Population-based study of α- and γ-tocopherol in plasma and adipose tissue as biomarkers of intake in Costa Rican adults[1–3]

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ABSTRACT

Background: γ-Tocopherol is the most abundant form of vitamin E in the US diet, but α-tocopherol concentrations are the highest in plasma and tissues. Although plasma and adipose tissue concentrations of α-tocopherol have been used as biomarkers of intake, the relation between γ-tocopherol intake and concentrations in plasma and adipose tissue is unknown.

Objective: Our goal was to investigate in a randomly selected population from Costa Rica whether plasma or adipose tissue concentrations of α- and γ-tocopherol are suitable biomarkers of intake.

Design: A total of 361 men ($\bar{x}$ ± SD age: 55 ± 11 y) and 121 women (aged 59 ± 10 y) completed a 135-item food-frequency questionnaire and provided a fasting blood sample and adipose tissue biopsy sample.

Results: Dietary γ-tocopherol correlated with adipose tissue ($r = 0.37$, $P < 0.001$) and plasma ($r = 0.42$, $P < 0.001$) concentrations, regardless of supplement use. Dietary α-tocopherol correlated poorly with adipose tissue ($r = 0.15$, $P < 0.01$) and plasma ($r = 0.16$, $P < 0.001$) concentrations, and these correlations were even lower when users of vitamin supplements ($n = 24$) were excluded (adipose tissue: $r = 0.10$, $P < 0.05$; plasma: $r = 0.09$, $P < 0.05$). Compared with subjects who reported palm shortening (36%) as the major type of fat used for cooking, subjects using soybean oil (52%) had higher amounts of both α- and γ-tocopherol in their diets. However, only γ-tocopherol concentrations were higher in the plasma and adipose tissue of soybean oil users.

Conclusions: Plasma and adipose tissue concentrations of γ-tocopherol are equally good biomarkers of intake. The weak associations between α-tocopherol intake and plasma or adipose tissue concentrations suggest that these biomarkers are influenced more by factors other than α-tocopherol intake. *Am J Clin Nutr* 2001;74:356–63.

KEY WORDS Vitamin E, biomarkers, α-tocopherol, γ-tocopherol, adipose tissue, α-tocopherol transfer protein, food-frequency questionnaire, Hispanics, Costa Rica

INTRODUCTION

The results of several studies suggest that vitamin E may protect against the development of coronary artery disease (1–5). It is not clear, however, whether protection can be conferred by vitamin E derived from foods or only by use of vitamin supplements (6). Most studies relating vitamin E to coronary artery disease focused on α-tocopherol, the most biologically active form of vitamin E and the one used in supplements. Food sources of vitamin E (mostly oils), however, include a variety of other tocopherols and tocotrienols (α, β, γ, and δ), the content of which varies considerably depending on the type and brand of oil (7). γ-Tocopherol is the most abundant form of vitamin E in the US diet, has approximately one-half the antioxidant activity of α-tocopherol (8), and can affect the metabolism of α-tocopherol (9, 10). Moreover, γ-tocopherol inhibits peroxynitrite-induced lipid peroxidation more effectively than does α-tocopherol by forming stable carbon-centered adducts through the nucleophilic 5-position, which is blocked in α-tocopherol (11).

Plasma concentrations of α-tocopherol correlate with intakes of vitamin E (12–15), although this association is significant only when users of vitamin supplements are included in the analysis (12–14). Adipose tissue concentrations of α-tocopherol are also sensitive to dietary changes (16). Nevertheless, the response to dietary modification is much slower in adipose tissue (>2 y to reach steady state) (17) than in plasma (1–2 d) (18). The slow turnover rate in adipose tissue suggests that adipose tissue vitamin E may be a better marker of long-term intake and the preferred biomarker in case-control studies (19). About 90% of vitamin E is contained in adipose tissue (20). One study showed that the relation between total dietary vitamin E and adipose tissue concentrations of α-tocopherol in subjects not taking vitamin supplements is relatively low ($r = 0.20$) (21), whereas there are no data from population studies of the relation between dietary γ-tocopherol and adipose tissue concentrations.

In addition to the variation in food sources, the bioavailability of tocopherols may depend on genetic differences in absorption and metabolism (22, 23). Future epidemiologic studies on gene-diet interactions will likely provide further insights into the role

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of vitamin E in coronary artery disease (24). But, because of the large number of subjects required for these studies, case-control study designs would be more suitable (25). However, differential recall between cases and controls may bias the results when dietary questionnaires are used retrospectively to assess intake (26). Thus, there is a need to establish reliable biomarkers of long-term intake. In this report, we examine the relation between dietary intake and plasma and adipose tissue concentrations of the 2 major forms of vitamin E, α- and γ-tocopherol, to determine whether these concentrations are suitable biomarkers.

