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Index-Based Dietary Patterns and Risk of Esophageal and Gastric Cancer in a Large Cohort Study

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Abstract

Background & Aims—Diet could affect risk for esophageal and gastric cancers, but associations have been inconsistent. The diet is complex, so studies of dietary patterns, rather than studies of individual foods, might be more likely to identify cancer risk factors. There is limited research on index-based dietary patterns and esophageal and gastric cancers. We prospectively evaluated associations between the Healthy Eating Index-2005 (HEI-2005) and alternate Mediterranean Diet (aMED) scores and risk of esophageal and gastric cancers.

Methods—We analyzed data from 494,968 participants in the National Institutes of Health (NIH)-AARP Diet and Health study, in which AARP members (51–70 y old) completed a self-administered baseline food frequency questionnaire between 1995 and 1996. Their answers were used to estimate scores for each index.

Results—During the follow-up period (1995–2006), participants developed 215 esophageal squamous cell carcinomas (ESCCs), 633 esophageal adenocarcinomas (EACs), 453 gastric cardia adenocarcinomas, and 501 gastric non-cardia adenocarcinomas. Higher scores from the HEI-2005 were associated with a reduced risk of ESCC (comparing the highest quintile with the lowest: hazard ratio [HR], 0.51; 95% confidence interval [CI], 0.31–0.86; P_{trend}=.001) and EAC (HR, 0.75; 95% CI, 0.57–0.98; P_{trend}=.01). We observed an inverse association between ESCC, but not

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EAC, and higher aMED score (meaning a higher-quality diet). HEI-2005 and aMED scores were not significantly associated with gastric cardia or noncardia adenocarcinomas.

Conclusions—Using data collected from 1995 through 2006 from the NIH-AARP Diet and Health Study, HEI-2005 and aMED scores were inversely associated with risk for esophageal cancers—particularly ESCC. Adherence to dietary recommendations might help prevent esophageal cancers.

Keywords

food habits; esophageal neoplasms; stomach neoplasms

Introduction

Esophageal cancer is the sixth and gastric cancer (GC) is the second leading cause of cancer deaths worldwide.[1] Esophageal cancer has two primary histologic types, esophageal squamous cell carcinoma (ESCC) and esophageal adenocarcinoma (EAC).[2–3] GC is usually subdivided to cardia and noncardia cancer by anatomic location.[1]

Although diet have been hypothesized to be associated with cancers of the esophagus and stomach,[2] few prospective studies have addressed these associations. Heavy alcohol intake has been associated with ESCC risk, but not with EAC or GC.[4–5] The consumption of total fruit and vegetables or fruit alone has been inversely correlated with ESCC, but evidence is yet weak for EAC and GC.[6–8] Salt and salted foods are listed as probable carcinogens in GC.[1–2] There is little convincing evidence of a role for other dietary items. Due to the complexity of foods and the likely interaction among components, dietary patterns reflecting the combination of multiple nutrients and foods may provide more insight into the association between diet and cancer.[9–10]

Some, mostly case-control,[11–17] studies have investigated the relationship between risk of esophageal and gastric cancers and dietary patterns developed using data-driven factor or cluster analysis.[11–19] In contrast, index-based dietary patterns are derived *a priori* based on dietary recommendations.[10] Few studies have evaluated risk of esophageal and gastric cancers by adherence to index-based dietary patterns.[20–21] We comprehensively examined associations between two diet quality indices, the Healthy Eating Index-2005 (HEI-2005), which is based on the 2005 Dietary Guidelines for Americans,[22] and the Alternate Mediterranean Diet Score (aMED), which reflects principles of the traditional Mediterranean diet adapted to the American population,[9] and risk of incident ESCC, EAC, and gastric cardia and noncardia adenocarcinomas in a prospective cohort of the National Institutes of Health (NIH)-AARP Diet and Health Study.

