Chapter 15
The Role of Vitamin E Forms in Cancer Prevention and Therapy – Studies in Human Intervention Trials and Animal Models

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Abstract Vitamin E is a generic term of eight structurally related molecules including α-, β-, γ-, δ-tocopherol and α-, β-, γ-, δ-tocotrienol, all of which are potent lipophilic antioxidants. Despite eight forms in the vitamin E family, most studies have traditionally focused on α-tocopherol (αT) until the last couple of decades. The role of αT in modulation of carcinogenesis and especially its supplementation in chemoprevention has been extensively investigated in numerous animal and human studies including large clinical trials. These studies have yielded inconsistent and disappointing outcomes regarding the protective role of αT in cancer. On the other hand, other vitamin E forms, despite low in tissues, are rich in different diets and have recently been shown to have unique properties independent of antioxidant activities which likely play a role in cancer prevention. Here we review recent development in the field of different forms of vitamin E and cancer development with emphasis on the results from large clinical intervention trials and animal cancer models. In addition, potential mechanisms of the actions by different vitamin E forms are discussed.

15.1 Introduction

Vitamin E is a generic term of eight structurally related molecules including α-, β-, γ-, δ-tocopherol (αT, βT, γT and δT) and α-, β-, γ-, δ-tocotrienol (Fig. 15.1), all of which are potent lipophilic antioxidants. Despite eight forms in the vitamin E family, most studies have traditionally focused on α-tocopherol (αT) until the last couple of decades. This is because αT is the predominant form of vitamin E in tissues and its deficiency results in vitamin E deficiency associated ataxia, increased risk of atherosclerosis and possibly immune dysfunction (Brigelius-Flohe and Traber 1999; Jiang et al. 2001; Reiter et al. 2007). The role of αT in modulation of carcinogenesis and especially its supplementation in chemoprevention has also been extensively investigated in animal and numerous human studies including large clinical trials. These studies have yielded inconsistent and disappointing outcomes regarding the

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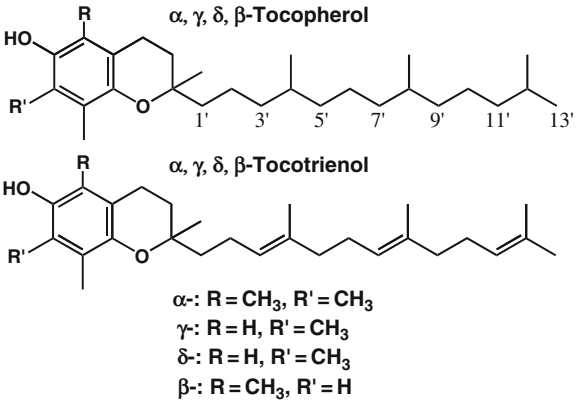

Fig. 15.1 Naturally occurring forms of vitamin E

protective role of αT in cancer. On the other hand, other vitamin E forms, despite low in tissues, are rich in different diets (Jiang et al. 2001) and have recently been shown to have unique properties independent of antioxidant activities which likely play a role in cancer prevention. In this chapter, we review recent development in the study of different forms of vitamin E and cancer development with emphasis on the results from large clinical intervention trials and animal cancer models. In addition, potential mechanisms of the actions by different vitamin E forms are briefly discussed.

15.2 Human Intervention Studies on the Role of Alpha-Tocopherol in Cancer Prevention and Therapy

15.2.1 Alpha-Tocopherol in Large Randomized Clinical Trials

All the clinical intervention studies related to vitamin E and cancer have exclusively focused on αT. Since 1994, eight large randomized clinical trials have been reported to investigate the role of αT or its combinations with other nutrition factors in cancer risk (summarized in Table 15.1). Four of these studies are primary prevention trials with apparently healthy subjects, i.e., SUVIMAX (Hercberg et al. 2004), WHS (Lee et al. 2005), SELECT (Lippman et al. 2009) and PHS II (Gaziano et al. 2009). The Linxian study (Blot et al. 1993) and the ATBC trial (The Alpha-Tocopherol BCCPSG, 1994) were conducted in high risk individuals for cancer including subjects with modest malnutrition or heavy smokers, respectively. In HOPE/HOPE-TOO (Lonn et al. 2005) and HPS (HPSCG, 2002) studies, participants with coronary diseases or diabetes were included. Since all these studies include relatively large population and provide valuable data in different populations (Table 15.1), it is important to reviewing them in great depth.

Linxian Study – The micronutrient intervention trial in Linxian, China (Blot et al. 1993) was designed to determine if supplementation with vitamins and minerals can lower cancer incidence, cancer mortality and mortality from other chronic diseases (primary outcomes). Linxian has a population with high rates of esophageal/gastric

Table 15.1 α-Tocopherol supplementation and the risk of cancer in large intervention trials

Study and locations	Characteristics of the subjects	Intervention	Major outcomes measured
Linxian study – Nutrition Intervention Trials. In Linxian, China. (Blot et al. 1993)	29,584 individuals aged from 40 to 69 years. Subclinical deficiencies of several micronutrients.	15 mg β-carotene, 30 mg α-tocopherol, and 50 μg selenium.	*Primary*: cancer incidence and mortality. *Secondary*: mortality from other diseases.
The α-Tocopherol, ß-Carotene Cancer Prevention Study (ATBC). Southwestern, Finland. (The Alpha-Tocopherol 1994)	29,133 men aged from 50 to 69 years. Heavy smokers.	50 mg/day *dl*-α-tocopheryl acetate. 50 mg/day *dl*-α-tocopheryl acetate + 20 mg/day β-carotene.	*Primary*: lung cancer. *Secondary*: prostate, bladder, colon and rectum, stomach, other.
Heart Protection Study MRC/BHF (HPS) United Kingdom. (HPSCG 2002)	20,536 individuals of aged from 40 to 80 years. Coronary disease, occlusive arterial disease, or diabetes.	600 mg vitamin E, 250 mg vitamin C, 20 mg β-carotene daily	*Primary*: major coronary events and fatal or non-fatal vascular events. *Secondary*: cancer and other major morbidity.
Supple'mentation en Vitamines et Miéraux Antioxydants (SUVIMAX) France. (Hercberg et al. 2004)	13,017 adults (women aged 35–60 years or men aged 45–60 years). Overall healthy	120 mg of ascorbic acid, 30 mg of vitamin E, 6 mg of β-carotene, 100 μg of selenium, and 20 mg of zinc, daily.	*Primary*: incidence of cancer and ischemic cardiovascular disease.
Women's Health Study (WHS). United States. (Lee et al. 2005)	39,876 apparently healthy US women ≥ 45 years. No previous history of coronary hearth disease, cerebro-vascular disease or cancer (except nonmelanoma skin cancer) or other major chronic illness.	600 IU natural source of α-tocopherol.	*Primary*: first major cardiovascular event. *Secondary*: individual cardiovascular events, stroke, and cardiovascular death and breast, lung and colon cancers.

Table 15.1 (continued)

Study and locations	Characteristics of the subjects	Intervention	Major outcomes
The Heart Outcomes Prevention Evaluation and The HOPE-The Ongoing Outcomes (HOPE and HOPE-TOO). Multi European countries and US. (Lonn et al. 2005)	7,030 patients ≥ 55 years with vascular disease or diabetes mellitus from the initial HOPE trial (1993–1999) and the HOPE-TOO extension (1999–2003).	400 IU/d RRR-α-tocopherol acetate.	*Primary*: cancer incidence, cancer deaths and major cardiovascular events.
Selenium and vitamin E Cancer Prevention Trial (SELECT). Canada, Puerto Rico, US. (Lippman et al. 2009)	35,533 men ≥50 y (African American) and ≥ 55 y (others). PSA ≤4 ng/ml and not suspicious for prostate cancer.	400 mg IU *all rac*-α-tocopheryl acetate. 200 μg/d L-selenomethionine + 400 mg IU *all rac*-α-tocopheryl acetate.	*Primary*: prostate cancer. *Secondary*: Lung, colorectal and overall primary cancer.
Physician's Health Study II (PHSII) United States. (Gaziano et al. 2009)	14,641 physicians ≥ 50 y including 1,307 men with history of prior cancer.	400 IU synthetic α-tocopherol every other day and vitamin C 500 mg daily.	*Primary*: prostate cancer for vitamin E and total cancer for vitamin C. *Secondary*: total cancer for vitamin E.

cardia cancer and persistently low intake of several micronutrients. As summarized in Table 15.1, one of the four treatments in the study included 15 mg β-carotene, 30 mg αT, and 50 μg selenium. This regimen led to a significant reduction in total mortality, mainly due to a lowered risk of cancer. Interestingly, this beneficial effect was still observed up to 10 years after the termination of supplementation (Qiao et al. 2009).