SUBJECTS AND METHODS

Study population

Participants in this study were the 531 control subjects from a case-control study of diet and heart disease in Costa Rica. The control subjects were randomly selected from the greater metropolitan area of San José and the surrounding 18 counties by using the national census information available at the National Census and Statistics Bureau of Costa Rica. Subjects were visited at their homes for recruitment and data collection and 90% of those selected participated. Subjects were ineligible if they reported a past diagnosis of myocardial infarction or if they were physically or mentally unable to answer the questionnaire because of a stroke or other serious illness. The total study area comprised 2225 km^2 and 1 092 000 persons who were ethnically Mestizo, as a result of 4 centuries of racial tripartite mixing (white-Indian-black), and culturally Hispanic American (27). All subjects gave informed consent and the study was approved by the Ethics Committee of the Harvard School of Public Health and the National Institute of Health Research at the University of Costa Rica.

Data collection

Data collection included a general questionnaire consisting of closed-ended questions regarding sociodemographic characteristics, smoking history, socioeconomic status, and medical history (including personal history of diabetes and hypertension). Self-reported diabetes and hypertension were validated by using the recommended definitions of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus (28) and the Third Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure (29). Anthropometric measurements were collected by trained fieldworkers while subjects wore light clothing and no shoes.

Dietary assessment

Dietary information was obtained by using a 135-item semiquantitative food-frequency questionnaire (FFQ) that was a modification of the Willett questionnaire (30) and was developed specifically for use in Costa Rica (31). This FFQ inquires about the intake of 135 food items; intake of 20 vitamin, mineral, and food supplements; types of fats used for cooking and frying; consumption of fried foods in and away from home; and food habits related to meat preparation during the past year. Energy and nutrient intakes were estimated from the US Department of Agriculture food-composition tables at the Channing Laboratory, as described previously (30). Subjects selected only one type of fat or oil that was used most frequently for cooking at home. The questionnaire was administered by trained interviewers. We carried out a validation study in which we compared this FFQ with 7-d, 24-h recalls in a subset of 120 subjects. For reproducibility, a second FFQ was administered 1 y after the first interview. The Pearson partial correlation coefficients for α- and γ-tocopherol between the average of the 2 FFQs and the mean of the 7-d, 24-h recalls were 0.48 and 0.29, respectively, and were 0.64 and 0.66 between the first and the second FFQ. The Costa Rican FFQ was also validated for cholesterol and fatty acid intakes by its ability to predict plasma lipids and apolipoproteins (31). The average macronutrient intakes assessed by this FFQ were also similar to the average intakes assessed by 24-h recall in the National Nutrition Survey in Costa Rica (31).

Biochemical analyses

Anthropometric measurements were made and biological specimens were collected in the morning at the subject's home after the subject had fasted overnight. A subcutaneous adipose tissue biopsy sample was collected from the upper buttock with a 16-gauge needle and disposable syringe following procedures previously described (32). Blood samples were collected in tubes containing 0.1% EDTA. Both samples were stored in a cooler with ice packs at 4 °C and transported to the fieldwork station within 4 h. Blood was centrifuged at 1430 × *g* for 20 min at 4 °C to separate the plasma. Adipose and plasma were stored at −80 °C and within 6 mo were transported on dry ice to the Harvard School of Public Health for analysis. The average yield of adipose tissue was 38 ± 33 mg ($\bar{x}$ ± SD).

Concentrations of α- and γ-tocopherol were measured by HPLC with use of a dual-wavelength Hitachi (San Jose, CA) HPLC system and data station (33). The L-4200 detector was set at a wavelength of 300 nm and injections were performed by the programmable AS-4000 autosampler. A single large sample of adipose tissue was used for between-run analytic variations. One adipose tissue aliquot from the core of the sample with similar weight to that of most of the unknown samples (20–60 mg) was included in every run. Every run also included one plasma pool sample. The CVs for adipose tissue α- and γ-tocopherol were 20.4% and 17.8%, respectively; those for plasma α- and γ-tocopherol were 9.4% and 10.1%, respectively. The minimum detection limits for α- and γ-tocopherol in a 30-mg adipose tissue sample were 1.19 and 1.72 μg/g, respectively. Plasma triacylglycerol, cholesterol, and HDL-cholesterol concentrations were measured by using enzymatic reagents (Boehringer Mannheim, Indianapolis) and a Cobas Mira Plus autoanalyzer (Roche Diagnostic Systems, Somerville, NJ). LDL cholesterol was calculated by using the Friedewald equation (34). Cholesterol measurements in our laboratory are standardized according to the program for research laboratories specified by the Centers for Disease Control and Prevention–National Heart, Lung, and Blood Institute.

