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Tocopherols in cancer: an update

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Abstract

Tocopherols exist in four forms designated as α, β, δ and γ. Due to their strong antioxidant properties, tocopherols have been suggested to reduce the risk of cancer. Cancer prevention studies with tocopherols have mostly utilized α-tocopherol. Large scale clinical trials with α-tocopherol provided inconsistent results regarding the cancer preventive activities of tocopherols. This review summarizes our current understanding of the anti-cancer activities of different forms of tocopherols based on follow up of the clinical trials, recent epidemiological evidences and experimental studies using in vitro and in vivo models. The experimental data provide strong evidence in support of the anti-cancer activities of δ-tocopherol,γ-tocopherol and the natural tocopherol mixture rich in γ-tocopherol, γ-TmT, over α-tocopherol. Such outcomes emphasize the need for detailed investigation into the cancer preventive activities of different forms of tocopherols to provide a strong rationale for intervention studies in the future.

Keywords

Tocopherols; vitamin E; cancer prevention

1. Introduction

Tocopherols, the major forms of vitamin E, are a group of fat soluble phenolic compounds. Each tocopherol consists of chromanol ring and a 16-carbon phytyl chain [1]. Depending on the number and position of methyl groups on the chromanol ring, tocopherols are designated as α, β, δ and γ [1].α-Tocopherol (T) is trimethylated at the 5-, 7-and 8-positions of the chromanol ring and β-T is dimethylated at 5- and 8-positions, whereas γ-T is dimethylated at the 7- and 8-positions and δ-T is methylated at the 8-position [1]. The unmethylated carbons at the 5- and 7-positions are electrophilic centers that can effectively trap reactive oxygen and nitrogen species (RONS). All tocopherols are strong antioxidants, however δ-T and γ-T are more effective in trapping reactive nitrogen species than α-T [2-5]. The major dietary sources of tocopherols are vegetable oils such as corn, soybean, sesame, cottonseed [6]. γ-T is the most abundant form of tocopherol in the US diet, being three to five times more abundant than α- and δ-T whereas β-T is present only in minute amounts [6]. A natural tocopherol mixture rich in γ-T, γ-TmT, can be easily obtained as a byproduct in the

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distillation of vegetable oil and usually contains (per gm) 115-130 mg α-T, 12-15 mg β-T, 561-568 mg γ-T and 223-243 mg δ-T [7-9].

Due to their strong antioxidant properties, tocopherols have been suggested to reduce the risk of cancer [10]. Several studies show that a lower vitamin E nutritional status is associated with an increased risk of certain cancers [11, 12]. α-T is considered to be the classic vitamin E as it is the major form of tocopherols found in blood and tissues [13]. Therefore, α-T has been the most widely used form of tocopherols for cancer prevention studies. However, results from large scale human intervention studies with α-T, such as the Alpha-Tocopherol Beta-Carotene Cancer Prevention (ATBC) Study and Selenium and Vitamin E Cancer Prevention Trial (SELECT), led to inconsistent conclusions about the cancer preventive activities of tocopherols [14, 15]. The 2009 report of the SELECT trial demonstrating that selenium and vitamin E failed to prevent prostate cancer in healthy men [15] raised questions and skepticism about the cancer preventive properties of tocopherols. In this review, we will summarize our current understanding of the chemopreventive effects of tocopherols after the SELECT report, based on recent intervention and follow up studies of ATBC and SELECT as well as epidemiological studies. We will also discuss the biological activities of different forms of tocopherols in cancer prevention with respect to current *in vitro* and *in vivo* studies.

2. Studies on Tocopherols and Human Cancers

2.1 Intervention Studies

The ATBC 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 [16]. Supplementation with α-T or β-carotene for 5-8 years did not have a beneficial effect on the incidence of lung cancer [16]. Men who received β-carotene were found to have lung cancer more frequently than those who did not receive β-carotene [14]. However, α-T supplementation and higher serum α-T was significantly associated with a reduced incidence of prostate cancer (as a secondary end point) [17]. Based on these results, the SELECT trial was launched, in which 35,533 men from 427 study sites in the United States, Canada and Puerto Rico were randomized into four groups and administered with 400 IU of all-racemic-α-tocopheryl acetate or 200 μg selenium from L-selenomethionine daily in a two-by-two design for an average of 5.5 years. However, the supplementations failed to prevent prostate or other cancers [15].

