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Vitamin E intake and Risk of Esophageal and Gastric Cancers in the NIH-AARP Diet and Health Study

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Abstract

We investigated the association of dietary α-tocopherol, γ-tocopherol, and supplemental vitamin E intake with the risk of esophageal squamous cell carcinoma (ESCC; n = 158), esophageal adenocarcinoma (EAC; n = 382), gastric cardia adenocarcinoma (GCA; n = 320), and gastric noncardia adenocarcinoma (GNCA; n = 327) in the NIH-AARP Diet and Health Study, a cohort of approximately 500,000 people. Data on dietary and supplemental vitamin E intake were collected using a validated questionnaire at baseline and were analyzed using Cox regression models. Intakes were analyzed as continuous variables and as quartiles.

For dietary α-tocopherol, we found some evidence of association with decreased ESCC and increased EAC risk in the continuous analyses, with adjusted hazard ratios (HR) and 95% confidence intervals (CI) of 0.90 (0.81 – 0.99) and 1.05 (1.00 – 1.11), respectively, per 1.17 mg (half the interquartile range) increased intake. However, in quartile analyses, the p-value for trend was non-significant for both of these cancers. There was no association between dietary α-tocopherol and GCA or GNCA. We observed no statistically significant associations with γ-tocopherol. For supplemental vitamin E, the results were mainly null, except for a significantly lower risk of GNCA with higher doses of supplemental vitamin E. An increase of 71 mg/day (half the interquartile range) in supplemental vitamin E had an HR (95% CI) of 0.92 (0.85–1.00) and the p-value for trend in the quartile analyses was 0.015.

Background

Upper gastrointestinal tract cancers, including esophageal and gastric cancers, cause over one million deaths worldwide each year.1 Nutritional factors may play an important role in the etiology of esophageal and gastric cancers. Higher intake of antioxidant vitamins, including vitamin A, vitamin E and carotenoids, may protect against cancer development. Vitamin E from foods and supplements may have different effects on the development of cancer, because of the differences in dose, bioavailability, and correlated intake of other nutritional factors, so it is useful to study their effects separately.

Prospective studies are essential in evaluating the role of nutritional factors in the etiology of cancers, because a diagnosis of cancer may systematically alter the retrospective reporting of

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diet prior to diagnosis. However, most prospective studies evaluating the role of vitamin E or other nutritional risk factors in the etiology of upper gastrointestinal tract cancers have had small numbers of cases, and results are often reported for aggregates of cancers at different sites and of different histologic types, which may obscure the results. Therefore, most of the previous prospective studies have not been sufficiently powered to examine nutritional associations in subtypes of esophageal or gastric cancer. In fact, the recent World Cancer Research Fund-American Institute for Cancer Research (WCRF-AICR) report notes that the evidence the evidence regarding vitamin E and esophageal cancer is mostly from case-control studies and of poor quality, and the report does not comment on vitamin E and stomach cancer 2.

The National Institutes of Health-AARP (NIH-AARP) Diet and Health Study is a large prospective cohort study, conducted in the United States, with relatively large numbers of esophageal and gastric cancers and extensive data on food and nutrient intake. We used data available in this study to analyze the effects of dietary α-tocopherol, the most bioactive form of vitamin E, γ-tocopherol, the most commonly consumed form, and supplementary vitamin E intake on the four primary types of esophageal or gastric carcinoma: esophageal squamous cell carcinoma (ESCC), esophageal adenocarcinoma (EAC), gastric cardia adenocarcinoma (GCA), and gastric non-cardia adenocarcinoma (GNCA).

Materials and Methods

Study Population

The details of the design of the NIH-AARP Cohort Study have been described previously.3 This study was initiated in 1995–1996 with the mailing of a 16-page baseline questionnaire to 3.5 million members of the AARP, age 50 to 71, living in six states (California, Florida, Pennsylvania, New Jersey, North Carolina, and Louisiana) and two metropolitan areas (Atlanta, Georgia and Detroit, Michigan). The baseline questionnaire was returned by 617,119 people, of whom 566,402 respondents completed the questionnaire in satisfactory detail and consented to be in the study. Exclusions were made for response by proxy (n=15,760), self-report of prostate (n=10,640), breast (n=10,875), colon (n=4,584), or other cancers (n=23,219), cancer diagnoses or death before baseline (n=1,899), extreme calorie intake (n=4,999), or extreme α-tocopherol intake (n=1,867; ref 4), resulting in a final analytic cohort of 492,559 study participants (293,775 men and 198,784 women).

