils; whereas β-T exists in only minute amounts. Upon inges-

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 α-T intake were 1.0, 0.63, 0.58, and 0.39, respectively (P trend < 0.0001; ref. 3). The authors concluded that α-T accounted for 34% to 53% reduction in lung cancer risk (3). Because 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, 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 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 U.S. women aged 45 years or older, the administration of 600 IU of α-T every other day 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 8 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-tocopherol 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 to 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 4 groups and took 400 IU all-rac-α-tocopherol acetate or 200 μg selenium from γ-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 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 α-T have obtained inconsistent results (2). On the other hand, our recent studies have showed 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-(methyl-nitrosamino)-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 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). 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'-deoxyguanosine (8-oxo-dG, a
marker for oxidative DNA damage), phosphorylated his-
tone 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; ref. 17). Dietary γ-TmT treat-
ment (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 showed the anti-
inflammatory and anticarcinogenic 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 azoxymethane-
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, 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
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-depen-
dent signaling pathways in mammary tumors were sig-
nificantly 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).

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 carcinogen-
isis and xenograft tumor growth, but α-T does not, an
important mechanistic issue is how γ-T and δ-T act differ-
cently 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 addi-
tion, γ-T and δ-T are 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 biologic
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, ω- or γ-carboxethyl hydroxy-
chroman (CEHC) and carboxymethylbutyl hydroxychro-
man (CMBHC) have been found in blood and tissues
(15, 18). These metabolites, without the hydrophobic side
chain, may effectively trap reactive oxygen and nitrogen
species in the cytosol.

It has been shown that PPARγ was more effectively
activated by γ-T and δ-T in comparison with α-T (20), and
this may be a mechanism for cancer prevention. Our results
suggest that the activation of PPARγ and the inhibition of ERα-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 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.

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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