Several follow up studies of the ATBC and SELECT trials have been reported in the recent years. A follow up study of ATBC examined whether vitamin E intake and serum α-T concentrations were prospectively associated with exocrine pancreatic cancer [18]. A cohort analysis of prediagnostic vitamin E intake (4 tocopherols and 4 tocotrienols), serum α-T concentrations and pancreatic cancer was conducted [18]. During a median follow up period of 16 years, higher serum α-T concentrations were associated with a significant 48% reduction in the risk of pancreatic cancer and the inverse serum α-T association was more pronounced in men with a higher polyunsaturated fat intake [18]. Another report examined whether serum α-T, β-carotene and retinol measured at study entry and after 3 years affected survival time in men diagnosed with prostate cancer while enrolled in the ATBC study [19].

Higher levels of serum α-T were found to increase overall prostate cancer survival while β-carotene and retinol had no effects [19]. A recent study evaluated the association of serum α-T, β-carotene and retinol with the incidence of liver cancer and chronic liver disease (CLD) mortality in a prospective cohort of male smokers from the ATBC study [20]. The findings suggest that higher serum β-carotene and retinol levels were inversely associated with incident liver cancer and death from CLD. Higher α-T levels had no association with liver cancer incidence, although a borderline statistically significant reduced risk was observed for CLD death [20]. To determine the post intervention effects of α-T and β-carotene in the ATBC study, 25,563 men were followed 18 years for cancer incidence and all causes of mortality [21]. Neither α-T nor β-carotene had significant effects on post-trial cancer incidence [21]. However, the preventive effect of α-T supplementation on prostate cancer continued several years post-trial, resulting in lower prostate cancer mortality [21].

A secondary analysis of SELECT assessed the effect of selenium and/or vitamin E (α-T) on bladder cancer incidence [22]. Contrary to the epidemiological and experimental evidences that selenium and vitamin E may prevent bladder cancer, this analysis showed that supplementation with selenium or vitamin E alone or in combination did not reduce the incidence of bladder cancer [22]. The SELECT trial demonstrated higher prostate cancer incidence upon supplementation with α-T [15]. A recent study evaluated whether plasma α-T or γ-T levels before supplementation were associated with prostate cancer in SELECT [23]. Men with the highest pre-randomization α-T concentrations were found to be twice as likely to be diagnosed with prostate cancer if they received the selenomethionine supplement in the trial [23]. However, pre-supplementation plasma α-T levels were unrelated to prostate cancer risk among men supplemented with only α-T, and γ-T had no association with prostate cancer [23]. These findings indicate that higher plasma α-T concentrations may interact with selenomethionine supplements to increase prostate cancer risk. The Physicians' Health Study II Randomized Control Trial evaluated the effects of long term vitamin E or C supplementation on the risk of prostate and total cancers in men [24]. Supplementation with vitamin E (400 IU of α-T every other day) or vitamin C (500 mg of synthetic ascorbic acid) for 8 years did not reduce the risk of prostrate or other cancers [24]. Four years post-trial follow up of this study revealed that vitamin E and C supplementation had no long term effects on the incidence of prostate or other site specific cancers [25].

High-grade prostatic intraepithelial neoplasia (HGPIN) is a putative precursor of invasive prostate cancer. Preclinical evidence suggests that vitamin E, selenium and soy protein may prevent progression of HGPIN to invasive prostate cancer [26]. This hypothesis was tested in a randomized phase III double-blind study including 303 men of median age 62.8 years in 12 Canadian centers supplemented daily with soy (40 g), vitamin E (800 IU) and selenium (200 μg) versus placebo. The results of this trial did not support the hypothesis that combination of vitamin E, selenium and soy prevents progression from HGPIN to invasive prostate cancer [27]. Till date, intervention studies have provided inconsistent conclusions about the cancer preventive activities of tocopherols, emphasizing the need for systematic future studies with different forms and effective doses of tocopherols to elucidate their role in cancer prevention.

2.2 Epidemiological studies

Although randomized controlled trials to assess the cancer preventive activities of vitamin E provided inconsistent results, several recent observational studies suggest an inverse association between vitamin E and cancer risk.

