

Cancer Prevention by Different Forms of Tocopherols

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Abstract Many epidemiological studies have suggested that a low vitamin E nutritional status is associated with increased cancer risk. However, several recent large-scale human trials with high doses of α -tocopherol (α -T) have produced disappointing results. This points out the need for a better understanding of the biological activities of the different forms of tocopherols. Using a naturally occurring tocopherol mixture (γ -TmT) that is rich in γ -T, we demonstrated the inhibition of chemically induced lung, colon, and mammary cancer formation as well as the growth of xenograft tumors derived from human lung and prostate cancer cells. This broad anticancer activity of γ -TmT has been attributed mainly to the trapping of reactive oxygen and nitrogen species and inhibition of arachidonic acid metabolism. Activation of peroxisome proliferator-activated receptor γ (PPAR γ) and the inhibition of estrogen signaling have also been observed in the inhibition of mammary cancer development. δ -T has been shown to be more active than γ -T in inhibiting the growth of human lung cancer cells in a xenograft tumor model and the development of aberrant crypt foci in azoxymethane-treated rats, whereas α -T is not effective in these models. The higher inhibitory activities of δ -T and γ -T (than α -T) are proposed to be due to their trapping of reactive nitrogen species and their capacity to generate side-chain degradation products, which retain the intact chromanol ring structure and could have cancer preventive activities.

Keywords Breast · Colon · Inhibition · Lung cancer · Prostate · Tocopherols · Vitamin E

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1 Introduction

Tocopherols, collectively known as vitamin E, are a family of fat-soluble phenolic compounds. 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) [1]. 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 hydrocarbon tail and ring structure provide the lipophilicity for tocopherols to be incorporated into the lipid bilayers of biological membranes. The phenolic group in the chromanol moiety effectively quenches lipid free radicals by one electron reduction. The resulting tocopherol phenoxy radical can be reduced by ascorbic acid or glutathione to regenerate the phenolic group. This is probably the most important physiological antioxidant mechanism to protect the integrity of biological membranes. The unmethylated carbons at 5- and 7-positions at the chromanol ring are electrophilic centers that effectively react with oxygen and nitrogen species (RONS). All the tocopherols are antioxidants; however, γ -T and δ -T are more effective than α -T in trapping reactive nitrogen species [2–4]. The formation of 5-nitro- γ -T, 5-nitro- δ -T, 7-nitro- δ -T, and 5,7-dinitro- δ -T have been reported [5].

The major dietary sources of tocopherols are vegetable oils, such as oils from corn, soybean, sesame, cottonseeds, and nuts [6, 7]. In these oils, γ -T is three to five times more abundant than α -T, and δ -T is as abundant as α -T, whereas β -T exists in only minute amounts. Upon ingestions, these tocopherols are incorporated into the chylomicrons and transported to the liver via the lymphatic system. The transfer of tocopherols in the liver to very low-density lipoproteins is mediated by a specific α -T transfer protein, which preferentially transfers α -T over γ -T, and δ -T is even less effectively transferred [8]. As a consequence, α -T is efficiently secreted into the circulation and transported to nonhepatic tissues, and is the most abundant form of vitamin E in the blood and tissues. The blood and tissue levels of γ -T are much lower, and those of δ -T are even lower.