Despite the positive outcomes, the authors suggest caution in extrapolating the findings to other populations due to the special characteristics of Linxian with relatively low micronutrients. In addition, as mentioned before, αT was given in combination with β-carotene and selenium, and therefore the effects found can not be attributed to a specific micronutrient. In an extended analysis of the Linxian trial (follow-up 13 years after intervention), liver cancer mortality was examined (Qu et al. 2007). No effect was found on liver cancer mortality among the supplements studied, including the combination of β-carotene, αT, and selenium.

The ATBC study – The α-Tocopherol, β-Carotene Cancer Prevention Study (ATBC) (The Alpha-Tocopherol BCCPSG, 1994) was designed to determine the effect of daily supplementation of αT alone or in combination with β-carotene on the incidence of lung (primary outcome) and other cancers, in male heavy smokers (20 cigarettes/day). Randomly assigned participants received 50 mg/day *dl*-α-tocopheryl acetate ($n = 7{,}286$), 20 mg/day β-carotene ($n = 7{,}282$), both supplements ($n = 7{,}278$) and placebo ($n = 7{,}287$) capsules. Compared with placebo controls, no significant effect of αT on the incidence of lung cancer was found, whereas β-carotene unexpectedly increased the risk of lung cancer and total mortality (1994). Interestingly, significant reduction in prostate cancer incidence by 32% was seen in participants receiving αT supplementation ($n = 14{,}564$) compared with those not receiving it ($n = 14{,}569$) (Heinonen et al. 1998). Mortality from prostate cancer was found to be 41% lower among men receiving αT than those non-recipients. It is noteworthy that the reduction was evident in clinical prostate cancer (stage II-IV) but not in relatively early stages (stage 0–1) (Heinonen et al. 1998). α-Tocopherol had no effect on total mortality, while men allocated in the αT group seemed to have more death from hemorragic stroke when compared to no αT group.

An additional report from ATBC study indicated increased colorectal cancer risk in those participants receiving αT supplementation as compared with those that did not receive it. However, the authors suspected of bias in the diagnostic process because supplementation with αT also caused more rectal bleeding and intestinal pain leading to more colonoscopies, which may consequently led to increased detection of the incidence of polyps (Malila et al. 1999). In addition, αT supplementation had no effect on the incidence of gastric cancer (Malila et al. 2002; Varis et al. 1998), urinary tract cancer (Virtamo et al. 2000), colorectal cancer (Albanes et al. 2000), aero digestive tract cancer (Wright et al. 2007) and oral mucosal lesions (Liede et al. 1998).

Although the protective effects on prostate cancer were observed with αT during its supplementation, in the 6–8 year ATBC post-intervention follow-up study aiming to valuate the duration of the intervention, the beneficial effects of αT and

the adverse effects of β-carotene disappeared (Virtamo et al. 2003). This suggests that the protective effect of αT may be transient and diminishing rapidly after termination of supplementation.

One of the caveats discussed in the literature for the ATBC study is that prostate cancer was not a pre-specified end point in the trial, and therefore the results could be due to confounding bias (Gann 2009). In addition, the ATBC study group suspected that the intervention period may be too short to inhibit the development of cancers resulting from life-long exposure to cigarette smoke and other carcinogens, and the dose of αT may be low (50 mg/day) (1994), especially if male smokers have inadequate vitamin E status previous to the supplementation.

Supplementary analysis from the ATBC trial, looking at baseline or serum levels of αT and other forms of vitamin E, have been reported. In a report during the trial intervention with only 317 cases, the relationship between baseline serum αT levels and prostate cancer risk was not significant (Hartman et al. 1998). But later, the ATBC group reported a significant inverse association between baseline serum αT and prostate cancer risk. A nested case-control analysis from ATBC trial reported that higher baseline serum levels of γ-tocopherol were also associated with lower prostate cancer risk in supplemented individuals (with αT or β-carotene) (Weinstein et al. 2005). In addition, a strong inverse relationships between baseline serum αT and prostate or pancreatic cancer risk were reported based on the data obtained from 19 years follow-up after ATBC intervention (Stolzenberg-Solomon et al. 2009; Weinstein et al. 2007).

The Heart Protection Study (HPSCG) (2002) was designed to investigate the effect of daily supplementation with a combination of antioxidant vitamins including αT on vascular events as the primary endpoints. Non-vascular events including cancer and other major morbidity were evaluated as secondary endpoints. The study included 20,536 British adults who had coronary diseases, other occlusive arterial disease or diabetes. These participants were randomly assigned to receive a combination of 600 mg vitamin E, 250 mg vitamin C, and 20 mg β-carotene daily ($n = 10{,}241$) or matching placebo ($n = 10{,}228$). After 5-year treatment, although this regime substantially increased blood concentrations of αT, ascorbate and β-carotene, no protective effect of the antioxidant vitamin combination was found on all-cause mortality, cancer incidence, cancer mortality, cancer in specific sites or other non-vascular outcomes. On the other hand, the authors concluded that the supplement appeared to be safe in the high-risk individuals studied. It is important to note that the primary endpoint of this study was vascular events (but not cancer incidence), which accordingly determined the time of intervention and follow-up time. As a result, the follow-up period may be too short for cancer events (incidence and mortality). Although the authors mentioned that the participants in this trial would be followed for several years, but to our knowledge no report has been published to date.

The Supple′mentation en Vitamines et Miéraux Antioxydants (SU.VI.MAX) (Hercberg et al. 2004) was designed to test the effect of what the authors called 'an adequate and well balanced intake of antioxidant nutrients' on the incidence of cancers and ischemic cardiovascular disease (CVD) in a middle-aged general

population. The study included 13,017 apparently healthy adults (35–60 years old) in France. Participants were randomly assigned to take a single daily capsule of a low-dose antioxidant supplementation containing ascorbic acid (20 mg), αT (30 mg), β-carotene (6 mg), selenium (100 μg) and zinc (20 mg), or a placebo in the controls. After a medium 7.5-year intervention, this low-dose antioxidant supplementation lowered total cancer incidence and all cause mortality in men but not in women. Interestingly, like the Linxian study in China, nutritional intake and concentrations of baseline β-carotene was lower in men than in women, which may potentially explain the effects limited to men (Blot et al. 1993).

In a post intervention analysis of the SUVIMAX study, the beneficial effects found in men disappeared during 5-year follow-up after antioxidant supplementation ceased (Hercberg et al. 2010). In contrast, the risk of skin cancer appeared to increase in women during the period of supplementation in SUVIMAX (Hercberg et al. 2007), although after a 5-year post-intervention follow up no increased risk of skin cancer was observed for either gender (Ezzedine et al. 2010).

The Heart Outcomes Prevention Evaluation (HOPE) and HOPE–The Ongoing Outcomes (HOPE-TOO) (Lonn et al. 2005) – HOPE trial was conducted for 4–5 years to test potential protective effects of αT supplementation on cardiovascular events and revealed a neutral effect on cardiovascular outcomes (Yusuf et al. 2000). HOPE-TOO study was 4-year extension of the HOPE study to assess whether longer duration of αT supplementation trial would prevent cancer and cardiovascular disease. The original HOPE study was an international, multicenter, double-blind, randomized, 2×2 factorial design trial that evaluates ramipril (10 mg/day) and vitamin E (RRR-α-tocopheryl acetate, 400 UI/day) in patients with high risk for cardiovascular events. The use of increased dose of αT (compared with Linxian and ATBC studies) was because of the lack of relation between vitamin E and coronary heart disease in the Linxian and ATBC studies (Yusuf et al. 2000). After the initial 5-year study showing significant beneficial effects from ramipril, the HOPE-TOO was extended for 4 more years with recommendation of ramipril for all participants. The primary outcomes in the HOPE-TOO trial included cancer incidence, cancer deaths, and major cardiovascular events. In final HOPE-TOO analysis, all patients from HOPE were included (final $n = 9{,}541$). No significant effect of αT supplementation was found on the incidence of cancers, cancer deaths, or major cardiovascular events, in patients with cardiovascular disease or diabetes mellitus. However, higher rates of heart failure and hospitalizations for heart failure were found in the αT supplementation group.