A nested case-control study of serum α-T and γ-Tlevels and prostate cancer risk in the Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial found that higher serum α-T levels reduce the risk of prostate cancer particularly among smokers while γ-T had no association with prostate cancer [28]. A meta-analysis of 9 nested case-control studies on blood α-T and γ-T levels and the risk of prostate cancer demonstrated that blood α-T levels, but not γ-T levels, were inversely associated with the risk of prostate cancer [29]. A recent study examined plasma carotenoid and tocopherol levels in relation to prostate specific antigen (PSA) levels among men with PSA-defined biochemical recurrence of prostate cancer [30]. Data analyzed from a 6-month diet, physical activity and stress-reduction intervention study showed that plasma levels of α-T and certain carotenoids are inversely related to PSA levels [30]. These findings suggest that greater intake of food containing these micronutrients might be beneficial to men with PSA-defined recurrent prostate cancer. The North Carolina-Louisiana Prostate Cancer Project (PCaP) examined whether dietary intake of tocopherols, vitamin E supplement use and adipose tissue biomarkers of tocopherols were associated with prostate cancer aggressiveness among African-American and European-American men [31]. Dietary intake of α-T and δ-T were inversely related to prostate cancer aggressiveness in European-Americans [31]. No significant association was observed between supplemental α-T or adipose tissue tocopherol levels and prostate cancer aggressiveness [31]. The Netherlands Cohort Study evaluated the relation between prostate cancer risk and intake of vegetables, fruits, carotenoids and vitamins C and E [32]. After 16.3 years of follow up, no association was observed between a high consumption of vegetables, fruits or the intake of carotenoids, vitamins (C and E) or vitamin supplements and prostate cancer risk [32]. Within the same study, the association of carotenoids, vitamins C and E with the risk of head-neck cancer subtypes was evaluated [33]. No significant association was observed between the intake of vitamin E (including supplements) and the risk of head-neck cancer [33].

A recent report based on 10 case-control studies to assess the association between vitamin E intake from natural sources and cancer of the oral cavity/pharynx and larynx found that vitamin E was inversely related to oral/pharyngeal cancer [34]. A nested case-control study within the European Prospective Investigation into Cancer and Nutrition (EPIC) investigating the relation of prediagnostic plasma levels of carotenoids, vitamin C, retinoids and tocopherols with the risk of pancreatic cancer showed that higher plasma concentrations of β-carotene, zeaxanthin and α-T may be inversely associated with pancreatic cancer risk [35]. A second case-control study within the EPIC examined the association of dietary consumption of carotenoids and vitamins A, C and E with the risk of colon and rectal cancer [36]. Inverse associations for dietary β-carotene and vitamins C and E with distal colon cancer were observed [36]. Repeated measurements of serum carotenoids, retinol and tocopherol levels in the Women's Health Initiative study revealed no association of retinoid and tocopherol levels with colorectal or colon cancer risk, although high serum levels of β-

carotene was inversely associated with the risk of colorectal and colon cancer in postmenopausal women [37]. A prospective investigation of the association between tocopherol intake from diet and supplements with lung cancer risk among Chinese female non-smokers participating in the Shanghai Women's Health Study was conducted [38]. After 12.02 years of follow up, total dietary consumption of tocopherol was inversely associated with lung cancer risk while vitamin E supplement was associated with increased lung cancer risk [38]. A dose response meta-analysis of 40 studies assessing the relation of vitamins C, D, and E with the risk of bladder cancer found that bladder cancer is inversely associated with vitamins D and E (especially α-T) in a linear dose response manner, but positively associated with γ-T [39].

A longitudinal study of serum carotenoid, retinol, and tocopherol concentrations in relation to breast cancer among postmenopausal women revealed that certain carotenoids reduce the risk of breast cancer, α-T has no association while γ-T has a positive association, increasing breast cancer risk [40]. The protective role of carotenoids, tocopherols and retinol in breast cancer was investigated in women subjects of the E3N study, the large French component of the EPIC. No significant associations between breast cancer risk and serum levels of these antioxidant micronutrients were observed [41]. A meta-analysis of 40 studies providing a comprehensive summary of the associations between plasma retinol, vitamins A, C, α-T and breast cancer risk reported that severe α-T deficiency could increase breast cancer risk [42]. A pooled analysis of 10 cohort studies in North America and Europe suggested that the intake of vitamins A, C, E and folate during adulthood does not affect the risk of ovarian cancer [43]. Although some epidemiological studies suggest the beneficial role of α-T in cancer prevention, overall epidemiological data do not provide clear evidence about the cancer preventive effects of tocopherols.

3. Experimental Studies with Tocopherols

Despite the fact that epidemiological and intervention studies did not provide consistent conclusions about the cancer preventive activities of tocopherols, *in vitro* and *in vivo* studies with different tocopherol forms demonstrate the anti-cancer activities of tocopherols. This indicates the need for more detailed investigation of the biological activities of individual forms of tocopherols.