Cohort follow-up and case ascertainment

Cohort follow-up has been described previously.5 Follow-up time (person-years) extended from study baseline (between 1995 and 1996) to diagnosis of the first upper-gastrointestinal tract cancer (head and neck, esophageal, or stomach cancer, as a diagnosis of one of these cancers would be associated with increased surveillance of the other sites), date of death, end of study (December 31, 2003), or the date moved out of registry ascertainment area. Ending follow-up time at the first cancer diagnosis, regardless of site, reduced case numbers slightly but did not appreciably affect the results. Incident cases of cancer were identified by linkage between the NIH-AARP cohort membership and eleven state cancer registry databases (8 states from baseline together with Arizona, Nevada, and Texas) each of which has been certified by the North American Association of Central Cancer Registries for meeting the highest standards of data quality. The estimated sensitivity and specificity of case identification using this methodology is about 90%.5

We used International Classification of Disease for Oncology (ICD-O), third edition for case definition. Tumors with ICD-O codes 15.0 – 15.9 were classified as esophageal cancer. Only esophageal tumors with diagnosis of EAC or ESCC were included for this analysis; other

histologies were excluded (n=24). Tumors with ICD-O code 16.0 were classified as gastric cardia cancers, and those with codes 16.1 – 16.9 were classified as gastric noncardia cancers. Cases that were reported as gastric adenocarcinoma without location information were treated as GNCA; non-adenocarcinomas were excluded.

Assessment of vitamin E intake

Our methods for the assessment of intake 4 and the validity of the questionnaire 6 have been described previously. The dietary component of the baseline questionnaire asked aboutthe frequency of consumption and corresponding portion sizesof 124 food items during the past 12 months. There were specificquestions on the consumption of nuts and seeds, salad dressing, butter, margarine, fats, and oils, which are major dietary sourcesof vitamin E. In addition, those who reported regular use of oil to fry or saute vegetables, eggs, or meat were askedabout the kinds of oils used, including corn, olive, safflower, sunflower, and canola. Daily dietary intakes of α- and γ-tocopherol were estimated using the method of Subarand colleagues,7 linking food codes from the U.S. Department ofAgriculture's 1994 to 1996 Continuing Survey of Food Intakeby Individuals (CSFII) to those from the Nutrition Data Systemsfor Research (NDS-R, University of Minnesota). This databasecontains values for individualtocopherols for an extensive number of foods and brand nameproducts. The reliability of the food-frequency questionnairewas tested using two non-consecutive 24-h recalls in 1953 participants. For dietary α-tocopherol, the energy adjusted Pearson correlations between the FFQ and the 24-hour recalls for men and women, respectively, were 0.40 and 0.36.6 The top five contributors to α-tocopherol intake were ready-to-eatcereals, salad dressings, margarine and butter, nuts and seeds, and potato/corn/other chips. The top 5 contributors to γ-tocopherol intake were margarine and butter, salad dressings, fried potatoes, oils (predominantly corn), and cookies and brownies.

Estimates of nutrient intakes from supplements were calculatedseparately from those from food. The baseline questionnaire askedabout the frequency of use of three types of multivitamins (Stress-tabstype, Therapeutic or Theragran-type, and One-a-day type) andfive single nutrient supplements, including vitamin E. Therewere five possible response categories (never, <1 time perweek, 1–3 times per week, 4–6 times per week, or every day), and the following frequencies were assigned to each: 0, 1 perweek, 2 per week, 5 per week, and 7 per week. The dose of each single nutrient supplement was also ascertained. For vitamin E, the possible response categories were < 100,100 to 250, 300 to 500, ≥600 IU, or unknown, and the followingdoses were assigned to each corresponding category: 100, 200,400, and 800 IU (individuals who reported vitamin E supplementuse but did not provide dose information were assigned a default value of 400 IU). Dosage was not queried for multivitamins. Average daily supplemental vitamin E intake was calculated for eachsubject by adding the amount obtained from individual vitaminE supplements (daily frequency of use × dose) plus the amount from multivitamin pills (daily frequency of use × 30 IU, thestandard amount of vitamin E assigned to multivitamins basedon nationally representative data from the Third National Healthand Nutrition Examination Survey).8 Each 100 IU of vitamin E was treated as 45 mg of vitamin E. Information on durationof supplement use was not available. We did not combine dietary α-tocopherol or γ-tocopherol with supplemental vitaminE as a measure of total vitamin E intake, as the average amounts obtainedfrom supplements greatly exceeded the average amounts obtained fromfood.