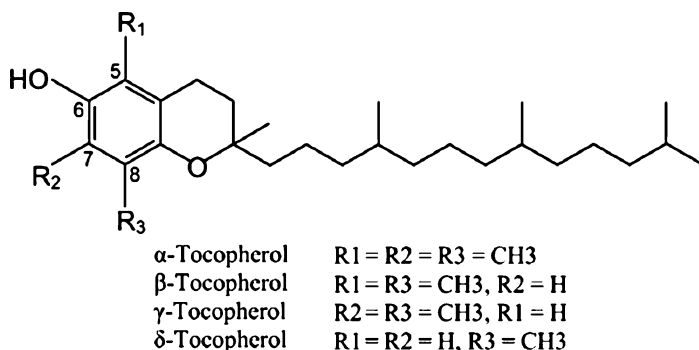


Fig. 1 Structures of tocopherols

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 -T is generally considered to be “the vitamin E.” Therefore, many studies on vitamin E have been conducted with α -tocopheryl acetate. However, the results of many of the animal studies are inconsistent, and the results of some of the human intervention studies are disappointing and at variance with those from observation epidemiological studies (reviewed in [9]). In recent years it has been recognized that γ -T and δ -T have beneficial health effects beyond α -T [9–12]. Our collaborative team at Rutgers has demonstrated the broad cancer preventive activities of a γ -T-rich mixture of tocopherols (γ -TmT) as well as pure δ -T and γ -T [13–20]. In this chapter we will discuss the cancer preventive activities of different forms of tocopherols, based on our recent results from animal studies, and their implications to human cancer prevention.

2 Studies on Tocopherols and Cancer in Humans

2.1 Observational Epidemiological Studies

Because of the involvement of RONS in carcinogenesis, the antioxidant nutrients tocopherols have been suggested to have cancer preventive functions. There are many studies that are in support of this concept, but some studies are not (reviewed in [9]). 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 [21–23]. In both of these studies, 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 [9]. In a recent case–control study, Mahabir et al. observed 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) [24]. The authors concluded that α -T accounts for 34–53% reduction in lung cancer risk [24]. 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. γ -T is three to four times more abundant than α -T and δ -T could also be more abundant than α -T in the American diet.

Of the six cohort studies on colorectal cancer reviewed, two studies showed an inverse association between vitamin E intake and colorectal cancer risk [25, 26]. For example, in the Iowa Women's Health Study [25], a high intake of vitamin E was associated with a low risk of colon cancer (P for trend <0.0001). This study also found that the protective effect was stronger in subjects under the age of 65 years than in subjects older than that. Of the two case–control studies, one found an inverse association between supplementary vitamin E intake and colorectal cancer risk [27], but the other did not find a protective effect of dietary or supplementary vitamin E against colorectal cancer [28].

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 [9]. 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 [29, 30]. In CLUE I, serum levels of γ -T were significantly lower in subjects who developed prostate cancers than subjects who did not ($P = 0.02$), but no dose-response trend was observed. In CLUE II, a strong inverse association between γ -T and prostate cancer risk was observed ($P = 0.0001$) [29]. Out of the six cohort studies examining the association between dietary or supplementary vitamin E intake and prostate cancer risk, none found any significant association. In the National Institutes of Health-American Association of Retired Persons Diet and Health Study, dietary γ -T and δ -T were found to be significantly related to a reduced risk of advanced prostate cancer (RR: 0.68; 95% CI: 0.56–0.84 for γ -T and RR: 0.8; 95% CI: 0.67–0.96 for δ -T), but supplemental vitamin E (α -T) intake beyond dietary sources was not related to prostate cancer risk [31].

In 24 case–control studies on the relationship between the use of vitamin E supplementation and breast cancer; 11 studies found a risk reduction; however, 13 studies did not find an association [32]. In the Shanghai Breast Cancer Study, it was found that vitamin E supplement may reduce the risk of breast cancer among women who have low dietary intake [33]. In 12 cohort studies there was no association between vitamin E supplementation and breast cancer risk [32]. In one cohort study, the European Prospective Investigation into Cancer and Nutrition (EPIC) trial observed that vitamin E did not reduce breast cancer risk, but there was a weak risk reduction in post-menopausal women [34]. Previously, detailed assessments revealed that vitamin E (α -T) supplements did not protect against breast cancer [35, 36]. Recently, Fulan et al. performed a meta-analysis on 38 studies between vitamin E and breast cancer [37]. For case–control studies, dietary vitamin E and total vitamin E reduced breast cancer risk by 18% and 11%, respectively [37]. When the cohort studies were pooled with the case–control studies, dietary vitamin E and total vitamin E both became nonsignificant [37]. Thus, a conclusion remains elusive between breast cancer and vitamin E. The term “vitamin E” is used loosely, and a

distinction in these case–control and cohort studies needs to clarify which variant of vitamin E is utilized. Thus, epidemiological evidence between different forms of vitamin E and breast cancer is limited.

2.2 *Intervention Trials with α -Tocopherol*

There have been many intervention trials to study the effects of vitamin E supplementation on cancer. However, the results from several large-scale intervention studies with α -T have been disappointing [38–41]. 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 [38]. 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 [39].

