Published in final edited form as:

Int J Cancer. 2012 September 15; 131(6): 1376–1387. doi:10.1002/ijc.27366.

Association of dietary fat intakes with risk of esophageal and gastric cancer in the NIH-AARP Diet and Health study

Mark G. O'Doherty^{1,2,*}, Neal D. Freedman², Albert R. Hollenbeck³, Arthur Schatzkin², Liam J. Murray¹, Marie M. Cantwell¹, and Christian C. Abnet²

¹Cancer Epidemiology Health Services Research Group, Centre for Public Health, Queens University Belfast, Belfast, Northern Ireland, BT12 6BA, UK.

²Division of Cancer Epidemiology and Genetics, National Cancer Institute, National Institutes of Health, Department of Health and Human Services, Rockville, MD 20852, USA.

³AARP, Washington, DC, USA.

Abstract

The aim of this study was to investigate whether intakes of total fat and fat subtypes were associated with esophageal adenocarcinoma (EAC), esophageal squamous cell carcinoma (ESCC), gastric cardia or gastric non-cardia adenocarcinoma. From 1995–1996, dietary intake data was reported by 494,978 participants of the NIH-AARP cohort. 630 EAC, 215 ESCC, 454 gastric cardia and 501 gastric non-cardia adenocarcinomas accrued to the cohort. Cox proportional hazards regression was used to examine the association between the dietary fat intakes, whilst adjusting for potential confounders. Though apparent associations were observed in energy-adjusted models, multivariate adjustment attenuated results to null (e.g. EAC energy adjusted hazard ratio (HR) and 95% confidence interval (95%CI) 1.66 (1.27–2.18) *P* for trend <0.01; EAC multivariate adjusted HR (95%CI) 1.17 (0.84–1.64) *P* for trend=0.58). Similar patterns were also observed for fat subtypes (e.g. EAC saturated fat, energy adjusted HR (95%CI) 1.79 (1.37–2.33) *P* for trend <0.01; EAC saturated fat, multivariate adjusted HR (95%CI) 1.27 (0.91–1.78) *P* for trend=0.28). However, in multivariate models an inverse association for polyunsaturated fat (continuous) was seen for EAC in subjects with a body mass index (BMI) in the normal range (18.5–<25 kg/m²) (HR (95%CI) 0.76 (0.63–0.92)), that was not present in overweight subjects (HR (95%CI) 1.04 (0.96–1.14)), or in unstratified analysis (HR (95%CI) 0.97 (0.90–1.05)). *P* for interaction=0.02. Overall, we found null associations between the dietary fat intakes with esophageal or gastric cancer risk; though a protective effect of polyunsaturated fat intake was seen for EAC in subjects with a normal BMI.

Keywords

cohort; dietary fat; esophageal neoplasms; stomach neoplasms; prospective

INTRODUCTION

Esophageal cancer is the sixth leading cause of cancer mortality worldwide and gastric cancer is the second [1]. The two main histological and etiological distinct types of esophageal cancer are esophageal adenocarcinoma (EAC) and esophageal squamous cell

*Corresponding author, Mark O'Doherty, Cancer Epidemiology Health Services Research Group, Centre for Public Health, Queens University Belfast, Institute of Clinical Sciences, Block B, Grosvenor Road, Belfast, BT12 6BA, UK. Tel: +44 (0) 2890632219; Fax: +44 (0) 2890231907; m.odoherty@qub.ac.uk.

carcinoma (ESCC). Although approximately 90% of gastric cancers are adenocarcinomas, these are usually subdivided according to anatomic location: cardia or non-cardia cancers [2].

Until the 1970s, ESCC accounted for the large majority of all esophageal cancer cases worldwide. However, incidence of EAC has dramatically increased since then, and this cancer is the most rapidly increasing cancer in the Western world [3–9]. Gastric cardia adenocarcinoma incidence rates have also been increasing, but the trend is not as prominent as with EAC [3, 6, 8]. It is possible that some of these increases may be due to better subsite classification of tumors rather than a true increase in incidence rates [10]. Additionally, because EAC and gastric cardia adenocarcinoma are adjacent tumors it is difficult to separate them clinically [11], and they have the potential of sharing many of the same risk factors.

Unfortunately, patients presenting with esophageal cancer do not commonly come to medical attention until the cancer is at an advanced stage and preventative treatment is near impossible [12]. Therefore, the identification of modifiable risk factors for the primary prevention of esophageal and gastric cancer is imperative. Several important risk factors for esophageal and gastric cancer have been identified. Gastro-esophageal reflux disease (GERD), white race, male sex, obesity [6], and cigarette smoking for EAC [13, 14]; alcohol consumption and smoking for ESCC [15–17]; *Helicobacter pylori* infection [18], obesity [19, 20], and cigarette smoking [14] for gastric cardia adenocarcinoma; and *Helicobacter pylori* infection [18], male sex and cigarette smoking [21] for gastric non-cardia adenocarcinoma. Diet is a potentially important modifiable risk factor that may influence the risk of developing both esophageal and gastric cancer. It has been hypothesized that dietary fat intake may be positively linked to reflux and reflux symptoms [22], thus an increased risk of EAC.

Several previous studies have reported associations between esophageal and gastric adenocarcinomas with dietary fat intake [23–27], although results from other studies have been inconsistent [28–32]. A recent review by De Ceglie et al. also reported a positive association between consumption of high-fat meals with EAC and esophagogastric junction adenocarcinomas [33]. Therefore, we examined the association between dietary fat intake with EAC, ESCC, gastric cardia adenocarcinoma and gastric non-cardia adenocarcinoma using the very large National Institutes of Health (NIH)–AARP Diet and Health study, a cohort of nearly 500,000 men and women.

MATERIALS AND METHODS

Study population

The establishment and recruitment procedures of the NIH-AARP Diet and Health study have been described [34]. Between 1995 and 1996, a baseline questionnaire was mailed to 3.5 million AARP (formerly known as the American Association of Retired Persons) members aged 50–71 years eliciting information on demographic characteristics, dietary intake and health-related behaviors. Members resided in six US states (California, Florida, Louisiana, New Jersey, North Carolina and Pennsylvania) and two metropolitan areas (Atlanta, Georgia and Detroit, Michigan). Of 617,119 questionnaires returned (17.6% of the 3.5 million mailed), a total of 566,401 respondents completed the survey in satisfactory detail and consented to be in the study. The comparability of the respondents and non-respondents and the external validity of the cohort have previously been discussed in detail [34]. Of these 566,401 respondents, we excluded subjects with a cancer diagnosis at baseline ($n = 51,234$) and proxy respondents ($n = 15,760$). Subjects who reported extreme (>2 times the interquartile ranges of sex-specific Box-Cox log-transformed) total energy intake ($n =$

4417) were also excluded. Those subjects who died or were diagnosed with cancer on the first day of follow-up were excluded (n = 12). The resulting cohort included 494,978 participants: 295,305 men and 199,673 women.

Cohort follow-up

Within the NIH–AARP study, addresses for members of the NIH-AARP cohort were updated annually by matching to the National Change of Address database maintained by the US Postal Service. Vital status was ascertained by linkage to the Social Security Administration Death Master File in the United States, follow-up searches of the National Death Index, cancer registries, questionnaire responses, and responses to other mailings. Follow-up time extended from study baseline (between 1995 and 1996) until December 31, 2006.