Prostate Cancer

The transgenic rat for adenocarcinoma of prostate (TRAP) model features development of high grade prostatic intraepithelial neoplasia (PIN) from 4 weeks of age and well differentiated adenocarcinoma by 15 weeks age [44]. Dietary γ-T suppressed the progression from PIN to adenocarcinoma in the TRAP model through the activation of caspase-3-mediated apoptosis [44]. γ-TmT, a natural tocopherol mixture rich in γ-T, has been reported to inhibit PIN and tumor incidence in the transgenic adenocarcinoma of the mouse prostate (TRAMP) model by upregulation of nuclear factor (erythroid derived 2)-like 2 (Nrf2) and its downstream detoxifying and antioxidant enzymes [45]. Nrf2 is known to be down regulated in human and TRAMP prostate cancer associated with excessive reactive oxygen species [46]. Nrf2 is epigenetically suppressed due to CpG hypermethylation in prostate tumors

from the TRAMP model. γ-TmT has been found to inhibit CpG methylation of the Nrf2 promoter in the prostate of TRAMP mice, leading to higher Nrf2 expression and prevention of tumorigenesis [47]. γ-TmT inhibited growth and induced apoptosis in LNCaP cells *in vitro* [48]. Treatment of severe combined immunodeficient (SCID) mice with dietary γ-TmT suppressed the formation and growth of LNCaP xenografted tumors [48]. A recent study demonstrated that treatment of human prostate cancer cells with δ-T resulted in strong growth inhibition and apoptosis stimulation, associated with suppression of androgen receptor (AR) activity and decreased levels of PSA, a downstream target of AR signaling [49]. In addition, δ-T inhibited the formation and growth of LNCaP xenografted prostate tumors in SCID mice [49]. Evaluation of the effects of lycopene, selenium and vitamin E (γ-T) alone and in combination on the growth of androgen-dependent transplantable Dunning R3327-H prostate rat tumors revealed that only selenium, but not lycopene or vitamin E decreased tumor growth [50]. γ-T has been reported to reduce tumor development in nude mice implanted with LNCaP cells, although less efficiently than γ-tocotrienol, a form of vitamin E with an unsaturated phytyl tail [51]. Previously, γ-T was shown to induce apoptosis in LNCaP cells interrupting sphingolipid synthesis [52]. A combination of γ-T and methaneseleninic acid (MSA) suppressed tumor growth in nu/nu mice xenografted with the human prostate cancer 22Rv1 cells, through upregulation of pro-apoptotic proteins, such as Bax and Bad, resulting in decreased cell proliferation and Ki-67 immunostaining in the tumors [53]. It has been reported that γ-T induces growth arrest in PC-3 prostate cancer cells through a peroxisome proliferator-activated receptor γ (PPARγ)-dependent mechanism [54]. γ-T has been shown not to be a direct PPARγ ligand, but it rather upregulates 15-S-HETE, an endogenous PPARγ ligand [54]. The vitamin E analogue α-tocopheryl succinate (α-TOS), a mitochondria targeting apoptotic agent, has been reported to inhibit autophagic survival of PC-3 cells induced by vitamin K3 (VK3) and ascorbate through triggering apoptosis [55]. In PC-3 xenografted immunodeficient mice, the combination of α-TOS, VK3 and ascorbate suppressed prostate tumor growth more efficiently than the single agents [55]. Tocopherols have been known to dephosphorylate Akt, a serine/threonine kinase that plays a pivotal role in cell growth, survival, metabolism and motility [56]. A recent study demonstrated that α-T and γ-T facilitate dephosphorylation of Akt in PTEN deficient 3 prostate cancer cells LNCaP and PC-3 through activation of PH domain leucine-rich repeat protein phosphatase, isoform 1 (PHLPP1), a phosphatase that dephosphorylates Akt at Ser^{473} [57].

Breast Cancer

γ-TmT has been reported to inhibit tumorigenesis in estrogen receptor (ER) positive *in vivo* models of breast cancer. γ-TmT inhibited N-methyl-N-nitrosourea (NMU)-induced mammary tumorigenesis in Sprague Dawley rats by downregulation of estrogen receptor α (ERα), Akt and activation of PPARγ[56]. δ-T and γ-T were shown to inhibit mammary tumor growth in NMU-induced Sprague Dawley rats, but did not prevent human epidermal growth factor receptor 2 (HER2/neu)-driven tumorigenesis [9]. In the August Copenhagen Irish (ACI) rat model, γ-TmT reduced oxidative and nitrosative stress and upregulated Nrf2-mediated antioxidant response in estrogen-induced early mammary hyperplasia [58]. At later stages of hyperplasia, dietary γ-TmT inhibited oxidative stress, inflammatory markers and regulated the expression of nuclear receptors ERα and PPARγ to inhibit cell proliferation in