Statistical analyses

All data were analyzed by using the SAS software package (version 8; SAS Institute Inc, Cary, NC). Of the 531 subjects recruited, those with missing or insufficient (<1 mg) adipose tissue samples for tocopherol analysis, those with missing plasma samples, or those missing both were excluded (n = 49). The final sample size of 482 subjects consisted of 361 men ($\bar{x}$ ± SD age: 56 ± 11 y) and 121 women (aged 60 ± 10 y). Spearman correlations and Wilcoxon's rank-sum tests were used to identify associations between tocopherol values and potential confounders. Where indicated, subjects taking vitamin E (α-tocopherol) supplements (n = 24) were excluded from the analysis. Intakes of

TABLE 1
General characteristics and dietary profile of the study population

Variable	Men (n = 361)	Women (n = 121)
Age (y)	56 ± 11[1]	60 ± 10[2]
Weight (kg)	71.1 ± 13.3	61.6 ± 10.9[2]
BMI (kg/m^2)	25.5 ± 4.0	26.1 ± 4.5
Waist-to-hip ratio	0.96 ± 0.06	0.87 ± 0.07[2]
Plasma triacylglycerol (mmol/L)	2.41 ± 1.38	2.27 ± 1.09
Plasma cholesterol (mmol/L)	5.14 ± 1.02	5.35 ± 1.02
HDL cholesterol (mmol/L)	1.03 ± 0.27	1.23 ± 0.33[2]
Diabetes (%)	8	21[2]
Hypertension (%)	23	37[3]
Angina (%)	4	8[4]
Smoking status (%)[5]		
Never smoker	21	74
Past smoker	45	17
Current smoker (<10 cigarettes/d)	16	5
Current smoker (≥10 cigarettes/d)	18	4
Energy intake (MJ/d)	10.10 ± 3.08	8.90 ± 2.40[2]
Total fat (% of energy)	33.1 ± 6.0	34.3 ± 6.2
Saturated (% of energy)	11.6 ± 2.8	12.3 ± 2.9[4]
Monounsaturated (% of energy)	12.3 ± 3.3	12.8 ± 3.9
Polyunsaturated (% of energy)	5.6 ± 1.5	5.5 ± 1.4
Protein (% of energy)	13.4 ± 2.4	13.9 ± 3.1
Carbohydrate (% of energy)	54.0 ± 8.1	54.8 ± 7.7
Dietary fiber (g/d)	24.7 ± 9.4	25.0 ± 9.9
Cholesterol (mg/d)	305 ± 178	252 ± 140
Vitamin E supplement users (%)	3.9	8.3

[1] $\bar{x}$ ± SD.
[2–4] Significantly different from men: [2] $P < 0.001$, [3] $P < 0.01$, [4] $P < 0.05$.
[5] Chi-square test of the overall distribution, $P < 0.001$.

tocopherols were adjusted for energy by calculating the residuals from regressing log dietary tocopherol amounts on total energy intake (19). Log plasma tocopherol concentrations were regressed on plasma triacylglycerol. Adjusting for total plasma cholesterol instead of plasma triacylglycerol gave similar results. Partial Spearman correlation coefficients adjusted for age, sex, body mass index (BMI; in kg/m^2), and smoking were calculated to determine associations between dietary, plasma, and adipose tissue tocopherol amounts. We calculated 95% CIs by using Fisher's z transformation. Multiple linear regression models were used to compare values between men and women and least-squares means were used to adjust for confounders.

Multiple linear regression models were also used to test for trends across quintiles and to compare the average values between quintiles. Test for trends were computed by assigning the median value of the corresponding quintile to each subject and entering that variable as a continuous one in the model. Robust estimators of the variance were used in regression models (35), thus eliminating the need for normalizing the dependent variable in the models described above. Analysis of variance with Bonferroni's adjustment for multiple comparisons was used to compare average α- and γ-tocopherol amounts in the diet, plasma, and adipose tissue between users of the different types of cooking oils or fats. The frequency of users of the different types of oils or fats within quintiles of plasma and adipose tissue tocopherols was compared by using the chi-square test. These analyses did not include oils used as salad dressing or the use of butter or margarine as spreads.

RESULTS

The general characteristics and macronutrient intakes of the study participants are shown in **Table 1**. Men were more likely to smoke than were women and had significantly higher energy intakes.

The values for dietary, plasma, and adipose tissue α- and γ-tocopherol in men and women are shown in **Table 2**. Intakes of α-tocopherol did not differ significantly between men and women, but women had higher plasma and adipose tissue concentrations than did men. Adipose tissue concentrations of γ-tocopherol were also greater in women than in men, although no significant differences in intake or plasma concentrations were observed. Adjustment for age, smoking, or BMI had no significant effect on any of the values in men and women.

Partial Spearman correlation coefficients between dietary, plasma, and adipose tissue tocopherols adjusted for age, sex, BMI, and smoking are shown in **Table 3**. Dietary α-tocopherol correlated poorly with plasma (r = 0.16) and adipose tissue (r = 0.15) concentrations. When supplement users were excluded, both correlations were attenuated. Plasma and adipose tissue concentrations of α-tocopherol were significantly correlated (r = 0.27), and this correlation did not change materially when supplement users were excluded. Dietary γ-tocopherol correlated with both plasma (r = 0.42) and adipose tissue (r = 0.37) concentrations. The strongest correlation was observed between plasma and adipose tissue concentrations of γ-tocopherol (r = 0.45).