MATERIALS AND METHODS

Study population

The NIH-AARP Diet and Health Study is a longitudinal cohort established between 1995 and 1996, when a total of 566,399 AARP members aged 50 to 71 years returned a mailed questionnaire enquiring about diet and lifestyle practices. The comparability of respondents and non-respondents and the external validity of the cohort have been detailed previously.[23]

We excluded proxy respondents (n=15,760), prevalent cancers at baseline (n=51,234), those with extreme total energy intake (exceeding two times the inter-quartile ranges of sex-specific Box-Cox log-transformed intake) (n=4,417), and those who died in the interval between questionnaire responses and study baseline (n=20). Totally 494,968 participants

(295,300 men and 199,668 women) were included. The study was approved by the Special Studies Institutional Review Board of the US National Cancer Institute.

Assessment of main exposure

Participants reported the frequency of consumption of 124 food items over the past year on the baseline food frequency questionnaire (FFQ), for which food items, portion sizes and nutrient databases were constructed using data from the 1994–1996 US Department of Agriculture's Continuing Survey of Food Intakes by Individuals. [23] The FFQ was calibrated using two nonconsecutive 24-hr dietary recalls in 1953 subjects.[24]

The HEI-2005 evaluates concordance with the 2005 Dietary Guidelines for Americans, scoring 12 components for a total of 100 points[22]. Components and scoring standards were measured per 1,000 kcal. Six components including total grains; whole grains; total vegetables; dark-green and orange vegetables, and legumes; total fruit; and whole fruits were awarded 0 to 5 each. Milk; meat and beans (including poultry, fish, nuts, and legumes); oils; saturated fat; and sodium were worth 0 to 10 each. One component, calories from solid fat, alcohol, and added sugar (SoFAAS), was worth 0 to 20. For saturated fat; sodium; and calories from SoFAAS, higher scores reflect lower intake. For the others, higher scores reflect higher intake.

The aMED is modified from the original MED,[9, 25] assessing 9 components with total scores of 9. Components were energy adjusted and standardized to 2,500 calories for men and 2,000 calories for women. Participants received 1 point for intake above the median for seven components (vegetables; legumes; fruit; nuts; whole grains; fish; and ratio of monounsaturated to saturated fat). Participants received 1 point for intake of red and processed meat below the median. For alcohol, one point was given for moderate alcohol intake (5–25g/day). In a sensitivity analysis, individuals with alcohol intake of 5–15g/day received 1 point.

Cohort follow-up and assessment of outcome

Vital status was ascertained by periodic linkage to the Social Security Administration Death Master File, linkage with cancer registries, questionnaire responses, and response to other mailings. Incident cancers were identified by linkage of cohort memberships to state cancer registry databases. Cancer sites were identified by anatomic site and histologic code of the International Classification of Disease for Oncology (ICD-O, third edition). Esophageal cancer included topography codes C15.0–C15.9, and was categorized as ESCC and EAC by histology codes. Gastric cardia and noncardia cancer had code C16.0 and C16.1–C16.9 respectively.

Statistical analysis

Person-years of follow-up were calculated from the baseline (1995–1996) to diagnosis of the first upper gastrointestinal (UGI) cancer (head and neck, esophageal or stomach cancer, as the diagnosis of one of these cancers would be associated with increased surveillance of the others), date of death, movement out of the study areas, or December 31, 2006, whichever came first.

Scores of HEI-2005 were categorized in quintiles. The aMED was divided into five categories: 0–2, 3, 4, 5–6, and 7–9. Cox regression analysis was performed to calculate the age and sex-adjusted, as well as multivariate-adjusted hazard ratios (HRs) and 95% confidence intervals (CIs), adjusting for age, sex, race or ethnic group, smoking (never, past with 1–20, past with ≥20, current with 1–20, or current with ≥20 cigarettes/day), education (<high school, high school, some college, completed college, or graduate school), body mass

index (BMI, <18.5, 18.5–24.9, 25.0–29.9, 30.0–34.9, or ≥35.0 kg/m^2), vigorous physical activity (never, rarely, 1–3 times/month, 1–2, 3–4, or ≥5 times/wk), usual activity throughout the day (sit without walking much, sit but walk fair amount, stand/walk a lot without lifting, lift/carry light loads or climb stairs/hills often, or do heavy work/carry loads), and total energy intake. Heavy alcohol intake (>3 drinks/day or not) was further adjusted for ESCC. Alternatively, we adjusted for alcohol using additional categories reflecting more modest intakes and the results were similar. We tested the proportional hazards assumption by including an interaction term for person-years and categories of each index and observed no significant deviations. We performed a lag analysis by excluding UGI cancers that occurred within the first three years of follow-up. Tests of linear trend across categories of each index were performed by assigning participants the median score of each category. Component analyses were conducted adjusting for the modified total score of other components. Because the numbers of women with the outcomes were small and associations did not differ between men and women, we chose only to show the overall rather than sex-specific results.