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-racemic- α -tocopheryl acetate and 20 mg of β -carotene in a two-by-two design [42]. Supplementation with α -T or β -carotene, or both, for 5–8 years did not produce a significant effect on the incidence of lung cancer [42]. However, α -T supplementation was significantly associated with the reduced incidence of prostate cancer (as a secondary endpoint) and higher serum α -T was associated with a reduced risk of prostate cancer (RR: 0.80; 95% CI: 0.66–0.96 for highest vs lowest quintile; P for trend = 0.03) [43–45]. These results encouraged the launching of the selenium and vitamin E cancer prevention trial (SELECT), in which 35,533 men from 427 study sites in the United States, Canada, and Puerto Rico were randomized between August 2001 and June 2004 [40]. These healthy individuals (ages >55 years old, and for blacks >50 years old) were allocated 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 [40]. It was noted that the α -T supplement caused a 50% decrease in median plasma γ -T levels [40]. In the recently published follow-up (for 7–12 years) results of this study, subjects receiving α -T had a hazard ratio of 1.17 for developing prostate cancer [41]. A possible interpretations of the result is that supplementation of a nutrient to a population that is already adequate in this nutrient may not produce any beneficial effects. It is also possible that supplementation of a large quantity of α -T decreases the blood and tissue levels of γ -T, which has been suggested to have stronger anti-inflammatory and cancer preventive activities [9–12, 46, 47]. Other possible mechanisms have also been discussed [48], but the exact reasons for these negative results are not known. Nevertheless, the disappointing outcome of these large-scale trials reflects our lack of 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.

3 Inhibition of Tumorigenesis by Single Forms and Mixtures of Tocopherol in Animal Models

Previous cancer prevention studies in different animal models with pure α -T have obtained inconsistent results [9]. On the other hand, recent studies from our research team at Rutgers University have demonstrated the inhibitory effect of γ -TmT against lung, colon, mammary gland, and prostate cancers [13–20]. γ -TmT is a by-product in the distillation of vegetable oil and usually contains (per gram) 130 mg α -T, 15 mg β -T, 568 mg γ -T, and 243 mg δ -T. Some of our studies are discussed in the following sections.

3.1 *Inhibition of Lung Carcinogenesis and Tumor Growth*

In studying the lung cancer preventive activity of γ -TmT, we treated A/J mice (6 weeks old) with a tobacco carcinogen, 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK), plus benzo[a]pyrene (B[a]P), a ubiquitous environmental pollutant, at doses of 2 μ mol each, by oral gavage weekly from weeks 1 to 8. At week 19, the mice in the control group (on the AIN93M diet) developed an average of 21 tumors per mouse [13]. Treatment of the mice with 0.3% γ -TmT in the diet during the entire experimental period lowered the tumor multiplicity to 14.8 (30% inhibition, $p < 0.05$). γ -TmT treatment also significantly reduced the average tumor volume and tumor burden by 50% and 55%, respectively [13]. In a second study, lung tumorigenesis was induced by i.p. injection of two doses of NNK (100 mg/kg on week 1 and 75 mg/kg on week 2). The 0.3% γ -TmT diet was given during the carcinogen-treatment stage, the post-initiation stage, or the entire experimental period. γ -TmT treatment during these three time periods all reduced the tumor multiplicity (17.1, 16.7, and 14.7 tumors per mouse, respectively, as compared to 20.8 in the control group; $p < 0.05$). Moreover, the tumor burden was significantly reduced by γ -TmT treatment given during the tumor initiation stage or during the entire experimental period by 36% and 43% inhibition, respectively [13].

