Review

Does γ-Tocopherol Play a Role in the Primary Prevention of Heart Disease and Cancer? A Review

Marion Dietrich, PhD, Maret G Traber, PhD, Paul F Jacques, DSc, Carroll E Cross, MD, Youqing Hu, Gladys Block, PhD

Jean Mayer United States Department of Agriculture, Human Nutrition Research Center on Aging at Tufts University, Boston, Massachusetts (M.D., P.F.J.), Department of Nutrition and Food Management, Linus Pauling Institute, Oregon State University, Corvallis, Oregon (M.G.T.), School of Medicine, University of California Davis, Sacramento (C.E.C), School of Public Health, University of California Berkeley, Berkeley (Y.H., G.B.), California.

Key words: γ-tocopherol, anti-inflammatory effects, dietary vitamin E, plasma γ-tocopherol, human cardiovascular disease, cancer

Vitamin E consists of a group of eight isomers, four tocopherols (α-, β-, γ-, δ-tocopherol) and four tocotrienols (α-, β-, γ-, δ-tocotrienol). While extensive literature has been published on the potential health benefits of α-tocopherol, little is known about γ-tocopherol, the major form of vitamin E in food in the U.S. γ-tocopherol has recently received more research attention based on findings from *in vitro* and animal studies indicating that it has potent anti-inflammatory and antioxidant properties. Based on these recent studies, it is important to investigate the possible health benefits of γ-tocopherol in humans. In this article, we review publications on dietary γ-tocopherol intake, plasma γ-tocopherol levels, cardiovascular disease and cancer risk in humans.

Key teaching points:

- It is estimated that approximately 70% of the vitamin E intake from food sources in the U.S. is in form of γ-tocopherol. This is largely due to the high intake of soybean and other vegetable oils rich in γ-tocopherol in the American diet.
- *In vitro* and animal studies show that γ-tocopherol has potent anti-inflammatory and anti-oxidant properties.
- With regard to *dietary γ-tocopherol intake* and coronary heart disease and stroke risk, findings are inconsistent, indicating protective effects in post-menopausal women only. To date, only one study on dietary γ-tocopherol intake and cancer risk has been published, and no protective effect was observed.
- With regard to *plasma γ-tocopherol levels* and risk for coronary heart disease, there is no evidence of a protective effect of high plasma γ-tocopherol levels. With regard to prostate cancer, studies suggest a protective effect of high plasma γ-tocopherol levels.
- More well-designed epidemiologic and intervention studies are needed, with measurement of plasma γ-tocopherol and explicit estimates of dietary γ-tocopherol.

INTRODUCTION

γ-tocopherol is a form of vitamin E that has recently received more research attention based on results from *in vitro* and animal studies regarding its antioxidant and anti-inflammatory properties [1–3]. Vitamin E consists of a group of eight isomers, four tocopherols (α-, β-, γ-, δ-tocopherol) and four tocotrienols (α-, β-, γ-, δ-tocotrienol). Within the vitamin E group, α-tocopherol is the predominant form in plasma and tissue and it therefore has been studied extensively in *in vitro* and *in vivo* studies [4]. Recent *in vitro* and animal studies suggest that the antioxidant properties of γ-tocopherol may actually exceed those of α-tocopherol [5] and also suggest that γ-tocopherol has anti-inflammatory properties. Qing et al. reported that γ-tocopherol at physiological concentrations reduced prostaglandin E_2 (PGE_2) synthesis through inhibition of

Address reprint requests to: Marion Dietrich, Ph.D., JM USDA HNRCA at Tufts University, Nutritional Epidemiology, 711 Washington Street, Boston, MA 02111. E-mail: Marion.Dietrich@tufts.edu

Journal of the American College of Nutrition, Vol. 25, No. 4, 292–299 (2006)
Published by the American College of Nutrition

COX-2 activity in macrophages and epithelial cells [1]. Prostaglandins play an important role as mediators in inflammatory processes. Using animal models, the same group also demonstrated that supplementing rodents with γ-tocopherol led to decreases in proinflammatory eicosanoids and inflammation-mediated parameters of tissue injury [2].

As both cardiovascular disease and many cancers have been associated with inflammation and/or evidences of oxidative stress, and as aforementioned data suggests a role for γ-tocopherol in the amelioration of both processes, it seems reasonable to explore the literature for associations between dietary intake or plasma levels of γ-tocopherol and the risk of human cardiovascular disease and cancer.