Statistical Analysis

General characteristics are reported by quartiles of α-tocopherol intake. We report numbers and percents for all categorical variables, and median values and interquartile ranges for all continuous variables. Dietary α-tocopherol was calculated from the baseline questionnaire and was adjusted for total energy intake using the method of residuals.9

Hazard ratios (HRs) and 95% confidence intervals (95% CIs) were determined using Cox Proportional Hazard models, once adjusting only for baseline age and sex, and once for age, sex, smoking status and dose, education (as a proxy for socioeconomic status), physical activity, alcohol consumption, body mass index (BMI), race, and calories as categorized in table 1. In this latter model, dietary intake of α-tocopherol and γ-tocopherol were adjusted for supplemental vitamin E intake. We will refer to this latter model as fully adjusted. Additional adjustment for the intake of fruit, vegetables, red meat, and white meat did not materially affect risk estimates (data not shown).

Dietary α-tocopherol, γ-tocopherol, and supplemental vitamin E intake were analyzed both as continuous variables and as categorical variables. For continuous analyses we scaled the variables to one-half the interquartile range, 1.17 mg/day for dietary α-tocopherol, 3.11 for γ-tocopherol, and 71 mg/day for supplementary vitamin E. For categorical analyses, dietary α-tocopherol and γ-tocopherol were divided into empiric quartiles, while supplementary vitamin E was divided into four groups of 0, 1–179, 180–359, ≥360 mg/day. These categorizations were chosen for supplements because 180 mg is the most common vitamin E supplement dose in the country and in the cohort.

We stratified the models on sex and current smoking status (smoker vs. nonsmoker) to check for interactions. Tests using cross-product terms found no statistically significant interactions. We found no deviations from the proportional hazard assumption for dietary α-tocopherol, γ-tocopherol, or supplemental vitamin E for ESCC, EAC, and GCA. We did find a significant deviation for dietary α-tocopherol intake and GNCA (p=0.011), but not for supplemental vitamin E (p=0.851). To examine the effect of the non-proportionality, we divided follow-up into before and after the first one, two, or three years of follow-up and compared the associations in each period separately. Finally, some noncardia gastric tumors were classified as overlapping lesion of the stomach (ICD-O site code C16.8) or were gastric tumors not otherwise specified (ICD-O site code C16.9), and we included these tumors (N = 131) in the GNCA category, which raises the possibility that cardia cancers might be present in the noncardia category. However, excluding these subjects from the analysis did not appreciably change the risk estimates so these cancers were retained with the GNCA (results not shown).

All *P* values are two-sided and *P*-values < 0.05 were considered as statistically significant. All analyses were done using SAS, version 9.1 (SAS Institute, Cary, NC).

Results

Over eight years (3,544,970 person-years) of follow-up, 158 ESCC cases, 382 EAC cases, 320 GCA cases, and 327 GNCA cases were diagnosed. Table 1 shows the association of α-tocopherol intake with vitamin E supplement use and potential confounding factors. Compared to study participants in the first quartile of dietary α-tocopherol, participants in the fourth quartile were more likely to take higher doses of vitamin E supplements, be female, abstain from smoking, use less alcohol, be physically active, and possess at least an undergraduate college degree.

Table 2 shows HRs (95% CIs) for the associations between dietary α-tocopherol and supplemental vitamin E intake and risk of the four upper gastrointestinal cancers. When analyzed as a continuous variable, dietary α-tocopherol (per increase of 1.17 mg/day, or half the interquartile range) showed significant inverse associations with ESCC risk, both in the age- and sex-adjusted model and in the fully adjusted model. The HR (95% CI) for the fully adjusted model was 0.90 (0.81–0.99) which was much closer to null than the estimate for the age- and sex-adjusted model. The quartile analyses showed a statistically significant inverse

dose-response association between dietary α-tocopherol intake and ESCC risk in models adjusted for age and sex, but when fully adjusted, the estimate for the fourth compared to the first quartile was reduced to 0.90 (0.58–1.40) and the trend was no longer significant (P = 0.64). A borderline significantly increased risk of EAC was seen in the fully adjusted continuous model, 1.05 (1.00–1.11), and a non-significant but monotonically increasing risk was seen across quartiles. Although there were inverse associations between α-tocopherol intake and GCA risk in the age- and sex-adjusted models, these associations disappeared in the fully adjusted models.

