REVIEW

Natural Forms of Vitamin E as Effective Agents for Cancer Prevention and Therapy

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ABSTRACT

Initial research on vitamin E and cancer has focused on α-tocopherol (αT), but recent clinical studies on cancer-preventive effects of αT supplementation have shown disappointing results, which has led to doubts about the role of vitamin E, including different vitamin E forms, in cancer prevention. However, accumulating mechanistic and preclinical animal studies show that other forms of vitamin E, such as γ-tocopherol (γT), δ-tocopherol (δT), γ-tocotrienol (γTE), and δ-tocotrienol (δTE), have far superior cancer-preventive activities than does αT. These vitamin E forms are much stronger than αT in inhibiting multiple cancer-promoting pathways, including cyclo-oxygenase (COX)– and 5-lipoxygenase (5-LOX)–catalyzed eicosanoids, and transcription factors such as nuclear transcription factor κB (NF-κB) and signal transducer and activator of transcription factor 3 (STAT3). These vitamin E forms, but not αT, cause pro-death or antiproliferation effects in cancer cells via modulating various signaling pathways, including sphingolipid metabolism. Unlike αT, these vitamin E forms are quickly metabolized to various carboxychromanols including 13′-carboxychromanols, which have even stronger anti-inflammatory and anticancer effects than some vitamin precursors. Consistent with mechanistic findings, γT, δT, γTE, and δTE, but not αT, have been shown to be effective for preventing the progression of various types of cancer in preclinical animal models. This review focuses on cancer-preventive effects and mechanisms of γT, δT, γTE, and δTE in cells and preclinical models and discusses current progress in clinical trials. The existing evidence strongly indicates that these lesser-known vitamin E forms are effective agents for cancer prevention or as adjuvants for improving prevention, therapy, and control of cancer. *Adv Nutr* 2017;8:850–67.

Keywords: long-chain carboxychromanol, tocopherol, tocotrienol, inflammation, food, cancer, adenomas, colitis, biology, medicine

Introduction

The number of diagnosed cancer cases is expected to grow worldwide from 13.3 million in 2010 to 20 million by 2030 (1). Because of the genetic heterogeneity and complexity of advanced cancer, cancer treatment has faced tremendous challenges, including drug resistance and a high frequency of recurrence. The development of effective prevention strategies, such as early detection and early interruption of the carcinogenic process, is important in reducing cancer mortality (2, 3). Chemoprevention, including the use of natural and synthetic compounds for preventing or delaying cancer development to a late stage, is an important public health strategy for decreasing cancer burden. Until recently, the study of vitamin E for cancer prevention has mostly centered on α-tocopherol (αT), the predominant form of vitamin E in tissues. Although epidemiologic studies have consistently reported an inverse association between αT and cancer risk, studies of the potential use of αT for preventing cancer have shown inconsistent and disappointing outcomes in many large randomized studies (4–6). The results of the Selenium and Vitamin E Cancer Prevention Trial (SELECT) surprisingly showed that dietary supplementation of αT at 400 IU/d appeared to increase the risk of prostate cancer in healthy men compared with placebo (7). In contrast, other forms of vitamin E and long-chain vitamin E metabolites have been shown to have robust cancer-prevention effects in mechanistic studies and preclinical cancer models, whereas αT often showed weak or ineffective anticancer effects in these studies. In this review, we focus on the role of different forms of vitamin E

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Abbreviations used: ACF, aberrant crypt foci; AOM, azoxymethane; CEHC, carboxyethyl-hydroxychroman; COOH, carboxychromanol; COX, cyclo-oxygenase; CRC, colorectal cancer; CSC, cancer stem cell; DNMT, DNA methyltransferase; DR, death receptor; DSS, dextran sodium sulfate; ER, estrogen receptor; HMG-CoA, β-hydroxy-β-methylglutaryl coenzyme A; LTB_4, leukotriene B_4; NMU, N-nitroso-N-methylurea; NSAID, nonsteroidal anti-inflammatory drug; PDA, pancreatic ductal adenocarcinoma; PhIP, 2-amino-1-methyl-6-phenylimidazo[4,5-b]pyridine; PIN, prostate intraepithelial neoplasia; STAT3, signal transducer and activator of transcription factor 3; TRAMP, transgenic adenocarcinoma of the mouse prostate; $T_{1/2}$, half-life; TRAIL, TNF-related apoptosis-inducing ligand; TRF, tocotrienol-rich fraction; αT, βT, γT, and δT, α-, β-, γ- and δ-tocopherol, respectively; αTE, βTE, γTE, and δTE, α-, β-, γ-, and δ-tocotrienol, respectively; γTmT, γT-rich mixed tocopherol; 5-LOX, 5-lipoxygenase.

[i.e., γ-tocopherol (γT), δ-tocopherol (δT), γ-tocotrienol (γTE), and δ-tocotrienol (δTE)] in cancer prevention and treatment in cell-based mechanistic studies and preclinical models as well as some human clinical studies that were inspired by the encouraging outcomes from basic and translational research.

Current Status of Knowledge

Vitamin E forms and metabolites

Natural forms of vitamin E include (RRR)-αT, β-tocopherol (βT), γT, and δT and (R)-α-tocotrienol (αTE), β-tocotrienol (βTE), γTE, and δTE, all of which have a chromanol ring and a phytyl side chain (**Figure 1**A). Although tocopherols have a saturated side chain, tocotrienols have 3 double bonds on the side chain. All vitamin E forms are lipophilic antioxidants because they have the phenolic group on the chromanol ring that can donate a hydrogen atom capable of scavenging lipid peroxide radicals (8). Vitamin E forms are naturally synthesized by plants and are rich in nuts, plant seeds, and plant oils (8–10). Humans and animals rely on these food sources to obtain vitamin E. Dietary amounts of specific vitamin E forms vary greatly among different food sources (8).

Despite sharing similar structures and antioxidant activities, vitamin E forms differ greatly in bioavailability and metabolism. Among the 8 members of naturally occurring vitamin E, αT is the predominant form of vitamin E in the blood and tissues and low intakes of this form result in vitamin E deficiency–associated ataxia (11). Serum concentrations of αT in humans can vary from <20 to >50 μM with a half-life ($T_{1/2}$) reported to be ~28–30 h, depending on the intake of this vitamin and food components, especially dietary fat contents (12). Compared with αT, other vitamin E forms have lowered bioavailability and a 4- to