Few epidemiologic studies have made explicit estimates of gamma tocopherol intake [6]. However, a number of studies have reported on health effects of food sources of vitamin E, as distinct from supplements. While supplemental vitamin E capsules consist of α-tocopherol, it is estimated that approximately 70% of the vitamin E intake in the U.S. from food sources is in form of γ-tocopherol [7,8]. This is largely due to the high intake of soybean and other vegetable oils rich in γ-tocopherol, such as canola rapeseed oil, in the American diet [9]. In soybean or corn oil γ-tocopherol concentrations are markedly higher compared to α-tocopherol concentrations (70 vs 8 mg and 70 vs 20 mg/100 g, respectively) [10]. In the year 2004 for example, 80% of all fats and oils consumed in the U.S. was soybean oil, with the majority of it consumed in form of baking and frying fat and salad or cooking oils [11]. Hardened soybean oil is used as the main fat source in baked goods. Other main dietary intake sources of γ-tocopherol are seeds, certain cereal grains, and walnuts [12]. For this review we will treat risk estimates of dietary vitamin E from food, exclusive of supplements, as indirect estimates of γ-tocopherol intake. The epidemiological data is buttressed by a number of epidemiologic studies that have actually measured plasma or serum γ-tocopherol levels, and investigated associations with both cardiovascular disease (CVD) and cancer.

EPIDEMIOLOGIC STUDIES

This review is limited to prospective studies, which only included subjects free of diagnosed CVD or cancer at the time that their diet or plasma γ-tocopherol concentrations were assessed. Subjects with diagnosed chronic diseases often change their dietary habits, and the presence of CVD or cancer, or their treatments, may influence plasma vitamin E levels. With regard to *dietary* vitamin E intake and chronic disease risks, we limit this review to human studies that have been conducted in the U.S. Diets in other countries such as countries in Europe, provide less γ-tocopherol due to the lower consumption of soybean oil, and therefore dietary vitamin E may not consist primarily of γ-tocopherol. With regard to epidemiological studies reporting *plasma or serum* γ-tocopherol levels and risk for CVD or cancer, studies available from all countries are included.

PLASMA γ-TOCOPHEROL

In the following section, we describe studies which examined the association between plasma (or serum) levels of γ-tocopherol with coronary heart disease and cancer.

Coronary Heart Disease and Myocardial Infarction (CHD and MI)

A prospective, nested case-control study by Evans et al. [13] involving 77 nonsmoking cases of nonfatal myocardial infarction (MI) and coronary heart disease (CHD) death and 158 healthy nonsmoking controls did not find differences in serum γ-tocopherol levels between cases and controls (Table 1). Analysis showed that the odds ratios for CHD death or MI were not significantly different when the highest versus the lowest quarter of serum γ-tocopherol levels were compared. The odds ratio for CHD for the highest versus the lowest quarter of serum γ-tocopherol among nonsmokers was 2.34 (95% CI = 0.56 to 9.81), and the odds ratio for nonfatal MI was 0.79 (95% CI = 0.14 to 4.58), in an analysis adjusted for lipoproteins. Although no significant associations were observed between γ-tocopherol and CHD death or non-fatal MI, confidence intervals were wide indicating low statistical power.

Results from the prospective nested case-control Physicians' Health Study published by Hak et al. [14] showed in a multivariate analysis that men with high plasma γ-tocopherol levels tended to have an increased risk of nonfatal and fatal MI (P for trend = 0.01). The authors suggest that since tocopherols are strongly associated with lipoproteins, residual confounding by elevated lipids could contribute to the observed positive association although statistical adjustment for those was conducted. Another possible explanation provided by the authors is that elevated plasma γ-tocopherol levels could be a marker of *trans* fat intake from partially hydrogenated soybean oil which in turn has been shown to represent a risk factor for cardiovascular diseases [15].

Cancer

Table 2 summarizes data from four publications which investigated the association of plasma or serum γ-tocopherol concentrations with cancer [16–19], one of which reported results from two studies, CLUE I and CLUE II [16].

Huang et al. [16] examined the association between serum γ-tocopherol levels and the subsequent risk of developing prostate cancer among participants of two prospective cohort studies conducted in 1974 and 1989 in Washington County, U.S (CLUE I and CLUE II). In nested case-control analyses, CLUE I included 182 matched (1:2) case-control sets, while CLUE II included 142 matched (1:2) sets. In both studies,

Table 1. Epidemiological Studies Investigating Plasma or Serum γ-Tocopherol Levels and Risk for Coronary Heart Disease Death and Myocardial Infarction (CHD Death and MI)