TABLE 2
Amounts of α- and γ-tocopherol in the diet, plasma, and adipose tissue of subjects[1]

	α-Tocopherol		γ-Tocopherol	
	Men (n = 347)	Women (n = 111)	Men (n = 347)	Women (n = 111)
Diet (mg/d)				
Energy adjusted	8.7 ± 0.2	9.7 ± 0.6	13.8 ± 0.4	13.9 ± 0.7
Multivariate adjusted[2]	8.6 ± 0.3	9.2 ± 0.6	13.4 ± 0.4	13.0 ± 0.8
Plasma (μmol/L)				
Triacylglycerol adjusted	28.6 ± 0.4	31.8 ± 0.8[3]	2.7 ± 0.1	2.7 ± 0.1
Multivariate adjusted[2]	28.2 ± 0.4	30.9 ± 1.1[3]	2.7 ± 0.1	2.6 ± 0.1
Adipose tissue (μg/g)				
Crude	82.9 ± 3.0	123.1 ± 6.6[3]	18.1 ± 0.6	20.9 ± 1.2[3]
Multivariate adjusted[2]	79.5 ± 3.2	118.7 ± 7.3[3]	18.1 ± 0.7	20.9 ± 1.4

[1] $\bar{x}$ ± SEM for subjects not taking vitamin supplements.
[2] Adjusted for age, smoking, and BMI.
[3] Significantly different from men, $P < 0.05$.

TABLE 3
Partial Spearman correlation coefficients (and 95% CIs) between dietary, plasma, and adipose tissue α- and γ-tocopherol[1]

	α-Tocopherol		γ-Tocopherol	
	Plasma	Adipose tissue	Plasma	Adipose tissue
α-Tocopherol				
Diet				
All subjects	0.16 (0.07, 0.25)	0.15 (0.06, 0.24)	0.24 (0.15, 0.32)	0.25 (0.16, 0.33)
Excluding supplement users	0.09 (0.00, 0.19)	0.10 (0.01, 0.19)	0.27 (0.19, 0.36)	0.25 (0.16, 0.34)
Plasma				
All subjects		0.27 (0.19, 0.35)		0.05 (−0.04, 0.14)
Excluding supplement users		0.26 (0.17, 0.34)		0.07 (−0.02, 0.16)
γ-Tocopherol				
Diet				
All subjects	−0.03 (−0.12, 0.06)	0.08 (−0.01, 0.17)	0.42 (0.34, 0.49)	0.37 (0.29, 0.45)
Excluding supplement users	−0.06 (−0.15, 0.04)	0.04 (−0.05, 0.13)	0.43 (0.35, 0.50)	0.37 (0.28, 0.44)
Plasma				
All subjects		0.07 (−0.02, 0.16)		0.45 (0.38, 0.52)
Excluding supplement users		0.08 (−0.01, 0.17)		0.44 (0.36, 0.51)

[1] Values are adjusted for age, sex, BMI, and smoking, for all subjects (n = 482) and excluding supplement users (n = 458). Dietary values were adjusted for energy and plasma values were adjusted for plasma triacylglycerol.

None of the correlations with γ-tocopherol changed materially when users of vitamin E supplements (n = 24) were excluded. We also examined the correlations between α- and γ-tocopherol within the diet, plasma, and adipose tissue. In all subjects, α-tocopherol correlated with γ-tocopherol in the diet (r = 0.40), plasma (r = 0.20), and adipose tissue (r = 0.58). When supplement users were excluded, these correlations did not change considerably (0.39, 0.25, and 0.58, respectively).

We next determined whether concentrations of α- and γ-tocopherol in plasma or adipose tissue could be used to discriminate between individuals with different intakes. Results are shown for all subjects and for subjects not taking vitamin E supplements. The average concentrations and 95% CIs of plasma and adipose tissue γ-tocopherol within each quintile of dietary γ-tocopherol intake are shown in **Figure 1**. A significant trend was observed across quintiles of intake for both plasma and adipose tissue concentrations. Excluding users of vitamin E supplements had no significant effect on this result. Plasma concentrations of γ-tocopherol appeared to be more sensitive to differences in intake at low intakes, whereas the adipose tissue concentration appeared to be a better discriminator of subjects with high intakes.

The associations between dietary α-tocopherol and plasma and adipose tissue concentrations of α-tocopherol are shown in **Figure 2**. When users of vitamin E supplements were included, there was a significant trend across quintiles of intake for both plasma and adipose tissue. This significant trend was mainly attributable to those in the highest quintile. When supplement users were excluded, the trend remained significant but neither plasma nor adipose tissue concentrations of α-tocopherol discriminated between those in the lowest and highest quintiles of intake. Therefore, plasma and adipose tissue concentrations of α-tocopherol are not sensitive to the small differences in intake within the range consumed in this population.