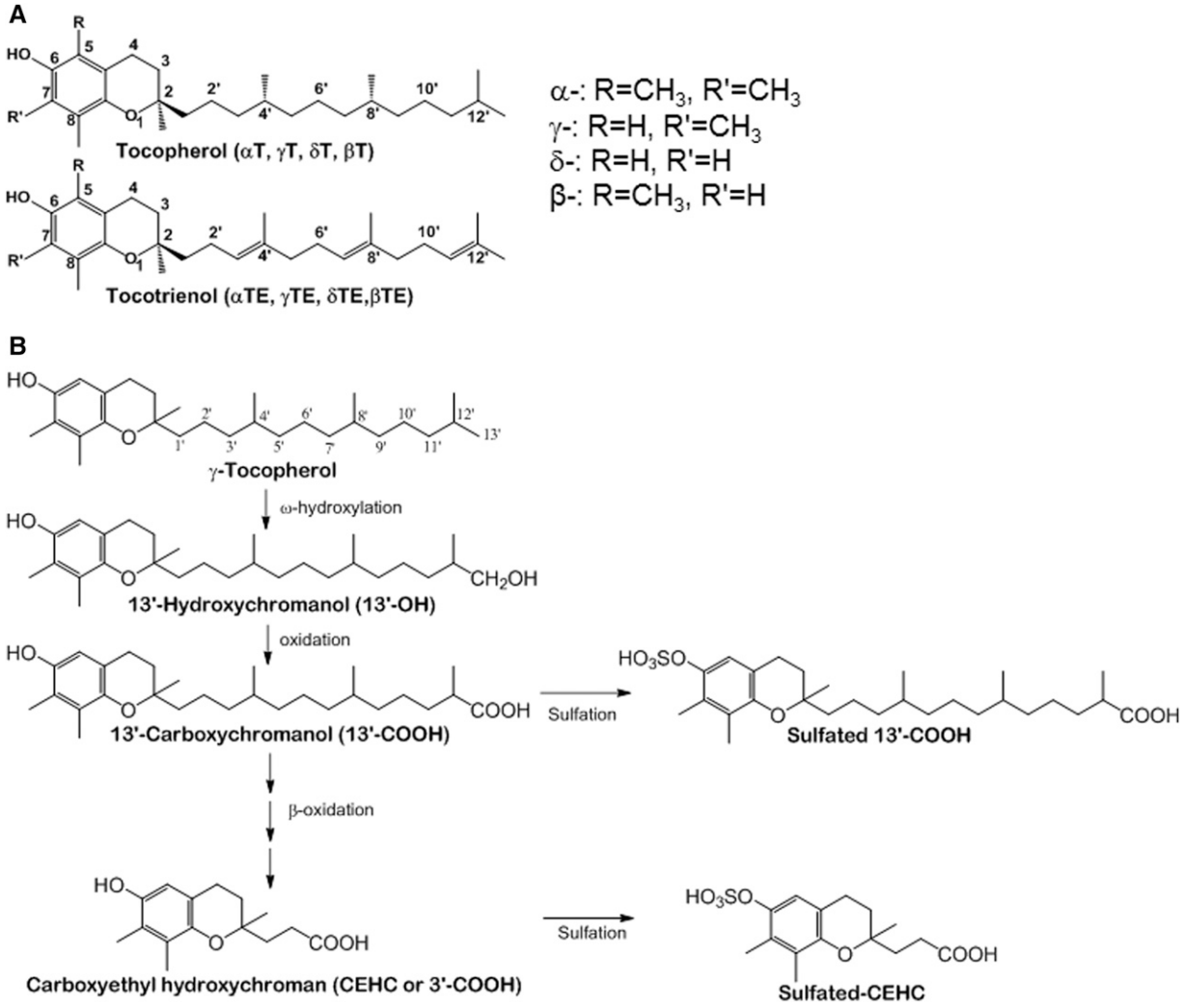

FIGURE 1 Chemical structures of vitamin E forms and vitamin E metabolism. (A) Structures of natural forms of vitamin E. (B) Vitamin E forms [e.g., γT (shown here)] are metabolized by side-chain oxidation to form various carboxychromanols and sulfated carboxychromanols. CEHC, carboxyethyl-hydroxychroman; COOH, carboxychromanol; αT, α-tocopherol; βT, β-tocopherol; δT, δ-tocopherol; γT, γ-tocopherol; αTE, α-tocotrienol; βTE, β-tocotrienol; δTE, δ-tocotrienol; γTE, γ-tocotrienol.

8-times shorter $T_{1/2}$. For instance, serum concentrations of γT range from 1–5 (diet intake) to 10–30 (supplementation) μM (13, 14) and δTE has maximum concentrations of 4–16 μM and $T_{1/2}$ of 3–4 h upon oral intake of 200–3200 mg of this form of vitamin E (15, 16). The high bioavailability of αT in tissues is a result of its binding to α-tocopherol transport protein (TTP), which prevents αT from being catabolized (8). Unlike αT, other vitamin E forms are readily metabolized via cytochrome P-450 (CYP4F2 or murine Cyp4f14)–catalyzed side-chain oxidation, including hydroxylation and oxidation of the terminal carbon 13′ in the endoplasmic reticulum to form 13′-hydroxychromanol (13′-OH) and 13′-carboxychromanol (13′-COOH). The subsequent degradation is believed to take place in the mitochondria or peroxisomes via β-oxidation to form various shorter chain COOHs, including 11′-, 9′-, 7′-, and 5′-COOHs as well as the terminal metabolite 3′-COOH, which is also called 3′-carboxyethyl-hydroxychroman (CEHC) (Figure 1B). Conjugated metabolites including sulfated long-chain COOHs and sulfated CEHCs are detected in circulation after supplementation of vitamin E forms, suggesting that sulfation takes place parallel to side-chain oxidation (17, 18).

Because some vitamin E metabolites have been shown to have anti-inflammatory and even anticancer effects (8), their bioavailability is of great interest for determining their contribution to the bioactive effects of vitamin E forms. γ-CEHC has been reported to reach ≤5–10 μM in the serum of humans after γT supplementation (13, 14); and CEHCs, conjugated CEHCs, and, to a lesser degree, 5-COOHs are the predominant metabolites found in urine (19). Long-chain metabolites, especially sulfated 11′-COOHs, have been reported in the circulation in rodents supplemented with vitamin E forms (18). Interestingly, CEHCs, 5-COOHs, and 11′-COOHs, whose conjugation status was unknown, have been found in the colon of mice supplemented with γT or δT (20). 13′-COOHs, which are low in the circulation, appear to be the predominant metabolites in feces of rodents fed tocopherols or tocotrienols (21, 22). Despite the reported bioavailability of various metabolites, much work is needed to determine metabolite concentrations, including maximum concentrations, in the circulation and different tissues in humans.

Anticancer mechanisms

All tocopherols and tocotrienols are powerful antioxidants and may block oxidative stress–induced DNA damage (8, 23). On the other hand, accumulating evidence has indicated that γT, δT, γTE, δTE, and 13′-COOHs have much superior anti-inflammatory and anticancer properties than αT. In particular, γT, δT, γTE, and δTE inhibit eicosanoid formation and 13′-COOHs are dual inhibitors of cyclo-oxygenases (COX-1 and -2) and 5-lipoxgenase (5-LOX). γTE and δTE also potently suppress activation of NF-κB or signal transducer and activator of transcription factor 3 (STAT3). These activities neutralize proinflammatory tumor microenvironments that favor cancer development, invasiveness, and resistance to treatment (**Figure 2**). Furthermore, these vitamin E forms and metabolites directly target cancer cells and cancer stem cells (CSCs) by promoting apoptosis, antiangiogenesis, and antiproliferation partially via modulating sphingolipids, epigenetic events, and other signaling pathways (Figure 2). In addition, emerging research suggests that tocotrienols appear to modulate immunity, which may also contribute to cancer prevention.

Anticancer effects via anti-inflammatory activities. Chronic inflammation contributes to cancer initiation, promotion, progression, and metastasis (24, 25). Inflammation-associated oxidative stress can cause damage and mutation to DNA, which constitutes a fundamental etiology of carcinogenesis. Inflammation also promotes epigenetic changes that contribute to cancer initiation and promotion (26). In the progression and late stages of cancer, immune cells often infiltrate to tumor tissues and interact with tumor cells to foster a proinflammatory tumor microenvironment, which promotes cancer development and even metastasis. Proinflammatory mediators such as eicosanoids and cytokines secreted by immune and tumor cells are known to facilitate tumor growth and render resistance to therapy (25, 27). This section focuses on the role of vitamin E forms and metabolites in modulating various proinflammatory mediators and regulators.

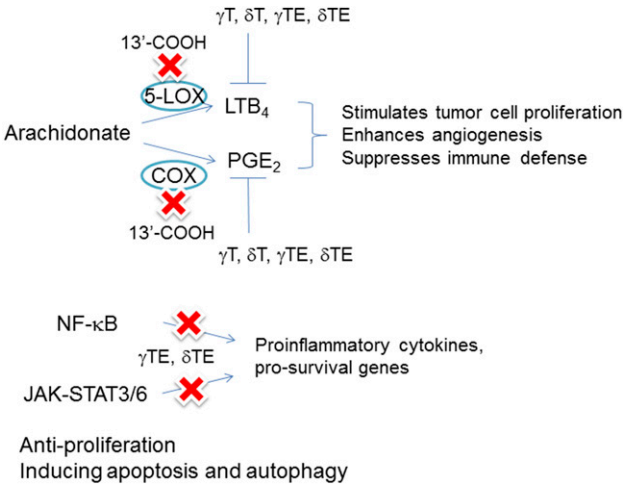

FIGURE 2 Molecular mechanisms underlying anticancer effects of vitamin E forms and 13′-COOH. γT, δT, γTE, δTE, and 13′-COOHs block multiple cancer-promoting pathways, including COX- and 5-LOX–mediated eicosanoids such as PGE_2 and LTB_4, respectively. 13′-COOHs are dual inhibitors of COXs and 5-LOX. γTE and δTE are potent inhibitors of NF-κB and STAT3. In addition, these vitamin E forms and 13′-COOHs can directly induce cancer cell death and inhibit proliferation. COX, cyclo-oxygenase; JAK-STAT3/6, Janus kinase-signal transducer and activator of transcription factor 3/6; LTB_4, leukotriene B_4; PGE2, prostaglandin E2; δT, δ-tocopherol; γT, γ-tocopherol; δTE, δ-tocotrienol; γTE, γ-tocotrienol; 5-LOX, 5-lipoxygenase; 13′-COOH, 13′-carboxychromanol.

Anticancer effects by inhibition of COX- and 5-LOX–catalyzed eicosanoids. It has been well recognized that prostaglandins and leukotrienes, which are synthesized by COX- (COX-1 and COX-2) and 5-LOX–catalyzed reactions, respectively, promote tumorigenesis, angiogenesis, and even metastasis (27). COX-2 and 5-LOX are often upregulated in tumor cells and cancer tissues (28–33). Overexpression of COX-2 accelerates colon cancer development (34) and reduces apoptotic susceptibility of colon cancer cells (35). COX-1 was also shown to promote angiogenesis and tumorigenesis (36, 37). Furthermore, PGE_2 is elevated in cancer cells and tissues (28–30) and has been shown to promote growth, angiogenesis, and resistance to apoptosis via PGE_2 (EP) receptor–mediated signaling in cancer cells (37, 38). In line with the procarcinogenic role of COXs and PGE_2, COX inhibitors, which are nonsteroidal anti-inflammatory drugs (NSAIDs), inhibit tumor development in numerous cancer models (39–41). In addition to PGE_2, blockage of the leukotriene B4 (LTB_4) signaling pathway results in antiproliferation and proapoptosis in colon cancer (27, 42). Zileuton, a specific 5-LOX inhibitor, suppressed tumor growth in a colon cancer xenograft model (33). Consistent with these mechanistic and preclinical studies, NSAIDs including aspirin and sulindac have proven effective in preventing colorectal cancer (CRC) in many clinical trials (2, 43–45). In addition, aspirin may prevent pancreatic cancer based on a meta-analysis of observational studies (46).