Identification of cancer cases

Incident cancer cases were identified by linkage between the NIH-AARP cohort membership and ten state cancer registry databases, including the eight original states/ metropolitan areas plus those of Texas and Arizona to capture subjects who moved to these states. A validation study showed that approximately 90% of all incident cancer cases in the NIH–AARP cohort were identified by using linkage to cancer registries [35]. Cancer sites were identified by anatomic site and histologic code of the International Classification of Disease for Oncology (ICD-O, third edition) [36]; esophageal cancer included topography codes: C15.0–C15.9, gastric cardia cancer included code: C16.0, and gastric non-cardia cancer included codes: C16.1–C16.7, as well as C16.8 (overlapping tumors) and C16.9 (not otherwise specified). Esophageal cancers were categorized as squamous cell carcinomas, which included histology codes: 8050–8076, and adenocarcinomas, which included: 8140, 8141, 8190–8231, 8260–8263, 8310, 8430, 8480–8490, 8560, and 8570–8572. Gastric cancers were restricted to adenocarcinomas. The NIH-AARP Diet and Health Study was approved by the Special Studies Institutional Review Board of the US National Cancer Institute (NCI).

Dietary data

The baseline questionnaire asked questions about demographics, health conditions, alcohol intake, tobacco smoking, physical activity, and included a food frequency questionnaire (FFQ). The FFQ was designed to assess usual diet by inquiring about the frequency of consumption of 124 food items over the past year (using ten categories ranging from never to 2+ times/day for solid foods and never to 6+ times/day for beverages) and also recorded typical portion size (presented as three ranges based on national dietary data for adults representing <25th, 25th–75th. And >75th percentiles of intake). The food items, portion sizes and nutrient database [37] used data from the 1994–1996 US Department of Agriculture's Continuing Survey of Food Intake by Individuals [38]. The nutrient and food database utilized a recipe file to disaggregate food mixtures into their component ingredients and assign them to the appropriate food groups. The FFQ was calibrated against two nonconsecutive 24-hour dietary recalls, that were administered by telephone within a year from the baseline questionnaire (n = 2053) [34, 39]. The estimated energy-adjusted Pearson correlation coefficients were 0.72 and 0.62 for total fat, 0.76 and 0.69 for saturated fat, 0.71 and 0.62 for monounsaturated fat, and 0.53 and 0.56 for polyunsaturated fat in men and women, respectively [39].

Statistical analysis

All analyses were carried out using SAS 9.1 (SAS Institute, Cary, NC). We interpreted P < 0.05 and/or 95% confidence intervals that excluded 1 as statistically significant. We used

two-sided tests exclusively. Follow-up time extended from the day of study entry to date of death, date of diagnosis of first upper gastrointestinal cancer or head and neck cancer, participant relocation out of the registry ascertainment area, or December 31, 2006, whichever date was earliest.

Hazard ratios (HR) and 95% confidence intervals (95% CI) were calculated using Cox proportional hazards regression [40], with person-years as the underlying time metric. We tested the proportional hazards assumption by modeling interaction terms of time and continuous total fat, saturated fat, monounsaturated fat, polyunsaturated fat, trans-fat, and omega-3 fatty acid intakes and found no statistically significant deviations. Excluding the first two or five years of follow-up did not affect risk estimates (data not shown).

We considered intakes of total fat and fat subtypes (saturated fat, monounsaturated fat, polyunsaturated fat, trans-fat and omega-3 fatty acids (total n-3 polyunsaturated fatty acids 18:3, 18:4, 20:5, 22:5, and 22:6)) as our exposures of interest. We used several energy adjustment methods to examine associations with total fat intake independent of energy intake [41]. Total fat intake is presented as the absolute amount per day (standard model), the residual of the regression of fat intake on non-alcohol energy intake (residual method), or the percentage of non-alcohol energy contributed by fat intake (density model) [41]. Fat subtypes were analyzed using the standard, residual, and density models also, but since results for both models were equivalent, data is presented for the density model only. As alcohol is a risk factor for ESCC [15–17], we used non-alcohol sources of energy to adjust for energy intake in all models and considered alcohol intake as a separate confounder in the multivariable models. We further examined specific food sources for each of the main fat types (total fat, saturated fat, monounsaturated fat, and polyunsaturated fat), including red meat, white meat, eggs, and dairy products.

We analyzed fat intake as both continuous and categorical variables. HRs on the continuous scale were calculated for a twofold increase in fat intake, for example, from 20% to 40% of energy from fat in the density models. In categorical analyses, quintiles of fat intake were based on the distribution observed in the study population at baseline. Tests for linear trend were performed by using the median intake level in each quintile. We included this trend variable in the Cox models and P values were obtained from the Wald test [42].

Our full multivariate models were adjusted for categorical variables of age (<55, 55 to <60, 60 to <65, 65 to <70, and ≥70 years); sex; alcohol intake (none, >0 to 0.5, >0.5 to 1, >1 to 2, >2 to 4, and >4 drinks per day); body mass index (BMI, kg/m²) (<18.5, 18.5 to <25, 25 to <30, 30 to 35, and ≥35); cigarette smoking (never smokers, former smokers who smoked ≤20 cigarettes/day, former smokers who smoked >20 cigarettes/day, current smokers who smoke ≤20 cigarettes/day and current smokers who smoke >20 cigarettes/day); education (high school graduate or less, post high school training or some college training, college graduate, and postgraduate education); ethnicity (non-Hispanic white, non-Hispanic black, Hispanic, and Asian/Pacific Islander/Native American); marital status (yes/no); self-reported diabetes (yes/no); vigorous physical activity (never, rarely, 1–3 times/month, 1–2 times/week, 3–4 times/week, 5 or more times per week), usual activity throughout the day (sit all day, sit much of the day/walk some times, stand/walk often/no lifting, lift/carry light loads and carry heavy loads); and continuous measures for intakes of fruit, vegetables, red meat, and total energy from non-alcohol sources. For the less than 4% of the cohort lacking data for a particular covariate, a separate indicator variable for missing was included in the models.

We further evaluated interactions with smoking (never, former, current), alcohol intake (never/ever), and BMI (normal 18.5 to <25 kg/m² or overweight ≥ 25 kg/m²) by performing stratified analysis and evaluating interaction terms with continuous fat intakes.

RESULTS

Table 1 presents cohort characteristics by quintiles of total fat intake, expressed as a proportion of total non-alcohol energy intake. Median intakes ranged from 20.8% in the lowest quintile to 40.5% in the highest quintile. Compared with subjects in the lowest quintile of percent energy from total fat, those in the highest quintile had fewer years of education, smoked more, reported less physical activity, consumed more calories and red meat per day, consumed less fruit and vegetables, and were more likely to report diabetes. Over an average follow-up of 9.7 years, we documented 630 cases of EAC; 215 cases of ESCC; 454 cases of gastric cardia adenocarcinoma; and 501 cases of gastric non-cardia adenocarcinoma.

Total fat intake

In the energy adjusted models, total fat intake was directly associated with risk of EAC, ESCC and gastric cardia adenocarcinoma, but not gastric non-cardia adenocarcinoma (Table 2). Multivariate adjustment, however, attenuated the majority of risk estimates to null. One exception was for the association for the highest versus the referent quintile of total fat intake with ESCC in the residual energy adjustment model. Yet little evidence was observed for a dose response (*P* for trend = 0.11) and the risk estimate for continuous fat intake was 1.01 (0.99–1.03) per two fold increase in total fat intake. No association was observed for fat intake with ESCC in either the standard or density energy adjustment models. Additionally, when we further adjusted for protein intake to estimate the effect of substituting total fat for carbohydrates, the hazard ratios for total fat remained unchanged (data not shown).