Publication	Study name and study design	Primary endpoint	Subjects #'s and characteristics	Supplement use	Results plasma/serum γ-tocopherol concentrations and Odds Ratios (OR)/Relative Risks (RR) for CHD or MI
Evans et al. [13]	Multiple Risk factor Intervention Trial (MRFIT) Prospective, nested case-control	CHD death and nonfatal MI	Cases: 44 CHD deaths; 33 nonfatal MI Controls: 158 Men Mean age: NR Age range: 35–57 yrs Results reported here are from nonsmokers only	NR*	Serum concentrations: No significant differences in serum γ-tocopherol levels among cases and controls for both CHD death and nonfatal MI: in CHD death subjects: 4.06 μg/ml ± 1.99 (mean ± SD); in nonfatal MI subjects: 3.53 μg/ml ± 1.69 (mean ± SD); in control subjects: 3.70 μg/ml ± 1.64 (mean ± SD); no P-values provided. OR: No significant associations between serum γ-tocopherol levels and CHD death or nonfatal MI: *CHD death:* 2.34 (95% CI: 0.56–9.81); highest quarter compared to lowest quarter. *Nonfatal MI:* 0.79 (95% CI: 0.14–4.58); highest quarter compared to lowest quarter.
Hak et al. [14]	Physicians' Health Study Prospective, nested case-control	MI (both fatal and nonfatal)	Cases: 531 Controls: 531 Men Age cases: 58.1 ± 8.6 yrs (mean ± SD) Age controls: 57.9 ± 8.5 yrs (mean ± SD) Smoking status matched between cases and controls	Current supplement use: Cases: 19.3% Controls: 21.4% Multivariate model did not include adjustment for multivitamin use.	Plasma concentrations: Baseline γ-tocopherol levels of cases and controls not presented. RR: Men with higher plasma γ-tocopherol levels had significantly increased RR of MI: 2.14 (95% CI: 1.18–3.87); P for trend = 0.01; highest fifth compared to lowest fifth.

* NR = not reported.

persons who subsequently developed cancer had significantly lower serum concentrations of γ-tocopherol than did the control subjects (P = 0.02 and P = 0.0001, respectively). The dose-response trend was non-significant in CLUE I (P for trend = 0.30), while a strong dose-response trend was observed in CLUE II (P for trend <0.001). Men in the highest fifth of the serum γ-tocopherol distribution in CLUE II had a five-fold reduction in the risk of developing prostate cancer compared with men in the lowest fifth (OR = 0.21, 95% CI = 0.08 to 0.54). Vitamin E or multivitamin users were not excluded from this analysis. However, the authors note that the result for each study was the same whether vitamin supplement users were excluded or included.

Another nested case control study on serum micronutrients and prostate cancer of similar size was conducted by Nomura et al. [17]. In their study, including 142 cases and 142 controls, lower serum levels of γ-tocopherol in cases compared to matched controls were found, but the differences were non-significant (P = 0.23). No significant dose-response trend with regard to prostate cancer risk was observed (P for trend = 0.27). Men in the two highest quarters of γ-tocopherol had lower odds ratios for prostate cancer when compared to the lowest quarter, although statistically non-significant (third quartile OR = 0.8, 95% CI = 0.8 to 1.8; fourth quartile OR = 0.7, 95% CI = 0.3 to 1.5).

Gann et al. [18] analyzed data from the Physicians' Health Study to investigate the association of prostate cancer risk with plasma antioxidant concentrations. In a nested case control study of 578 prostate cancer cases and 1294 matched controls, no significant differences in plasma γ-tocopherol levels between cases and controls were seen (P = 0.50). No reduced risk for prostate cancer was seen with higher plasma γ-tocopherol levels (P for trend = 0.89).

Nomura et al. [19] also examined the association of serum γ-tocopherol and cancer of the upper aerodigestive tract in the same cohort in which they investigated prostate cancer [17]. In a nested case-control analysis, sixty-nine cases were matched to

Table 2. Epidemiological Studies Investigating Plasma or Serum γ-Tocopherol Levels and Cancer