Although randomized trials support the chemopreventive effectiveness of NSAIDs for CRC (47, 48), the long-term use of NSAIDs is limited because of associated side effects, including gastrointestinal bleeding and increased risk of cardiovascular diseases (49–52). Furthermore, aspirin showed modest protective effects in some clinical trials (2). To this end, blocking both COX and 5-LOX pathways may be a better strategy than targeting either enzyme alone due to blocking multiple cancer-promoting pathways. Consistently, the inhibition of 5-LOX augments the antitumor activity of COX inhibitors (31). In addition, the inhibition of COXs and 5-LOX may attenuate the adverse effects of COX inhibitors by preventing shunt of arachidonate metabolism to 5-LOX–mediated leukotrienes, which are cytotoxic, proinflammatory, and tumorigenic (31, 53, 54). Thus, 5-LOX inhibitors alleviate gastric lesions induced by aspirin or indomethacin (53) and the inhibition of 5-LOX augments the antitumor activity of COX inhibitors (31). Licofelone, a dual 5-LOX/COX inhibitor, suppressed colon cancer development in a preclinical model (55) and shows a favorable safety profile (56, 57). Interestingly, simultaneously targeting both COXs and 5-LOX blocks the progression of pancreatic ductal adenocarcinoma (58). As a whole, targeting both COX- and 5-LOX–mediated eicosanoids may offer improved cancer-preventing effects compared with NSAIDs.

Various forms of vitamin E and novel long-chain metabolites have been shown to inhibit COX- and 5-LOX–catalyzed eicosanoids. Specifically, γT, δT, and γTE at physiologically relevant concentrations [the concentration of an inhibitor causing 50% inhibition (IC_{50}): 2.5–10 μM], but not αT, inhibited COX-2–mediated PGE_2 in cellular environments, although they did not directly inhibit the enzyme activity, indicating vitamin E forms are weak COX-2 inhibitors (59, 60). γT, δT, and γTE inhibit calcium (Ca^{2+}) ionophore–stimulated LTB_4 via blocking calcium influx, whereas tocopherols do not directly inhibit human 5-LOX activity (61). Consistent with cell-based studies, γT decreased PGE_2 and LTB_4 and attenuated inflammation in various models in rodents (62–67). Interestingly, we recently showed that long-chain metabolites of vitamin E, for example, δT-13′-COOH and δTE-13′-COOH, which are metabolites of δT and δTE (68–70), respectively, are potent dual inhibitors of COX-2 (IC_{50}: 4 and 9.8 μM, respectively) and 5-LOX (IC_{50}: 1–2 μM) and that δT-13′-COOH competitively inhibits COXs (60, 61, 71). In agreement with the dual inhibition of COXs and 5-LOX, δTE-13′-COOH suppressed azoxymethane (AOM)/dextran sodium sulfate (DSS)–induced colon tumorigenesis more effectively than γT in mice (71). It is interesting to note that high concentrations of 13′-COOHs are found in feces of mice supplemented with γT (17, 18, 21, 22). These results indicate that vitamin E forms and metabolites may exert cancer-preventive effects via decreasing COX- and 5-LOX–mediated eicosanoids.

Inhibition of NF-κB or STAT3 in immune and cancer cells. In addition to eicosanoids, proinflammatory cytokines can drive tumor growth and invasiveness. Tumor-promoting cytokines are often secreted by various types of cells in the tumor microenvironment, including tumor-associated macrophages. Cytokines can also be secreted by cancer cells themselves and promote cell growth in autocrine matter. These cytokines, such as IL-6, TNF-α and IL-1, activate NF-κB and STAT3 in cancer cells. More rarely, NF-κB or STAT3 is activated through mutational activation of upstream signaling in tumors. In both scenarios, activated NF-κB or STAT3 acts as a nonclassical oncogene by upregulating genes that promote cell survival, proliferation, angiogenesis, and invasiveness (25, 72). Consistently, the inhibition of NF-κB or STAT3 activation has been shown to suppress cancer development in animal models (73, 74). Therefore, blocking NF-κB or STAT3 and their regulated cytokines is considered to be a potentially effective strategy to preclude tumor progression.

Vitamin E forms have been shown to block NF-κB or STAT3 activation and their regulated genes in macrophages and cancer cells (8). For instance, tocopherols and tocotrienols inhibited LPS-stimulated IL-6 in macrophages and γTE is stronger than tocopherols in this activity (75–77). Mechanistic studies indicate that γTE decreased LPS-induced IL-6 by blocking the activation of NF-κB and inhibiting upregulation of C/EBPβ and C/EBPδ (75). In cancer cells, the inhibition of NF-κB and STAT3 by γTE and δTE prevents upregulation of survival genes and sensitizes tumor cells to therapeutic drugs (78, 79). In particular, γTE or its combination with gemcitabine or DHA downregulated NF-κB or STAT3 target proteins, including

cyclin D1, MMP-9, c-Myc, and CXCR4, which promote tumor growth and invasiveness (80, 81). We recently showed that γTE inhibits TNF-α–stimulated NF-κB by inducing its negative regulator A20 (82), which is recognized as a tumor suppressor gene in various types of cancer (83). Consistent with mechanistic and cell-based studies, γTE and δTE have been shown to inhibit NF-κB or STAT3 in preclinical models (78, 79). These observations indicate that the inhibition of these key regulators likely contributes to the anticancer effects of γTE and δTE, potentially overcoming drug resistance as discussed in the section entitled "Combination and adjuvant therapies: molecular mechanisms and evidence."

Immunomodulation for cancer prevention. Immune surveillance has long been recognized to play an important role in defense against cancer by detecting and killing tumor cells. Specific tocotrienols have been reported to modulate immune response. For instance, supplementation of tocotrienol mixtures enhanced lymphocyte proliferation without affecting major cytokines in old but not young C57BL/6 mice (84). This result suggests that tocotrienols may help improve age-associated impairment of immune functions. Radhakrishnan et al. (85) examined the potential effects of αT, δTE, and mixed tocotrienols on tetanus toxoid immunization in mice and found that δTE and mixed tocotrienols were stronger than αT in enhancing the production of antibodies against tetanus toxoid. Interestingly, while increasing IFN-γ and IL-4, these vitamin E forms decreased TNF-α in stimulated splenocytes. Furthermore, in a double-blinded, placebo-controlled clinical trial, tocotrienol-rich supplementation in healthy volunteers resulted in enhanced production of anti–tetanus toxoid antibody, IL-4, and IFN-γ induced by tetanus toxoid vaccine challenge, but reduced IL-6 compared with placebo (86). These data suggest that tocotrienols may be capable of preventing cancer via immune modulation, although this hypothesis remains to be further tested.

Anticancer effects via directly targeting cancer cells.

Antiproliferation, induction of death, and inhibition of invasiveness. γT, δT, γTE, δTE, and 13′-COOHs have been shown to induce growth arrest and apoptosis and autophagy in various types of cancer cells. In these activities, γTE, δTE, and 13′-COOHs (IC_{50}: 10–20 μM) appear to be stronger than γT and δT (IC_{50}: ≥25–50 μM) (87–92), all of which are much stronger than αT (72, 93). One potential explanation for these observed differential activities is that tocotrienols such as γTE appear to be accumulated at much higher concentrations in cells than their tocopherol counterparts (88). Tocotrienols have also been shown to accumulate in cancer but not in normal tissues in vivo (94, 95).

In numerous cell-based studies, biochemical events associated with γT- and tocotrienol-induced anticancer actions have been extensively characterized and reviewed elsewhere (6, 23, 96). These actions include the activation of various pathways associated with antiproliferation and cell stress and death, such as upregulation of PPAR-γ expression (97), inhibition of PI3K-mediated AKT phosphorylation (88–92, 98), and elevation of mitochondria-related apoptosis proteins such as caspase 9 cleavage (94), autophagy marker LC3II, and endoplasmic reticulum stress markers such as c-Jun N-terminal kinase (JNK) phosphorylation, CCAAT/enhancer binding protein homologous protein (CHOP), and death receptor (DR) 5 (DR5) proapoptotic pathway (99). Blocking NF-κB and STAT3 by tocotrienols in cancer cells also contributes to the anticancer activities (see section entitled "Inhibition of NF-κB or STAT3 in immune and cancer cells"). In addition, δTE but not αTE inhibited tumor cell–induced angiogenesis in an in vivo mouse angiogenesis assay (100).

Evidence suggests that these biochemical events induced by vitamin E forms and 13′-COOHs may be partially rooted in their modulating sphingolipids. Sphingolipids such as dihydroceramides, dihydrosphoingosine, and ceramides play important roles in regulating cell death and survival, and persistent elevation of these sphingolipids is known to cause stress, inhibit cell growth and induce apoptosis (101–103). γT, γTE, and 13′-COOHs have been shown to readily elevate dihydrosphingosine and dihydroceramides as well as ceramides in prostate, colon, pancreatic, and breast cancer cells; and the modulation of these sphingolipids precedes or coincides with biochemical events associated with cell death (71, 93, 99, 104). Further mechanistic studiesshowed that γTE and 13′-COOHs inhibited dihydroceramide desaturase activity in the pathway of de novo synthesis of sphingolipids and elevated ceramides during prolonged treatment, possibly by activation of sphingomyelinase-catalyzed sphingomyelin hydrolysis (71, 104). Consistently, blocking the de novo synthesis of sphingolipids partially reverses γT- or γTE-caused anticancer effects in cancer cells (93, 99, 104). In breast cancer cells, the chemical inhibition of de novo sphingolipid synthesis counteracted the ability of γT and γTE to induce apoptosis and to activate the JNK/CHOP/DR5 proapoptotic pathway (99). These data indicate a molecular interaction between vitamin E–related compounds and sphingolipids, which in part explains their anticancer actions and activations of signals of cell death. Further research is needed to elucidate the nature of the interaction and to verify whether sphingolipid modulation can be observed in vivo.