Because vegetable oils can be a major source of vitamin E (7), the frequencies of users of the different types of oil or fat were compared within each quintile of plasma and adipose tissue

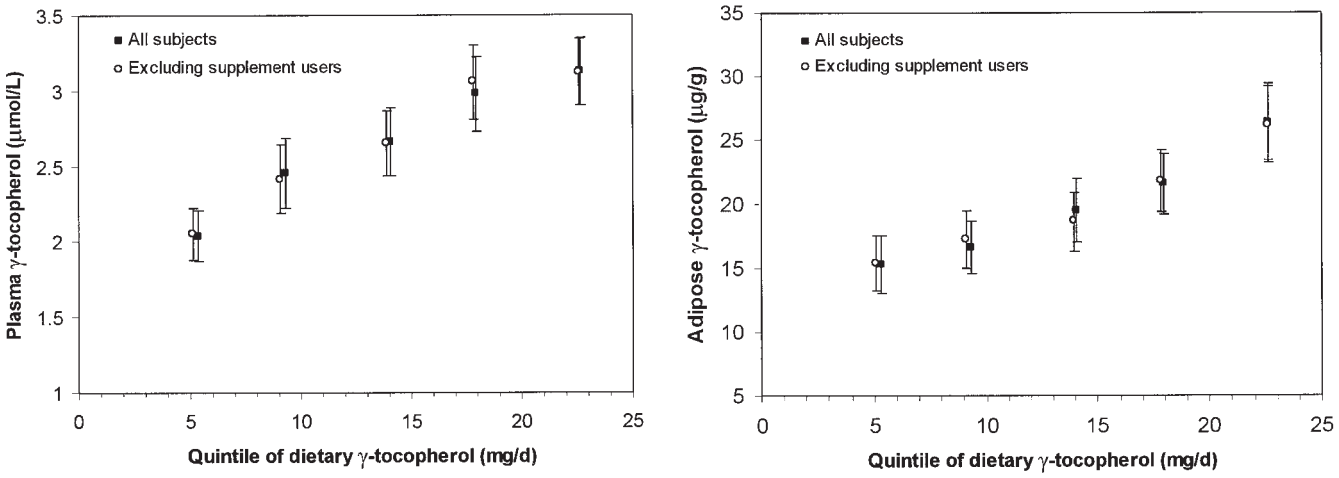

FIGURE 1. Concentrations of γ-tocopherol in plasma and adipose tissue by quintile of dietary γ-tocopherol intake. Data are presented for all subjects and excluding users of vitamin supplements (n = 24). Values are the mean ± 95% CI plotted against the median value for each quintile. P for trend for both plasma and adipose tissue, with and without supplement users: <0.001.

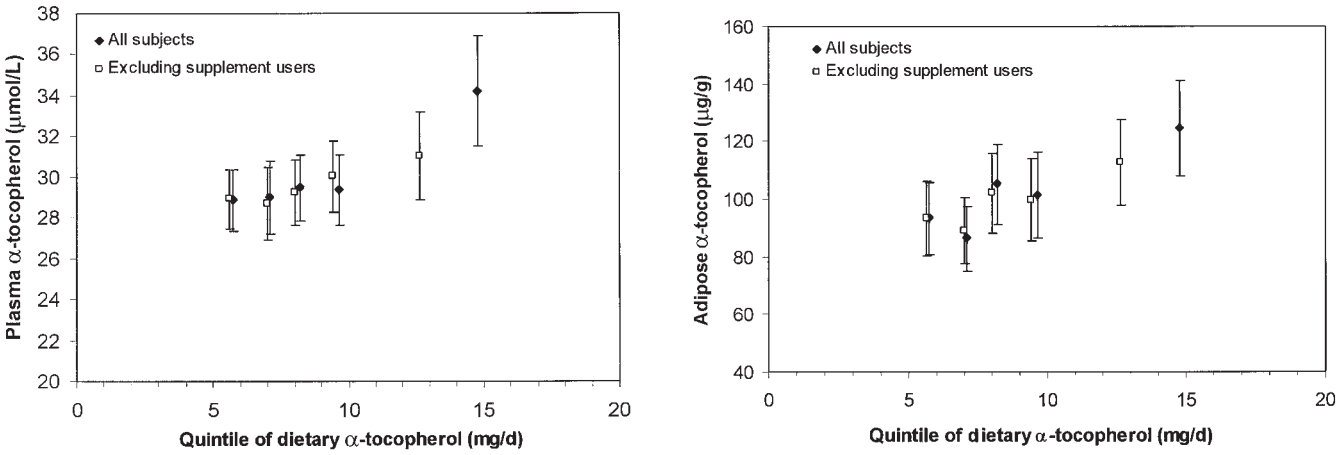

FIGURE 2. Concentrations of α-tocopherol in plasma and adipose tissue by quintile of dietary α-tocopherol intake. Data are presented for all subjects and excluding users of vitamin supplements ($n = 24$). Values are the mean ± 95% CI plotted against the median value for each quintile. P for trend: <0.001 (all subjects, plasma and adipose tissue), <0.03 (excluding supplement users, plasma), <0.01 (excluding supplement users, adipose tissue).