Publication	Study name and study design	Primary endpoint	Subjects #'s and characteristics	Supplement use	Results γ-tocopherol concentrations and Odds Ratios (OR)/relative risks (RR) for CANCER
Huang et al. [16]	CLUE I and II Nested case-control	Prostate cancer	CLUE I: Cases: 182 Controls: 364 Men Age cases: 54 ± 9 yrs Age controls: 54 ± 9 yrs (mean ± SD)	CLUE I: Vitamin E supp use: Cases: 2.2% Controls: 1.6% Multivitamin use: Cases: data not collected Controls: data not collected	CLUE 1: Plasma: Plasma γ-tocopherol was significantly lower in cases than in controls (0.20 vs. 0.24 mg/dl [median], P = 0.02). OR OR = 0.77 (95% CI 0.42–1.43; p for trend = 0.30) for highest fifth of serum g-toc concentration compared to lowest fifth.
			CLUE II: Cases: 142 Controls: 284 Men Age cases: 66 ± 8 yrs Age controls: 66 ± 8 yrs (mean ± SD) Cases and controls were not significantly different in history of cigarette smoking in both cohorts (CLUE I and II).	CLUE II: Vitamin E supp use: Cases: 1.4% Controls: 2.5% Multivitamin use: Cases: 18.6% Controls: 11.2%	CLUE II: Plasma: Plasma γ-tocopherol was significantly lower in cases than in controls (0.25 vs. 0.29 mg/dl [median], P = 0.0001). OR: OR = 0.21 (95% CI 0.08–0.54; p for trend <0.001) for highest fifth of serum g-toc concentration compared to lowest fifth.
Nomura [17]	Nested case-control	Prostate cancer	Cases: 142 Controls: 142 Men Age matched cases and controls 62 yrs (mean) (range: 52–74 yrs) Cases and controls were not significantly different in history of cigarette smoking (p = 0.18)	NR*	Serum: No statistically significant difference in serum γ-tocopherol levels were found between cases and controls (1.34 μg/ml versus 1.50 μg/ml, respectively, P = 0.23) OR: OR = 0.7 (95% CI 0.3–1.5; p for trend = 0.27) for highest quarter of serum g-toc concentration compared to lowest quarter.
Gann [18]	Physician's Health Study Nested case-control	Prostate cancer	Cases: 578 controls: 1294 Men Cases: 60.7 yrs Controls: 61.5 yrs (mean age) Cases and controls matched on smoking status	Vitamin A supplement users excluded. ORs adjusted for multivitamin supplement use.	Plasma: No statistically significant difference in γ-tocopherol levels between cases and controls (1.66 μg/ml versus 1.70 μg/ml, respectively, P = 0.50). OR: No association between γ-tocopherol levels and prostate cancer risk: OR = 0.98 (95% CI 0.71–1.35; p for trend = 0.89) for highest fifth of plasma g-toc concentration compared to lowest fifth.
Nomura [19]	Nested case-control	Upper aerodigestive tract cancer	Cases: 69 controls: 138 Men Cases and controls: 52–75 yrs (range) Cases and controls matched on cigarette smoking history		Plasma: Significantly lower γ-tocopherol levels in upper aerodigestive tract cancer cases than in controls (1.14 ± 0.10 vs. 1.33 ± 0.07 μg/ml [mean ± SE], P = 0.001). OR: significantly decreased risk for aerodigestive tract cancer with high g-toc serum levels: OR = 0.39 (95% CI 0.19–0.80; p for trend <0.01) for highest third of serum g-toc concentration compared to lowest third.

* NR = not reported.

138 controls. They found significantly lower serum γ-tocopherol levels in the 69 upper aerodigestive tract cancer patients than in their controls (P = 0.001). The protective trend in risk for aerodigestive tract cancer by tertiles of serum γ-tocopherol level was significant (P <0.01).

DIETARY VITAMIN E/γ-TOCOPHEROL INTAKE AND CVD AND CANCER

Table 3 summarizes literature data regarding dietary intake of vitamin E by quintiles and risks of selected cardiovascular diseases and cancer.

Coronary Heart Disease (CHD)

Kushi et al. [20] observed in the Iowa Women's Health Study, a prospective cohort study of 34,486 U.S. postmenopausal women, that dietary intake of vitamin E was significantly inversely associated with the risk of death from coronary heart disease (CHD). In a subgroup of 19,687 women who did not consume vitamin supplements, the relative risks (RR) from lowest to highest fifth of intake were, 1.0, 0.70, 0.76, 0.32, and

Table 3. Dietary Vitamin E Intake (Without Supplements) by Quintiles and Relative Risks of Coronary Heart Disease, Death from Stroke, or Prostate Cancer according to Quintiles of Dietary Intake of Vitamin E