ACI rats [59]. Recently, γ-TmT has been reported to suppress estrogen-mediated mammary tumor growth in ACI rats and MCF7-xenografted immunodeficient mice [8]. In ACI rats, γ-TmT inhibited mammary tumorigenesis by modulating cytochrome P450 1A1 (CYP1A1)-mediated estrogen metabolism, Nrf2-dependent antioxidant response and arresting cell proliferation through activation of PPARγ [8]. Several studies have investigated the effects of tocopherol analogues in breast cancer. α-Tocopheryloxyacteic acid (α-TEA) has been shown to enhance the cytotoxic activity of trastuzumab in HER2/neu positive murine mammary tumor cells and human breast cancer cells [60]. In a xenograft model, the combination of α-TEA and trastuzumab resulted in more effective mammary tumor regression and increase in tumor free animals than trastuzumab alone [60]. In the human breast cancer cells, MCF-7 and HCC-1954, α-TEA has been reported to act synergistically in combination with pharmacological inhibitors of mitogen-activated protein kinase (MEK) and mammalian target of rapamycin (mTOR), inducing apoptosis by targeting insulin receptor substrate-1 (IRS-1)/PI3K pathways [61].α-TEA induced apoptosis in MCF-7 and HCC-1954 via tumor necrosis factor-related apoptosis inducing ligand (TRAIL)/death receptor-5 (DR5) pathway and downregulation of cellular FLICE-like inhibitory protein (c-FLIP) [62]. Recently, the mitochondria targeting vitamin E analogue (Mito-chromanol, Mito-ChM) and its acetylated ester analogue (Mito-ChMAc) have been shown to exhibit anti-proliferative and cytotoxic effects in multiple breast cancer cell lines [63]. Furthermore, Mito-ChM selectively accumulated in tumor tissue and inhibited tumor growth in a xenograft model of human breast cancer [63]. $_{D}$-alpha-tocopheryl polyethylene glycol succinate (TGPS) is a vitamin E derivative that has been extensively used as a vehicle for delivery of anti-cancer drugs. TGPS has been found to act as anti-cancer agent alone or in combination with chemotherapeutic drugs [64]. TGPS induced G1/S cell cycle arrest and apoptosis in MCF-7 and MDA-MB-231 breast cancer cell lines by inhibition of Akt and downregulation of the anti-apoptotic proteins, survivin and Bcl2 [65]. The α-T derivative ESeroS-GS (γ-L-glutamyl-S-[2-[[[3,4- dihydro-2,5,7,8-tetramethyl-2-(4,8,12-trimethyltridecyl)-2H-1-benzopyran-6-yl]oxy] carbonyl]-3-[[2-(1H-indol-3-yl) ethyl] amino]-3-oxopropyl]-L-cysteinylglycine sodium salt) has been shown to induce cell death and inhibit viability, migration and invasion of breast cancer cells [66].

Colon Cancer

The effect of dietary γ-TmT on the colon of mice treated with azoxymethane (AOM) and dextran sulfate sodium (DSS) was studied at different time points [7]. γ-TmT lowered colon inflammation at day 7, reduced the number of colon adenomas at week 7 and inhibited formation of adenoma and adenocarcinoma in the colon at week 21 [7]. In male BALB/c mice, γ-T or tocopherol mixtures (rich in γ-T and δ-T) did not show any significant effect on colon tumorigenesis induced by AOM followed by 3 cycles of DSS [67]. However, when AOM-initiated carcinogenesis was promoted by relatively mild colitis induced by 1 cycle of DSS, γ-T decreased tumor multiplicity demonstrating that γ-T is able to alleviate moderate but not severe colitis promoted tumorigenesis [67]. Administration of different doses of vitamin E in a 1, 2-dimethylhydrazine (DMH)-induced model of colorectal carcinogenesis in male Wistar rats demonstrated that 1500 IU of vitamin E is hazardous, whereas 225 IU of vitamin E has beneficial effects on colorectal carcinogenesis associated with reduced aberrant crypt foci and decreased cyclooxygenase 2 (COX2) expression [68]. Investigation

of the growth inhibitory effects of different forms of tocopherols, tocopheryl phosphates (TP) and tocopherol quinones (TQ) on human colon cancer cells, HCT116 and HT29, revealed that TP and TQ had higher inhibitory activities than their parent compounds [69]. δ-T was more active than γ-T in inhibiting cell growth, colony formation and inducing apoptosis, while α-T was ineffective [69]. Recently, γ-T has been found to enhance the apoptotic effects of lovastatin, a HMG (3-hydroxy-3-methyl-glutaryl)-CoA reductase inhibitor, in the human colorectal carcinoma cell line HT29 by induction of mitochondrial membrane potential collapse, cytochrome c release and caspase 3 activation [70].