In this population, the main food sources contributing to saturated fat intake were margarine (25.1%), dairy (23.9%) and red meat (22.3%) (mean percentage of saturated fat intake). Major foods contributing to monounsaturated fat intake were margarine (38.6%) and red meat (22.1%) (mean percentage of monounsaturated fat intake); and for polyunsaturated fat intake was margarine (52.5%) (mean percentage of polyunsaturated fat intake) (data not shown).

The Spearman correlation coefficients between saturated fat, monounsaturated fat, polyunsaturated fat, trans-fat and omega-3 fatty acids in the total population were 0.8, 0.4, 0.5, and 0.4, respectively; between monounsaturated fat, polyunsaturated fat, trans-fat and omega-3 fatty acids were 0.7, 0.7, and 0.5, respectively; between polyunsaturated fat, trans-fat and omega-3 fatty acids were 0.5 and 0.8, respectively; between trans-fat and omega-3 fatty acids was 0.3.

Fat subtypes

In the energy adjusted models, saturated fat and monounsaturated fat intakes were directly associated with risk of EAC, ESCC and gastric cardia adenocarcinoma, but not gastric non-cardia adenocarcinoma (Table 3). Yet, as with total fat intake, multivariate adjustment attenuated hazard ratios to null for saturated fat intake (HR (95%CI) 1.27 (0.91–1.78), 0.96 (0.56–1.65) and 1.02 (0.70–1.50), respectively) and monounsaturated fat intake (HR (95%CI) 1.18 (0.84–1.66), 1.59 (0.91–2.80) and 1.03 (0.71–1.51), respectively).

Before multivariate adjustment, polyunsaturated fat intake was directly associated with risk of ESCC (95%CI 1.60 (1.02–2.50)), though not with other examined cancer sites. However, multivariate adjustment attenuated this association to null (HR (95%CI) 1.18 (0.74–1.89)).

When we included the fat subtypes (saturated, monounsaturated and polyunsaturated) with protein in the models to estimate the effect of substituting the intake of a given fat subtype for carbohydrate intake, none of the hazard ratios changed on the continuous scale (data not shown).

In the energy adjusted models, trans-fat intake was directly associated with risk of EAC, ESCC and gastric cardia adenocarcinoma, but not gastric non-cardia adenocarcinoma. Adjusting for the other confounding variables in the multivariate models attenuated the hazard ratios for EAC and gastric cardia adenocarcinoma to null (HR (95%CI) 1.24 (0.92–1.68) and 1.03 (0.74–1.43), respectively), but a borderline significant association persisted for ESCC (HR (95%CI) 1.68 (1.00–2.81)). Nevertheless, the tests for trend were not significant (all *P* for trend > 0.05) and the risk estimates for continuous intakes per two fold increase were also attenuated to null.

No consistent associations were seen for EAC, ESCC, gastric cardia adenocarcinoma or gastric non-cardia adenocarcinoma with omega-3 fatty acid intakes, either in energy adjusted or multivariate adjusted models.

We also investigated association with fat types from different food sources. However, no evidence was observed for associations for fat subtypes from different sources, e.g. saturated fat from red meat, with any of the examined outcomes (data not shown).

There were no statistically significant deviations from the proportional hazards assumption. But to further examine the robustness of the associations, we deleted two and five years of follow-up and fit the models using quintiles from the density model for the different fat intakes. Overall, the point estimates for associations between fat intakes and cancer risk were unaffected. For example, EAC subjects in the highest versus the referent quintile of saturated fat intake – (HR (95%CI) no lag, 1.27 (0.91–1.78); 2-years lag, 1.30 (0.91–1.86); 5-years lag, 1.08 (0.70–1.66); ESCC subjects in the highest versus the referent quintile of monounsaturated fat intake – (HR (95%CI) no lag, 1.59 (0.91–2.80); 2-years lag, 1.51 (0.83–2.74); 5-years lag, 1.27 (0.66–2.47)).

The association of fat intakes (continuous variable) with cancer risk was also examined by stratum of cigarette use (never, former, or current), alcohol use (drinkers and non-drinkers), and BMI (normal 18.5–<25 kg/m² or overweight ≥ 25 kg/m²). We observed little difference by smoking status, and the risk estimates were similar in alcohol drinkers and non-drinkers (data not shown). Formal tests for interaction failed to reach statistical significance for either cigarette smoking or alcohol use (*P* for interaction > 0.05) (data not shown). However, an inverse association for polyunsaturated fat was seen for risk of EAC in subjects with normal BMI (HR (95%CI) 0.76 (0.63–0.92)), that was not present in overweight subjects (HR (95%CI) 1.04 (0.96–1.14)), or in unstratified analysis (HR (95%CI) 0.97 (0.90–1.05)). Also, the formal test for interaction reached statistical significance in this analysis (*P* for interaction = 0.02).

DISCUSSION

In the prospective NIH-AARP cohort, we found no consistent associations between total fat intake and fat subtypes with risk of EAC, ESCC, gastric cardia and gastric non-cardia adenocarcinoma; though a protective effect of polyunsaturated fat intake was seen for EAC in subjects with a normal BMI.

Although several previous studies have reported associations between esophageal and gastric adenocarcinomas, and dietary fat intakes [23–27], results from other studies have been inconsistent [28–32]. Many of these previous studies have been hindered due to their

relatively small case numbers and their case-control design [23–31], and some required the grouping of different sites together [26, 27, 30]. To our knowledge, only one other prospective cohort study examined fat intake with esophageal cancer risk [32]. Even though their results appear to support our findings, their cohort was limited by small case numbers ($n = 101$), of which 68 were ESCC cases, 8 were EAC cases, 1 case was classified as other and 24 had unknown histological types.

Furthermore, few previous studies have comprehensively investigated fat intake, with data particularly limited for intake of trans-fat and omega-3 fatty acids, which we included within this current study. However, we did not find any consistent associations between either trans-fat or omega-3 fatty acid intakes with EAC, ESCC, gastric cardia adenocarcinoma or gastric non-cardia adenocarcinoma. Future studies are needed to confirm these findings.

Obese individuals are thought to have higher prevalence of GERD, a potential risk factor for EAC, due to increased intra-abdominal pressure on the lower esophageal sphincter [43–45]. In some, but not all previous studies, dietary fat has been positively linked to reflux and reflux symptoms [22], presumably through relaxation of the lower esophageal sphincter [31, 46]. Though we lacked assessment of reflux, our findings indicating no association between dietary fat intakes and EAC risk does not appear to support a hypothesis linking dietary fat intakes and EAC through reflux.

We tested for effect modification of fat intake by smoking, alcohol, and BMI for each of the four cancer outcomes. We found one significant interaction that suggested higher intake of polyunsaturated fat was associated with reduced risk of EAC only among normal BMI subjects and no association in subjects who were overweight or obese. This result may be spurious due to the number of interactions we tested and confirmation of this result should be sought in future analyses. Omega-3 fatty acids did not display a similar association to that of polyunsaturated fat intakes and formal tests for interaction failed to reach statistical significance.