Publication	Quintile of dietary vitamin E intake					p for trend
	1	2	3	4	5	
Kushi et al., 1996, Iowa Women's Health Study [20]						
34,486 postmenopausal women, 55–69 yrs of age, mean age 61 yrs, 7 years follow up						
Dietary vitamin E intake						
Ranges (no medians provided) (IU/day)	<4.91	4.92–6.24	6.25–7.62	7.63–9.63	>9.64	—
RR of death from CHD (95% CI)						
Multivariate adjusted	1.0	0.70 (0.41–1.18)	0.76 (0.44–1.29)	0.32 (0.17–0.63)	0.38 (0.18–0.80)	0.004
Rimm et al., 1993, Health Professionals Study [21]						
39,910 men, 40–75 yrs of age, mean age not reported, 4 years follow up						—
Dietary vitamin E intake						
Ranges (no medians provided) (IU/day)	1.6–6.9	7.0–8.1	8.2–9.3	9.4–11.0	11.1	
RR of CHD (95% CI) Multivariate adjusted	1.0	1.10 (0.80–1.51)	1.17 (0.84–1.62)	0.97 (0.69–1.37)	0.79 (0.54–1.15)	0.11
Stampfer et al., 1993, Nurses Health Study [22]						
87,245 women, 34–59 yrs of age, mean age not reported, 8 years follow up						
Dietary vitamin E intake						
Ranges (IU/day)	0.3–3.1	3.2–3.9	4.0–4.8	4.9–6.2	6.3–100	
Medians	2.6	3.6	4.4	5.4	7.7	—
RR of nonfatal MI and death due to coronary disease (95% CI)						
Adjusted for age and smoking	1.0	1.04 (0.8–1.35)	0.87 (0.66–1.14)	1.14 (0.89–1.47)	0.95 (0.72–1.23)	0.99
Yochum et al., 2000, Iowa Women's Health Study [23]						
34,492 postmenopausal women, 55–69 yrs of age, mean age 61 yrs, 7 years follow up						
Dietary intake						
Medians (IU/day)* (no ranges provided)	2.9	4.0	5.0	6.0	8.2	—
RR of death from stroke (95% CI)						
Multivariate adjusted	1.0	0.8 (0.51, 1.26)	0.93 (0.58, 1.49)	0.67 (0.39, 1.14)	0.40 (0.20, 0.80)	0.008
Kirsh et al., 2006, [6] PLCO trial						
29,361 men, mean age 63 yrs, age range not reported, 8 years follow up						
Dietary intake Medians (mg/day)**	8.6	10.2	11.3	12.6	15.8	
RR of prostate cancer (95% CI)						
Multivariate adjusted	1.0	0.92 (0.77, 1.09)	0.94 (0.79, 1.13)	0.87 (0.72, 1.05)	0.93 (0.78, 1.12)	0.33

* The original literature reported the dietary intake in mg/day. For comparison reasons, we multiplied the mg/day data with the conversion factor of 0.67 for alpha-tocopherol to receive IUs. The mg/day intakes were 4.4, 6.0, 7.4, 9.0, and 12.3 for the first, second, third, fourth, and fifth quintile respectively.

** Measured as milligrams of total alpha-tocopherol equivalents. It was not possible to convert into IUs since only total alpha-tocopherol equivalents were reported in the original literature.

0.38 (P for trend = 0.004) in multivariate analysis (Table 3). The authors note that further adjusting for micronutrients in food, such as carotenoids and folate, did not substantially alter the inverse association observed with vitamin E. When investigating the association of relative risk of death from CHD with vitamin E intake from food and supplements combined, or from supplements alone, the inverse association was not seen. When the intake of certain foods containing vitamin E was investigated in a multivariate analysis, intake of margarine, and nuts and seeds, was significantly inversely associated with risk of death from CHD (P for trend 0.05 and 0.02, respectively). Nuts and seeds contain polyunsaturated fatty acids (PUFAs) which could also contribute to the observed protective effect on cardiovascular health.

Rimm et al. [21] observed in the Health's Professional Study, which included 39,910 U.S. male health professionals aged 40 to 75 years, that a higher intake of dietary vitamin E was associated with an inverse but non-significant reduction in the risk of coronary heart disease for the highest intake group as compared with the lowest intake group (P for trend = 0.11). During four years of follow-up among men who did not take supplemental vitamin E, the multivariate relative risk of CHD was nonsignificantly decreased (RR = 0.79, 95% CI = 0.54 to 1.15 highest fifth compared to lowest fifth).

Stampfer et al. [22], analyzing data from the Nurses Health Study, did not find a significant reduction in risk of coronary heart disease with high dietary vitamin E intake in women free of CVD aged 34 to 59 years (P for trend = 0.99).

Cerebrovascular Disease (Stroke)

Kushi's group also examined the relation between risk of death from stroke and dietary vitamin E intake in the Iowa Women's Health study [23]. A significant inverse association was seen between death from stroke and vitamin E intake from food (RR from lowest to highest fifth of intake, 1.0, 0.80, 0.93, 0.67, and 0.40; P for trend = 0.008) in women with a mean age of 61 years. No other U.S. studies investigating the association of dietary vitamin E intake with cerebrovascular disease could be identified.