We performed stratified analyses by subgroups of age, sex, BMI, smoking, alcohol intake, and education. Likelihood ratio tests were performed to evaluate the interactions between each index and the subgroup variable. We additionally explored the possibility of additive interactions by estimating the synergy index specifically for interactions with smoking and alcohol. As sensitivity analyses, those with type 2 diabetes or heart disease or reporting poor or fair health at baseline were excluded.

Results

Participants with higher HEI-2005 or aMED scores tended to be older and perform vigorous physical activity, have more education, report a lower total caloric intake, and report having heart disease at baseline (Table 1). They were less likely to smoke currently, drink heavily, and engage in heavy work, or report poor or fair health.

Over an average follow-up of 9.7 years, we identified 215 incident ESCC, 633 EAC, 453 gastric cardia, and 501 noncardia adenocarcinomas. Higher HEI-2005 scores were associated with significantly reduced risk of ESCC (the highest quintile compared to the lowest: HR=0.51, 95% CI: 0.31–0.86, P for trend (P_{trend}) =0.001), and EAC (HR=0.75, 95% CI: 0.57–0.98, P_{trend}=0.01) (Table 2). In contrast, HEI-2005 scores were not associated with risk of either gastric cardia or noncardia cancer in multivariate-adjusted analyses.

ESCC risk decreased with increasing aMED (P_{trend} =0.03); the HR (95% CI) for the score of 7–9 compared with a score of 0–2 was 0.44 (0.22–0.88). We did not observe significant association with EAC risk after adjusting for covariates, particularly smoking. Analyses did not reveal significant association of either gastric cardia or noncardia cancer with aMED (Table 3). Assigning 1 point for alcohol intake of 5–15g/day did not appreciably alter the effect estimates.

The components of total grains, whole grains, and calories from SoFAAS within HEI-2005, as well as whole grains and total fruit within aMED were significantly associated with decreased ESCC risk (Table 4 and 5). Total grains within HEI-2005 and legumes within aMED were inversely related to EAC risk. For gastric cardia cancer, total fruit was a significant component of the two indices (Supplementary Tables 1 and 2).

We observed an interaction between education and aMED on EAC (P_{int}=0.02), with a stronger inverse association observed for those not attending college. There were borderline effect modifications by smoking or alcohol intake on the association between HEI-2005 and ESCC (Supplementary Figures 1 and 2). We further explored the synergy index for

interactions of each index with smoking and alcohol intake and the 95% CIs all included 1 (data not shown).

We performed a lag analysis excluding UGI cancers occurring within the first three years. The HR (95% CI) for the highest quintile (category) was 0.47 (0.26–0.86) for HEI-2005 and ESCC, 0.72 (0.53–0.99) for HEI-2005 and EAC, 0.45 (0.21–0.98) for aMED and ESCC, and 0.91 (0.64–1.29) for aMED and EAC. In sensitivity analyses, modifying each index by removing alcohol part and adjusting for it, excluding individuals reporting type 2 diabetes or heart disease, or excluding those reporting poor or fair health did not materially change the associations either.

Discussion

Associations between esophageal and gastric cancers and several individual food groups have been described, with total fruit and vegetable consumption widely considered a protective factor and alcohol intake a risk factor of ESCC.[4, 6, 8] Evidence regarding dietary factors and risk of EAC and GC is inconsistent.[4–8] In addition, it is less clear whether adherence to dietary patterns is associated with decreased risk of these cancers and consistent evidence is sparse.[18–21] In this study, we observed that participants with a higher adherence to HEI-2005 had a reduced risk of ESCC and EAC, and those adhering to aMED had a reduced risk of ESCC, highlighting the effect of adherence to dietary guidance in prevention of esophageal cancers. In contrast, no associations of each index were found with gastric cardia or noncardia adenocarcinomas.