Lung Cancer

Investigation of the growth inhibitory effects of γ-TmT against CL13 murine lung cancer cells *in vitro* and subcutaneous tumors in A/J mice showed that γ-TmT weakly inhibited the growth of CL13 cells after 5 days but significantly inhibited the growth of CL13 tumors after 50 days of dietary administration [71]. Dietary γ-TmT reduced tumor multiplicity and tumor burden in 4-(methylnitrosoamino)-1-(3-pyridyl)-1-butanone (NNK) or NNK plus benzo[a]pyrene (B[a]P)-induced lung cancer in A/J mice [72]. In a xenograft model of human lung cancer H1299 cells in nu/nu mice, γ-TmT decreased tumor volume and tumor weight [72]. In another study of H1299 xenograft in nu/nu mice, δ-T was found to be more active than γ-T in inhibiting lung tumorigenesis, while α-T was not active [73].

Other cancers

RRR-α-tocopheryl succinate induces apoptosis in the human gastric cancer cell line, SGC-7901, by inhibition of NFκB signaling and BCL2 family members and induction of cleaved caspase-3 and -9 [74]. In a mouse model of acute promyelocytic leukemia (APL) derived from hCG-PML-RARα transgenic mice, the vitamin E derivative α-TOS was as effective as arsenic trioxide or all-trans retinoic acid, the current gold standards of therapy [75]. α-TOS induced early dissipation of mitochondrial membrane potential by inhibiting the mitochondrial respiratory chain complex I [75]. Supplementation with vitamin E/selenium for different stages in N-nitrosomethylbenzylamine (NMBA)-induced esophageal carcinogenesis in Fischer 344 rats demonstrated that the chemopreventive efficacy of vitamin E/selenium is time selective and that supplementation during the early stages is effective in preventing the cancer while that during late stages had no effect [76]. A recent study investigated the effects of topical α-T alone as well as α-T combined with vitamin C and ferulic acid in UVB induced skin tumors in SKH-1 mice. The combination of α-T, vitamin C and ferulic acid decreased tumor multiplicity and tumor burden while α-T promoted carcinogenesis when applied on chronically UVB-damaged skin [77]. Although some studies demonstrated the anti-cancer activities of synthetic α-T derivatives, the experimental studies suggest the favorable chemopreventive effects of natural forms of δ-T and γ-T over α-T *in vitro* and *in vivo*.

Possible mechanisms of action

Several mechanisms have been proposed for the actions of tocopherols. Since recent studies show that unlike α-T, δ-T and γ-T are effective in inhibiting carcinogenesis and tumor growth in experimental animal models, it is important to address why δ-T and γ-T have higher anti-cancer properties than δ-T. All tocopherols are antioxidants. However, the

unmethylated 5-position of the chromanol ring enables δ-T and γ-T to trap reactive nitrogen species [5]. In addition, δ-T and γ-T are less effectively transported to the blood and are prone to side chain degradation. The resulting long chain metabolites have been shown to inhibit COX2 activity [78]. Modulation of nuclear receptors by tocopherols may contribute to their chemopreventive activity. PPARγ is known to be important for inhibition of cell proliferation and induction of apoptosis in breast cancer [79]. δ-Tand γ-T have been shown to be more effective than α-T in upregulating PPARγ [9]. Downregulation of ERα-dependent estrogen signaling by δ-T and γ-T may play a role in the inhibition of mammary tumorigenesis [9]. δ-T and γ-T downregulate the cell survival marker Akt [57]. δ-T and γ-T are more potent than α-T in inhibiting growth and inducing apoptosis in different cancer cell lines [10], causing cell cycle arrest at S phase by downregulating key regulators of G1-S transition, cyclin D1 and cyclin E and upregulating p21 and p27 [10]. For the induction of apoptosis, activation of caspase- 3 and caspase-9, caspase independent pathways [80] and interruption of de novo synthesis of sphingolipids have been proposed as key mechanisms [52].

4. Conclusion

This review summarizes the recent reports on the cancer preventive activities of tocopherols based on epidemiological and intervention studies as well as experimental studies. Some epidemiological studies suggest that α-T could be beneficial for the prevention of certain cancers. However, large scale clinical trials with α-T have provided inconsistent conclusions regarding its cancer preventive activity. The high dose of α-T (400 IU/d) used in SELECT may have been less effective than a lower dose of 50 IU/d that exerted secondary chemopreventive effects against prostate cancer in the ATBC study. High pharmacological doses of α-T may have adverse effects on cytochrome P450 enzymes and other regulatory mechanisms [81]. Besides, high doses of α-T have been demonstrated to decrease the levels of potentially beneficial γ-T in the blood [15]. α-T is the most abundant form of tocopherols in human blood and tissues. Hence, supplementation with a nutrient that is already abundant in the human body might not be effective for the prevention of cancer. Results from *in vitro* and *in vivo* studies suggest that γ-T and δ-T could be more potent anti-cancer agents compared to α-T. Future human cancer prevention trials with pure δ-T and γ-T or tocopherol mixtures rich in δ-T and γ-T could be very important. Due to its broad cancer preventive activity and availability, the naturally occuring tocopherol mixture rich in γ-T, γ-TmT, or similar tocopherol mixtures may have a high potential for practical application. In light of the recent studies elucidating the role of antioxidants in cancer progression, tocopherols should be administered at early or pre-cancerous stages for effective chemoprevention. In future intervention studies, it would be important to evaluate the cancer preventive effects and the effective doses of the different forms of tocopherols.