The Women's Health Study (WHS) (Lee et al. 2005) – The study was designed to test whether vitamin E supplementation for 10 years decreases the risk of major cardiovascular diseases (nonfatal myocardial infarction, nonfatal stroke or cardiovascular death) and total invasive cancer (primary outcomes) in healthy women (39,876 women aged al least 45 y). In a 2×2 factorial design, apparently healthy US women were randomly assigned to receive 600 IU natural source of αT or placebo and 100 mg of aspirin or placebo every other day. The use of 600 IU was based on previous reports where individuals with high vitamin E intake have lower rates of cardiovascular disease and cancer than those with low vitamin E intake

(Rexrode et al. 2000). After 10-year supplementation, αT did not show significant effect on the incidences of major cardiovascular events (myocardial infarction, stroke, or ischemic or hemorrhagic stroke) or incidences of cancer or cancer deaths, including total invasive cancer or main site-specific cancers (lung, breast, colon cancers). Although there was a significant 24% reduction of cardiovascular death in αT supplemented group, the authors concluded that this observation was likely due to chance arising from multiple comparisons as no effects on the incidence of any major cardiovascular events were observed in the current study or other previous studies (Eidelman et al. 2004; Vivekananthan et al. 2003). It is interesting to note that unlike observations in ATBC, HOPE-TOO studies or meta-analysis (Miller et al. 2005), no significant adverse effects, e.g., increased hemorrhagic strokes or all-cause mortality, were observed related to αT supplementation in the WHS.

The Selenium and Vitamin E Cancer Prevention Trial (SELECT) – The SELECT trial (Lippman et al. 2009) was prompted by the reported beneficial effects of αT in the ATBC study (1994) and selenium in the Nutritional Prevention of Cancer (Clark et al. 1996), as well as the reduction of overall cancer mortality in the Linxian study by supplementation of selenium, αT and β-carotene (Blot et al. 1993). The main objective of SELECT was to assess whether selenium (200 μg/day from L-selenomethionine), vitamin E (400 UI/day of all *rac*-*α*-tocopheryl acetate) or their combination could prevent prostate cancer and other diseases in healthy men. The study included healthy, low-cancer-risk men who have prostate specific antigen (PSA) values ≤ 4 ng/ml, have no prior prostate cancer diagnosis and are not suspicious for cancer during a digital rectal examination. Prostate cancer incidences were reported by participants and were further confirmed by medical records, prostate biopsy and pathology laboratory. After 5.46-year supplementation, there were no differences in the rates of prostate cancer among the treatment groups and placebo; Specifically, 416 prostate cancer cases were diagnosed during the trial in the patients receiving placebo, 473 receiving αT alone, 432 in the selenium alone group, and 437 in the group that received the combination of αT and selenium. Among all groups, more than 95% diagnosed prostate cancer was in early stage, e.g., ∼70 and 25% in stage T1 and T2, respectively. In sharp contrast to the ATBC study, there was a non-significant ($P = 0.06$) increase in stage-one prostate cancer in αT alone group.

In addition, no effect of treatments was found for any pre-specified secondary cancer endpoints including lung, colorectal and overall primary cancer. The numbers of deaths from any cause were similar in all treatment groups. No significant effects were found on the overall incidence of cardiovascular events.

The Physicians' Health Study II (PHS II) – Unlike the SELECT trial that is focused on low-risk subjects, the PHS II (Gaziano et al. 2009) was designed to test whether αT prevents prostate cancer in men, regardless current risk of prostate cancer or previous history of cancer. PHS II included 14,641 male physicians at 50 years or older from the American Medical Association, approximately 9% of whom have previous history of cancer, myocardial infarction or stroke. The main goal of the study was to evaluate whether long-term vitamin E (400 IU αT every other day) or vitamin C (500 mg ascorbic acid daily) decreases the risk of prostate cancer or total cancer among men. After the mean 8 years follow-up, neither αT nor vitamin C

supplementation reduced the risk of prostate cancer, total cancer, and site-specific cancer incidence or total mortality. On the other hand, a greater number of hemorrhagic strokes were observed among those assigned to vitamin E (39 *vs.* 23 events; HR, 1.74; 95% CI, 1.04–2.91) compared with placebo. Similar adverse effects were also reported in the ATBC (1994) and the HOPE-TOO study (Lonn et al. 2005).

15.2.2 Summary of Large Intervention Studies

Three out of the eight large intervention studies have found that αT or its combination with other antioxidants reduced cancer risk, which include the Linxian study in China where supplementation of β-carotene, αT and selenium significantly reduced total cancer incidence and mortality of cancer, the ATBC study which showed reduction in the incidence of prostate cancer among heavy smokers, and the SUVIMAX where reduction of total cancer incidence and all mortality cause was seen in men but not women. It is important to note that these studies were conducted in different but yet very specific populations with distinct characteristics; Specifically, the Linxian study has population with subclinical deficiencies of micronutrients (Blot et al. 1993), and the subjects in the ATBC and SUVIMAX include heavy smokers who likely have increased oxidative stress, or men with low plasma levels of antioxidant levels, respectively. Interestingly, compared with other large trials, these three used low doses of αT (e.g., 30–50 mg of αT) alone or combined with other nutrients. The protective effects of low-dose supplementation on cancer in high cancer-risk populations can be explained by the notion that mild malnutrition or unbalanced antioxidant status due to heavy smoking may result in increased DNA damage and compromised DNA repair system, which may consequently lead to increased risk for cancer development compared with healthy populations (Ames et al. 2002). It is therefore conceivable that in these 'abnormal' populations, supplementation of even low-dose αT and/or its combinations with other nutrients would be sufficient to suppress the increased risk.

In contrast to the subjects with sub-adequate nutrient or unbalanced antioxidant characteristics, participants in the other large trials have sufficient nutrients with limited number of current smokers. The subjects in the SELECT trial, the WHS and PHS II include low-risk and apparently healthy individuals, although the PHS II also included less than 9% men with previous cancer or vascular diseases. Unlike the ATBC, which has 100% heavy smokers, the SELECT and PHS II included <8% current smokers. In these studies, long-term supplementation of high doses of αT (>400 IU) or its combination with other antioxidants failed to show any beneficial effects on cancer risk or cancer mortality. Similarly, in the HOPE-TOO and HPS study where subjects are patients with vascular diseases or diabetes mellitus, high doses of αT did not show any benefits to cancer or cardiovascular incidence. These results are consistent with animal studies (Sections below) showing that high-dose supplementations with αT do not seem to show consistent protective effects on cancer development compared with controls, which have adequate dietary intake of αT.

It is worth mentioning that four of the eight large trials indicate potential adverse effects from high-dose αT supplementation, including greater number of hemorrhagic strokes (PHS II), and ATBC, non-significant ($P = 0.06$) increase in stage-one prostate cancer in αT alone group (SELECT), or higher rates of heart failure and hospitalizations for heart failure in the αT supplementation group (HOPE-TOO). Interestingly, potential adverse effects associated with higher dose of αT, e.g., 400 IU or higher, were also pointed out by a meta analyses that take consideration of large and small clinical trials (Miller et al. 2005). Since high dose of αT has been shown to modulate the expression of cytochrome P450s and pregnane-X-receptor (Brigelius-Flohe 2005), which are among the key players for drug metabolism, it is reasonable to speculate that high dose of αT may potentially modulate drug metabolism. This may partially explain adverse effects in patients on multiple drugs due to high-dose αT supplementation. In addition, αT supplementation is known to suppress γ-tocopherol (Jiang et al. 2001), which has been shown to have unique health benefits based on mechanistic and animal studies (Jiang et al. 2001; Reiter et al. 2007).