Cancer (Prostate Cancer)

A very recent publication from the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial (PLCO Trial) reports no association between prostate cancer risk and dietary vitamin E intake (RR = 0.93, 95% CI = 0.79 to 1.12; P for trend = 0.33) [6]. This is the only published U.S. study investigating the association of dietary vitamin E intake with risk for cancer to date. The authors also conducted the analysis separately by dietary gamma-tocopherol intake and no statistically significant association was found (RR = 0.87, 95% CI: 0.70 to 1.09; P for trend = 0.34).

DISCUSSION

All of the reviewed plasma studies were nested case-control studies and therefore have collected plasma prior to the diagnosis of stroke, CHD, or cancer. Thus, the disease itself is unlikely to have influenced the observed plasma γ-tocopherol levels. The very limited available data on the association of CHD death and myocardial infarction with plasma γ-tocopherol concentrations provide no evidence of a protective effect of γ-tocopherol [13,14]. One of the two available studies even suggests a higher risk for MI with higher γ-tocopherol concentrations [14].

With regard to cancer, three out of five nested case-control studies on prostate and upper aerodigestive tract cancer found significantly inverse associations with plasma γ-tocopherol levels [16,19]. This result may suggest that low levels are associated with the development of the disease. In summary, for cancer, the data from plasma studies is suggestive of a protective effect of gamma-tocopherol. However, this finding can only be applied to men since the majority of these cancer studies investigated prostate cancer.

Studies of CHD events and stroke using dietary vitamin E as a proxy for γ-tocopherol intake provide mixed results. The two analyses conducted in the Iowa Women's Health Study found significant inverse associations with dietary vitamin E in postmenopausal women, whereas the other two studies, the Health Professionals Follow-up Study in men and the Nurses' Health Study, did not find statistically significant associations. One major difference between the Iowa Women's Health Study and the Nurses Health Study is that in the former, all women were post-menopausal, while only approximately one-third of the women in the Nurses' Health Study were post-menopausal. It may be possible that a high γ-tocopherol intake is only protective against CHD or death from stroke in postmenopausal women. In summary, results with regard to the role of dietary vitamin E in the protection of CHD and stroke are inconclusive and still too limited, but based on the literature, a possible protective effect can not be dismissed.

Only one study on dietary vitamin E intake and cancer (prostate cancer) risk has been published to date [6]. No protective effect was observed when dietary vitamin E intake expressed as total alpha-tocopherol equivalents (which include all four tocopherol isomers including gamma-tocopherol) or gamma-tocopherol specifically was investigated. Future epidemiological studies should stratify by gender, and in women also on menopausal status, if sample sizes allow this.

There are methodological limitations when investigating the association of dietary intake of vitamin E with risk for chronic disease development. For example, other components in food, including α-tocopherol, are correlated with γ-tocopherol and may be responsible for the observed associations. Vitamin E derived from food may be only a marker for those other components. For example, the highly consumed vegetable oils in the U.S., soybean oil and canola rapeseed oil are rich in

γ-tocopherol and are also good sources of the n-3 polyunsaturated fatty acid α-linolenic acid (ALA). High intake of ALA has been linked to reduced coronary heart disease risk in several epidemiological studies [24,25]. Further, most of the analyses reviewed here included adjustment for lipid soluble components such as triglycerides and lipoproteins. However, residual confounding by these factors and other nutrients may still be influencing the results. Inaccuracies in measurement of dietary nutrient intake are further limitations of such studies.

To our knowledge, no intervention studies of γ-tocopherol with clinical disease endpoints have been conducted to date. Two intervention studies investigating biomarkers for inflammation and oxidative stress have been conducted. One small human supplementation study investigated the effect of γ-tocopherol on plasma C-reactive protein levels (CRP) [26]. CRP is a biomarker of inflammation and a well recognized risk factor for cardiovascular disease. In that intervention study [26] 14 days of gamma-enriched tocopherols lowered median CRP levels significantly in nine hemodialysis patients ($P < 0.02$). Our research group conducted a larger, double-blind, randomized intervention study in healthy smokers and nonsmokers who were lightly exposed to second hand smoke, using plasma F_2-isoprostanes as a biomarker of oxidative stress. We administered γ-tocopherol but in combination with α-tocopherol, tocotrienols (alpha-, gamma-, and delta-tocotrienols), vitamin C and alpha-lipoic acid (antioxidant-cocktail pills) [27,28]. No effect of antioxidant cocktail supplementation was observed in the smokers, but in the second hand smokers a significant decrease in F_2-isoprostanes was observed when compared to the placebo group ($P = 0.008$). However, since the cocktail pills also contained other components besides γ-tocopherol, it can not be determined which component was responsible of the observed effect.