tocopherols. The 3 major types of oils or fats used for cooking and frying were soybean oil (50%), palm shortening (36%), and corn oil (10%). The other types of oil used by the remaining 4% of the population were canola, olive, and sunflower oils. Subjects in the lowest quintile of plasma γ-tocopherol concentrations were more likely to use palm shortening (82%) than soybean oil (12%), whereas the opposite was observed in the highest quintile (11% and 77%, respectively) (**Figure 3**). Similarly, in the lowest quintile of adipose tissue γ-tocopherol concentrations, 70% of the subjects used palm shortening and 25% used soybean oil, whereas in the highest quintile, 17% used palm shortening and 69% used soybean oil. No associations were observed between the type of oil or fat used for cooking and the frequency of users within each quintile of plasma or adipose tissue α-tocopherol concentrations (**Figure 4**).

Shown in **Table 4** are the average amounts of α- and γ-tocopherol in the diet, plasma, and adipose tissue by type of oil used for cooking, excluding users of vitamin E supplements. As expected from the nutrient compositions, users of corn oil had the highest dietary α-tocopherol intake, followed by users of soybean oil and palm shortening. However, no significant differences in plasma or adipose tissue concentrations of α-tocopherol were observed among the users of the different types of oil. Compared with users of palm shortening, users of soybean and corn oils had significantly higher amounts of γ-tocopherol in their diet, plasma, and adipose tissue. Thus, users of vegetable oils that are rich in γ-tocopherol have higher γ-tocopherol concentrations in their plasma and adipose tissue. Higher α-tocopherol intake from corn oil was not associated with α-tocopherol concentrations in plasma and adipose tissue.

DISCUSSION

Our findings show that plasma and adipose tissue provide better biomarkers of intake for γ-tocopherol than for α-tocopherol. This difference could be explained by the ability of α-tocopherol transfer protein (α-TTP) to discriminate between these 2 major forms of vitamin E in the liver, suggesting that plasma concentrations of

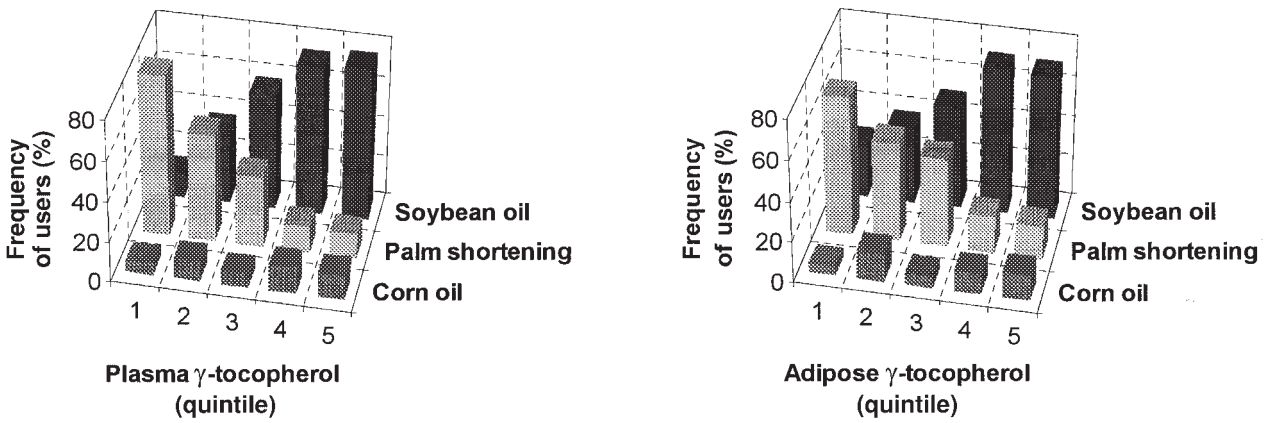

FIGURE 3. Distribution of subjects who reported using soybean oil, palm shortening, or corn oil as the major source of cooking fat, by quintile of γ-tocopherol concentration in plasma and adipose tissue. Subjects taking vitamin supplements were excluded. The frequency of users of each type of oil or fat within each quintile was compared by chi-square test. For both plasma and adipose tissue, users of palm shortening were more likely to be in the lowest quintile, whereas users of soybean oil were more likely to be in the highest quintile, $P < 0.05$.