The protective effects of low-dose αT supplementation in subjects with moderate malnutrition or heavy smokers underscores the importance of long-term maintenance of healthy nutrient status in prevention of cancer and possibly other chronic diseases. This aspect has been proven by other nutrition factors including folate whose deficiency has been shown to increase the risk of cancer (Ames et al. 2002; Kim 2008). In the meanwhile, the lack of significant protection from high-dose supplementation of αT strongly suggests that essential nutrient factors may have limited role in directly intervening carcinogenesis that is promoted by factors beyond nutrient deficiency. These notions are elaborated in an elegant study by Suarna et al. (2006) showing that low-dose supplementation of αT significantly attenuated αT-deficiency induced exaggeration of atherosclerosis development, whereas high-dose supplementation of αT did not offer further benefits.

15.3 Case-Control Studies of Different Vitamin E Forms

The evidence of beneficial effect of tocopherols on cancer in case-control studies is controversial. From 21 studies reviewed (number of cases ranging from 67 to 1,072), seven showed that higher αT levels were associated with reduced risk of various types of cancer, such as bladder (Liang et al. 2008), cervical neoplasia (Cho et al. 2009), esophagus and noncardia (Taylor et al. 2003), gastric (Jenab et al. 2006), lung (Goodman et al. 2003), pancreas (Stolzenberg-Solomon et al. 2009) and prostate cancer (Goodman et al. 2003; Weinstein et al. 2007). Four case-control studies reported that high plasma concentrations of γ-tocopherol were negatively associated with the risk of aerogastric tract cancer (Nomura et al. 1997), cervical neoplasia (Cho et al. 2009) and prostate cancer (Helzlsouer et al. 2000; Weinstein et al. 2007). However, two studies showed γ-tocopherol (Kabat et al. 2009) or both αT and γT levels (Kim et al. 2010) are associated with increased risk of breast

cancer. Ingles et al. (Ingles et al. 1998) found negative association between the α-tocopherol/γ-tocopherol ratio and the risk of colorectal cancer, but not with the individual vitamin E forms.

Unlike large double-blind placebo controlled intervention trials that are considered as 'gold standard' for studying drug efficacy, conclusions based correlation data obtained from case-control studies are often weakened by several weaknesses due to the nature of this type of studies. One caveat to be considered in case-control studies is bias. Secondly, a single determination of micronutrients at a single time point may not reflect the long-term exposure to micronutrients. Thirdly, when blood samples are collected at the time of cancer diagnosis or after, it is possible that the associations observed may be due to the disease that could consequently change overall metabolism in the body. In the studies reviewed here, five included analyses from serum of patients already diagnosed with cancer, three of them showing negative association between αT and cancers (Cho et al. 2009; Ingles et al. 1998; Liang et al. 2008), one reporting positive association (Kim et al. 2010), whereas the other one found negative association of the α-tocopherol:γ-tocopherol ratio with decreased risk of cancer (Ingles et al. 1998). In addition, the measured nutrients such as αT or γT might merely serve as a marker of other important factors such as dietary fat contents because both of them are associated with high fat intake. As a result, the associations observed based on case-control studies must be interpreted with considering these limitations.

15.4 Alpha-Tocopherol and Analogs in Various Cancer Models

Like human clinical intervention studies, most early animal studies on vitamin E and cancer exclusively focused on αT. Potential protective effects of αT supplementation have been investigated in broad ranges of cancer models including skin, prostate, colon and breast cancer. These studies, however, have revealed inconsistent results regarding the beneficial effects of αT on cancer risk. For instance, although many studies have reported protective effects of αT when administered alone (Ichikawa et al. 1993; McVean and Liebler 1997; Mizumoto et al. 1994; Moore et al. 1987; Yano et al. 1994) or in combination with other compounds (Battalora et al. 1993; Bissett et al. 1990; Burke et al. 2000; Chen et al. 2000; Factor et al. 2000; Hirose et al. 1986, 1993; Kakizaki et al. 2001; Limpens et al. 2006; Nakadate et al. 1984; Perchellet et al. 1985, 1987; Sarna et al. 2000; Shamberger and Rudolph 1966; Trickler and Shklar 1987; Wang et al. 1989; Weber et al. 2002; Yam et al. 2001; Yu et al. 2008, 2009), there are plenty of studies also reporting no protective effects (Al-Johar et al. 2008; Berton et al. 1998; Chen et al. 2000; Chung et al. 2003; Hirose et al. 1986, 2002; Hirose et al. 1995; Masui et al. 1986; McCormick et al. 2010; Nakamura et al. 1991; Ogasawara et al. 2007; Ozten et al. 2010; Wenger et al. 2001). In addition, several groups have also reported tumor-promoting activity by αT (Hirose et al. 1993; Kolaja and Klaunig 1997; Mitchel and McCann 1993; Miyauchi et al. 2002; Moore et al. 1987).

Besides naturally occurring RRR-αT, several derivatives from this vitamin E form have been shown to have anticancer effects. For instance, α-tocopheryl succinate (α-TOS) is a redox-inactive αT derivative and can be hydrolyzed in vivo to αT and succinate. Recently, several non-hydrolyzable ether acetic acid derivatives from αT including αTEA (2,5,7,8-tetramethyl-2R-(4R,8R,12-trimethyltridecyl)chroman-6-yloxyacetic acid) have been shown to have potent anticancer effects. In addition, distinctive features between synthetic αT which is composed of mixed stereoisomers of αT (*dl*-α-tocopherol acetate, or *all-rac*-α-tocopheryl acetate) and naturally occurring RRR-αT have also been suggested.

15.4.1 RRR-α-Tocopherols

Skin cancer – Shamberger in 1966 (Shamberger and Rudolph 1966) reported for the first time that topical application of αT reduced skin tumor formation induced by with 3,2′-dimethyl-4-aminobifenyl (DMBA) in mice. Similarly, in a two-stage mouse skin carcinogenesis model, topical application of 40 μmol of *d*-α-tocopherol reversed the effect of the tumor promoter on ornithine decarboxylase and glutathione peroxidase activities, with the concomitant reduction of the incidence of skin tumors (Battalora et al. 1993; Nakadate et al. 1984; Perchellet et al. 1985, 1987). On the other hand, when 80 μmol of topical αT used in the same skin carcinogenesis model, αT acted as a tumor promoter, with similar efficiency as 12-O-tetradecanoylphorbol-13-acetate (TPA) (Mitchel and McCann 1993, 2003).

The extent of topical application of αT in photodamage prevention has also been investigated. αT dispersion (1% in neutral vehicle cream) inhibited the formation of thymine dimers with greater efficacy than α-tocopherol acetate, α-tocopherol methyl ester, γ-tocopherol and δ-tocopherol (McVean and Liebler 1997). In addition, αT inhibited UV irradiation induced DNA damage and p53 expression, but was not effective in preventing UV-induced proliferation and tumor formation (Berton et al. 1998). Interestingly, topical administration of αT (5% solution) reduced UVB-radiation induced skin wrinkling, skin tumor incidence and tumor onset (Bissett et al. 1990).

Prostate cancer – Based on the hypothesis that αT may have potential anti-cancer effect against prostate cancer, Nakamura et al. (1991) studied the effect of dietary αT (1% by weight) on 3,2′-dimethyl-4-aminobifenyl (DMAB)-initiated prostate carcinogenesis in rats. However, these investigators found no significant effect of αT on the incidence of tumors in the prostate or any other organs analyzed, including small and large intestines, pancreas, skin, subcutis, preputial and zymbal glands. Ozten et al. (Ozten et al. 2010) examined the effect of selenomethionine and *dl*-α-tocopherol acetate on prostate cancer in estradiol-treated NBL rats. In this study, αT at 0.2 and 0.4% by weight did not show any effect on the development of prostate carcinomas. Similarly, McCormick et al. (2010) did not find beneficial effect of the same dietary treatments (αT at 2000 and 4000 mg/kg diet) on prostate cancer incidence in rats where prostate epithelial cell proliferation was stimulated by sequential administration of oral cyproterone acetate (for 21 consecutive days), subcutaneous

injection of testosterone propionate (for 3 days), followed by a single dose of the carcinogen N-methyl-N-nitrosurea and subcutaneous implantation of testosterone capsules during the study for chronic androgen stimulation.