Our study had several strengths, including its prospective nature and large size, which allowed for a wide range of reported intakes. Unlike case-control studies, the prospective nature of this study also limited the possibility of recall and selection bias, as diet was assessed before cancer diagnosis. Information was also available for a wide selection of possible confounders and we comprehensively investigated fat intakes. However, our study also had several limitations. We lacked information on possibly important confounders, such as GERD symptoms and *Helicobacter pylori* infection, a cause of gastric non-cardia adenocarcinoma, but which also may be protective against EAC [47]. The intake distributions for respondents differed from those observed in national surveys. The AARP respondents to the questionnaire consumed less fat and red meat and more fiber and fruits and vegetables than comparably aged adults in the general US population, on average. However, the intake distributions for these dietary factors were wider than those in the national surveys. Additionally, the AARP respondents were predominantly White and more educated than the general US population [34]. We also assessed fat intakes at a single time-point with the use of a FFQ, which is subject to potential reporting errors [48]. This was highlighted quite well by Bingham et al. [49] who demonstrated a significant positive risk of breast cancer with saturated fat intake measured with a food diary, but not with saturated fat measured with a FFQ. Thus, it is possible that measurement error prevented us from observing an association in our study. Clearly the identification of suitable biomarkers for fat intake (currently exist for only a few nutrients or nutrient combinations such as short-term total energy, protein, sodium, and potassium) would substantially improve exposure assessment. Nevertheless, it should be noted that in large scale cohorts, such as the NIH-

AARP cohort, FFQs continue to be the most practical, less burdensome, and most cost-effective method for the reporting of food consumption.

In summary, we found null associations between total fat intake and fat subtypes with risk of EAC, ESCC, gastric cardia adenocarcinoma or gastric non-cardia adenocarcinoma in a large US prospective cohort; though a possible protective effect of polyunsaturated fat intake was seen for EAC in subjects with a normal BMI.

Novelty

Previous epidemiological studies have examined the association between dietary fat intake with esophageal and gastric cancer risk. However, results have not been consistent and many studies did not differentiate between specific cancers e.g. esophageal adenocarcinoma and esophageal squamous cell carcinoma. Additionally, many of these previous studies have been hindered due to their relatively small case numbers and case-control design. However, this large prospective cohort afforded us the opportunity to investigate associations between intake of total fat and fat subtypes with risk of esophageal adenocarcinoma, esophageal squamous cell carcinoma, gastric cardia adenocarcinoma, and gastric non-cardia adenocarcinoma.

Impact

Esophageal cancer is the sixth leading cause of cancer mortality worldwide and gastric cancer is the second. Unfortunately, patients presenting with esophageal cancer do not commonly come to medical attention until the cancer is at an advanced stage and preventative treatment is near impossible. Therefore, the identification of modifiable risk factors for the primary prevention of esophageal and gastric cancer is imperative, with diet being one such potentially important modifiable risk factor. The results of this large prospective cohort study demonstrated a lack of an association between intake of total fat or fat subtypes with risk of esophageal adenocarcinoma, esophageal squamous cell carcinoma, gastric cardia adenocarcinoma, or gastric non-cardia adenocarcinoma. Therefore, interventions to reduce the intake of dietary fats may not help reduce incidence of esophageal or gastric cancers.

Acknowledgments

This research was supported [in part] by the all-Ireland National Cancer Institute Cancer Consortium Joint Research Project in Cancer, supported by the Health and Social Care Research & Development Office (Belfast, Northern Ireland) and the Intramural Research Program of the NIH, National Cancer Institute (Bethesda, MD, USA). No conflicts of interest to declare. Cancer incidence data from the Atlanta metropolitan area were collected by the Georgia Center for Cancer Statistics, Department of Epidemiology, Rollins School of Public Health, Emory University. Cancer incidence data from California were collected by the California Department of Health Services, Cancer Surveillance Section. Cancer incidence data from the Detroit metropolitan area were collected by the Michigan Cancer Surveillance Program, Community Health Administration, State of Michigan. The Florida cancer incidence data used in this report were collected by the Florida Cancer Data System (FCDC) under contract with the Florida Department of Health (FDOH). The views expressed herein are solely those of the authors and do not necessarily reflect those of the FCDC or FDOH. Cancer incidence data from Louisiana were collected by the Louisiana Tumor Registry, Louisiana State University Medical Center in New Orleans. Cancer incidence data from New Jersey were collected by the New Jersey State Cancer Registry, Cancer Epidemiology Services, New Jersey State Department of Health and Senior Services. Cancer incidence data from North Carolina were collected by the North Carolina Central Cancer Registry. Cancer incidence data from Pennsylvania were supplied by the Division of Health Statistics and Research, Pennsylvania Department of Health, Harrisburg, Pennsylvania. The Pennsylvania Department of Health specifically disclaims responsibility for any analyses, interpretations or conclusions. Cancer incidence data from Arizona were collected by the Arizona Cancer Registry, Division of Public Health Services, Arizona Department of Health Services. Cancer incidence data from Texas were collected by the Texas Cancer Registry, Cancer Epidemiology and Surveillance Branch, Texas Department of State Health Services.

Abbreviations used

95%CI	95% confidence interval
BMI	body mass index
EAC	esophageal adenocarcinoma
ESCC	esophageal squamous cell carcinoma
FFQ	food frequency questionnaire
GERD	gastro-esophageal reflux disease
HR	hazard ratio
NCI	National Cancer Institute
NIH	National Institutes of Health

REFERENCES

1. Ferlay, J.; Shin, HR.; Bray, F.; Forman, D.; Mathers, C.; Parkin, DM. GLOBOCAN 2008, Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 10. Lyon: International Agency for Research on Cancer; 2010. Available from: <http://globocan.iarc.fr>.
2. Crew KD, Neugut AI. Epidemiology of gastric cancer. *World J Gastroenterol*. 2006; 12:354–362. [PubMed: 16489633]
3. Blot WJ, Devesa SS, Kneller RW, Fraumeni JF Jr. Rising incidence of adenocarcinoma of the esophagus and gastric cardia. *JAMA*. 1991; 265:1287–1289. [PubMed: 1995976]
4. Brown LM, Devesa SS, Chow WH. Incidence of adenocarcinoma of the esophagus among white Americans by sex, stage, and age. *J Natl Cancer Inst*. 2008; 100:1184–1187. [PubMed: 18695138]
5. Bollschweiler E, Wolfgarten E, Gutschow C, Holscher AH. Demographic variations in the rising incidence of esophageal adenocarcinoma in white males. *Cancer*. 2001; 92:549–555. [PubMed: 11505399]
6. World Cancer Research Fund & American Institute for Cancer Research. Food, Nutrition, Physical Activity, and the Prevention of Cancer: a Global Perspective. Washington, DC: American Institute for Cancer Research; 2007.
7. Cook MB, Chow WH, Devesa SS. Oesophageal cancer incidence in the United States by race, sex, and histologic type, 1977–2005. *Br J Cancer*. 2009; 101:855–859. [PubMed: 19672254]
8. Brown LM, Devesa SS. Epidemiologic trends in esophageal and gastric cancer in the United States. *Surg Oncol Clin N Am*. 2002; 11:235–256. [PubMed: 12424848]
9. Bosetti C, Levi F, Ferlay J, Garavello W, Lucchini F, Bertuccio P, Negri E, La Vecchia C. Trends in oesophageal cancer incidence and mortality in Europe. *Int J Cancer*. 2008; 122:1118–1129. [PubMed: 17990321]
10. Corley DA, Kubo A. Influence of site classification on cancer incidence rates: an analysis of gastric cardia carcinomas. *J Natl Cancer Inst*. 2004; 96:1383–1387. [PubMed: 15367571]
11. Lindblad M, Ye W, Lindgren A, Lagergren J. Disparities in the classification of esophageal and cardia adenocarcinomas and their influence on reported incidence rates. *Ann Surg*. 2006; 243:479–485. [PubMed: 16552198]
12. Enzinger PC, Mayer RJ. Esophageal cancer. *N Engl J Med*. 2003; 349:2241–2252. [PubMed: 14657432]
13. Cook MB, Kamangar F, Whitman DC, Freedman ND, Gammon MD, Bernstein L, Brown LM, Risch HA, Ye W, Sharp L, Pandeya N, Webb PM, et al. Cigarette smoking and adenocarcinomas of the esophagus and esophagogastric junction: a pooled analysis from the international BEACON consortium. *J Natl Cancer Inst*. 2010; 102:1344–1353. [PubMed: 20716718]
14. Tramacere I, La Vecchia C, Negri E. Tobacco Smoking and Esophageal and Gastric Cardia Adenocarcinoma: A Meta-analysis. *Epidemiology*. 2011; 22:344–349. [PubMed: 21330928]