Targeting CSCs. γTE may target CSCs, which are believed to play important roles in resistance to cancer therapy (105). Specifically, γTE downregulated the expression of prostate CSC markers CD133/CD44 in androgen-independent prostate cancer cells and inhibited the formation of spheroids (106). Interestingly, although CSC-enriched PC-3 cells (CD133-positive) were resistant to docetaxel, these cells and CD133-negative cells were sensitive to γTE treatment (106). Husain et al. (107) showed that δTE inhibited the growth of pancreatic stemlike cells and prevented pancreatic cancer

metastasis. Gopalan et al. (108) showed that γTE eliminated CSC enrichment in drug-resistant human breast cancer cells via suppressing STAT3 signaling and activation of the de novo ceramide synthesis pathway. They also found that the combination of γTE with simvastatin synergistically enhanced these effects (108). In addition, γTE or its combination with DHA decreased aldehyde dehydrogenase (ALDH; a CSC marker)–positive cells and STAT3 activation via upregulation of Src homology region 2 domain-containing protein tyrosine phosphatase 1 (SHP-1) in human triple-negative breast cancer cells (81). These observations strongly suggest that tocotrienols are capable of targeting CSCs that are often the source of drug resistance, but the role of this action in the whole-body environment and the underlying mechanisms remain to be determined.

Modulation of epigenetic mechanisms. Emerging evidence suggests that vitamin E forms may have an impact on epigenetic events, which play critical roles in cancer development. δTE suppressed the Notch-1 pathway by upregulating miR-34a in non–small cell lung cancer cells, which appears to be partially responsible for induction of apoptosis and inhibition of cell growth and invasiveness (109). δTE suppressed radiation-induced microRNA-30 and protected mice from radiation injury (110). In the transgenic adenocarcinoma of the mouse prostate (TRAMP) model, γT-rich mixed tocopherols inhibited CpG methylation in the promoter of nuclear factor erythroid 2–related factor (Nrf2) compared with control and decreased the expression of DNA methyltransferases (DNMTs), including DNMT1, DNMT3A, and DNMT3B, in the prostate of mice (111). In addition, a tocotrienol mixture inhibited prostate tumor growth, which was associated with epigenetic modification, including acetylation of CDK inhibitors p21 and p27 (112). Despite these interesting observations, little is known about the mechanisms underlying epigenetic modulation by vitamin E forms and to what extent these effects contribute to anticancer effects in vivo.

Combination and adjuvant therapies: molecular mechanisms and evidence

The potential use of γTE and δTE as an adjuvant for enhancing the effectiveness of chemotherapeutic drugs has been investigated in cells and preclinical models. First, tumor cells have altered lipid metabolism, including elevated cholesterol synthesis, compared with nontransformed cells. Excessive lipids and cholesterol in cancer cells appear to be associated with cancer aggressiveness and recurrence (113–115). Therefore, blocking cholesterol synthesis may improve therapeutic efficacy. To this end, γTE or δTE, combined with statins that are inhibitors of β-hydroxy-β-methylglutaryl coenzyme A (HMG-CoA) reductase in cholesterol synthesis, synergistically decreased the growth of colon (116), breast (117), and pancreatic and melanoma (118, 119) cancer cells. γTE or δTE has been shown to cause degradation of HMG-CoA reductase and thus decrease cholesterol synthesis in liver cells (120). The synergy of γTE and statins was explained by the fact that γTE inhibited statin-induced upregulation of HMG-CoA reductase (116). Second, TNF-related apoptosis-inducing ligand (TRAIL) is a promising chemotherapeutic agent, but its anticancer efficacy is limited by drug resistance. It has been shown that a combination of γTE and TRAIL synergistically exerted anticancer effects via induction of the TRAIL receptors, including DR4 and DR5 (121). Third, activated NF-κB and STAT3 in cancer cells are known to contribute to drug resistance. γTE was found to promote anticancer effects of chemotherapeutic drugs such as paclitaxel, capecitabine (oral precursor of 5-fluorouracil), and doxorubicin via downregulation of NF-κB–dependent antiapoptotic genes in vitro and in vivo (78, 80, 122). These results strongly suggest that γTE and δTE may be useful in combination or as adjuvant therapy for enhancing the effectiveness of cancer treatment and sensitizing cancer cells to chemotherapeutic drugs.

Anticancer efficacy of tocopherols in preclinical models

On the basis of the anti-inflammatory and anticancer activities observed in mechanistic studies, γT has been proposed to be potentially effective for cancer prevention and is likely superior to αT in anticancer efficacy (5, 123). Over the past decade, the anticancer efficacy of γT-, δT-, and γT-rich mixed tocopherols (γTmTs) has been tested in various preclinical models, and some studies compared the effect of these vitamin E forms with αT (**Table 1**). The effect of these tocopherols on tumor initiation and promotion has been tested in cancer models induced by carcinogens such as N-nitroso-N-methylurea (NMU), 2-amino-1-methyl-6-phenylimidazo[4,5-b]pyridine (PhIP), or AOM. Xenograft models with implanted cancer cells in mice were used to evaluate the effect on tumor growth in late-stage cancer. There were also studies that used genetically engineered murine cancer models to examine the effectiveness of tocopherols for cancer prevention.

Prostate cancer. The effect of γT or γTmTs on prostate cancer development has been examined in many preclinical models, including carcinogen (NMU, PhIP)-induced prostate epithelial dysplasia, genetically engineered spontaneous [transgenic rat for adenocarcinoma of prostate (TRAP), TRAMP] prostate cancer, xenograft models with implanted human prostate cancer cells (LNCaP, 22Rv1), and prostate Dunning R3327H adenocarcinoma in male Copenhagen rats (Table 1). Because these models recapitulate different-stage prostate cancer development, the impact of tocopherols on the disease in these models indicates their potential role in preventing cancer from early precancerous lesions to relatively late-stage tumor development.

In the NMU or PhIP-induced prostate cancer models, γT, δT and γTmT inhibited mouse prostate intraepithelial neoplasia (PIN), an early precancerous lesion. In the PhIP-induced model, δT was more effective than γT or αT in preventing PINs (125). In the TRAP and TRAMP model

TABLE 1 Cancer-preventive effects of tocopherols in preclinical models[1]