While risk of GNCA was not associated with dietary α-tocopherol intake overall (Table 2), we observed differences in the results for cancers diagnosed at the beginning of follow-up and those in later years. When tested in the first one, two, or three years of follow-up, we found that higher dietary α-tocopherol intake significantly increased risk of GNCA. For example, there were 105 cases of GNCA diagnosed in the first two years and the fully adjusted HR (95% CI) for the continuous variable was 1.11 (1.03–1.20). In the remaining years of follow-up there were 222 cases of GNCA and the fully adjusted HR (95% CI) for the continuous variable was 0.95 (0.88–1.03).

We found no associations between higher doses of supplementary vitamin E and risk of esophageal cancer of either cell type. For GCA, the continuous estimate (per 71 mg/day, or half the interquartile range) was 1.06 (0.93–1.14) and the fourth category showed significantly elevated risk, 1.57 (1.03–3.28), but the trend was not significant (P = 0.12). In contrast, supplementary Vitamin E intake appeared to reduce the risk of GNCA in both the continuous and categorical models.

Finally, as γ-tocopherol is also frequently consumed in the diet, we examined associations between γ-tocopherol intake and each cancer type. We found no associations. For example, per increase of 3.11 mg/day (half the interquartile range), the risk estimate was 1.14 (0.73–1.77) for ESCC, 1.03 (0.97–1.11) for EAC, 1.04 (0.97–1.12) for GCA, and 0.97 (0.91–1.05) for GNCA.

Discussion

Prior to the 1980s, ESCC constituted the large majority of esophageal cancer cases in the United States. But, in the past few decades rates of EAC have sharply increased while ESCC rates have decreased.10 Therefore, earlier epidemiologic studies of esophageal cancer were mostly focused on ESCC, but the rising numbers of cases now allow investigation of EAC risk factors as well. Likewise, GCA was uncommon in the past, but rates may have increased and more research is being conducted to identify specific risk factors for this cancer.10 Availability of relatively large numbers of cases in the NIH-AARP study made it possible to examine the associations between vitamin E intake and each of these cancers separately. The results of this study suggest that vitamin E may have different effects on different subtypes of esophageal and gastric cancer. Dietary α-tocopherol had a significant inverse association with ESCC and GCA risk in age- and sex-adjusted models but this was substantially attenuated in our fully adjusted models. Therefore, these apparent associations may be due to residual confounding. In contrast, we found that supplementary vitamin E use significantly increased the risk of GCA among the users of ≥360 mg/day, but there was no apparent trend across categories of supplement dose, so this result should be interpreted with caution. Fully adjusted models for supplementary vitamin E use suggested reduced risk of GNCA with higher doses of supplements, although only about 5% of the cohort took doses in the top category.

Previous case-control studies have consistently shown a strong association between vitamin E intake and reduced ESCC risk11–16, but case-control design is not the preferred design for testing nutritional associations. Our results showed reduced risk of ESCC in age-and sex-adjusted models, but this was substantially attenuated in fully adjusted models and our adjustments may not have fully accounted for confounding. So, we found little evidence for the association in our study.

The results of a meta-analysis of retrospective case-control studies suggested an inverse association between vitamin E intake and EAC risk17, but we found no evidence for this in our prospective study. In fact, our continuous model showed significantly elevated risk associated with higher intake of dietary α-tocopherol, but no association with vitamin E supplement use even at high doses.

Results from case-control studies for GCA have been mixed, showing marginally significantly protective associations 14,18 or no association15 with dietary intake of vitamin E. Results from a previous cohort in Finland reported an increased risk of GCA with higher intake of α-tocopherol.19 Results of our study showed no clear pattern of association, with no effect of dietary α-tocopherol, but a suggestion of increased risk with high dose supplementary vitamin E intake. Separation of adenocarcinomas at the esophagogastric junction into EAC versus GCA is difficult. 20 Combining these two cancer sites into a single entity would produce null results throughout this study (data not shown).