15. Morita M, Kumashiro R, Kubo N, Nakashima Y, Yoshida R, Yoshinaga K, Saeki H, Emi Y, Kakeji Y, Sakaguchi Y, Toh Y, Maehara Y. Alcohol drinking, cigarette smoking, and the development of squamous cell carcinoma of the esophagus: epidemiology, clinical findings, and prevention. *Int J Clin Oncol*. 2010; 15:126–134. [PubMed: 20224884]
16. Toh Y, Oki E, Ohgaki K, Sakamoto Y, Ito S, Egashira A, Saeki H, Kakeji Y, Morita M, Sakaguchi Y, Okamura T, Maehara Y. Alcohol drinking, cigarette smoking, and the development of squamous cell carcinoma of the esophagus: molecular mechanisms of carcinogenesis. *Int J Clin Oncol*. 2010; 15:135–144. [PubMed: 20224883]
17. Freedman ND, Murray LJ, Kamangar F, Abnet CC, Cook MB, Nyrén O, Ye W, Wu AH, Bernstein L, Brown LM, Ward MH, Pandeya N, et al. Alcohol intake and risk of oesophageal adenocarcinoma: a pooled analysis from the BEACON Consortium. *Gut*. 2011; 60:1029–1037. [PubMed: 21406386]
18. Cavaleiro-Pinto M, Peleteiro B, Lunet N, Barros H. *Helicobacter pylori* infection and gastric cardia cancer: systematic review and meta-analysis. *Cancer Causes Control*. 2011; 22:375–387. [PubMed: 21184266]
19. Abnet CC, Freedman ND, Hollenbeck AR, Fraumeni JF Jr, Leitzmann M, Schatzkin A. A prospective study of BMI and risk of oesophageal and gastric adenocarcinoma. *Eur J Cancer*. 2008; 44:465–471. [PubMed: 18221867]
20. Merry AH, Schouten LJ, Goldbohm RA, van den Brandt PA. Body mass index, height and risk of adenocarcinoma of the oesophagus and gastric cardia: a prospective cohort study. *Gut*. 2007; 56:1503–1511. [PubMed: 17337464]
21. Brenner H, Rothenbacher D, Arndt V. Epidemiology of stomach cancer. *Methods Mol Biol*. 2009; 472:467–477. [PubMed: 19107449]
22. Fox M, Barr C, Nolan S, Lomer M, Anggiansah A, Wong T. The effects of dietary fat and calorie density on esophageal acid exposure and reflux symptoms. *Clin Gastroenterol Hepatol*. 2007; 5:439–444. [PubMed: 17363334]
23. O'Doherty MG, Cantwell MM, Murray LJ, Anderson LA, Abnet CC. on behalf of the FINBAR study group. Dietary fat and meat intakes and risk of reflux esophagitis, Barrett's esophagus and esophageal adenocarcinoma. *Int J Cancer*. 2011; 129:1493–1502. [PubMed: 21455992]
24. Mayne ST, Risch HA, Dubrow R, Chow WH, Gammon MD, Vaughan TL, Farrow DC, Schoenberg JB, Stanford JL, Ahsan H, West AB, Rotterdam H, et al. Nutrient intake and risk of subtypes of esophageal and gastric cancer. *Cancer Epidemiol Biomarkers Prev*. 2001; 10:1055–1062. [PubMed: 11588131]
25. Chen H, Tucker KL, Graubard BI, Heineman EF, Markin RS, Potischman NA, Russell RM, Weisenburger DD, Ward MH. Nutrient intakes and adenocarcinoma of the esophagus and distal stomach. *Nutr Cancer*. 2002; 42:33–40. [PubMed: 12235648]
26. Zhang ZF, Kurtz RC, Yu GP, Sun M, Gargon N, Karpeh M Jr, Fein JS, Harlap S. Adenocarcinomas of the esophagus and gastric cardia: the role of diet. *Nutr Cancer*. 1997; 27:298–309. [PubMed: 9101561]
27. Kabat GC, Ng SK, Wynder EL. Tobacco, alcohol intake, and diet in relation to adenocarcinoma of the esophagus and gastric cardia. *Cancer Causes Control*. 1993; 4:123–132. [PubMed: 8481491]
28. Tzonou A, Lipworth L, Garidou A, Signorello LB, Lagiou P, Hsieh C, Trichopoulos D. Diet and risk of esophageal cancer by histologic type in a low-risk population. *Int J Cancer*. 1996; 68:300–304. [PubMed: 8903470]
29. Wu AH, Tseng CC, Hankin J, Bernstein L. Fiber intake and risk of adenocarcinomas of the esophagus and stomach. *Cancer Causes Control*. 2007; 18:713–722. [PubMed: 17562192]
30. Brown LM, Swanson CA, Gridley G, Swanson GM, Schoenberg JB, Greenberg RS, Silverman DT, Pottern LM, Hayes RB, Schwartz AG, Liff JM, Fraumeni JF Jr, et al. Adenocarcinoma of the esophagus: role of obesity and diet. *J Natl Cancer Inst*. 1995; 87:104–109. [PubMed: 7707381]
31. Terry P, Lagergren J, Wolk A, Nyren O. Reflux-inducing dietary factors and risk of adenocarcinoma of the esophagus and gastric cardia. *Nutr Cancer*. 2000; 38:186–191. [PubMed: 11525596]
32. Fan Y, Yuan JM, Wang R, Gao YT, Yu MC. Alcohol, tobacco, and diet in relation to esophageal cancer: the Shanghai Cohort Study. *Nutr Cancer*. 2008; 60:354–363. [PubMed: 18444169]