It is well-established that α-tocopherol supplementation results in significantly lower circulating γ-tocopherol levels [29]. It is therefore possible that in administering the alpha form of the vitamin, potentially effective γ-tocopherol levels and pathways are disrupted. Importantly, however, human plasma α- and γ-tocopherol concentrations reflect differences in their kinetics, especially influenced by vitamin E metabolism. Studies using deuterium labeled tocopherols demonstrated that plasma fractional disappearance rates for γ-tocopherol were more than triple than those of α-tocopherol ($p < 0.001$), but similar for both d_2-γ-tocopherol and its metabolite d_2-γ-carboxyethyl-hydroxychroman (d_2-γ-CEHC) [30]. No d_2-α-CEHC was detected. These results indicate that γ-tocopherol is rapidly metabolized to γ-CEHC, while α-tocopherol is maintained in the plasma and little is metabolized to α-CEHC. These comparisons reinforce the importance of vitamin E metabolism in regulating plasma γ-tocopherol metabolism. Based on its protein structure [31], α-tocopherol is the vitamin E form preferred by the tocopherol transfer protein. Thus, γ-tocopherol does not bind well to the protein and is preferentially metabolized leading to its short plasma half-lives. Nonetheless, the potential anti-inflammatory effects of γ-tocopherol remain of great interest.

In order to better understand the potential role of γ-tocopherol in chronic disease, more well-designed epidemiologic and intervention studies are needed, with measurement of plasma γ-tocopherol and explicit estimates of dietary γ-tocopherol.

ACKNOWLEDGMENTS

This work was supported by the Clinical Nutrition NIH grant DK07651-17, USDA (2003-00915) and NIH (ES01 1985) grants, and by Pharmavite LLC, Makers of Nature Made Vitamins.

REFERENCES

1. Jiang Q, Elson-Schwab I, Courtemanche C, Ames BN: Gamma-tocopherol and its major metabolite, in contrast to alpha-tocopherol, inhibit cyclooxygenase activity in macrophages and epithelial cells. Proc Natl Acad Sci 97:11494–11499, 2000.
2. Jiang Q, Ames BN: Gamma-tocopherol, but not alpha-tocopherol, decreases proinflammatory eicosanoids and inflammation damage in rats. FASEB J 17:816–822, 2003.
3. Jiang Q, Lykkesfeldt J, Shigenaga MK, Shigeno ET, Christen S, Ames BN: Gamma-tocopherol supplementation inhibits protein nitration and ascorbate oxidation in rats with inflammation. Free Radic Biol Med 33:1534–1542, 2002.
4. Singh U, Jialal I: Anti-inflammatory effects of alpha-tocopherol. Ann N Y Acad Sci 1031:195–203, 2004.
5. Christen S, Woodall AA, Shigenaga MK, Southwell-Keely PT, Duncan MW, Ames BN: γ-tocopherol traps mutagenic electrophiles such as NOx and complements α-tocopherol: physiological implications. Proc Natl Acad Sci 94:3217–3222, 1997.
6. Kirsh VA, Hayes RB, Mayne ST, Chatterjee N, Subar AF, Dixon LB, Albanes D, Andriole GL, Urban DA, Peters U, PLCO Trial: Supplemental and dietary vitamin E, beta-carotene, and vitamin C intakes and prostate cancer risk. J Natl Cancer Inst 98:245–54, 2006.
7. McLaughlin PJ, Weihrauch JL: Vitamin E content of foods. Research 75:647–665, 1979.
8. Handelman GJ, Machlin LJ, Fitch K, Weiter JJ, Dratz EA: Oral α-tocopherol supplements decrease plasma γ-tocopherol levels in humans. J Nutr 115:807–813, 1985.
9. Lehmann J, Martin HL, Lashley EL, Marshall MW, Judd JT: Vitamin E in foods from high and low linoleic acid diets. J Am Dietet Assn 86:1208–1216, 1986.
10. Eitenmiller R, Lee J: "Vitamin E: Food Chemistry, Composition, and Analysis." New York: Marcel Dekker, Inc., 2004.
11. U.S. Department of Commerce and U.S. Bureau of the Census: Fats and Oils: Production, Consumption, and Stocks 2004. 2005.
12. Amaral JS, Alves MR, Seabra RM, Oliveira BP: Vitamin E composition of walnuts (Juglans regia L.): a 3-year comparative study of different cultivars. J Agric Food Chem 29:5467–5472, 2005.