Most prior studies employed a case-control design and used data-driven approaches.[11–17] Prospective studies using data-driven methods have been limited and reported inconsistent results.[18–19] For example, results from one Japanese study found a decreased risk of GC associated with a healthy dietary pattern loaded with fruit and vegetables, and an increased risk associated with a traditional Japanese dietary pattern among women,[18] whereas a second Japanese study found no association.[19] Of the limited studies assessing adherence to dietary recommendations,[20–21] one prospective European study suggested a beneficial role for adherence to the relative MED, which used an 18-point scale incorporating 9 components, in relation to gastric cardia adenocarcinoma (P_{trend}=0.04).[20]

We prospectively evaluated the association between aMED and HEI and risk of esophageal and gastric cancers. We found significantly decreased risk of esophageal cancer, particularly ESCC, associated with higher HEI-2005 scores. Higher aMED scores were inversely associated only with ESCC risk but not with EAC. ESCC and EAC have distinct histopathologic manifestations and changing incidence patterns worldwide, suggesting different etiologies.[1] Although tobacco smoking is a risk factor for both ESCC and EAC, associations for many other factors have differed.[1, 4, 6] For example, total fruit and vegetable consumption decreases ESCC risk and alcohol intake increases ESCC risk, but the association for these factors with EAC is inconsistent.[4, 6, 8] Although scores of HEI-2005 and aMED are closely correlated, they highlight distinct components and award optimal scores using different approaches.[9, 22] We observed distinct associations of individual components with ESCC and EAC. These reasons could partly explain the differential results for ESCC and EAC associated with the dietary pattern indices.

Esophageal and gastric cancers arise from anatomically adjacent organs. Numerous studies have evaluated their environmental exposures, but, other than smoking, association with most environmental factors differed between them[4, 6–7]. The present study also failed to identify dietary patterns associated with GC. Scores of dietary pattern indices have been inversely related to levels of chronic inflammation and oxidative stress,[9, 26–27] whether the

distinct effects by adherence to dietary pattern indices reflects the differential anti-inflammatory or antioxidant capacity of the diet in esophagus and stomach or other biological mechanisms remain to be seen in further functional studies.

Previous reports have highlighted a reduced risk of esophageal cancer by a dietary pattern loaded with fruit and vegetables.[11, 17] In our study, total fruit in aMED was associated with reduced ESCC risk. The component of whole grains in the two indices, though operationalized differently, was associated with reduced ESCC risk. Whole grains are a major source of dietary fiber and several vitamins, minerals, and phytochemicals. Past studies have reported inverse associations between intake of dietary fiber and vitamins and ESCC.[16] As individual constituents are correlated with each other, it is difficult to assign results for each overall score to particular constituents, which underscores the major rationale for our investigation of dietary patterns in the first place.

We placed special emphasis on alcohol intake, as heavy alcohol intake is an established risk factor for ESCC, yet moderate alcohol intake has been associated with better health,[4, 28] and plays a role in each dietary index. Moderate alcohol intake is considered an optimal component in aMED. HEI-2005 considers alcohol as part of the discretionary calories from SoFAAS. We observed that persons with higher HEI-2005 or aMED score tended to drink less, suggesting that confounding by heavy alcohol intake was of potential concern. As such, we adjusted ESCC risk estimates for heavy alcohol consumption, which only slightly attenuated, but not materially changed the magnitude of associations. We also modified scores of HEI-2005 and aMED by removing the alcohol parts, which did not change the results appreciably either. Moreover, we observed similar associations within strata of alcohol intake. Tobacco smoking is also a strong risk factor for these cancers; however associations with dietary indices persisted after adjusting for smoking and in subgroup analyses, among never-smokers. The synergy index also did not indicate additives interactions with alcohol and smoking. Together, these results suggest an inverse association between each dietary index and ESCC, irrespective of alcohol intake and tobacco smoking.

We observed significantly inverse association only among those with lower education, who tended to have unfavorable socioeconomic status. It is possible that exposure to other factors correlated with favorable socioeconomic status could have overwhelmed the inverse association to null among those with high education. However, as we examined a number of interactions, such differences could be due to chance and further replication is required.