Unlike αT alone, combination of αT with lycopene seems to show some beneficial results. In the human PC346-C prostate xenograft model in nude mice, αT (*all-rac*-α-tocopheryl acetate) in combination with lycopene (5 mg/kg body weight of each component by oral gavage) suppressed the growth of the prostate xenograft by 75%, and increase median survival by 40% (Limpens et al. 2006). Consistently, in Copenhagen rats injected with MatLyLu Dunning prostate cancer cells, dietary αT and lycopene increased prostate tumor necrotic areas to 36.3, and 35.97%, respectively. On the other hand, αT/lycopene co-treated group had a non-significant increase on the percentage of tumor necrotic area (Siler et al. 2004).

Colon cancer – Most studies regarding the effects of αT on colon cancer revealed no beneficial effects. In F344 male rats which were injected with azoymethane (AOM) to induce colon cancer, dietary vitamin E did not have any effect on colon carcinogenesis, as measured by aberrant crypt foci (ACF, a pre-cancer lesion) (Yao et al. 1996) or tumor incidence or multiplicity (Reddy and Tanaka 1986). Similarly, in Sprague Dawley rats (Maziere et al. 1998), Swiss mice (Temple and el-Khatib 1987), or CD-1 (ICR) BR mice (Chester et al. 1986) injected with 1,2-dimethylhydrazine to initiate colon carcinogenesis, αT did not have inhibitory effect on colon tumor development. In addition, dietary treatments of *dl*-α-tocopheryl acetate at 30 mg/kg or 500 mg/kg diet before induction of colon tumorigenesis by i.p. injection of AOM, did not have any effect on the formation of ACF in young or old C57L/6 mice (Chung et al. 2003). Similarly, in Sprague Dawley rats, dietary treatment of *dl*-α-tocopherol at 100 mg/kg diet and vitamin A at 1.2 mg/kg diet did not show significant effect on ACF formation ($p>0.05$) in AOM-induced tumorogenesis (Al-Johar et al. 2008). In addition, dietary αT at 0.5% diet did not suppress colon carcinogenesis induced by 2-amino-1-methyl-6-phenylimidazol[4,5-b]pyridine (PhIP) in rats (Hagiwara et al. 1999).

Despite being ineffective in most studies with colon cancer models, supplementation of αT appeared to be capable of reducing colon cancer risk associated with vitamin E deficiency or high fat plus low fiber intake. Thus, dietary vitamin E (90 mg/kg diet) decreased the incidence of AOM-induced colonic tumors and tumor multiplicity in Fischer-344 rats fed low fiber/high fat diet (Shivapurkar et al. 1995). Cook et al. showed that in LACA mice, compared with animals fed a low vitamin E diet (10 mg/kg diet), dietary vitamin E at 600 mg/kg diet reduced the incidence of 1,2-dimethyl hydrazine-induced adenomas and the number of invasive carcinomas in the colon (Cook and McNamara 1980).

In contrast, *dl*-α-tocopheryl acetate at 4% in diet enhanced the tumorigenicity induced by 1,2-dimethylhydrazine dihydrochloride in Swiss mice, as indicated by increased incidences of tumors in the duodenum, cecum, colon, rectum, and anus (Toth and Patil 1983).

Recently, Ogasawara et al. tested whether antioxidants including αT can modulate lung metastasis of colon cancer cells (Ogasawara et al. 2007). In this study, αT was administered via 5 consecutive i.p. injections of 20 μl, 100 mM stock solution,

3 days before tumor inoculation. This treatment did not have inhibitory activity against lung tumor metastasis of murine colon 26-L5 carcinoma cells. Similarly, β-carotene and ascorbic acid were also tested, but had not inhibitory effect on tumor lung metastasis. On the other hand, epigallocatechin gallate, gallocatechin gallate, and genistein reduced tumor nodules in the lungs by 77, 46, and 44%, respectively.

Lung cancer – The effects of αT on lung cancer varied with animal models. In urethane-induced lung carcinogenesis in A/J mice, αT administered via i.p. at 1000 mg/kg body weight did not affect tumor development (Witschi et al. 1981). Consistently, αT did not inhibit tumor growth in nude mice implanted with human lung cancer cells (Li et al. 2011). However, inhaled αT aerosol but not inhaled αT acetate, decreased lung inflammation markers in rats with inflammation caused by bacterial lipopolysaccharide (Hybertson et al. 2005). α-Tocopherol (100 mg/kg) decreased concentrations of thiobarbituric acid reactive substances (TBARS), hydroperoxides, and conjugated dienes in liver, lungs and hearts of nicotine-treated male albino rats (Helen et al. 2003). Similarly, αT administered in diet (at 550.9 mg/kg diet) inhibited TBARS and DNA single strand breaks in lungs of mice treated with 4-nitroquinoline 1-oxide (Ichikawa et al. 1993; Yano et al. 1994). Interestingly, this dietary treatment also reduced lung tumor incidence and multiplicity in spontaneous lung tumorigenesis in A/J mice (Yano et al. 1994). Similarly, dietary αT combined with fish oil and vitamin C led to slower rate of tumor growth and lower metastatic load in mice inoculated with a highly metastatic clone of the 3LL Lewis lung carcinoma cells (Yam et al. 2001).

In addition, the combination of β-carotene, αT and ascorbic acid protected against 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone-induced lung carcinogenesis in smoke-exposed ferrets (Kim et al. 2006, 2007). A combination of αT and ascorbic acid prevented the smoke-induced lung squamous metaplasia in ferrets (Kim et al. 2011).

Breast cancer – Dietary αT at 1.5 or 1% diet did not inhibit rat mammary carcinogenesis induced by 7, 12-dimethylbenz[a]anthracene (DMBA) (Hirose et al. 1986) or 2-Amino-1-methyl-6-phenylimidazo[4,5-b]pyridine (PhIP) (Hirose et al. 2002), respectively. At 0.5% diet, αT did not reduce the incidence of mammary tumors (the number of rats bearing tumors) induced by injection of PhIP, but decrease the number of tumors per rat (multiplicity) (Hagiwara et al. 1999). Interestingly, in the daunorubicin-induced mammary tumor model in Sprague-Dawley rats, i.p. injection of 1.8 g of α-tocopheryl acetate/m^2/day lowered the incidence of mammary tumors and delayed the onset of tumor formation (Wang et al. 1989). Yu et al. (2008) found that only the synthetic forms of αT (*all-rac*-α-tocopherol and *all-rac*-α-tocopheryl acetate), but not RRR-αT inhibited mammary tumor growth and lung metastases using the transplantable mouse 66c1-4-GFP mammary cancer cells in BALB/c mice.

Liver and other cancers – Although several studies have found that dietary αT exerts antitumor activities in chemically-induced hepatocarcinogenesis (Hirose et al. 1995; Kolaja and Klaunig 1997; Mizumoto et al. 1994; Moore et al. 1987; Tsuda et al. 1994), and in transgenic mice models (Factor et al. 2000; Kakizaki et al. 2001), others report no effect of dietary αT on chemically-induced liver cancer (Lii et al. 1999; Masui et al. 1986).

α-Tocopherol administration has been reported to inhibit chemically-induced oral and esophageal carcinogenesis (Chen et al. 2000; Odukoya et al. 1984; Trickler and Shklar 1987), as well as the incidence and multiplicity of kidney atypical tubules (Hirose et al. 1993), but had no effect on chemically-induced pancreatic adenocarcinoma (Wenger et al. 2001). On the other hand, the administration of αT induced hyperplastic and papillomatous lesions in the forestomach (Hirose et al. 1993; Miyauchi et al. 2002; Moore et al. 1987), and enhanced tumor growth and metastasis in retrovirus-induced cancers (Kline and Sanders 1989).