Animal model	Vitamin E forms and doses	Outcomes
Prostate cancer		
NMU-induced epithelial dysplasia in the rat ventral prostate	γT-enriched diet (20 mg/kg) for 4 mo (124)	γT ↓ NMU-induced epithelial dysplasia by 38% and cell proliferation, COX-2, and MMP-9 in the ventral prostate
PhIP-induced prostate carcinogenesis in hCYP1A mice	γTmTs (0.3%) or tocopherols (i.e., γT, δT, or αT at 0.2% in diet) (125)	γTmTs or tocopherols ↓ PhIP-induced mouse PINs by 66%; δT was stronger than γT or αT in this effect
TRAP	γT at 50, 100, and 200 mg/kg diet for 7–10 wk; αT at 50 mg/kg diet (126)	γT, not αT, dose-dependently ↓ PIN to adenocarcinoma and ↑ apoptosis in prostate tissue
TRAMP mice	γTmTs at 0.1% in diet (113, 127)	γTmTs ↓ palpable tumor incidence by 75% and PINs and ↑ Nrf2 and its targeted genes by ↓ CpG methylation
LNCaP-xenograft model in nude mice	γT at 125 mg/kg bw 3 times/wk for 4 wk (88); αT or δT at 0.3% of diet for 48 d (128)	γT and δT, but not αT, ↓ the growth of LNCaP tumor by 30% and induced apoptosis in tumors
Dunning R3327H adenocarcinoma cells implanted in male Copenhagen rats	γT at 200 mg/kg or its combination with lycopene (250 mg/kg diet) (129)	Neither γT or its combination with lycopene had a significant impact on tumor growth
Human PCa cell 22Rv1-implanted tumor in Nu/J mice	MSA (40.95 μg/kg bw), γT at 20.83 or 41.66 mg/kg bw in corn oil, alone or in combinations by gavage (130)	Combination of MSA with γT showed the strongest ↓ tumor volume (~25%), serum PSA and Ki67
Colon cancer		
AOM-induced ACF formation in the colon of male F344 rats	γTmTs at 0.1% of diet (131); δT, γT, αT, or γTmTs at 0.2% of diet (20); *dl*-α-tocopheryl acetate (500 mg/kg) (132)	γT, δT, or γTmTs (131) ↓ ACF with relative efficacy of δT (62%) > γT ~γTmTs (48%) (20), whereas αT ↔ ACF (20, 132)
AOM-induced and DSS-promoted colon cancer in mice (polyps as endpoints)	γT at 0.1% of diet in male Balb/c mice (21); γTmTs at 0.17% and 0.3% in male CF-1 mice (133)	γT ↓ moderate colitis–promoted large-size tumors by 36–80% (21); γTmTs ↓ tumorigenesis, nitrotyrosine, PGE_2, and LTB_4 (133)
Colon tumorigenesis induced by PhIP/DSS in hCYP1A mice	γT, δT, or αT at 0.2% of diet starting 1 wk before PhIP administration and continuing until being killed; in some studies, δT intervention started after PhIP and DSS (134)	γT and δT (but not αT) ↓ tumor multiplicity by 45% and 64%, but not tumor volume, and ↓ oxidative stress, NF-κB, and STAT3; when intervention started after PhIP/DSS, δT was much less effective
Breast cancer		
NMU-induced hormone-dependent mammary tumor in female Sprague-Dawley rats	γTmTs at 0.1%, 0.3%, and 0.5% (135, 136); αT, δT, or γT (0.3% diet) or γTmTs (0.3%) (137)	γTmTs ↓ tumor growth and multiplicity by 38%, 50%, and 80% and ↑ p21, p27, caspase 3, and PPAR-γ (136); δT and γT (not αT), ↓ tumor multiplicity or weight and ↑ apoptosis (137)
Estrogen 17β-estradiol E2-promoted mammary hyperplasia and tumor in ACI rats	γTmTs at 0.3% of diet for 1, 3, 7, and 14 d after estrogen implantation (138); γTmTs at 0.05%, 0.1%, 0.3%, and 0.5% of diet for 31 wk (139)	γTmTs ↔ E2-induced mammary hyperplasia, but ↓ oxidative stress (138); γTmTs (0.3% or 0.5%) ↓ tumor size by 52% or 42% and serum estradiol; ↑ CYP1A1 (metabolizing estrogen), ↑ Nrf2, and ↑ PPAR-γ (139)
ER^+ MCF7 cancer cells orthotopically implanted in immunodeficient mice implanted with estrogen pellets	γTmTs at 0.05%, 0.1%, 0.3%, and 0.5% of diet for 9 wk (139)	γTmTs at all doses ↓ mammary tumor and appeared to be more effective in this model than ACI rats
MMTV/ErbB2/neu female transgenic mice that overexpress Her-2	αT, γT, or δT (0.3% of diet) or γTmTs (0.3% of diet) for 35 wk (137)	Only γT diet ↑ the median tumor latency, but none of the treatment was effective in reducing tumor weight
Murine 66c1-4 GFP or MDA-MB231-GFP breast cancer cells implanted into mice	RRR-αT, synthetic αT, or RRR-γT at 358 or 2000 mg/kg diet (140, 141)	γT and synthetic αT, but not natural RRR-αT, ↓ mammary cancer growth and lung metastasis by 57%, whereas αT counteracted γT's anticancer effect
Lung cancer		
H1299 human lung cancer cell xenografts in NCr Nu/Nu mice	αT, γT, δT, and γTmTs at 0.17% or 0.3% of diet (142)	δT, γT, or γTmTs (not αT) ↓ tumor size by 50%, 35%, and 40%, respectively; ↓ DNA damage and nitrotyrosine; ↑ apoptosis
CL13 murine lung cancer cells implanted (subcutaneously) in A/J mice	γTmTs at 0.1% or 0.3% (143)	γTmTs ↓ the growth of CL13 tumors by 50–80%

[1] The typical formula of γTmTs contains 57–60% γT, 21–24% δT, 12–13% αT, and 0.5–1.5% βT. ACF, aberrant crypt foci; AOM, azoxymethan; bw, body weight; COX-2, cyclo-oxygenase 2; CYP1A1, cytochrome P4501A1; DSS, dextran sodium sulfate; ER^+, estrogen receptor positive; hCYP1A, humanized CYP1A; LTB_4, leukotriene B_4; MMP-9, matrix metallopeptidase 9; MSA, methaneseleninic acid; NMU, N-methyl-N-nitrosourea; Nrf2, nuclear factor erythroid 2–related factor; PCa, prostate cancer; PhIP, 2-amino-1-methyl-6-phenylimidazo[4,5-b] pyridine; PIN, prostate intraepithelial neoplasia; PSA, prostate specific antigen; STAT3, signal transducer and activator of transcription factor 3; TRAMP, transgenic adenocarcinoma of the mouse prostate; TRAP, transgenic rat for adenocarcinoma of prostate; αT, α-tocopherol; βT, β-tocopherol; δT, δ-tocopherol; γT, γ-tocopherol; γTmT, γT-rich mixed tocopherol; ↓, suppressed or inhibited; ↑, increased or enhanced; ↔, showed no effect.

that captures the development of neoplasia to tumor, γT or mixed tocopherols suppressed cancer progression from PIN to adenocarcinoma and decreased palpable tumor incidence, which was accompanied by increased apoptosis and enhanced Nrf2 via modulating DNA methylation (111, 126, 127). In LNCaP- or 22Rvl-implanted xenograft models that mimic late-stage tumor, γT modestly suppressed tumor growth, and its combination with methaneselenic acid more strongly inhibited tumor development than either agent alone. On the other hand, in the study in Dunning R3327H adenocarcinoma rats, which represented slow-growing prostate cancer (adenocarcinoma or beyond) (144), γT or its combination with lycopene did not have a significant impact on tumor growth, probably because of the relatively low dose used (0.02% of diet) or lack of efficacy in blocking further progression of adenocarcinoma to advanced cancer.

Overall, γT-, δT-, or γT-rich tocopherols appeared to be capable of inhibiting initiation and early-stage prostate intraepithelial neoplasia formation and suppressing progression from prostate intraepithelial neoplasias to adenocarcinoma, whereas they only modestly slowed the growth of relatively late-stage tumors. Therefore, γT, δT, and γTmTs are likely promising agents for preventing relatively early-stage prostate cancer.

CRC. The chemopreventive effectiveness of αT, γT, δT, and γTmTs has been extensively studied in carcinogen-induced CRC models, including AOM-induced aberrant crypt foci (ACF), a surrogate marker of precancerous lesions. In this model, γT, δT, and γTmTs significantly inhibited ACF formation and δT appeared to be stronger than γT or γTmTs in this effect, whereas αT was found to be ineffective (Table 1). αT was also not effective toward colon tumorigenesis induced by meat-derived PhIP (145). In addition to AOM-induced ACF formation, AOM combined with DSS, which causes colon inflammation, has been shown to accelerate tumor formation in the colon. The AOM-DSS model is considered to mimic inflammatory bowel disease–promoted colorectal cancer in humans (146, 147). In the AOM-DSS-induced model, γT or γTmTs suppressed the multiplicity of polyps that are adenomas or adenocarcinomas, although their anticancer effectiveness appeared to depend on the severity of colitis. In particular, γT was more effective in attenuating tumor formation with moderate colitis than with severe colitis (21). In a recent study, γT and δT but not αT were found to significantly reduce colon tumor formation that was induced by PhIP and promoted by DSS-induced colitis in CYP1A-humanized (hCYP1A) mice. In this model, the chemopreventive effects were much stronger when tocopherol intervention started before PhIP-DSS was administered than after initiation and promotion of carcinogenesis (134). These results indicate that γT, δT, or γTmTs, but not αT, are able to suppress chemically induced colon tumorigenesis.

Breast cancer. The effect of tocopherols on breast cancer development varied with animal models. For instance, γT or δT, but not αT, suppressed estrogen receptor (ER)-positive breast cancer induced by NMU in female Sprague-Dawley rats. In this model, γTmTs also dose-dependently suppressed NMU-induced mammary tumors (Table 1). Furthermore, γTmTs (at 0.3% or 0.5%) suppressed estrogen-induced hyperplasia and mammary tumor in ACI rats, via decreasing serum estradiol, by inducing the estrogen-metabolizing enzyme CYP1A1 (139). γT and γTmTs, but not αT, were effective in suppressing xenograft MDA-MB231 (ER-negative, low HER-2) or MCF7 (ER-positive, low HER-2) human breast cancer growth in nude mice (148). It is noticeable that an estrogen-sensitive MCF7 xenograft appeared to be more responsive to the treatment of γTmTs than the ER-negative MDA-MB231 tumor. On the other hand, none of αT, γT, δT, or γTmTs had a significant impact on tumor multiplicity or weight in MMTV-Erb2/neu transgenic mice with HER-2 overexpression, although γT significantly increased the median mammary tumor latency. These data indicate that γT, δT, and γTmTs, but not αT, are capable of preventing estrogen-dependent mammary tumors, but none of these is effective in inhibiting HER-2–positive breast cancer.

Lung cancer. γT, δT, and γTmTs, but not αT, have been reported to inhibit tumor growth and decrease oxidative stress markers in lung cancer xenograft models (Table 1).

Anticancer efficacy of tocotrienols in animal models

Early animal studies on tocotrienols for chemoprevention have focused on tocotrienol-rich fractions (TRFs) extracted from palm oil (4). These TRFs showed anticancer effects in xenograft breast cancer studies in nude mice (149), spontaneous hepatocarcinogenesis, induced lung cancer (150), and UV-B–damaged skin (95, 151). Here we will focus on recent research on the in vivo anticancer effects of γTE, δTE, and TRFs from various sources (palm oil, rice bran, and annatto), as well as their use as adjuvant therapy for sensitizing chemotherapeutic agents or radiation therapy (**Table 2**).