13. Evans RW, Shaten BJ, Day BW, Kuller LH: Prospective association between lipid soluble antioxidants and coronary heart disease in men. Am J Epidemiol 147:180–186, 1998.
14. Hak AE, Stampfer MJ, Campos H, Sesso HD, Gaziano JM, Willett W, Ma J: Plasma carotenoids and tocopherols and risk of myocardial infarction in a low-risk population of US made physicians. Circulation 108:E9012–E9013, 2003.
15. Steinhart H, Rickert R, Winkler K: Trans fatty acids (TFA): analysis, occurrence, intake and clinical relevance. Eur J Med Res 8:358–362, 2003.
16. Huang H-Y, Alberg AJ, Norkus EP, Hoffman SC, Comstock GW, Helzlsouer KJ: Prospective study of antioxidant micronutrients in the blood and the risk of developing prostate cancer. Am J Epidemiol 157:335–344, 2003.
17. Nomura AMY, Stemmermann GN, Lee J, Craft NE: Serum micronutrients and prostate cancer in Japanese Americans in Hawaii. Cancer Epidemiol Biomarkers Prev 6:487–491, 1997.
18. Gann PH, Ma J, Giovannucci E, Willett W, Sacks FM, Hennekens CH, Stampfer MJ: Lower prostate cancer risk in men with elevated plasma lycopene levels: results of a prospective analysis. Cancer Res 59:1225–1230, 1999.
19. Nomura AMY, Ziegler RG, Stemmermann GN, Chyou P-H, Craft NE: Serum micronutrients and upper aerodigestive tract cancer. Cancer Epidemiol Biomarkers Prev 6:407–412, 1997.
20. Kushi LH, Folsom AR, Prineas RJ, Mink PJ, Wu Y, Bostick RM: Dietary antioxidant vitamins and death from coronary heart disease in postmenopausal women. N Engl J Med 334:1156–1162, 1996.
21. Rimm EB, Stampfer MJ, Ascherio A, Giovannucci EL, Colditz GA, Willett WC: Vitamin E consumption and the risk of coronary heart disease in men. N Engl J Med 328:1450–1456, 1993.
22. Stampfer MJ, Hennekens CH, Manson JE, Colditz GA, Rosner B, Willett WC: Vitamin E consumption and the risk of coronary disease in women. N Engl J Med 328:1444–1449, 1993.
23. Yochum LA, Folsom AR, Kushi LH: Intake of antioxidant vitamins and risk of death from stroke in postmenopausal women. Am J Clin Nutr 72:476–483, 2000.
24. Hu FB, Stampfer MJ, Manson JE, Rimm EB, Wolk A, Colditz GA, Hennekens CH, Willett WC: Dietary intake of alpha-linolenic acid and risk of ischemic heart disease among women. Am J Clin Nutr 69:890–897, 1999.
25. Ascherio A, Rimm EB, Giovannucci EL, Spiegelman D, Stampfer MJ, Willett WC: Dietary fat and risk of coronary heart disease in men: cohort follow up study in the United States. Br Med J 313:84–90, 1996.
26. Himmelfarb J, Kane J, McMonagle E, Zaltas E, Bobzin S, Boddupalli S, Phinney S, Miller G: Alpha and gamma tocopherol metabolism in healthy subjects and patients with end-stage renal disease. Kidney Int 64:978–991, 2003.
27. Dietrich M, Block G, Hudes M, Morrow JD, Norkus EP, Traber MG, Cross CE, Packer L: Antioxidant supplementation decreases lipid peroxidation biomarker F2-isoprostanes in plasma of smokers. Cancer Epidemiol Biomark Prev 11:7–13, 2002.
28. Dietrich M, Block G, Benowitz NL, Morrow JD, Hudes M, Jacob P, Norkus EP, Packer L: Vitamin C supplementation decreases oxidative stress biomarker F2-isoprostanes in plasma of nonsmokers exposed to environmental tobacco smoke. Nutr Cancer 45:176–184, 2003.
29. Huang H-Y, Appel LJ: Supplementation of diets with α-tocopherol reduces serum concentrations of γ- and δ-tocopherol in humans. J Nutr 133:3137–140, 2003.
30. Leonard SW, Paterson E, Atkinson JK, Ramakrishnan R, Cross CE, Traber MG: Studies in humans using deuterium-labeled alpha- and gamma-tocopherol demonstrate faster plasma gamma-tocopherol disappearance and greater gamma-metabolite production. Free Rad Biol Med 38:857–866, 2005.
31. Min KC, Kovall RA, Hendrickson WA: Crystal structure of human alpha-tocopherol transfer protein bound to its ligand: Implications for ataxia with vitamin E deficiency. Proc Natl Acad Sci USA 100:14713–14718, 2003.

Received April 18, 2006; revision accepted June 21, 2006.