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Abbreviations

ATBC	Alpha Tocopherol Beta Carotene Cancer Prevention Study
ACI	August Copenhagen Irish
AOM	azoxymethane
α-TEA	α-tocopheryl acetic acid
α-TOS	α-tocopheryl succinate
APL	acute promyelocytic leukemia
B[a]P	benzo[a]pyrene
Bcl2	B-cell lymphoma 2
CYP1A1	cytochrome P450 1A1
c-caspase-3	cleaved caspase-3
c-FLIP	cellular FLICE-like inhibitory protein
COX2	cyclooxygenase 2
DSS	dextran sulfate sodium

DR5	death receptor-5
DMH	1,2-dimethylhydrazine
EPIC	European Prospective Investigation into Cancer and Nutrition
ESeroSGS	γ-L-glutamyl-S-[2-[[[3,4- dihydro-2,5,7,8-tetramethyl-2-(4,8,12-trimethyltridecyl)-2H-1-benzopyran-6-yl]oxy] carbonyl]-3-[[2-(1H-indol-3-yl) ethyl] amino]-3-oxopropyl]-L-cysteinylglycine sodium salt
ERα	estrogen receptor α
GPx	glutathione peroxidase
HGPIN	high-grade prostatic intraepithelial neoplasia
HMOX1	hemeoxygenase1
IRS-1	insulin receptor substrate-1
MEK	mitogen-activated protein kinase
mTOR	mammalian target of rapamycin
MSA	methaneseleninic acid
NMU	N-methyl-N-nitrosourea
Mito-ChM	Mito-chromanol
Nrf2	nuclear factor (erythroid derived 2)-like 2
NMBA	N-nitrosomethylbenzylamine
NNK	4-(methylnitrosoamino)-1-(3-pyridyl)-1-butanone
PTEN	phosphatase and tensin homologue
p-Akt	phosphorylated Akt
PI3K	phosphatidylinositol-4,5-bisphosphate 3-kinase
PSA	prostate specific antigen
PPARγ	peroxisome proliferator-activated receptor γ
PGE2	prostaglandin E2
ROS	reactive oxygen species
RONS	reactive oxygen and nitrogen species
SELECT	Selenium and Vitamin E Cancer Prevention Trial

T	tocopherol
TRAP	transgenic rat for adenocarcinoma of prostate
TRAMP	the transgenic adenocarcinoma of the mouse prostate
TGPS	$_{D}$-alpha-tocopheryl polyethylene glycol succinate
TRAIL	tumor necrosis factor-related apoptosis inducing ligand
TP	tocopherol phosphates
TQ	tocopherol quinones
VK3	vitamin K3