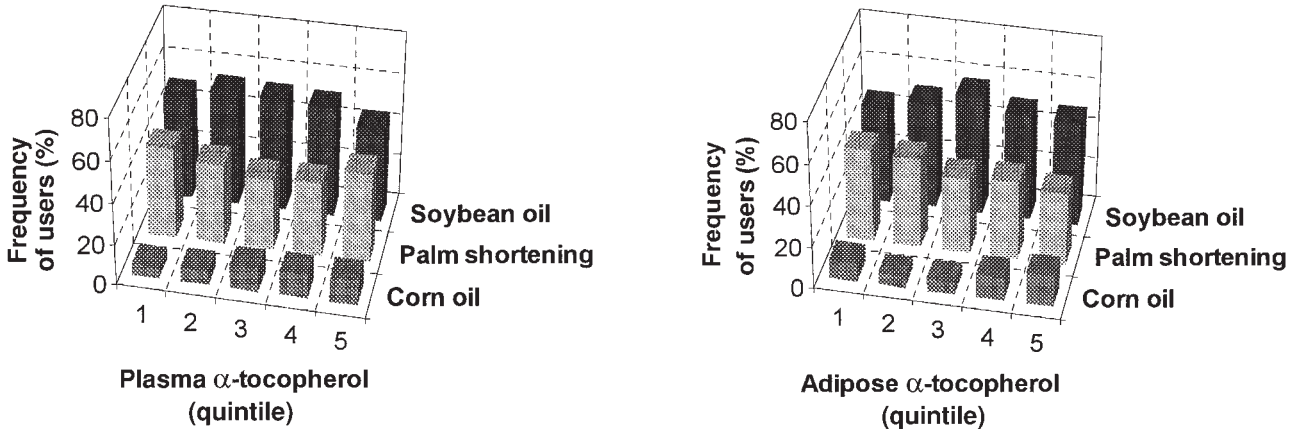

FIGURE 4. Distribution of subjects who reported using soybean oil, palm shortening, or corn oil as the major source of cooking fat, by quintile of α-tocopherol concentration in plasma and adipose tissue. Subjects taking vitamin supplements were excluded. The frequency of users of each type of oil or fat within each quintile was compared by chi-square test. There were no significant differences.

α-tocopherol are more highly regulated and may not reflect differences in intake. The average daily intake of α-tocopherol in the Costa Rican population is similar to values previously reported for other populations (36, 37) and to the recommended dietary allowances of vitamin E for men (10 mg/d) and women (8 mg/d) set by the Food and Nutrition Board of the National Research Council (38).

The associations between intakes of γ-tocopherol and plasma concentrations were previously examined only in small numbers of subjects fed defined diets (39, 40), and no study previously compared intake with adipose tissue concentrations. In one study in which subjects were fed varying amounts of α- and γ-tocopherol, the plasma concentrations of γ-tocopherol increased with dietary intake after 12 h, whereas the concentrations of α-tocopherol did not (39). This observation is consistent with our data showing that plasma concentrations of γ-tocopherol reflect different intake, whereas α-tocopherol concentrations do not. In a more recent study, subjects were fed diets that contained ≈20 mg α-tocopherol/d and either 2 or 100 mg γ-tocopherol/d for 2 wk (40). This 5-fold difference in γ-tocopherol intake was associated with a marked difference in plasma concentrations of γ-tocopherol, but only a small difference in plasma concentrations of α-tocopherol (40).

To our knowledge, the present study is the first to compare γ-tocopherol intake from a variety of foods assessed by an FFQ with γ-tocopherol concentrations in either plasma or adipose tissue. Dietary γ-tocopherol was significantly correlated with both plasma and adipose tissue concentrations. Because none of the vitamin supplements used by the study participants contained γ-tocopherol, it is not surprising that the correlations with γ-tocopherol were not altered when supplement users were excluded. In other studies, the use of vitamin supplements containing α-tocopherol was shown to decrease the concentration of γ-tocopherol in plasma (41, 42) and adipose tissue (17). In the present study, however, dietary α-tocopherol was positively correlated with γ-tocopherol in plasma and adipose tissue. The inverse association between dietary α-tocopherol and plasma γ-tocopherol observed by others appears to be due to those subjects taking vitamin supplements (13, 43).

Vitamin E intake is not correlated with plasma concentrations of α-tocopherol when vitamin supplements are excluded (12–15). Consistent with these findings, we found a small correlation between dietary and plasma α-tocopherol ($r = 0.16$) that became even smaller ($r = 0.09$) when supplement users were excluded. This smaller correlation may be due, at least in part, to the relatively narrow range of vitamin E intake from foods found in this and other studies (2–34 mg/d) (6). Nevertheless,

TABLE 4
Comparison between intake, plasma, and adipose tissue amounts of α- and γ-tocopherol in subjects reporting use of soybean oil, palm shortening, or corn oil as the major fat in cooking[1]