Pancreatic cancer. The potential chemoprevention effect of δTE against pancreatic cancer has been examined in various transgenic mouse models. Mutations in the KRAS proto-oncogene are found in >90% of invasive pancreatic ductal adenocarcinomas (PDAs) and are believed to represent a key initiating event of pancreatic cancer (168). LSL-*K-ras*^{G12D};PDX-1*Cre* mice bear the *Kras* mutation in pancreas epithelium, which therefore mimics the most common genetic lesion of the human PDA. Importantly, these mice developed preinvasive and invasive ductal pancreatic cancers that were histologically indistinguishable from those observed in patients with PDA (168). In this model, δTE at 200 mg/kg body weight 2 times/d resulted in increased median survival, decreased incidence of invasive cancer, and suppressed pancreatic intraepithelial neoplasm progression (152). In addition to this model, δTE or its combination with gemcitabine was

TABLE 2 In vivo anticancer effects of tocotrienols and their potential use as adjuvants in chemotherapy[1]

Animal model	Vitamin E forms and doses	Outcomes
Pancreatic cancer		
LSL-*Kras*(G12D)/+;Pdx-1-Cre (KPC) pancreatic cancer mouse model	δTE at 200 mg/kg, po, twice a day for 12 mo (152)	δTE ↑ median survival (11.1 mo vs. 9.7 mo in controls), ↓ PanIN progression, and ↓ incidence of invasive cancer
LSL-*Kras*(G12D)/+;LSL*Trp53*(R172H)/+;Pdx-1-Cre (KPC) transgenic mouse model of pancreatic cancer	δTE (200 mg/kg), po, twice a day, or δTE (oral) combined with gemcitabine (100 mg/kg, i.p twice a week) (153)	δTE or the combination ↑ survival rate (70% or 90%) compared with 30% with gemcitabine alone, ↓ epithelial-to-mesenchymal transition, and ↑ antiproliferation markers (p21, p27)
Human MIA PaCa2 pancreatic cancer cells orthotopically implanted in athymic Nu/Nu mice.	γTE at 400 mg/kg bw, po, daily or γTE with gemcitabine at 25 mg/kg via i.p. twice a week (78)	γTE ↓ tumor growth (by 40%) and ↓ NF-κB; the combination was stronger than either agent
Human pancreatic cancer AsPc-1 xenograft model in female NIH SCID nude mice	αTE, βTE, γTE and δTE at 200 mg/kg (in olive oil) gavaged twice daily for 4 wk; or δTE plus gemcitabine (100 mg/kg, i.p, twice a week) (79)	δTE > γTE > other tocotrienols in ↓ tumor development. δTE ↓ NF-κB and targeted genes in tumors; the combination ↓ (50%) pancreatic tumor more strongly than δTE (40%)
Human pancreatic cancer (PANC-1) implanted in nude mice	γTE (50 mg/kg, i.p.) or its combination with gemcitabine (50 mg/kg, i.v) (23)	γTE did not affect tumor growth but the combination ↓ tumor growth by ∼50%
An orthotopic xenograft model of human PDA stem-like cells	δTE at 200 mg/kg, po, twice a day with or without gemcitabine (100 mg/kg, i.p., twice a week) for 4 wk (107)	δTE ↓ the growth (volume by 45%) and metastasis of gemcitabine-resistant PDA human stem-like cells.
Prostate cancer		
PC3 human AIPCa in xenograft model	γTE at 50 mg/kg, i.p., 5 times/wk alone or coadminstered with docetaxel (7.5 mg/kg, i.p.) (154)	γTE or its combination with docetaxel ↓ tumor growth by 52% and 61%, respectively; γTE accumulated in tumors, ↑ apoptosis, and ↓ proliferation
LNCaP human prostate cancer xenograft model in Nu/Nu mice	γT or γTE at 125 mg/kg bw by oral gavage 3 times/wk for 5 wk (88)	γTE was stronger than γT in ↓ the growth of LNCaP xenograft (by 50%) in nude mice
VCaP human hormone-refractory prostate cancer xenograft model in NCr immunodeficient mice	mTEs containing αTE, βTE, δTE, γTE, and αT at 8.3, 1.5, 4.6, 11.4, and 6 g out of 100 g) at 200 or 400 mg/kg bw, by gavage 3 times/wk for 8 wk (112)	The mTEs dose-dependently ↓ tumor growth and ↑ CDK inhibitors p21 and p27 and ↑ H3K9 acetylation at their promoters with ↓ expression of histone deacetylase
Human prostate cancer bone metastasizing PC3 cells implanted in athymic mice	γTE at 400 mg/kg bw was injected subcutaneously in the necks of nude mice, which were then irradiated at the rear part of the body including the location of tumor (155)	The size of the tumors was ↓ by ∼40% only in γTE- injected and irradiated mice, whereas there was ↑ lipid peroxidation in tumors and kidney (potential side effect in kidney)
TRAMP mice	γTE-rich mTEs containing 13%, 1%, 19%, 5%, and 13% αTE, βTE, γTE, δTE, and αT, respectively, at 0.1%, 0.3%, and 1% in an AIN-76A diet (156)	Tocotrienols dose-dependently ↓ tumor incidence (50–70%), weight (by 75%), and high-grade neoplastic lesions, and ↑ BAD, caspase-3, p21, and p27
Breast cancer		
Spontaneous mammary tumors in FVB/N HER-2/neu transgenic mice	Annatto tocotrienols (δTE and γTE at 9:1) at 50 or 100 mg/kg bw in olive oil by gavage 3 times/wk (157)	Tocotrienols dose-dependently ↓ tumor size/mass by 75% and lung metastases; ↑ apoptosis and cell senescence in mammary glands
Human breast cancer MDA-MB-231 xenograft model in nude mice	γTE (50 mg/kg, i.p.) or its combination with docetaxel (2 mg/kg, i.p.) (23)	The combination was much stronger than either alone in ↓ tumor growth by ≤80% and 40–50%, respectively.
Female Balb/c mice inoculated with 4T1 cells in mammary pad to induce tumor	TRF from palm oil (1 mg/d, oral) alone with i.v. injection of DCs pulsed with tumor lysate (158)	Although DC injection ↓ tumor growth, TRF plus DC impulse with tumor lysate showed stronger antitumor effects
Melanoma and skin cancer		
Aggressive melanoma B6(F10) implanted in C57BL female mice	Study 1: γTE at 116 and 924 μmol/kg diet given 10 d before and 28 d after tumor cell implantation; study 2: γTE at 2 mmol/kg diet given after melanomas were established	γTE delayed and ↓ melanoma growth; γTE at 2 mmol/kg prolonged the survival of mice by 30%; the combination of δTE and lovastatin ↓ tumor weight but not either alone

(Continued)

TABLE 2 (*Continued*)

Animal model	Vitamin E forms and doses	Outcomes
	(159); δTE at 62.5 mg/kg bw + lovastatin at 12.5 mg/kg bw in diet (160)	
B6(F10) melanoma or A431 human epidermoid carcinoma cells implanted in female immunodeficient Balb/c mice	Transferrin-bearing, multilamellar vesicles entrapping tocotrienol for improving uptake by cancer cells that overexpress transferrin receptors; daily tail vein injection of 10 μg TRF (αTE, γTE, δTE, and αT at 17.6%, 23.1%, 15.1%, and 15.3%) (161)	The novel tocotrienol formulation, but not free agent, led to complete tumor eradication for 40% of B16-F10 melanoma tumors and 20% of A431 epidermoid carcinoma tumors
Mice xenografted with A375 melanoma cells	δTE at 100 mg/kg gavaged in olive oil, daily, 5 d/wk (162)	δTE ↓ (by 60.6%) the growth and progression of melanoma
Liver, colon, and gastric cancer		
Murine hepatoma MH134 xenograft in C3H/HeN mice	γTE and δTE (0.1%) in diet (95)	γTE and δTE ↓ the growth of hepatoma by 45% and 55% and were accumulated in tumor but not in normal tissues
AOM-DSS-induced colon cancer in male C57BL/6 mice	Supplementation with TRF with 0.03% tocopherols (mainly αT) + 0.07% mTEs; δTE/γTE (8:1) at 0.075% in diet for 77 d (163)	Compared with a control diet, a δTE/γTE diet ↓ tumor multiplicity by 42%, whereas TRF nonsignificantly affected tumor number
Orthotopic HCC patient xenograft model in Balb/c nude female mice	γTE at 3.25 mg/mouse via daily gavage (164)	γTE ↓ tumor growth by 65% and suppressed angiogenesis
Colon adenocarcinoma (DLD-1) xenograft in nude mice	Rice bran tocotrienols at 10 mg/mouse containing αTE, γTE, and δTE at 0.36, 9.22, and 0.42 mg via daily gavage (165)	Tocotrienols ↓ tumor growth and ↑ p21, p27, and caspase 3/9; ↓ Akt phosphorylation; δTE was stronger against hypoxic tumor cells than nomoxic cells
SW620 colon cancer cell–implanted xenograft model in Balb/c nude mice	TRFs from palm oil (αT, αTE, βTE, γTE, and δTE at 0.4%, 9.8%, 4.1%, 45.6%, and 40%) at 5, 10, and 20 mg/kg by gavage (166)	TRFs ↓ tumor growth by ≤70–80% and ↓ β-catenin and Wnt-1 expression in tumors
HCT116 human colon cancer cell–implanted tumor in athymic nu/nu mice	γTE at 100 mg/kg, po, or γTE with capecitabine (60 mg/kg, twice a week); corn oil as vehicle (167)	The combination of γTE and capecitabine was stronger than either agent alone in inhibition of tumor growth
SNU-5 gastric cancer cells implanted xenograft model	γTE at 1 mg/kg or its combination with capecitabine at 60 mg/kg via i.p. injection (122)	γTE ↓ gastric tumor growth by 66% and the combination was more effective (by >90%) in this effect