A number of studies have specifically addressed the associations between either dietary or supplemental vitamin E intake and future risk of GNCA using observational designs. Others, however, have not distinguished between GCA and GNCA and have reported only combined results. As GNCA tumors constitute the large majority of gastric cancers in most studies, we believe that the results of studies that have not distinguished between GCA and GNCA are best grouped with other GNCA studies. Results for case-control studies have been mixed,18,21–28 whereas most prospective studies have found no association between baseline dietary intake of vitamin E,29 or supplemental intake of vitamin E 30 and future risk of GNCA. Our results showed no statistically significant association between dietary intake of α-tocopherol and GNCA, except for an increased risk among cases diagnosed in the first few years. This may reflect a real change in risk or could be due to chance. In contrast, we found an inverse association between use of higher-doses of vitamin E supplements and risk of GNCA.

Several randomized trials have examined the association between supplemental vitamin E intake and the risk of gastric cancer. A chemoprevention trial in Finland 31 found no association between five years of daily supplementation with 50 mg α-tocopherol and GCA or GNCA risk. Another trial in Linxian, China,32 where people are deficient for several vitamins and minerals, showed no effect of daily supplementation for 5.25 years with a combination of 30 mg α-tocopherol, 50 μg selenium and 15 mg β-carotene on ESCC, but this same combination did significantly reduce the risk of gastric cancer mortality. In a UK study, daily supplementation with 600 mg vitamin E, 250 mg vitamin C, and 20 mg β-carotene for five years had no significant effect on GNCA mortality.33

Other studies have examined the association between serum α-tocopherol concentration and the risk of upper gastrointestinal cancers.19,34,35 and some have shown that higher serum concentrations were associated with higher risk of GNCA. The correlation between estimated dietary intake of vitamin E and concentrations measured in the blood varies widely in different studies. Because blood concentrations reflect intake and interpersonal variation in uptake and metabolism, studies using serum concentrations as a biomarker of

vitamin E status should be examined separately from those using dietary intake and we could not measure serum concentrations in our study.

The strengths of this study include its prospective design, a large sample size, the use of a validated questionnaire, and the ability to adjust for potential confounders. One major limitation of this study is the potential misclassification of intake associated with the use of food frequency questionnaires.36 Also, the lack of *H. pylori* data is a potential limitation and this may be important because a previous study reported non-significantly different greater protection from higher vitamin E intake for gastric cancer in subjects positive for *H. pylori* infection.18

In conclusion, the results of our study showed little evidence for associations between dietary α-tocopherol and risk of ESCC, EAC, or GCA, but higher intake was positively associated with GNCA risk in analyses restricted to the first few years of follow-up. We found no association between dietary γ-tocopherol intake and risk of any of these cancers. For supplemental vitamin E, the results were also mainly null, with the exception of an inverse association between high doses of supplemental vitamin E and GNCA risk. Overall, the association of vitamin E with risk of upper gastrointestinal tract cancers is unclear. Results from this and other observational studies of intake have been mixed as are results from intervention trials, using multiple agent interventions which included vitamin E. For these reasons, future work is needed to delineate the association between vitamin E intake and risk of upper gastrointestinal tract cancers.

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Table 1

Distributions of subject characteristics in the NIH-AARP Diet and Health Study cohort by dietary α-tocopherol intake in quartiles