15.4.2 α-Tocopherol Derivatives

Both redox-active and redox-inactive αT derivatives have been investigated regarding their anticancer effects. α-Tocopheryl succinate (α-TOS), a redox-inactive analogue of vitamin E, has been shown to be a stronger inducer of apoptosis than αT in cell-based studies. Potential anticancer efficacy of α-TOS has been tested in some animal models, which was recently reviewed (Neuzil et al. 2007; Tomasetti and Neuzil 2007). Weber et al. (2002) found that α-TOS is a potent antitumor agent in a xenograft model implanted with human HCT116 colon cancer cells in nude mice. These investigators found that α-TOS and αT (50 μL of 200 mM every 3rd day) resulted in inhibition of tumor growth by 80 and 35% respectively. In addition to the antiproliferative action, α-TOS also has pro-apoptotic activity that may explain its higher efficiency when compared to αT. Other xenograft studies have reported that α-TOS suppressed the growth of tumors implanted from breast cancer cells (Malafa and Neitzel 2000), lung cancer cells (Dong et al. 2009; Quin et al. 2005), prostate cancer cells (Basu et al. 2007; Yin et al. 2009), head and neck squamous cell carcinoma (Gu et al. 2008), and bladder cancer cells (Kanai et al. 2010). Studies in allograft models also support the anticancer effects of α-TOS (Barnett et al. 2002; Hahn et al. 2006; Hrzenjak et al. 2004; Kogure et al. 2005; Malafa et al. 2002; Ramanathapuram et al. 2005). Moreover, antitumor activity of α-TOS has also been reported in chemically-induced tumors (Wu et al. 2001) and protective effect against γ-radiation (Singh et al. 2011).

Besides the hydrolyzable αT derivatives, several non-hydrolyzable αT derivatives have recently been developed and shown to have anticancer properties, such as the non-hydrolyzable RRR-αT ether acetic acid analog (α-TEA) (Hahn et al. 2006; Lawson et al. 2004), α-tocopheryl malonate (Kogure et al. 2005), RRR-α-tocopheryloxybutyl sulfonic acid (Ni et al. 2009), α-tocopheryl melamide (Turanek et al. 2009), and amphiphilic α-tocopherol oligochitosan conjugates (Noh et al. 2011).

Yu et al. (2008, 2009) compared antitumor activity of naturally occurring tocopherols with synthetic αT, i.e., *all-rac*-αT and *all-rac*-α-tocopheryl acetate (*all-rac*-αTAc) that contain a mixture of eight stereoisomers and are commonly used in supplements. In two mammary cancer models, these investigators also compared naturally occurring αT (RRR-αT) and γ-tocopherol (RRR-γT). In these studies, RRR-αT ether-linked acetic acid analog (αTEA), the non-hydrolyzable ether analog

of αT, was included as a positive control. In one of the mammary cancer models, murine 66c1-4 GFP mammary cancer cells were inoculated into BALB/c mice, after 10 days of oral administration of 6 mg of the synthetic forms of vitamin E/day and 5 mg of the natural forms of vitamin E/day (Yu et al. 2008). Compared with controls, the synthetic forms of vitamin E (*all-rac*-αT and *all-rac*-α-TAc) and the positive control (αTEA) reduced tumor volume. αTEA and *all-rac*-αT also reduced macroscopic lung tumor metastasis, and the number of macroscopic lung tumor foci. As to the naturally occurring RRR-αT and RRR-γT, only γT reduced tumor growth in comparison with control. In a follow-up study, these investigators examined these vitamin E related compounds in another xenograft breast cancer model where human breast cancer MDA-MB 231-GPF cells were subcutaneous injected into nude mice. The supplementation regime included 378 mg RRR-αT/kg diet; 358 mg RRR-γT/kg diet; 400 mg *all-rac*-αT/kg diet, 243 mg α-TEA/kg diet and 456 mg RRR-αT + 506 mg RRR-γT/kg diet. Significant reduction of tumor volume was observed in RRR-γT, *all-rac*-αT and αTEA dietary groups as compared to basal control diet. No differences in tumor volumes in RRR-αT and RRR-αT+RRR-γT groups were found in comparison with control groups (Yu et al. 2009). These results suggest that the natural form of αT does not possess antitumor activity and appears to block the antitumor efficacy of γT.

15.5 γ-Tocopherol and γT-Rich Mixed Tocopherols in Cancer Models

15.5.1 Mechanistic Bases for Potential Anticancer Activities of γT

Despite αT has drawn most attention in most studies in the past, studies by us and others during the last 15 years have demonstrated that γT, the major form of vitamin E in US diet, has unique activities that are not shared by αT but are potentially important for cancer prevention and therapy (Jiang and Ames 2003; Jiang et al. 2000, 2001). We have found that γT and its terminal metabolite γ-CEHC, unlike αT, exhibit anti-inflammatory effects by inhibition of cyclooxygenase (COX)-catalyzed formation of prostaglandin E2 (PGE_2) in LPS-treated macrophages and IL-1β activated epithelial cells, as well as in carrageenan-induced inflammation model in rats (Jiang and Ames 2003). In this rat inflammation model, γT but not αT also inhibited 5-lipoxygenase (5-LOX)-catalyzed formation of LTB_4 and TNFα (Jiang and Ames 2003). Our recent studies have demonstrated that 13'-carboxychromanol, which is a novel long-chain metabolite of vitamin E forms and is substantially excreted in feces, is a much more potent inhibitor of COX-1, COX-2 and 5-LOX than the unmetabolized vitamin E forms (Jiang et al. 2008; Jiang et al. 2011b).

In addition to its anti-inflammatory properties, γT is better than αT in trapping electrophilic reactive nitrogen oxide species, such as nitrogen dioxide (Cooney et al. 1993, 1995) and peroxynitrite (Christen et al. 1997, 2002), to form a stable adduct, 5-nitro-γ-tocopherol. Thus, γT inhibits methylcholanthrene-induced

neoplastic transformation more effectively than αT in C3H/10T1/2 murine fibroblasts, a process believed to be mediated by reactive nitrogen species (Cooney et al. 1993).

We recently showed that γT but not αT inhibits growth and induces apoptosis in prostate cancer cells, but had no effect on healthy prostate epithelial cells (Jiang et al. 2004). This effect appears to stem from interruption of de novo synthesis of sphingolipids by γT, which results in an accumulation of dihydrosphingosine and dihydroceramide (Jiang et al. 2004). Gysin et al. showed that γT is stronger than αT in inhibition of prostate cell proliferation by down-regulation of cyclin D (Gysin et al. 2002). In addition, γT inhibited growth and induced apoptosis in colon cancer cell lines, although the mechanism was not well understood (Campbell et al. 2006).

Based on these exciting mechanistic studies which strongly suggest that γT and possibly other tocopherols may be useful anticancer agents and is likely better than αT, potential anticancer activities of γT have been tested in some animal models. In addition, several groups recently conducted animal studies to investigate whether γT-enriched mixed tocopherols may have chemoprevention activities against various types of cancer, including prostate, colon and breast cancer.

15.5.2 High Pure γ-Tocopherol

As of today, six studies have been conducted to test potential benefits from high-pure γT (>90%) in animal cancer models. Five of these studies indicated beneficial outcomes from γT supplementation against cancer.

Stone et al. (2002) compared the effects of dietary RRR-α-tocopherol and RRR-γ-tocopherol (at 65–66 mg/kg diet) on iron-induced oxidative stress and *ras*-p21 expression in the colon of rats. After 22 weeks on experimental diets, rats fed with γT-containing diet had lower levels of *ras*-p21 in colonocytes, an oncogenic protein that is over-expressed in patients with advanced colorectal cancer, than those fed with αT supplement or αT-deficient diets.