33. De Ceglie A, Fisher DA, Filiberti R, Bianchi S, Conio M. Barrett's esophagus, esophageal and esophagogastric junction adenocarcinomas: The role of diet. *Clin Res Hepatol Gastroenterol*. 2011; 35:7–16. [PubMed: 20970272]
34. Schatzkin A, Subar AF, Thompson FE, Harlan LC, Tangrea J, Hollenbeck AR, Hurwitz PE, Coyle L, Schussler N, Michaud DS, Freedman LS, Brown CC, et al. Design and serendipity in establishing a large cohort with wide dietary intake distributions : the National Institutes of Health-American Association of Retired Persons Diet and Health Study. *Am J Epidemiol*. 2001; 154:1119–1125. [PubMed: 11744517]
35. Michaud DS, Midthune D, Hermansen S, Leitzmann M, Harlan LC, Kipnis V, Schatzkin A. Comparison of cancer registry case ascertainment with SEER estimates and self-reporting in a subset of the NIH-AARP diet and health study. *J Registry Manag*. 2005; 32:70–75.
36. Fritz, AG.; Percy, C.; Jack, A.; Shanmugaratnam, K.; Sobin, L.; Parkin, DM.; Whelan, S., editors. International classification of diseases for oncology: ICD-O. 3rd edition. Geneva: World Health Organization; 2000.
37. Subar AF, Midthune D, Kulldorff M, Brown CC, Thompson FE, Kipnis V, Schatzkin A. Evaluation of alternative approaches to assign nutrient values to food groups in food frequency questionnaires. *Am J Epidemiol*. 2000; 152:279–286. [PubMed: 10933275]
38. Tippet, KS.; Cypel, YS. Design and Operation: Continuing Survey of Food Intakes by Individuals and Diet and Health Knowledge Survey, 1994–96. No. 96–1. Beltsville, MD: U.S. Department of Agriculture; 1998.
39. Thompson FE, Kipnis V, Midthune D, Freedman LS, Carroll RJ, Subar AF, Brown CC, Butcher MS, Mouw T, Leitzmann M, Schatzkin A. Performance of a food-frequency questionnaire in the US NIH-AARP (National Institutes of Health-American Association of Retired Persons) Diet and Health Study. *Public Health Nutr*. 2008; 11:183–195. [PubMed: 17610761]
40. Cox DR. Regression models and life-tables. *J R Stat Soc Series B Stat Methodol*. 1972; 34:187.
41. Willett W, Stampfer MJ. Total energy intake: implications for epidemiologic analyses. *Am J Epidemiol*. 1986; 124:17–27. [PubMed: 3521261]
42. Greenland, S.; Rothman, KJ. Fundamentals of Epidemiologic Data Analysis. In: Greenland, S.; Rothman, KJ., editors. *Modern Epidemiology*. 2nd ed. Philadelphia, PA: Lippincott-Raven; 1998. p. 201-229.
43. Kim R, Weissfeld JL, Reynolds JC, Kuller LH. Etiology of Barrett's metaplasia and esophageal adenocarcinoma. *Cancer Epidemiol Biomarkers Prev*. 1997; 6:369–377. [PubMed: 9149898]
44. Murray L, Johnston B, Lane A, Harvey I, Donovan J, Nair P, Harvey R. Relationship between body mass and gastro-oesophageal reflux symptoms: The Bristol Helicobacter Project. *Int J Epidemiol*. 2003; 32:645–650. [PubMed: 12913045]
45. Corley DA, Kubo A, Zhao W. Abdominal obesity, ethnicity and gastro-oesophageal reflux symptoms. *Gut*. 2007; 56:756–762. [PubMed: 17047097]
46. Becker DJ, Sinclair J, Castell DO, Wu WC. A comparison of high and low fat meals on postprandial esophageal acid exposure. *Am J Gastroenterol*. 1989; 84:782–786. [PubMed: 2741888]
47. Islami F, Kamangar F. Helicobacter pylori and esophageal cancer risk: a meta-analysis. *Cancer Prev Res (Phila)*. 2008; 1:329–338. [PubMed: 19138977]
48. Schaefer EJ, Augustin JL, Schaefer MM, Rasmussen H, Ordovas JM, Dallal GE, Dwyer JT. Lack of efficacy of a food-frequency questionnaire in assessing dietary macronutrient intakes in subjects consuming diets of known composition. *Am J Clin Nutr*. 2000; 71:746–751. [PubMed: 10702168]
49. Bingham SA, Luben R, Welch A, Wareham N, Khaw KT, Day N. Are imprecise methods obscuring a relation between fat and breast cancer? *Lancet*. 2003; 362:212–214. [PubMed: 12885485]

Table 1

Baseline characteristics by quintile of total fat intake as a percentage of energy among 494,978 participants in the NIH-AARP Diet and Health Study¹

Characteristic	Quintile of percentage energy from total fat (median)				
	Quintile 1 (20.8)	Quintile 2 (26.8)	Quintile 3 (31.0)	Quintile 4 (35.0)	Quintile 5 (40.5)
Number	98,995	98,996	98,996	98,996	98,995
Sex, Men, N (%)	52,152 (52.7)	55,890 (56.5)	60,063 (60.7)	63,341 (64.0)	63,859 (64.5)
Age, mean (SD)	62.2 (5.4)	62.1 (5.4)	62.1 (5.4)	62.0 (5.4)	61.8 (5.4)
Body mass index (kg/m ²), mean (SD)	26.0 (4.7)	26.8 (4.8)	27.3 (5.0)	27.5 (5.0)	27.9 (5.5)
<i>Race/ethnicity</i>					
Non-Hispanic white, %	90.1	91.9	92.7	93.4	94.2
Non-Hispanic black, %	4.5	4.1	4.0	3.7	3.5
Hispanic, %	2.7	2.2	1.9	1.6	1.3
Other, %	2.8	1.8	1.4	1.3	1.1
<i>Education</i>					
High school or less, %	23.0	25.1	26.6	27.7	29.0
Post high school, %	9.1	10.0	10.4	10.5	10.7
Some college, %	23.0	23.3	23.5	24.1	25.6
College and post graduate, %	44.8	41.8	39.5	37.7	34.8
<i>Smoking</i>					
Never smoked, %	41.9	39.5	37.2	34.3	29.5
Former 20 cigarettes/day, %	30.1	29.5	28.4	26.8	23.6
Former > 20 cigarettes/day, %	19.8	20.6	21.5	22.4	23.8
Current 20 cigarettes/day, %	6.1	7.5	8.8	10.6	13.2
Current > 20 cigarettes/day, %	2.1	2.9	4.2	6.0	10.0
<i>Vigorous physical activity</i>					
Never, %	3.4	3.7	4.2	4.6	6.5
Rarely, %	9.8	11.8	13.5	15.2	18.2
1–3 times/month, %	10.2	12.6	14.0	15.2	16.5
1–2 times/week, %	18.2	21.5	22.8	23.6	22.5
3–4 times/week, %	31.1	29.6	27.5	25.2	21.7
5 times/week, %	27.3	20.8	18.0	16.2	14.7

Characteristic	Quintile of percentage energy from total fat (median)				
	Quintile 1 (20.8)	Quintile 2 (26.8)	Quintile 3 (31.0)	Quintile 4 (35.0)	Quintile 5 (40.5)
<i>Activity throughout the day</i>					
Sit during day, not much walking, %	7.1	7.5	7.8	8.3	9.7
Sit much of day, walk a fair amount, %	32.3	33.0	33.1	33.1	33.1
Stand/walk a lot, no lifting, %	40.5	39.7	38.8	37.7	36.0
Lift/carry light loads, %	17.5	17.3	17.5	17.8	17.6
Heavy work, %	2.5	2.5	2.9	3.2	3.6
Married, Yes, %	64.1	68.3	70.5	72.0	70.6
Self-reported diabetes, %	6.4	8.1	9.0	9.7	12.0
Energy from non-alcohol sources (kcal/day), mean (SD)	1,623 (694)	1,692 (701)	1,781 (739)	1,879 (790)	1,970 (864)
Fruit (servings/1000 kcal), mean (SD)	2.8 (1.5)	2.0 (1.0)	1.6 (0.9)	1.3 (0.7)	0.9 (0.6)
Vegetables (servings/1000kcal), mean (SD)	2.6 (1.5)	2.4 (1.2)	2.2 (1.0)	2.1 (1.0)	2.0 (0.9)
Red meat (grams/1000 kcal), mean (SD)	18.0 (12.9)	29.0 (16.1)	36.3 (18.3)	43.1 (20.8)	51.5 (25.6)
Alcohol (drinks/day), mean (SD)	0.9 (3.2)	0.8 (2.2)	0.9 (2.1)	0.9 (2.1)	1.0 (2.1)
<i>Cancer sites</i>					
Esophageal adenocarcinoma, N	83	126	117	150	154
Esophageal squamous cell carcinoma, N	25	38	44	49	59
Gastric cardia adenocarcinoma, N	78	75	103	86	112
Gastric non-cardia adenocarcinoma, N	89	104	96	119	93

[†] Some columns may not total 100% due to rounding.