Dietary α-tocopherol[1], mg/day	**Quartile 1 ≤ 5.43**	**Quartile 2 5.44–6.51**	**Quartile 3 6.52–7.78**	**Quartile 4 ≥7.79**
Number (%)[2,3]	123139 (25)	123140 (25)	123140 (25)	123140 (25)
Dietary α-tocopherol, mg/day, Median (IQR)	4.68 (4.06–5.10)	5.99 (5.72–6.25)	7.07 (6.78–7.39)	8.92 (8.25–10.1)
Supplementary Vitamin E in mg/day, median (IQR)	13.5 (0–104)	13.5 (0–140)	13.5 (0–180)	13.5 (0–180)
Supplementary Vitamin E groups in mg/day, N (%)				
0 (non-users)	48459 (39)	44151 (36)	41946 (34)	39827 (32)
<180	48286 (39)	49231 (40)	49790 (40)	48842 (40)
180–359	20291 (16)	23165 (19)	24479 (20)	26294 (21)
≥360	6103 (5)	6593 (5)	6925 (6)	8177 (7)
Age at Baseline, years, median (IQR)	62 (57–66)	62 (58–67)	63 (58–67)	63 (58–67)
Sex, N (%) Male	77345 (63)	75679 (62)	72888 (59)	67863 (55)
Race, N (%) Caucasian	113232 (92)	115272 (94)	114757 (93)	112814 (92)
Smoking Status, N (%):				
Never	38908 (33)	43499 (37)	45039 (38)	45520 (38)
Former, ≤ 20 cigarettes/day	29762 (25)	32981 (28)	33671 (28)	34767 (29)
Former, > 20 cigarettes/day	26304 (22)	25844 (22)	25487 (21)	24669 (21)
Current, ≤ 20 cigarettes/day	13846 (12)	10574 (9)	9793 (8)	9398 (8)
Current, > 20 cigarettes/day	9106 (8)	5847 (5)	4790 (4)	4052 (3)
Alcohol, servings/day, N (%)				
0	28149 (23)	28600 (23)	29485 (24)	32090 (26)
0.01–1.00	56397 (46)	66111 (54)	69121 (56)	69347 (57)
1.01–3.00	17452 (14)	19958 (16)	19258 (16)	17868 (15)
> 3.00	20529 (17)	8060 (7)	4859 (4)	3234 (3)
Body Mass Index, kg/m^2, N (%)				
< 18.5	1395 (1)	1167 (1)	1101 (1)	1335 (1)
18.5–24.9	40933 (34)	40318 (33)	40618 (34)	43397 (36)
25–29.9	51565 (43)	52084 (43)	51433 (43)	49662 (41)
30–34.9	8956 (16)	19322 (16)	19318 (16)	18060 (15)
≥ 35	7117 (6)	7491 (6)	7968 (7)	7533 (6)
Physical Activity, N (%)				
Never	7549 (6)	5090 (4)	4555 (4)	4639 (4)
Rarely	20748 (17)	16654 (14)	15085 (12)	14150 (12)
1–2 times per month	19052 (16)	17133 (14)	16094 (13)	14499 (12)
1–2 times per week	25853 (21)	27436 (22)	27255 (22)	25391 (21)
3–4 times per week	28522 (23)	32959 (27)	34756 (28)	35519 (29)

Dietary α-tocopherol[1], mg/day	**Quartile 1 ≤ 5.43**	**Quartile 2 5.44–6.51**	**Quartile 3 6.52–7.78**	**Quartile 4 ≥7.79**
5 or more times per week	19726 (16)	22706 (19)	24238 (20)	27590 (23)
Education, N (%)				
Less than high school	8757 (7)	6977 (6)	6622 (6)	6891 (6)
Completed high school	26985 (23)	23948 (20)	22965 (19)	22275 (19)
Some post-high school training	41673 (35)	41033 (34)	40267 (34)	39731 (33)
Completed college	21559 (18)	23541 (20)	23995 (20)	23641 (20)
Completed postgraduate education	20107 (17)	24396 (20)	25937 (22)	26865 (23)
Cancer Cases, N (row %)				
Esophageal squamous cell carcinoma (ESCC)	64 (41)	30 (19)	29 (18)	35 (22)
Esophageal adenocarcinoma (EAC)	93 (24)	98 (26)	97 (25)	94 (25)
Gastric cardia adenocarcinoma (GCA)	91 (28)	81 (25)	90 (28)	58 (18)
Gastric Noncardia adenocarcinoma (GNCA)	85 (26)	85 (26)	85 (26)	72 (22)

[1] All dietary intakes are adjusted for calorie intake using the residual method. The median (IQR) for daily calorie intake was 1684 (1274–2209)

[2] All percentages reported are column percents, except for cancer cases, which are presented as row percents. exposure category

[3] Counts may not add to 492,559, the analytic cohort size, due to missing data

Table 2

Hazard Ratios (95% CI) for the association between dietary α-tocopherol or supplementary vitamin E and risk of esophageal squamous cell carcinoma (ESCC), esophageal adenocarcinoma (EAC), gastric cardia adenocarcinoma (GCA), or gastric noncardia adenocarcinoma (GNCA) in the NIH-AARP Diet and Health Study cohort[1]