The effects of high pure γT have been studied in three different prostate cancer models. Takahashi et al. used the transgenic rat for adenocarcinoma of prostate (TRAP) model, which is characterized by development of high-grade prostatic intraepithelial neoplasia (PIN) from 4 weeks of age and high incidence of well-moderately differentiated adenocarcinomas by 15 weeks of age (Takahashi et al. 2009). In this model, dietary γT (at 50, 100 or 200 mg/kg diet), but not αT, dose-dependently suppressed tumor progression from prostatic intraepithelial neoplasia to adenocarcinoma in the ventral lobe and led to activation of caspase-3 and 7 in the ventral prostate of rats. Jiang et al. (2011a) recently showed that γT at 125 mg/kg body weight three times a week (540 mg/kg diet daily) decreased the growth of LNCaP xenograft in nude mice, although being less potent than its tocotrienol analog. In contrast, dietary γT at 200 mg/kg diet or its combination with lycopene did not reduce the growth of prostate tumor that was implanted with Dunning R3327H adenocarcinoma in male Copenhagen rats (Lindshield et al. 2010).

In addition, as discussed in 15.4.1, Yu et al. (2008, 2009) reported that γT supplementation suppressed breast cancer development in two xenograft models, whereas αT did not show any protection. Interestingly, the results from these studies suggest that αT appears to block the anticancer capability of γT when these two are co-administered, which warrants future investigation.

15.5.3 γT-Rich Mixed Tocopherols

The use of γT-rich mixed tocopherols (γ-TmT) was in part due to the lack of economic sources of high-pure individual vitamin E forms including γT. On the other hand, the mixed tocopherols are often obtained from a byproduct of soybean and are therefore relatively cheap. The typical tocopherol composition of γ-TmT includes 50–70% γ-tocopherol, 20–25% δ-tocopherol, ~10% α-tocopherol, and ~0.5–1.5% β-tocopherol. Remarkably, all the seven studies conducted to test the effect of γ-TmT on carcinogenesis in different models, including colon, breast, lung and prostate, showed protective effects.

Based on the evidence that γT and its metabolites suppress COX-stimulated PGE_2, Newmark et al. (2006) hypothesized that γ-TmT may show protective effects against colon cancer because targeting COXs and eicosanoids has been recognized as one of the most promising anticancer strategies (Wang and Dubois 2010). These investigators found that compared with control diet (AIN76A), dietary γ-TmT (at 0.1% in AIN76A diet) reduced AOM-induced ACF (a pre-cancer lesion) by 55% in male F344 rats. To further examining the anti-inflammatory activity, these investigators showed that the mixed tocopherols appeared to attenuate TPA-caused inflammation (Newmark et al. 2006). In a follow-up study, γ-TmT was tested in an inflammation enhanced mouse colon cancer model in male CF-1 mice where colon tumorogenesis was induced by AOM and promoted by dextran sulfate sodium (DSS) that is known to caused colon inflammation. The results showed that mice fed AIN93M diets containing γ-TmT at 0.17–0.3% (w/w diet) had reduced number of colon adenomas compared with controls, although the outcomes were somewhat dependent upon the way of AOM injection (Ju et al. 2009). Interestingly, the γ-TmT regimen appeared to suppress DSS-induced inflammation only when mice were also co-injected with AOM, but seemed to worsen the inflammation caused by DSS alone.

Besides colon cancer, the similar supplementation of γ-TmT was also tested in other cancer models. Suh et al. (Lee et al. 2009; Suh et al. 2007) showed that γ-TmT supplementation at 0.1, 0.3 and 0.5% in diet inhibited the development of mammary tumors that were induced by N-methyl-N-nitrosourea injection in female Sprague Dawley rats. These regimens suppressed mammary tumor growth and tumor multiplicity, and increased the expression of p21, p27 caspase-3 and peroxisome proliferator activated receptor-γ. The studies on lung cancer models (Lambert et al. 2009; Lu et al. 2010) also found that γ-TmT containing diets inhibited growth and reduced volume of lung tumors in mice. In addition, the beneficial effect of γ-TmT (at 0.1%) was also found in transgenic murine prostate cancer model (TRAMP) where γ-TmT significantly suppressed the incidence of palpable tumor

and prostate intraepithelial neoplasia development (Barve et al. 2009). Interestingly, γ-TmT treatment significantly up-regulated the transcription factor Nrf2 and consequently up-regulated several phase II detoxifying antioxidant enzymes, which provides plausible explanations for the observed tumor suppression effects by the tocopherol mixtures.

15.6 Tocotrienols

15.6.1 Molecular Bases of Tocotrienols as Potential Anticancer Agents

Besides tocopherols, tocotrienols, especially γ-tocotrienol and δ-tocotrienol, respective analogs of γT and δT with an unsaturated side chain and abundant in palm oil, have been reported to exhibit potent anticancer effects in various types of cancer cells (Shah and Sylvester 2004, 2005; Sylvester et al. 2005; Wali et al. 2009; Yap et al. 2008). In cell-based studies, γ-tocotrienol appears to show stronger efficacy than γT in the anti-proliferation and pro-apoptotic activity (Jiang et al. 2011a; Yap et al. 2008). δ-tocotrienol appears to have similar or slightly stronger anticancer efficacy than γ-tocotrienol. Biochemical events associated with γ-tocotrienol-induced anticancer actions have been well characterized, including its activation of caspase-8 or JNK, induction of endoplasmic reticulum (ER) stress and inhibition of PI3K-mediated AKT phosphorylation (Park et al. (2010); Shah and Sylvester 2004, 2005; Sylvester et al. 2005; Wali et al. 2009; Yap et al. 2008). γ-tocotrienol has also been shown to inhibit NFkB in various types of cells (Ahn et al. 2007). Compared with tocopherols, γ-tocotrienol showed similar or stronger anti-inflammatory activity by modulation of COX- and 5-LOX-mediated reactions (Jiang et al. 2008, 2011b). Long-chain metabolites of γ-tocotrienol appears to be potent inhibitor of COXs (Jiang et al. 2008). Recently Jiang et al. (2011a) showed that γ-tocotrienol induces apoptosis and autophagy by causing intracellular accumulation of dihydrosphingosine and dihydroceramide and is more potent than γT in these activities. In addition, combinations of tocotrienols (γ-tocotrienol or δ-tocotrienol) with statins have been shown to synergistically inhibit cancer cell growth in cell based studies (Wali and Sylvester 2007; Wali et al. 2009), which is partially explained by the fact that γ-tocotrienol is capable of suppressing statin-promoted up-regulation HMG-CoA reductase (Yang et al. 2010). These interesting cell-related studies have prompted many groups to investigate potential anticancer effects of tocotrienols in different animal cancer models.

15.6.2 Tocotrienol Mixtures

Dietary palm oil, a rich source of carotenoids, tocotrienols, and tocopherols, appears to have antitumor activity in chemically-induced mammary tumor in rats (Sundram et al. 1989; Sylvester et al. 1986), and attenuates TPA-promoted skin tumors (Kausar et al. 2003). A caveat with these studies using palm oil is that the effects cannot be

attributed to a single component. Subsequent studies have therefore investigated potential anti-carcinogenic properties of tocotrienol-enriched fractions from palm oil and found beneficial effects in different cancer models such as chemically-induced hepatocarcinogenesis (Makpol et al. 1997; Ngah et al. 1991; Shamaan et al. 1993), xenograft breast cancer studies in nude mice (Nesaretnam et al. 2004), spontaneous hepatocarcinogenesis and chemically-induced lung cancer (Wada et al. 2005), ultraviolet B damaged-skin (Shibata et al. 2010; Yamada et al. 2008), and angiogenesis (Nakagawa et al. 2007). Since these tocotrienol-enriched products derived from palm oil have varied compositions and amounts of tocotrienols and may also contain other active compounds such as tocopherols, the anticancer effects cannot be attributable to a single tocotrienol form.

15.6.3 γ-Tocotrienol

Six studies have been reported on in vivo anti-cancer effects of high-pure γ-tocotrienol (≥ 95%), all of which used xenograft models. In 1997, He et al. (1997) studied the effect of dietary γ-tocotrienol on the growth of mouse melanoma B16(F10)-implanted in female C57BL mice. Dietary treatments, which included α-tocopherol (97%) and γ-tocotrienol (98%) at 116 and 924 μmol/kg diet levels, were given 10 days prior to and 28 days following tumor-cell implantation. Compared with αT supplemented group, γ-tocotrienol significantly delayed the onset of tumor detection and reduced tumor weight. In addition, the effect of these dietary treatments on the survival of mice bearing implanted melanoma was studied, where mice were given diets containing 2 or 4 mmol γ-tocotrienol/kg diet 14 days after the implantation. Compared with control fed animals, γ-tocotrienol containing diets prolonged the survival of mice bearing implanted melanomas by increasing the mean duration of survival by 30%.