We acknowledge several limitations. First, the high scores of dietary pattern indices may be associated with non-dietary aspects of a healthy lifestyle and reflect a high socioeconomic status, which raises a potential concern about residual confounding. To address this, we adjusted for potential confounders comprehensively. Associations also generally appeared similar across stratum of each of these factors. However, an observational study cannot rule out the possibility of residual confounding by additionally unmeasured or imperfectly measured confounders. We did not, for example, have information on gastroesophageal reflux disease symptoms or *Helicobacter pylori* infection.[1] Second, although the calibration study indicated reasonably good validity, information on dietary intake at a single time may not reflect long-term patterns. Misclassification may have been caused by the changing dietary intake during the follow-up. However, this would likely be non-differential resulting in a conservative effect estimate. Although we used energy adjustment to reduce measurement error inherent in self-reported FFQs, future work is needed to enable measurement correction. Fourth, almost 75% of the accrued esophageal cancers were EAC, which is higher than the EAC proportion in total esophageal cancers in the US, despite steadily increasing trends of EAC rates among US whites since the 1970s[3]. This may be due to the predominance of White and more highly educated participants in the cohort compared

to the general US population and extrapolation of the results should be cautious. Fifth, further functional studies are warranted to elucidate the mechanisms underlying the observed associations.

In conclusion, our prospective study demonstrates that two index-based diet quality patterns, HEI-2005 and aMED, are inversely associated with ESCC, and the HEI-2005 is inversely associated with EAC, providing evidence regarding a beneficial role of adherence to dietary patterns that are consistent with given dietary guidelines in prevention of esophageal cancers. Our findings may provide health professionals with further information to encourage the public to adhere to the dietary recommendations for prevention of esophageal cancers.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

aMED	Alternate Mediterranean Diet Score
BMI	body mass index
CI	confidence interval
EAC	esophageal adenocarcinoma
ESCC	esophageal squamous cell carcinoma
FFQ	food frequency questionnaire
HR	hazard ratio

HEI-2005	Healthy Eating Index-2005
SoFAAS	solid fats, alcoholic beverages, and added sugars
UGI	upper gastrointestinal

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Table 1

Baseline characteristics of the participants, according to distribution of diet-quality scores

	Healthy Eating Index-2005			Alternate Mediterranean Diet Score		
	Quintile 1	**Quintile 3**	**Quintile 5**	**Score 0–2**	**Score 4**	**Score 7–9**
n	98,993	98,994	98,993	81,866	106,728	49,538
Score median	50	69	80	2	4	7
Age, year, mean (SD)	61.4 (5.5)	62.0 (5.3)	62.6 (5.3)	61.5 (5.5)	62.0 (5.4)	62.5 (5.2)
Male (%)	72.2	60.0	46.3	56.5	57.2	71.1
BMI, kg/m^2, mean (SD)	27.2 (4.9)	27.2 (4.8)	26.7 (4.7)	27.6 (5.2)	27.3 (4.9)	26.2 (4.1)
Race (non-Hispanic white, %)	93.4	92.3	92.0	93.8	91.8	93.1
Current smoking (%)	25.4	9.9	5.4	22.4	12.2	4.5
Heavy alcohol intake (>3 drinks/day, %)	25.0	3.3	0.2	16.9	6.7	1.6
Usual activity (heavy work, %)	4.6	2.7	1.9	4.1	2.9	2.1
Vigorous physical activity (≥5 times/wk, %)	14.4	19.1	24.7	13.5	18.2	28.3
Education (college graduate, %)	31.5	41.4	44.7	28.9	38.1	54.7
Total calories intake, kcal/day, mean (SD)	2,169 (997)	1,786 (740)	1,622 (630)	2,025 (949)	1,810 (794)	1,750 (664)
Health status (poor or fair, %)	14.4	11.9	11.2	15.7	12.8	7.7
Heart disease (%)	11.2	14.0	16.0	11.5	13.3	17.6
Diabetes (%)	5.9	9.0	12.1	8.3	9.8	7.1

Table 2

Association of the Healthy Eating In dex-2005 in quintiles with incident ESCC, EAC, gastric cardia and noncardia adenocarcinoma