[1] AIPCa, androgen-independent prostate cancer; AOM, azoxymethan; BAD, Bcl-2-associated death promoter; bw, body weight; CDK, cyclin-dependent kinase; DC, dendritic cell; DSS, dextran sodium sulfate; HCC, human hepatocellular carcinoma; HER-2, human epidermal growth factor receptor 2; mTE, mixed tocotrienol; PanIN, pancreatic intraepithelial neoplasm; PDA, pancreatic ductal adenocarcinoma; po, orally; SCID, severe-combined immunodeficient; TRAMP, transgenic adenocarcinoma of the mouse prostate; TRF, tocotrienol-rich fraction; αT, α-tocopherol; αTE, α-tocotrienol; βTE, β-tocotrienol; δTE, δ-tocotrienol; γTE, γ-tocotrienol; ↓, suppressed or inhibited; ↑, increased or enhanced; ↔, showed no effect.

also tested in a more aggressive pancreatic model, LSL-*Kras*(G12D)/+;LSL*Trp53*(R172H)/+;Pdx-1-Cre (KPC), in which mice are genetically engineered with double mutations (i.e., oncogenic *Kras* and tumor suppressor *p53*) (153). In this model, δTE and its combination with gemcitabine suppressed tumor development and markedly enhanced survival compared with control or even gemcitabine-treated mice.

In addition to the role in chemoprevention, tocotrienols or their combinations with chemotherapeutic drugs have been tested for the treatment of pancreatic cancer in various xenograft models. To this end, both γTE and δTE have been reported to inhibit pancreatic tumor growth and enhanced the antitumor efficacy of gemcitabine in nude mice that were orthotopically implanted with different types of human pancreatic tumors (Table 1). The mechanisms underlying these anticancer actions include inhibition of NF-κB and cell proliferation and induction of apoptosis.

Prostate cancer. The effect of tocotrienols on prostate tumor growth has been evaluated in various xenograft models that represent relatively late-stage prostate cancer, although one study tested mixed tocotrienols in TRAMP mice, which resemble relatively aggressive prostate cancer development. Specifically, γTE inhibits tumor development in nude mice implanted with androgen-sensitive human prostate adenocarcinoma (LNCaP) xenografts and is stronger than γT in this effect (88). γTE alone inhibited androgen-independent PC3 prostate tumor growth in nude mice, and its combination with docetaxel showed an even stronger inhibition of tumor growth (154). In another xenograft model, mixed tocotrienols in diets inhibited prostate tumor development and increased CDK inhibitors p21 and p27 via elevating H3K9 acetylation of their promoters (112). In addition, mixed tocotrienols have been shown to suppress prostate tumor development in the TRAMP model (156). These results indicate that γTE or mixed tocotrienols may be effective for slowing down prostate cancer progression, although their efficacy should be further tested in patient-derived xenograft models.

Breast cancer. A δTE/γTE mixture inhibited spontaneous breast cancer development and lung metastasis in HER-2/neu transgenic mice (157), which suggests that tocotrienols may be stronger than tocopherols, which failed to inhibit the growth of HER-2 overexpression mammary tumors (137). In nude mice implanted with breast and pancreatic cancer cells, the combination of γTE and docetaxel led to much stronger suppression of tumor growth than either agent alone (23). In addition, a TRF enhanced anticancer effectiveness of dendritic cell–based immunotherapy in a xenograft model in immunocompetent mice (158).

Melanoma and skin cancer. γTE and δTE or a tocotrienol mixture have been shown to delay and suppress tumor growth compared with vehicle control groups in B16 (F10)- or A375-implanted melanoma in mice (159, 162). Interestingly, the delivery of a tocotrienol mixture via targeting transferrin receptors on tumor cells resulted in enhanced anticancer efficacy (161). In addition, a combination of dietary δTE and lovastatin suppressed the growth of implanted mouse melanoma B16(F10) more strongly than either agent alone in C57BL female mice (160).

Liver, colon, and gastric cancer. γTE and δTE have been reported to inhibit the growth of hepatoma in xenograft models, and tocotrienols were found to be accumulated specifically in tumors but not in normal tissues (95, 164). Tocotrienols extracted from rice and palm oil have been shown to block colon cancer growth in 2 xenograft models in mice (165, 166). A δTE and γTE (8:1) mixture is stronger than TRF (γTE rich) in the inhibition of AOM-DSS-induced colon cancer in mice (163). γTE improved capecitabine's anticancer effects in an HCT116 xenograft model (**Table 3**). In addition, γTE was found to improve the anticancer efficacy of capecitabine in a human gastric cancer–xenograft mouse model (122).

γTE as an adjuvant in radiation therapy. Tocotrinols have been shown to enhance the efficacy of cancer radiation therapy. Kumar et al. (155) reported that γ-irradiation combined with γTE at 400 mg/kg body weight (via subcutaneous injection in the neck), but not radiation or γTE alone, reduced the size of established tumors and increased lipid peroxidation in tumors in athymic mice implanted with human prostate cancer PC-3 cells. Meanwhile, γTE at 200 mg/kg body weight administered subcutaneously before radiation protected hematopoietic stem and progenitor cells in mice after total-body irradiation (170) and accelerated the recovery of white blood cells in irradiated mice (171). Consistently, δTE at 400 mg/kg (subcutaneous) protected 100% of CD2F1 mice from total-body irradiation-induced death, increased regeneration of hematopoietic microfoci and stem and progenitor cells in irradiated mouse bone marrow, and protected human $CD34^+$ cells from radiation-induced damage (172). In addition, γTE (400 mg/kg) improved postirradiation survival, enhanced hematopoietic recovery, and reduced intestinal radiation injury in mice (173). These studies strongly suggest that tocotrienols may be useful for adjuvant therapy for increasing treatment efficacy and reducing irradiation-associated adverse effects, including decreased white blood cell counts.

Toxicity of tocopherols and tocotrienols

When tocopherols and tocotrienols are considered for long-term use for cancer prevention, it is important to systemically evaluate the safety of these compounds. Tasaki et al. (174, 175) investigated the potential toxicity of long-term (≤2 y) exposure to a tocotrienol mixture in Wistar Hannover rats. The tocotrienol mixture contained αTE 21.4%, βTE 3.5%, γTE 36.5%, δTE 8.6%, αT 20.5%,

TABLE 3 Published and ongoing clinical studies on tocopherols and tocotrienols for cancer prevention or therapy[1]

Study design (ref)	Subjects or purpose of study	Vitamin E forms	Outcomes
Breast cancer			
TRF on breast cancer: double-blinded, placebo-controlled intervention (169)	Women aged 40–60 y, with tumor node metastases stage I or II breast cancer or estrogen receptor; 120 subjects in each group; the study lasted for 5 y	Control: 20 mg TAM with placebo (soybean oil); intervention: TRF at 200 mg + 20 mg TAM	No statistical difference between TAM and TAM + tocotrienols in mortality rate
Tocotrienols in combination with neoadjuvant chemotherapy (NCT02909751)	Whether tocotrienols can improve the efficacy and reduce the side effects of chemotherapy before surgery for breast cancer	Tocotrienol, daily 300 mg ×3 along with chemotherapy drugs	Correlation of changes in NK cells, or ctDNA, with pathological response; grade 3–4 side effects
Pancreatic cancer			
Window-of-opportunity preoperative trial: open-label, phase I trial (16)	25 patients for curative surgical resection with presumptive premalignant or malignant neoplasms of exocrine pancreas	δTE at escalation doses of 200–3200 mg/d for 2 wk before surgery	δTE is generally safe and induced apoptosis in dysplastic or malignant tissues from pancreas
CRC			
γTmTs on CRC: randomized early phase I trial (NCT00905918)	Patients undergoing surgery for colorectal cancer	γTmTs for 1 or 2 wk	Bioavailability, plasma F2-isoprostane, inflammation markers
Tocotrienols as adjuvants for treatment of CRC, randomized and double-blinded (NCT02705300)	Side effects to Folfoxiri + tocotrienol/placebo as first-line treatment of metastatic colorectal cancer	Standard chemotherapy plus tocotrienol, daily 300 mg ×3	Side effects and survival benefits
Prostate cancer			
γTmTs on prostate cancer: randomized early phase I trial (NCT00895115)	Patients at risk of prostate cancer or who have prostate cancer	γTmTs for 1 or 2 wk	Bioavailability, plasma PSA, F2-isoprostane, inflammation markers
Ovarian cancer			
Cabazitaxel vs. tocotrienol: a phase 2 randomized, open-label study; crossover (NCT02560337)	Patients with recurrent ovarian cancer after failure of standard therapy	Cabazitaxel (25 mg/m^2) vs. tocotrienol (300 mg ×3); 3 mo	Survival rate and cancer progression
Tocotrienols as a nutritional supplement with bevacizumab; phase 2, single-group assignment (NCT02399592)	Patients with advanced ovarian cancer	Bevacizumab plus tocotrienol, 300 mg	Disease progression
Lung cancer			
Tocotrienols as nutritional supplement; randomized, double-blind (NCT02644252)	In patients with advanced NSCLC	Tocotrienol, 300 mg ×3 plus standard chemotherapy	Disease progression–free survival