Table 1
Effects of tocopherol treatment in experimental cancer models

Type of Cancer	Treatment	Experimental Model	Effects	Ref
Prostate Cancer	γ-T	TRAP rats	↓Adenocarcinoma ↑Apoptosis	[44]
	γ-TmT	TRAMP mice	↓Tumor incidence, PIN ↑Nrf2, HMOX1, GPx, SOD	[45]
	γ-TmT	TRAMP mice	↓Tumor incidence, Nrf2 methylation ↑Nrf2	[47]
	γ-TmT	LNCaP cells LNCaP xenograft	↑Apoptosis ↓Tumor growth	[48]
	δ-T	LNCaP, VCaP cells LNCaP xenograft	↓AR activity, PSA ↑Apoptosis ↓Tumor growth	[49]
	γ-T	LNCaP xenograft	↓Tumor growth	[52]
	γ-T + MSA	22Rv1 xenograft	↓Tumor growth, Ki67 ↑Bax, Bad, apoptosis	[53]
	γ-T	PC-3 cells	↓Cell growth ↑PPARγ, 15-S-HETE	[54]
	α-TOS	PC-3 cells	↓Autophagy	[55]
	α-TOS+VK3+ascorbate	PC-3 xenograft	↓Tumor growth	
	α-T, γ-T	LNCaP, PC-3 cells	↓p-Akt ↑PHLPP1	[57]
Breast Cancer	γ-TmT	NMU-treated rats	↓Tumor growth, p-Akt, ERα ↑PPARγ	[56]
	δ-T, γ-T	NMU-treated rats	↓Tumor growth, p-Akt, ERα ↑PPARγ, Nrf2, p21, p27, c-caspase-3	[9]
	γ-TmT	ACI rat early hyperplasia	↓8-oxo-dG, 8-isoprostane, nitrotyrosine ↑Nrf2, GPx, catalase, SOD	[58]
	γ-TmT	ACI rat hyperplasia	↓8-isoprostane, PGE2, COX2, ERα ↑Nrf2, PPARγ	[59]
	γ-TmT	ACI rats	↓Tumor growth, PCNA ↑CYP1A1, Nrf2, PPARγ	[8]
	α-TEA + trastuzumab	MDA-MB-453 xenograft	↑Tumor regression, apoptosis	[60]
	α-TEA + MEK/mTOR inhibitors	MCF-7, HCC-1954 cells	↓p-Akt, p-Erk, p-mTOR, IRS-1 ↑Apoptosis	[61]
	α-TEA	MCF-7, HCC-1954 cells	↓c-FLIP ↑TRAIL, DR5, apoptosis	[62]
	Mito-ChM	9 breast cancer cell lines MDA-MB-231 xenograft	↓Cell growth ↓Tumor growth	[63]
	TGPS	MCF-7, MDA-MB-231cells	↓p-Akt, Bcl2	[65]

Type of Cancer	Treatment	Experimental Model	Effects	Ref
			↑G1/S arrest, apoptosis	
	ESeroS-GS	MDA-MB-231 cells	↓Cell growth, migration, invasion	[66]
Colon Cancer	γ-TmT	AOM + DSS-treated mice	↓Inflammation, adenocarcinoma	[7]
	γ-T	AOM + DSS-treated mice	↓Inflammation, tumor multiplicity	[67]
	α-TOA	DMH-treated rats	↓Aberrant crypt foci, COX2	[68]
	γ-T, δ-T, TP, TQ	HCT116, HT29 cells	↓Cell growth, colony formation	[69]
			↑Apoptosis	
	γ-T + lovastatin	HT29 cells	↑c-caspase-3, apoptosis	[70]
Lung Cancer	γ-TmT	CL-13 tumors A/J mice	↓Tumor growth	[71]
	γ-TmT	NNK + B[a]P-treated mice	↓Tumor multiplicity, tumor growth	[72]
		H1299 xenograft	↓Tumor growth	
	γ-T, δ-T	H1299 xenograft	↓Tumor growth, 8-oxo-dG, γ-H2AX	[73]
			↑c-caspase-3	
Other Cancers				
Gastric	α-TOS	SGC-7901 cells	↓NFκB, Bcl2 family proteins	[74]
			↑c-caspase-3, 9	
Leukemia	α-TOS	APL mice	↓Leukemia, MRC complex I	[75]
			↑ROS, caspases, apoptosis	
Esophageal	Vitamin E + selenium	NMBA-treated rats	↓Tumor growth, NFκB, proliferation	[76]
Skin	α-T + vitamin C + ferulic acid	UVB-treated SKH-1 mice	↓Tumor growth, tumor multiplicity	[77]

Abbreviations: γ-TmT, a natural tocopherol mixture rich in γ-T; T, tocopherol; MSA, methaneseleninic acid; α-TOS, α-tocopheryl succinate; VK3, vitamin K3; α-TEA, α-tocopheryl acetic acid; Mito-ChM, Mito-chromanol; TRAP, transgenic rat for adenocarcinoma of prostate; TRAMP, the transgenic adenocarcinoma of the mouse prostate; NMU, N-methyl-N-nitrosourea; ACI, August Copenhagen Irish; AOM, azoxymethane; DSS, dextran sulfate sodium; DMH, 1,2-dimethylhydrazine; NNK, 4-(methylnitrosoamino)-1-(3-pyridyl)-1-butanone; B[a]P, benzo[a]pyrene; TGPS, D-alpha-tocopheryl polyethylene glycol succinate; ESeroSGS, γ-L-glutamyl-S-[2-[[[3,4- dihydro-2,5,7,8-tetramethyl-2-(4,8,12-trimethyltridecyl)-2H-1-benzopyran-6-yl]oxy] carbonyl]-3-[[2-(1H-indol-3-yl) ethyl] amino]-3-oxopropyl]-L-cysteinylglycine sodium salt; TP, tocopherol phosphates; TQ, tocopherol quinones; NMBA, N-nitrosomethylbenzylamine.