	Quintile 1 (n=98,993)	Quintile 2 (n=98,994)	Quintile 3 (n=98,994)	Quintile 4 (n=98,994)	Quintile 5 (n=98,993)	*P* value for trend
ESCC						
No. of Cases	96	41	32	23	23	
Age and sex-adjusted HR (95% CI)	1.00	0.41 (0.29–0.59)	0.32 (0.21–0.47)	0.23 (0.14–0.36)	0.22 (0.14–0.35)	<0.0001
Multivariate-adjusted HR† (95% CI)	1.00	0.54 (0.37–0.78)	0.46 (0.30–0.70)	0.35 (0.22–0.57)	0.36 (0.22–0.59)	<0.0001
Multivariate-adjusted HR* (95% CI)	1.00	0.67 (0.46–0.98)	0.62 (0.40–0.96)	0.49 (0.30–0.81)	0.51 (0.31–0.86)	0.001
EAC						
No. of Cases	187	145	107	108	86	
Age and sex-adjusted HR (95% CI)	1.00	0.81 (0.65–1.00)	0.63 (0.49–0.80)	0.67 (0.53–0.85)	0.59 (0.46–0.77)	<0.0001
Multivariate-adjusted HR† (95% CI)	1.00	0.88 (0.71–1.10)	0.73 (0.57–0.93)	0.81 (0.63–1.04)	0.75 (0.57–0.98)	0.01
Cardia adenocarcinoma						
No. of Cases	112	103	91	79	68	
Age and sex-adjusted HR (95% CI)	1.00	0.95 (0.73–1.24)	0.88 (0.66–1.16)	0.80 (0.60–1.06)	0.75 (0.55–1.01)	0.03
Multivariate-adjusted HR† (95% CI)	1.00	1.02 (0.78–1.34)	0.99 (0.74–1.31)	0.94 (0.69–1.27)	0.92 (0.67–1.27)	0.56
Noncardia adenocarcinoma						
No. of Cases	109	127	102	82	81	
Age and sex-adjusted HR (95% CI)	1.00	1.13 (0.88–1.46)	0.91 (0.69–1.19)	0.73 (0.55–0.98)	0.72 (0.54–0.96)	0.002
Multivariate-adjusted HR† (95% CI)	1.00	1.23 (0.95–1.60)	1.03 (0.78–1.36)	0.86 (0.63–1.15)	0.88 (0.65–1.20)	0.15

†Adjusted for age, sex, race, smoking, alcohol intake, education, BMI, vigorous physical activity, usual activity, and total energy intake.

*Additionally adjusted for alcohol intake.

Table 3

Association of the alternate Mediterranean Diet Score with incident ESCC, EAC, gastric cardia and noncardia adenocarcinoma

	Score 0–2 (n=81,866)	Score 3 (n=88,570)	Score 4 (n=106,728)	Score 5–6 (n=168,266)	Score 7–9 (n=49,538)	*P* value for trend
ESCC						
No. of Cases	67	39	37	62	10	
Age and sex-adjusted HR (95% CI)	1.00	0.53 (0.35–0.78)	0.40 (0.27–0.60)	0.41 (0.29–0.59)	0.22 (0.11–0.42)	<0.0001
Multivariate-adjusted HR† (95% CI)	1.00	0.61 (0.41–0.92)	0.52 (0.34–0.78)	0.58 (0.40–0.83)	0.32 (0.16–0.63)	0.0003
Multivariate-adjusted HR* (95% CI)	1.00	0.68 (0.46–1.02)	0.62 (0.41–0.94)	0.74 (0.51–1.08)	0.44 (0.22–0.88)	0.03
EAC						
No. of Cases	117	121	133	198	64	
Age and sex-adjusted HR (95% CI)	1.00	0.94 (0.73–1.21)	0.82 (0.64–1.05)	0.71 (0.57–0.90)	0.67 (0.50–0.92)	0.0006
Multivariate-adjusted HR† (95% CI)	1.00	1.00 (0.78–1.30)	0.93 (0.72–1.19)	0.86 (0.68–1.10)	0.91 (0.66–1.25)	0.25
Cardia adenocarcinoma						
No. of Cases	75	81	106	142	49	
Age and sex-adjusted HR (95% CI)	1.00	0.98 (0.72–1.34)	1.03 (0.76–1.38)	0.81 (0.61–1.07)	0.83 (0.58–1.20)	0.10
Multivariate-adjusted HR† (95% CI)	1.00	1.04 (0.76–1.42)	1.13 (0.84–1.53)	0.96 (0.72–1.29)	1.10 (0.76–1.61)	0.90
Noncardia adenocarcinoma						
No. of Cases	94	93	109	163	42	
Age and sex-adjusted HR (95% CI)	1.00	0.88 (0.66–1.17)	0.83 (0.63–1.09)	0.75 (0.58–0.96)	0.60 (0.42–0.87)	0.002
Multivariate-adjusted HR† (95% CI)	1.00	0.91 (0.69–1.22)	0.89 (0.67–1.18)	0.85 (0.65–1.10)	0.75 (0.52–1.09)	0.11