	Continuous[2]		**Categorical**				
			HR (95% CI)				
	HR (95% CI)	***P***	**Quartile 1**	**Quartile 2**	**Quartile 3**	**Quartile 4**	P_{trend}[3]
Dietary α-tocopherol (mg/day)							
ESCC (N = 158)							
Age and sex adjusted	0.76 (0.69–0.85)[7]	<0.0001	1.00	0.46 (0.30–0.71)	0.44 (0.28–0.68)	0.53 (0.35–0.80)	0.0025
Fully adjusted[4]	0.90 (0.81–0.99)	0.023	1.00	0.69 (0.44–1.07)	0.73 (0.46–1.15)	0.90 (0.58–1.40)	0.64
EAC (N = 382)							
Age and sex adjusted	1.02 (0.97–1.07)	0.39	1.00	1.05 (0.79–1.39)	1.06 (0.79–1.40)	1.07 (0.80–1.42)	0.69
Fully adjusted[4]	1.05 (1.00–1.11)	0.041	1.00	1.16 (0.87–1.55)	1.21 (0.90–1.63)	1.27 (0.94–1.72)	0.12
GCA (N = 320)							
Age and sex adjusted	0.93 (0.88–0.99)	0.031	1.00	0.89 (0.66–1.20)	1.00 (0.75–1.34)	0.67 (0.48–0.93)	0.033
Fully adjusted[4]	0.96 (0.90–1.02)	0.19	1.00	0.97 (0.72–1.32)	1.13 (0.84–1.53)	0.77 (0.55–1.09)	0.22
GNCA (N = 327)[5]							
Age and sex adjusted	1.01 (0.96–1.07)	0.72	1.00	0.98 (0.73–1.32)	0.97 (0.72–1.31)	0.82 (0.60–1.13)	0.23
Fully adjusted[4]	1.01 (0.96–1.07)	0.62	1.00	1.02 (0.75–1.38)	1.01 (0.74–1.37)	0.84 (0.61–1.16)	0.26
Supplementary Vitamin E (mg/day)			0	< 180	180–359	≥ 360	
ESCC (N = 158)							
Age and sex adjusted	0.91 (0.80–1.02)	0.10	1.00	1.34 (0.94–1.92)	0.77 (0.47–1.27)	0.99 (0.47–2.09)	0.16
Fully adjusted[6]	0.92 (0.82–1.04)	0.17	1.00	1.40 (0.98–2.00)	0.83 (0.50–1.39)	1.03 (0.49–2.19)	0.23
EAC (N = 382)							
Age and sex adjusted	0.99 (0.92–1.06)	0.69	1.00	0.92 (0.73–1.16)	1.01 (0.76–1.33)	0.86 (0.53–1.41)	0.90
Fully adjusted[6]	1.00 (0.93–1.08)	0.98	1.00	0.98 (0.78–1.24)	1.10 (0.83–1.45)	0.91 (0.56–1.48)	0.83
GCA (N = 320)							
Age and sex adjusted	1.04 (0.97–1.12)	0.26	1.00	0.82 (0.64–1.06)	0.80 (0.58–1.10)	1.46 (0.96–2.20)	0.28

	Continuous[2]		Categorical				
			HR (95% CI)				
	HR (95% CI)	*P*	Quartile 1	Quartile 2	Quartile 3	Quartile 4	P_{trend}[3]
Fully adjusted[6]	1.06 (0.99–1.14)	0.091	1.00	0.89 (0.69–1.15)	0.89 (0.65– 1.23)	1.57 (1.03–2.38)	0.12
GNCA (N = 327)							
Age and sex adjusted	0.90 (0.83–0.98)	0.011	1.00	1.18 (0.93–1.50)	0.72 (0.51–1.01)	0.61 (0.33–1.12)	0.0028
Fully adjusted[6]	0.92 (0.85–1.00)	0.057	1.00	1.24 (0.98–1.59)	0.80 (0.57–1.13)	0.68 (0.36–1.26)	0.015

[1] Cohort N = 492,559

[2] For continuous models variables were scaled to the IQR/2, 1.17 mg/day for dietary α-tocopherol and 71 mg/day for supplemental Vitamin E

[3] *P*-values come from models where the median value of intake for each subject's quartile is entered as a continuous variable

[4] Adjusted for age, sex, supplementary vitamin E, smoking, education, physical activity, alcohol consumption, BMI, and total calorie intake

[5] Models for dietary α-tocopheroland GNCA showed evidence of non-proportionality and models stratified on follow-up time are presented in the text

[6] Adjusted for age, sex, dietary α-tocopherol, smoking, education, physical activity, alcohol consumption, BMI, and total calorie intake