Energy- and multivariate-adjusted hazard ratios and 95% confidence intervals (HR 95%CI) for esophageal adenocarcinoma, esophageal squamous cell carcinoma, gastric cardia adenocarcinoma and gastric non-cardia adenocarcinoma risk in association with total fat intake among 494,978 participants in the NIH-AARP Diet and Health Study¹

Table 2

Energy adjustment model	Quintile of total fat intake ²					P _{trend} [†]	Total fat intake as a continuous variable [‡]
	1	2	3	4	5		
Esophageal adenocarcinoma							
Standard [§]							
Cases (n)	98	90	131	145	166		
Energy adjusted, HR (95%CI)	1.00 (Ref)	0.82 (0.61–1.10)	1.13 (0.85–1.49)	1.21 (0.89–1.63)	1.46 (1.00–2.13)	0.01	1.02 (1.01–1.03)
Multivariate adjusted, HR (95%CI)	1.00 (Ref)	0.74 (0.55–0.99)	0.93 (0.70–1.26)	0.91 (0.65–1.26)	0.92 (0.60–1.42)	0.81	1.01 (1.00–1.02)
Residual							
Cases (n)	89	122	125	140	154		
Energy adjusted, HR (95%CI)	1.00 (Ref)	1.31 (1.00–1.73)	1.30 (0.99–1.70)	1.42 (1.09–1.85)	1.65 (1.27–2.14)	<0.01	1.02 (1.01–1.03)
Multivariate adjusted, HR (95%CI)	1.00 (Ref)	1.17 (0.88–1.55)	1.08 (0.81–1.46)	1.10 (0.81–1.50)	1.16 (0.84–1.61)	0.54	1.00 (0.99–1.02)
Density [¶]							
Cases (n)	83	126	117	150	154		
Energy adjusted, HR (95%CI)	1.00 (Ref)	1.45 (1.10–1.91)	1.28 (0.97–1.70)	1.59 (1.21–2.08)	1.66 (1.27–2.18)	<0.01	1.04 (1.02–1.07)
Multivariate adjusted, HR (95%CI)	1.00 (Ref)	1.30 (0.97–1.73)	1.07 (0.79–1.46)	1.24 (0.91–1.69)	1.17 (0.84–1.64)	0.58	1.01 (0.98–1.04)
Esophageal squamous cell carcinoma							
Standard [§]							
Cases (n)	41	35	38	51	50		
Energy adjusted, HR (95%CI)	1.00 (Ref)	0.94 (0.59–1.49)	1.10 (0.68–1.77)	1.64 (0.98–2.72)	2.08 (1.07–4.05)	0.01	1.03 (1.01–1.04)
Multivariate adjusted, HR (95%CI)	1.00 (Ref)	0.78 (0.49–1.25)	0.80 (0.49–1.32)	1.02 (0.59–1.74)	0.95 (0.46–1.98)	0.76	1.00 (0.98–1.02)
Residual							
Cases (n)	22	42	42	44	65		
Energy adjusted, HR (95%CI)	1.00 (Ref)	1.91 (1.14–3.20)	1.90 (1.14–3.19)	2.00 (1.20–3.34)	3.02 (1.86–4.90)	<0.01	1.04 (1.02–1.06)
Multivariate adjusted, HR (95%CI)	1.00 (Ref)	1.82 (1.08–3.09)	1.67 (0.97–2.87)	1.56 (0.89–2.73)	1.89 (1.07–3.33)	0.11	1.01 (0.99–1.03)
Density [¶]							
Cases (n)	25	38	44	49	59		

Energy adjustment model	Quintile of total fat intake ²					P _{trend} [†]	Total fat intake as a continuous variable [‡]
	1	2	3	4	5		
Gastric cardia adenocarcinoma							
Standard [§]							
Cases (n)	73	72	105	102	102		
Energy adjusted, HR (95%CI)	1.00 (Ref)	1.53 (0.92–2.53)	1.77 (1.08–2.90)	1.98 (1.22–3.22)	2.45 (1.53–3.93)	<0.01	1.07 (1.03–1.11)
Multivariate adjusted, HR (95%CI)	1.00 (Ref)	1.41 (0.84–2.36)	1.49 (0.89–2.51)	1.47 (0.86–2.52)	1.43 (0.82–2.51)	0.32	1.01 (0.97–1.06)
Residual							
Cases (n)	77	75	103	88	111		
Energy adjusted, HR (95%CI)	1.00 (Ref)	0.95 (0.68–1.32)	1.38 (0.99–1.91)	1.37 (0.96–1.97)	1.62 (1.02–2.58)	0.02	1.02 (1.00–1.03)
Multivariate adjusted, HR (95%CI)	1.00 (Ref)	0.90 (0.64–1.27)	1.25 (0.88–1.77)	1.16 (0.78–1.73)	1.20 (0.70–2.05)	0.41	1.00 (0.99–1.02)
Density [¶]							
Cases (n)	78	75	103	86	112		
Energy adjusted, HR (95%CI)	1.00 (Ref)	0.93 (0.68–1.28)	1.24 (0.92–1.67)	1.02 (0.75–1.38)	1.36 (1.02–1.82)	0.03	1.04 (1.01–1.07)
Multivariate adjusted, HR (95%CI)	1.00 (Ref)	0.85 (0.61–1.18)	1.08 (0.78–1.49)	0.83 (0.58–1.18)	0.99 (0.68–1.44)	0.97	1.02 (0.99–1.05)
Gastric non-cardia adenocarcinoma							
Standard [§]							
Cases (n)	89	80	121	102	109		
Energy adjusted, HR (95%CI)	1.00 (Ref)	0.83 (0.61–1.13)	1.20 (0.89–1.61)	0.96 (0.69–1.34)	0.94 (0.61–1.45)	0.91	1.00 (0.99–1.01)
Multivariate adjusted, HR (95%CI)	1.00 (Ref)	0.88 (0.64–1.20)	1.28 (0.93–1.75)	1.02 (0.71–1.48)	0.96 (0.59–1.59)	0.60	1.00 (0.99–1.01)
Residual							
Cases (n)	97	97	101	114	92		
Energy adjusted, HR (95%CI)	1.00 (Ref)	0.99 (0.75–1.32)	1.02 (0.77–1.35)	1.15 (0.88–1.51)	0.97 (0.73–1.29)	0.82	1.00 (0.99–1.02)
Multivariate adjusted, HR (95%CI)	1.00 (Ref)	1.00 (0.75–1.35)	1.02 (0.75–1.39)	1.13 (0.82–1.56)	0.91 (0.64–1.30)	0.81	1.00 (0.99–1.02)
Density [¶]							
Cases (n)	89	104	96	119	93		
Energy adjusted, HR (95%CI)	1.00 (Ref)	1.16 (0.87–1.54)	1.05 (0.79–1.40)	1.29 (0.98–1.70)	1.02 (0.76–1.37)	0.65	1.01 (0.98–1.03)
Multivariate adjusted, HR (95%CI)	1.00 (Ref)	1.18 (0.88–1.59)	1.07 (0.78–1.46)	1.29 (0.93–1.79)	0.99 (0.69–1.43)	0.92	1.00 (0.97–1.03)

Cox proportional hazards regression was used to estimate hazard ratios (HR) and 95% confidence intervals (95%CI).