In the NNK plus B[a]P-treated model, dietary γ -TmT treatment significantly increased the apoptotic index (based on cleaved-caspase 3 positive cells) from 0.09% to 0.25% in the lung tumors, whereas the treatment did not affect apoptosis in nontumorous lung tissues. Dietary γ -TmT treatment also significantly decreased the percentage of cells with positive immunostaining for 8-hydroxydeoxyguanine (8-oxo-dG) (from 26% to 17%), a marker for oxidative DNA damage, as well as for γ -H2AX (from 0.51% to 0.23%), a reflection of double-strand break-induced DNA repair. The plasma levels of prostaglandin E2 (PGE2) and leukotriene B4 (LTB4) were markedly elevated in the tumor-bearing A/J mice at week 19 as compared to mice that received no carcinogen treatment. γ -TmT treatment resulted in lower plasma levels of PGE2 (by 61%, $p < 0.05$) and LTB4 (by 12.7%, $p < 0.1$). These results demonstrate the antioxidant and anti-inflammatory activities of γ -TmT.

The antiangiogenic activity of dietary γ -TmT was demonstrated with antiendothelial cell CD31 antibodies. CD31-labeled capillary clusters and blood vessels were observed mainly in the peripheral area of the lung adenomas, and dietary γ -TmT reduced the microvessel density (blood vessels/mm²) from 375 to 208 ($p < 0.05$) [13].

When 0.3% γ -TmT was given to NCr nu/nu mice in the diet 1 day after implantation of human lung H1299 cells (1×10^6 cells injected subcutaneously per site to both flanks of the mouse), an inhibition of xenograft tumor growth was observed [13]. After 6 weeks, the tumor size and weight were significantly reduced by 56% and 47%, respectively, as compared to the control group. The γ -TmT treatment also caused a 3.3-fold increase in apoptotic index as well as a 52% decrease in 8-oxo-dG-positive cells and a 57% decrease in γ -H2AX-positive cells in the xenograft tumors. Strong cytoplasm staining of nitrotyrosine was observed in xenograft tumors, and the staining intensity was decreased by 44% in mice that received γ -TmT. The γ -TmT treatment also reduced the plasma LTB4 level by 36.5% ($p < 0.05$) [13].

In a similar experiment, the effectiveness of different forms of pure tocopherols in the inhibition of H1299 xenograft tumor growth was compared [14]. Pure 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 [13]. In another transplanted tumor study, dietary 0.1% and 0.3% γ -TmT were found to inhibit the growth of subcutaneous tumors (formed by injection of murine lung cancer CL13 cells) in A/J mice by 54% and 80%, respectively, on day 50 [15].

3.2 Inhibition of Colon Inflammation and Tumorigenesis

Previous studies concerning the effect of α -T on colon carcinogenesis have yielded mostly negative results [9]. 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) [16]. Dietary γ -TmT treatment (0.3% in the diet) resulted in a significantly lowered colon inflammation index (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, LTB4, and nitrotyrosine levels in the colon, and lower PGE2, LTB4, and 8-isoprostane levels in the plasma on week 7. In the 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). In the third experiment, mice received dietary treatment with 0%, 0.1%, and 0.3% γ -TmT in the AIN 93 M basal diet. One week later, 1% DSS was given to mice in drinking water for 1 week to induce inflammation, and a dose-dependent anti-inflammation by γ -TmT treatment was also observed [16]. These studies demonstrate the anti-inflammatory and anticarcinogenic activities of γ -TmT in the colon.

3.3 *Inhibition of Mammary Carcinogenesis*

In previous studies on mammary carcinogenesis, four studies showed a protective effect of α -T [49–52], but one study showed no effect [53]. Recently, we demonstrated that dietary administration of γ -TmT significantly inhibited *N*-methyl-*N*-nitrosourea-induced mammary tumorigenesis in rats [17, 18]. 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 [17]. The inhibition of mammary tumorigenesis was associated with increased expression of p21, p27, cleaved caspase-3, and PPAR- γ , whereas Akt and the estrogen-dependent signaling pathways in mammary tumors were significantly decreased by γ -TmT treatment [17]. Furthermore, in *N*-methyl-*N*-nitrosourea-treated rats, dietary γ -TmT, γ -T, and δ -T decreased PCNA levels while increasing the levels of cleaved-caspase 3 in mammary tumors, but α -T was not active [32].