[1] Data were from published data and https://clinicaltrials.gov. This table shows non-αT vitamin E forms for cancer prevention or treatment in ongoing or published trials, whereas large trials that focus on αT have been extensively reviewed elsewhere (4, 6). This table does not include the studies whose sole purpose is for obtaining pharmacokinetic data, in which vitamin E forms are used as part of other dietary factors or antioxidants, or where the vitamin E form was not clearly identified. For those ongoing (unpublished) studies, the clinicaltrials.gov identifiers (NCT) are indicated. CRC, colorectal cancer; ctDNA, circulating tumor DNA; NSCLC, non–small cell lung cancer; PSA, prostate specific antigen; ref, reference; TAM, tamoxifen; TRF, tocotrienol-rich fraction; αT, α-tocopherol; γTmT, γT-rich mixed tocopherol; δTE, δ-tocotrienol; X3, 3 times/d.

βT 0.7%, γT 1.0%, and δT 0.5%. It was observed that 1-y chronic exposure to 2% tocotrienol mixture diets resulted in a reduction in the survival rate by 42% in rats. A 2-y exposure to a 1–2% tocotrienol mixture induced highly proliferative liver lesions (nodular hepatocellular hyperplasia), although no obvious neoplastic characteristics were found from increased exposure. In a 13-wk feeding study, Nakamura et al. (176) reported that a similar tocotrienol mixture did not cause any observable adverse effects at 120 mg/kg body weight, although there slight adverse effects shown at 473 mg/kg and adverse effects including decreased body weight at 1895 mg/kg body weight. In addition, Yap et al. (154) determined the acute toxicity of γTE by single intraperitoneal injection of escalating doses in C57BL/6 black male mice and found that γTE at 800 mg/kg body weight did not cause any deaths among 5 injected mice, whereas deaths started to occur when 1000 mg/kg was used. In addition to research in animals, the safety of relatively high doses of γT and δTE has been examined in healthy humans. Supplementation of γT at ≤1.2 g for 8 d did not result in obvious adverse effects in healthy subjects (14). In a multiple-dose study, δTE was found to be well tolerated at doses ≤3.2 g for 14 d, although some subjects experienced grade 1 or 2 adverse events (19). These results indicate that vitamin E forms are generally safe in healthy subjects. On the other hand, the safety of these compounds under

disease conditions or in the presence of other drugs remains to be determined.

Anticancer effects in human intervention studies

All of the large randomized trials on vitamin E focused only on αT with regard to cancer-preventive potential and have shown inconsistent and disappointing outcomes, which have been extensively reviewed elsewhere (4, 6). With regard to other vitamin E forms, there are observational studies that reported both positive and negative associations between their intake and cancer risk. Given the potential confounding factors in diets, limited conclusions can be drawn on the basis of the epidemiologic data. In this review, we focus on published intervention trials and currently ongoing clinical human studies (based on https://clinicaltrials.gov) that aim to test the safety and anticancer efficacy of tocotrienols and (non-aT) tocopherols (Table 3).

In a double-blinded, placebo-controlled clinical trial, potentially improved therapeutic outcomes from a combination of a TRF with tamoxifen were tested in women with early-stage breast cancer. After 5 y of follow-up, tocotrienol adjuvant therapy did not significantly improve breast cancer–specific survival rate compared with tamoxifen-placebo controls, although there was a nonsignificant 60% decrease in the risk of mortality due to breast cancer in the tocotrienol group compared with the tamoxifen-alone control group (169). In an open-label, dose-escalation phase I trial, patients with presumptive premalignant or malignant neoplasms of the exocrine pancreas for curative surgical resection were given various doses of δTE at 200–3200 mg 2 times/d for 13 d. The endpoints of this study included pharmacokinetics, general safety, and the effect of supplements on cell apoptosis in pancreatic tissues. The key findings include that δTE was generally safe and induced apoptosis in dysplastic or malignant tissues from the pancreas (16). In addition to these 2 published studies, there are several ongoing trials investigating the effect of γTmTs on colon and prostate cancer or tocotrienols on cancer treatment (Table 3).

Conclusions

Because αT supplementation failed to show cancer-preventive effects in many clinical studies but was reported to increase prostate cancer risk in the SELECT, the role of other tocopherols and tocotrienols in cancer prevention has also been questioned. However, as reviewed here, accumulating cell-based and preclinical studies indicate that the form and metabolism of vitamin E are critically important factors for vitamin E–related cancer prevention. In particular, mechanistic and cell-based studies have shown that γT, δT, γTE, and δTE are much stronger than αT in blocking multiple cancer-promoting pathways, including COX- and 5-LOX–catalzyed eicosanoids, and γTE and δTE inhibit key transcription factors such as NF-κB and STAT3 (8). These vitamin E forms, but not αT, inhibit cancer cell proliferation and induce cancer cell death via modulating various signaling pathways, including sphingolipids. Unlike αT, which is largely unmetabolized, γT, δT, γTE, and δTE are readily metabolized and their long-chain metabolite 13′-COOHs are unique dual inhibitors of COXs and 5-LOX and have stronger anti-inflammatory and anticancer effects than some unmetabolized vitamers (60, 61, 71). Consistently, γT, δT, γTE, and δTE have been shown to suppress tumor development in relevant animal cancer models, whereas αT was often ineffective in similar preclinical studies. Therefore, it is noteworthy that the lack of anticancer effects of αT in preclinical models is in agreement with no beneficial effect of its supplementation observed in many randomized clinical trials (4–6).

Studies in preclinical animal models have shown that γT, δT, γTE, and δTE exhibit varied anticancer efficacy, and γTE and δTE often appear to be stronger than tocopherols in these effects. The relative effectiveness also depends on the stage and severity of tumorigenesis. For instance, γT, δT, and γTmTs are effective in preventing early-stage cancer progression but show modest protection of relatively advanced or aggressive stages of cancer. γT, δT, and γTmTs significantly suppressed tumorigenesis or precancerous lesions when the intervention started before carcinogenesis was initiated, whereas they were less effective if supplementation began after the cancer-promotion phase. These tocopherols inhibited estrogen-dependent breast cancer but were ineffective in HER-2–positive breast cancer, whereas γTE was able to suppress *Her2*-positive breast cancer in transgenic mice. γTE was stronger than γT in inhibiting the growth of prostate LNCaP xenograft tumor. Furthermore, δTE inhibited pancreatic cancer in genetic models with aggressive driver mutations. These preclinical observations are in agreement with those in cell-based studies in which tocotrienols exhibited stronger anticancer and anti-inflammatory effects than tocopherols, which may be attributed to the fact that tocotrienols are accumulated at higher concentrations in some cancer cells or tumors than tocopherols and are more readily metabolized to bioactive metabolites in vivo (68).

Although different vitamin E forms clearly have anticancer potential, in the future more preclinical studies are needed to validate and optimize their efficacy for cancer prevention and therapy, with an emphasis on translation from bench to bedside. First, with the exception of δTE on pancreatic cancer, more preclinical work should be conducted to examine the cancer-prevention efficacy of vitamin E forms in genetically engineered "humanized" models that have driver mutations found in human cancers. In these studies, anticancer efficacy should be tested at different stages of cancer development. Second, combinations of vitamin E forms with other preventive agents such as statins or NSAIDs should be explored to achieve enhanced chemoprevention effects. Because vitamin E forms are rich in different foods and dietary components may have a profound impact on vitamin E's anticancer effects and bioavailability, it is important to examine and compare the use of food approaches with supplementation for cancer prevention. Furthermore, the potential use of tocotrienols in adjuvant chemotherapy for enhancing treatment efficacy of traditional therapeutic agents should be further tested in patient-derived cancer

models. In addition, the use of nutrition factors for cancer control or preventing recurrence after chemo- or radiation therapy is a largely uncharted territory. I propose that vitamin E forms hold tremendous promise in cancer control, which warrants investigation. Whether vitamin E forms are capable of enhancing immunotherapy should also be examined.

With strong preclinical data and further studies in animal models, vitamin E forms or their combinations with other agents should be examined in secondary and even tertiary prevention trials in individuals who are at high risk of cancer (e.g., those who have multiple precancerous, genetically cancer-driven mutations; familial adenomatous polyposis; or chronic conditions that promote cancer such as colitis) (177). With regard to treatment, the following areas can be explored: the use of vitamin E forms as adjuvant therapy for improving traditional chemotherapy or radiation therapy or the use of vitamin E forms for cancer control and prevention of recurrence as well as improving cancer patients' quality of life and survival rate. In addition to efficacy, potential toxicity or side effects of vitamin E forms alone or in combinations with other agents should be extensively investigated before they can generally be recommended as chemoprevention or therapeutic agents.

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