	Soybean oil ($n = 227$)	Palm shortening ($n = 173$)	Corn oil ($n = 41$)	ANOVA
Diet (mg/d)				
α-Tocopherol	8.8 ± 0.2[a]	7.4 ± 0.3[b]	13.2 ± 0.8[c]	<0.0001
γ-Tocopherol	17.9 ± 0.3[a]	7.6 ± 0.3[b]	17.5 ± 1.0[a]	<0.0001
Plasma (μmol/L)				
α-Tocopherol	28.5 ± 0.5	29.1 ± 0.6	31.7 ± 1.4	0.089
γ-Tocopherol	3.2 ± 0.1[a]	2.1 ± 0.1[b]	3.0 ± 0.2[a]	<0.0001
Adipose tissue (μg/g)				
α-Tocopherol	94.3 ± 4.2	85.4 ± 4.4	112.7 ± 11.0	0.048
γ-Tocopherol	22.1 ± 0.8[a]	13.7 ± 0.6[b]	21.3 ± 1.7[a]	<0.0001

[1] $\bar{x}$ ± SEM. Dietary values were adjusted for energy and plasma values were adjusted for triacylglycerol. Analysis includes only subjects who did not report intake of vitamin supplements (347 men and 111 women). Values in the same row with different superscript letters are significantly different, $P < 0.05$.

plasma α-tocopherol does not appear to be a reliable biomarker of dietary intake. Genetic differences in absorption and metabolism may contribute to the poor correlation between dietary and plasma α-tocopherol. Studies examining gene-diet interactions will likely provide a greater understanding of the large interindividual variations that have been reported (44, 45). For example, subjects with rare mutations in the *α-TTP* gene have extremely low plasma concentrations of α-tocopherol despite normal intakes (23). Polymorphisms in this or other genes may, therefore, be important determinants of the plasma response to dietary α-tocopherol.

Adipose tissue concentrations of fat-soluble vitamins have been proposed as biomarkers of intake (46), but few studies have examined the relation between dietary vitamin E and adipose tissue concentrations (16, 21, 36). In a study of a small number of subjects that included users of vitamin supplements, Schäfer and Overvad (16) showed that intakes of total tocopherols as assessed by a diet history interview were highly correlated ($r = 0.76$) with adipose tissue concentrations of total tocopherols. However, no distinction was made between α-tocopherol and γ-tocopherol in either the diet or adipose tissue. In the only study to examine subjects who were not taking vitamin supplements, intakes of vitamin E correlated with α-tocopherol concentrations in adipose tissue ($r = 0.24$), but not in plasma ($r = 0.05$) (21). Recently, a study of 125 men from Norway found no associations between intakes of α-tocopherol, as assessed by either a 180-item FFQ or 14-d weighed-food record, and the concentration of α-tocopherol in either adipose tissue or serum (36). Therefore, there is no clear evidence that adipose tissue α-tocopherol is a better biomarker of long-term intake than is plasma α-tocopherol.

Because of the many oil types and brands used by most populations for cooking, it has been difficult in epidemiologic studies to assess the contribution of different types of dietary fat to concentrations of tocopherol in plasma or adipose tissue. Most (96%) of the Costa Rican population was found to use either soybean oil (2 brands), palm shortening (1 brand), or corn oil (2 brands) for cooking and frying at home. Those who used soybean oil had significantly higher amounts of γ-tocopherol in their diet, plasma, and adipose tissue than did those who used palm shortening. Despite different intakes of α-tocopherol among the users of the different types of oil, no associations were observed between oil type and the concentration of α-tocopherol in either plasma or adipose tissue. This observation provides further evidence that plasma and adipose tissue concentrations of α-tocopherol, unlike γ-tocopherol, do not adequately reflect intake from food sources. Indeed, subjects taking a single dose of 1000 mg each of α- and γ-tocopherol showed a much greater relative increase in plasma concentrations of γ-tocopherol than in α-tocopherol (42). Furthermore, daily supplementation with 50 mg α-tocopherol for 3 y produced only a 40% increase in plasma concentrations (47), and daily supplementation with either 440, 880, or 1320 mg α-tocopherol for 28 d produced the same (≈80%) increase in plasma concentrations (45). Thus, plasma and adipose tissue concentrations of γ-tocopherol appear to be more responsive to changes in dietary intake than the corresponding concentrations of α-tocopherol.

In summary, both plasma and adipose tissue concentrations of γ-tocopherol are equally good biomarkers of γ-tocopherol intake. The low correlations between dietary α-tocopherol and plasma or adipose tissue concentrations make these biomarkers poor predictors of intake. Although most studies relating vitamin E and chronic diseases have focused on α-tocopherol, recent studies suggest that γ-tocopherol may also play an important role (11, 48, 49). Future epidemiologic studies involving vitamin E should, therefore, include separate analyses of α- and γ-tocopherol. Furthermore, the differences we observed between α- and γ-tocopherol highlight the importance of validating studies that use biomarkers to investigate the role of diet in the development of chronic diseases.

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