Our in vitro data showed that treatment with γ -TmT, γ -, and δ -T inhibited cell proliferation in MCF-7 breast cancer cells in a dose-dependent manner, while α -T did not [17]. In MCF-7 and T47D breast cancer cells, γ -TmT, γ -T, and, more strongly, δ -T enhance the transactivation of peroxisome proliferator-activated receptor (PPAR)- γ [17]. Since PPAR γ transactivation can be suppressed by ER α binding to the PPAR response element [54], the inhibition of ER α expression by tocopherols may result in the activation of PPAR γ . Thus, tocopherols may indirectly activate PPAR γ , and possibly through this pathway may interfere with ER- α expression, inhibit cell cycle progression, and induce apoptosis to prevent breast cancer. The inhibitory activities of γ -T and δ -T, but not α -T, have also been demonstrated in breast cancer cell lines by other authors [41, 54–56]. In a xenograft model, γ -T treatment inhibited tumor growth and enhanced apoptosis of tumor cells [57].

3.4 *Inhibition of Prostate Carcinogenesis and Tumor Growth*

Barve et al. demonstrated the inhibition of prostate carcinogenesis in the TRAMP model by 0.1% γ -TmT in the diet [20]. During the development of prostate cancer in the TRAMP mouse, loss of expression of Nrf2 and related cell protective enzymes was observed, and γ -TmT treatment prevented the loss [20]. 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 (TRAP) model [58] and the inhibitory action was associated with enhanced apoptosis (activation of caspase-3 and caspase-7). In collaboration with Dr. Xi Zheng and others, we also 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

immunodeficient (SCID) mice [19]. The inhibition was associated with suppressed cell mitosis and stimulated apoptosis (activation of caspase-3).

4 Possible Mechanisms of Action

As reviewed previously [9], 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 why γ -T and δ -T are more active than α -T. All tocopherols are antioxidant. However, the unmethylated 5-position of the chromanol ring enables γ -T and δ -T to quench reactive nitrogen species. In addition, because γ -T and δ -T are less effectively transported to the blood, they are prone to 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 [9, 12]. The long chain metabolites have been shown to inhibit cyclooxygenase-2 activity [59]. In mice and rats receiving δ -T or γ -T supplementation, short-chain metabolites, δ - or γ -carboxyethyl hydroxychroman, and carboxymethylbutyl hydroxychroman have been found in blood and tissues at micromolar concentrations [14]. These metabolites, without the hydrophobic phytyl chain, may effectively trap RONS in the cytosol.

The activation of PPAR γ and the inhibition of ER α -dependent estrogen signaling may play a role in the inhibition of mammary carcinogenesis. It has been shown that PPAR γ was more effectively activated by γ -T and δ -T in comparison to α -T [17]. 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 [9]. For the former action, cell cycle arrest at the S phase and related decrease in cyclin D1, cyclin E, p27, p21, and p16 have been reported [9, 17]. For the induction of apoptosis, activation of caspase-2 and caspase-9, the involvement of caspase-independent pathways, and interruption of de novo synthesis of sphingolipids, have been proposed [9]. Other mechanisms for cancer prevention that contribute to the high activity of δ -T over γ -T in contrast to the very low or null activity of α -T still remain to be discovered.

5 Concluding Remarks

Based on epidemiological and animal studies, we may suggest that at the nutritional level, α -T, being an antioxidant nutrient, contributes to the cancer preventive activity. At the supra-nutritional level, however, γ -T and δ -T are cancer preventive, but α -T is not. The lack of cancer preventive activity of α -T is consistent with many previous studies in animal models [9] and may explain why disappointing results were observed in some recent large scale human trials with α -T [38–41, 60]. The decrease

of γ -T levels in the blood and nonhepatic tissues by high doses of α -T has been well demonstrated in animal models and humans [9, 40]. When a high dose of α -T is used, it may decrease the blood and tissue levels of γ -T and diminish its cancer preventive activity [40, 41]. α -T may also increase the cancer incidence if it competes with γ -T and δ -T for binding to molecular targets that are important for cancer prevention. In future intervention trials, high doses of γ -T may also not be suitable because this may decrease the blood and tissue levels of α -T, as has been shown in animals [14]. In the light of the broad cancer preventive activity of γ -TmT and its general availability, this or similar tocopherol mixtures may have a high potential for practical application. These mixtures, with different tocopherols, existing at ratios approximately equal to those in our diet, may have an advantage over pure tocopherols.

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