†Adjusted for the above-mentioned variables in table 2(†).

*Additionally adjusted for alcohol intake.

Table 4

Association of components in Health Eating Index-2005 with incident ESCC and EAC

	Criteria for optimal score	ESCC, HR[†*] (95% CI)	EAC, HR[†] (95% CI)
Total grains	≥3 ounces/1,000 kcal	0.86 (0.76–0.99)	0.92 (0.85–0.99)
Whole grains	≥1.5 ounces/1,000 kcal	0.85 (0.74–0.97)	1.01 (0.94–1.08)
Total vegetables	≥1.1 cups/1,000 kcal	1.07 (0.95–1.21)	1.03 (0.96–1.11)
Dark-green and orange vegetables and legumes	≥0.4 cups/1,000 kcal	1.02 (0.93–1.13)	1.01 (0.95–1.07)
Total fruit	≥0.8 cups/1,000 kcal	0.92 (0.84–1.02)	1.00 (0.94–1.06)
Whole fruits (not juice)	≥0.4 cups/1,000 kcal	0.95 (0.86–1.05)	1.00 (0.94–1.06)
Milk	≥1.3 cups/1,000 kcal	0.96 (0.91–1.01)	0.99 (0.96–1.02)
Meat and beans	≥2.5 ounces/1,000 kcal	1.01 (0.94–1.09)	1.01 (0.96–1.06)
Oils	≥12 g/1,000 kcal	1.01 (0.96–1.07)	0.99 (0.96–1.02)
Saturated fat	≤7% kcal	1.00 (0.95–1.05)	0.99 (0.96–1.01)
Sodium	≤700 mg/1,000 kcal	0.94 (0.88–1.01)	0.97 (0.93–1.01)
Calories from Solid Fats, Alcoholic beverages, and Added Sugars	≤20% kcal	0.96 (0.93–0.99)	0.99 (0.97–1.01)

[†] HR associated with 1 score of each component adjusted for other components and the above-mentioned covariates in table 2.

[*] Additionally adjusted for alcohol intake.

Table 5

Association of components in the alternate Mediterranean Diet Score with incident ESCC and EAC

	Criteria for optimal score	ESCC, HR[†*] (95% CI)	EAC, HR[†] (95% CI)
Whole grains	≥median: 1.09 ounces	0.60 (0.44–0.81)	0.91 (0.78–1.07)
Vegetables (no white potatoes)	≥median: 1.86 cups	1.05 (0.78–1.40)	1.00 (0.85–1.17)
Fruit	≥median: 2.30 cups	0.65 (0.48–0.88)	0.94 (0.79–1.10)
Fish	≥median: 0.60 ounces	1.00 (0.76–1.32)	0.94 (0.80–1.11)
Red and processed meat	≥median: 2.45 ounces	0.91 (0.68–1.21)	0.96 (0.81–1.13)
Legumes	≥median: 0.08 cups	1.02 (0.77–1.34)	0.84 (0.72–0.99)
Nuts	≥median: 0.30 ounces	0.91 (0.69–1.20)	1.12 (0.95–1.31)
Ratio of monounsaturated: saturated fat	<median: 1.24	1.04 (0.80–1.37)	1.06 (0.90–1.24)
Alcohol	5–25g/day	0.79 (0.56–1.11)	0.99 (0.83–1.19)

† HR associated with 1 point of each component adjusted for other components and the above-mentioned variable in table 2(†).

* Additionally adjusted for alcohol intake except for analysis of the alcohol component.