Potential protective effects of γ-tocotrienol on prostate cancer have been investigated. Jiang et al. (2011a) recently showed that γ-tocotrienol (125 mg/kg body weight administered by gavage three times a week during 5 weeks) significantly inhibited tumor development in nude mice implanted with androgen-sensitive human prostate adenocarcinoma (LNCaP) cells. The study also showed that γ-tocotrienol exhibited stronger anticancer activity than γ-tocopherol in the xenograft model, which paralleled with much higher cellular accumulation of γ-tocotrienol. Yap et al. reported that γ-tocotrienol (50 mg/kg /day five times a week for 2 weeks) inhibits androgen-independent prostate cancer (AIPCa) tumor growth in a xenograft model. The antitumor capacity of γ-tocotrienol was enhanced when co-administered with docetaxel (Yap et al. 2010). These investigators also indicated that γ-tocotrienol appeared to be selectively accumulated in tumor tissues, which may account for its high anticancer efficacy in vivo. In an earlier study, Kumar et al. examined the anti-tumor properties of γ-tocotrienol in a model where human prostate cancer bone metastasizing (PC3) cells were injected to athymic male CBy.Cg.*Foxnl*^{nu} mice and γ-tocotrienol at 400 mg/kg body weight was injected subcutaneously in the neck of nude mice (Kumar et al. 2006). Mice were then irradiated

(5 Gy/min for a final dose of 12 Gy) at the rear part of the body including the location of the tumor. The results indicated that the size of the tumors was decreased by almost 40% only in γ-tocotrienol injected and irradiated mice. Lipid peroxidation increased in tumors from mice irradiated and treated with γ-tocotrienol. Surprisingly, although rectum tissue was not affected by the treatments, kidney tissue was equally sensitized to lipid peroxidation as the tumors when both irradiation and γ-tocotrienol were given. The increase in lipid peroxidation in tumors is associated to their destruction, but the mechanism(s) involved is not fully understood. This study suggests that if sensitivity of kidney can be resolved, the combination of irradiation and γ-tocotrienol may be an useful therapy for advanced prostate cancer.

Kunnumakkara et al. (2010) showed that oral administration of γ-tocotrienol (400 mg/kg BW) inhibited the growth of pancreatic tumor that was formed from human pancreatic cancer cells (MIA PaCa2) implanted in athymic nu/nu mice. In addition, γ-tocotrienol treatment enhanced the antitumor properties of gemcitabine, a standard treatment drug for pancreatic cancer.

Hiura et al. (2009) reported that dietary γ-tocotrienol or δ-tocotrienol (0.1% by weight) similarly delayed the growth of hepatoma MH134 cells in C3H/HeN mice. These investigators also found that tocotrienols are accumulated specifically in tumor but not in normal tissues. Kulkarni et al. (2010) showed that γ-tocotrienol appeared to have radioprotective effects on hematopoietic stem and progenitor cells, and therefore may serve as potential adjuvant to radiotherapy for cancer. Specifically, γ-tocotrienol at a dose of 200 mg/kg body weight, which was subcutaneously injected in CD2F1 mice 24 h prior to irradiation, provided protection of hematopoietic tissues from radiotherapy.

15.6.4 δ-Tocotrienol

In most cell-based studies, δ-tocotrienol showed similar or slightly more potent anticancer effects than γ-tocotrienol with respect to the anti-proliferation and pro-death activities (He et al. 1997). Three studies have been carried out using ≥ 98% pure δ-tocotrienol to examine its in vivo anticancer activity. Hiura et al. (2009) reported that dietary δ-tocotrienol and γ-tocotrienol (0.1% by weight) similarly delayed tumor growth in C3H/HeN mice implanted with murine hepatoma MH134. Both of these tocotrienols appeared to accumulate specifically in tumor tissues but not other normal tissues.

McAnally et al. (2007) studied the effect of dietary δ-tocotrienol on the growth of mouse melanoma B16(F10) implanted in C57BL female mice. Dietary δ-tocotrienol reduced tumor weight only in combination with lovastatin in the diet (62.5 mg δ-tocotrienol/kg body weight per day + 12.5 mg lovastatin/kg body weight per day), when compared to non-supplemented control group.

Shibata et al. (2009) studied the antiangiogenic potential of δ-tocotrienol as compared to αT in an in vivo mouse angiogenesis assay. δ-Tocotrienol (30 μg) but not α-tocopherol inhibited tumor cell-induced angiogenesis formation.

15.6.5 Toxicity of Tocotrienols

Nakamura et al. (2001) reported that in a 13-week feeding study which investigates potential toxicity from a tocotrienol mixture (α-tocotrienol 21.4%, β-tocotrienol 3.5%, γ-tocotrienol 36.5%, δ- tocotrienol 8.6%, α-tocopherol 20.5%, β-tocopherol 0.7%, γ-tocopherol 1.0% and δ-tocopherol 0.5%), the no-observed-adverse-effect level for tocotrienols was daily 120 mg/kg BW, slight adverse effect was seen at doses of 473 mg/kg BW, and more adverse effect including suppression of body weight was observed at 1,895 mg/kg BW. Takaski et al. (2008, 2009) studied potential toxicological effects of long term (1–2 years) exposure to tocotrienol mixture in rats. One-year chronic exposure of rats to 2% tocotrienol mixture diets induced highly proliferative liver lesions, nodular hepatocellular hyperplasia (NHH). However, NHH did not harbor neoplastic characteristics from increased exposure despite sustained high cellular proliferation. The tocotrienol mixture did not induce tumor in any other organ besides the liver. In addition, Yap et al. determined acute toxicity of γ-tocotrienol by single i.p. injection of escalating doses of this compound in C57BL/6 black male mice and found that γ-tocotrienol at 800 mg/kg did not cause any death among five-injected mice, whereas death starts to be seen when 1,000 mg/kg was used (Yap et al. 2010).

15.7 Conclusion Remarks

The large clinical trials and recent animal studies strongly indicate that different forms of vitamin E appear to play distinct roles in cancer prevention and treatment. αT, the major form of vitamin E in tissues and the only vitamin E form known to be required to have adequate dietary intake to prevent nutrient deficiency, may be useful in prevention of cancers that are promoted by nutrient deficiency, increased oxidative stress related to heavy smokers as well as poor diets such as high fat combined with low-fiber diets. On the other hand, αT supplementation may be futile to individuals who have adequate antioxidant levels and non-heavy smokers. In contrast, due to the unique anti-inflammatory and anticancer activities of other forms of vitamin E, γT, δT and tocotrienols are likely better than αT in cancer prevention and may even be useful in chemotherapy. In particular, γT and tocotrienols have been shown to inhibit COX- and 5-LOX-mediated eicosanoid formation and induce cancer cell death by modulating sphingolipid metabolism, whereas αT is much less efficient in these activities. Based on these exciting mechanistic observations, animal studies have been undertaken to examine potential anticancer efficacy of these vitamin E forms in vivo. Emerging evidence from various animal models already indicates promising anticancer effects of these compounds.

In the future, studies using cancer models that bear genetic lesions and/or mimic human cancer development are needed to further evaluate the role of different vitamin E forms in cancer prevention and treatment. Given that long-chain carboxychromanols are even stronger than the unmetabolized vitamin E forms in inhibition of COX- and 5-LOX-catalized reactions and induction of cancer cell death (Jiang Q,

Jang Yumi, Jiang Z, Wang Y and Kuah S, unpublished observations), these vitamin E metabolites and analogs may be more effective than their vitamin E precursors as anticancer agents, which warrants further investigation. Furthermore, combination therapies that include combinations of tocotrienols and statins or other chemotherapeutic agents may represent new promising and effective strategies against relatively advanced cancers.

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