¹Energy adjusted Cox regression models adjusted for age, sex and non-alcohol energy intake. Multivariate Cox proportional hazards regression models adjusted for age, sex, non-alcohol energy intake, body mass index, education, ethnicity, alcohol, cigarette smoking, diabetes, physical activity, fruit and vegetable intake, and red meat intake.

²Median values; standard model (grams/day), Q1 (27.3), Q2 (41.7), Q3 (55.2), Q4 (72.5), Q5 (106.0); residual model (grams/day), Q1 (35.4), Q2 (48.9), Q3 (58.3), Q4 (67.2), Q5 (73.6); density model (percentage of non-alcohol energy), Q1 (20.8), Q2 (26.8), Q3 (31.0), Q4 (35.0), Q5 (40.5).

³Two-sided Wald χ^2 test for linear trend using median intake in each quintile.

⁴Hazard ratios presented for a twofold increase in total fat intake.

⁵Standard models contain total fat as the absolute amount per day.

⁶Residual models contain the residual of the regression of total fat intake on non-alcohol energy intake (with predicted mean added).

⁷Density models contain the percentage of non-alcohol energy contributed by total fat intake.

Energy- and multivariate-adjusted hazard ratios and 95% confidence intervals (HR 95%CI) for esophageal adenocarcinoma, esophageal squamous cell carcinoma, gastric cardia adenocarcinoma and gastric non-cardia adenocarcinoma risk in association with intakes of fat subtypes among 494,978 participants in the NIH-AARP Diet and Health Study¹

Table 3

Energy adjustment model	Quintile of intake ²					<i>P</i> _{trend} [†]	Fat intake as a continuous variable [‡]
	1	2	3	4	5		
Esophageal adenocarcinoma							
<i>Saturated fat</i>							
Cases (n)	85	124	117	137	167		
Energy adjusted, HR (95%CI)	1.00 (Ref)	1.40 (1.07–1.85)	1.27 (0.96–1.68)	1.45 (1.10–1.90)	1.79 (1.37–2.33)	<0.01	1.13 (1.07–1.19)
Multivariate adjusted, HR (95%CI)	1.00 (Ref)	1.25 (0.94–1.67)	1.06 (0.78–1.44)	1.13 (0.82–1.55)	1.27 (0.91–1.78)	0.28	1.05 (0.98–1.12)
<i>Monounsaturated fat</i>							
Cases (n)	85	114	135	123	173		
Energy adjusted, HR (95%CI)	1.00 (Ref)	1.26 (0.95–1.67)	1.42 (1.08–1.85)	1.22 (0.93–1.61)	1.69 (1.30–2.20)	<0.01	1.11 (1.06–1.17)
Multivariate adjusted, HR (95%CI)	1.00 (Ref)	1.12 (0.84–1.50)	1.18 (0.88–1.60)	0.95 (0.69–1.31)	1.18 (0.84–1.66)	0.61	1.04 (0.97–1.11)
<i>Polysaturated fat</i>							
Cases (n)	115	136	130	122	127		
Energy adjusted, HR (95%CI)	1.00 (Ref)	1.12 (0.88–1.44)	1.06 (0.82–1.36)	1.00 (0.77–1.29)	1.12 (0.87–1.44)	0.65	1.03 (0.96–1.11)
Multivariate adjusted, HR (95%CI)	1.00 (Ref)	1.02 (0.79–1.31)	0.92 (0.71–1.19)	0.83 (0.64–1.09)	0.91 (0.70–1.19)	0.27	0.97 (0.90–1.05)
<i>Trans fat</i>							
Cases (n)	85	122	135	136	152		
Energy adjusted, HR (95%CI)	1.00 (Ref)	1.35 (1.02–1.78)	1.42 (1.08–1.87)	1.38 (1.05–1.81)	1.55 (1.19–2.02)	<0.01	1.36 (1.14–1.63)
Multivariate adjusted, HR (95%CI)	1.00 (Ref)	1.21 (0.91–1.61)	1.21 (0.91–1.62)	1.13 (0.84–1.52)	1.24 (0.92–1.68)	0.36	1.19 (0.97–1.46)
<i>Omega-3 fatty acid</i>							
Cases (n)	116	149	123	123	119		
Energy adjusted, HR (95%CI)	1.00 (Ref)	1.26 (0.99–1.61)	1.04 (0.81–1.34)	1.08 (0.84–1.39)	1.16 (0.90–1.50)	0.61	1.24 (0.61–2.54)
Multivariate adjusted, HR (95%CI)	1.00 (Ref)	1.16 (0.91–1.49)	0.93 (0.71–1.20)	0.93 (0.72–1.22)	0.98 (0.75–1.29)	0.46	0.78 (0.35–1.71)
Esophageal squamous cell carcinoma							
<i>Saturated fat</i>							
Cases (n)	32	37	40	52	54		
Energy adjusted, HR (95%CI)	1.00 (Ref)	1.17 (0.73–1.88)	1.27 (0.80–2.03)	1.67 (1.07–2.61)	1.77 (1.14–2.76)	<0.01	1.17 (1.08–1.28)

Energy adjustment model		Quintile of intake ²					P _{trend} [†]	Fat intake as a continuous variable [‡]
1	2	3	4	5				
Monounsaturated fat								
Multivariate adjusted, HR (95%CI)	1.00 (Ref)	1.02 (0.63–1.67)	0.98 (0.59–1.62)	1.14 (0.69–1.89)	0.96 (0.56–1.65)	0.92	1.02 (0.92–1.14)	
Cases (n)	26	31	45	50	63			
Energy adjusted, HR (95%CI)	1.00 (Ref)	1.20 (0.71–2.02)	1.75 (1.08–2.83)	1.94 (1.21–3.13)	2.50 (1.58–3.97)	<0.01	1.20 (1.10–1.30)	
Multivariate adjusted, HR (95%CI)	1.00 (Ref)	1.11 (0.65–1.90)	1.50 (0.89–2.52)	1.49 (0.87–2.55)	1.59 (0.91–2.80)	0.08	1.06 (0.95–1.19)	
Polyunsaturated fat								
Cases (n)	31	41	41	53	49			
Energy adjusted, HR (95%CI)	1.00 (Ref)	1.31 (0.82–2.09)	1.31 (0.82–2.09)	1.70 (1.09–2.64)	1.60 (1.02–2.50)	0.02	1.12 (1.00–1.25)	
Multivariate adjusted, HR (95%CI)	1.00 (Ref)	1.27 (0.79–2.03)	1.21 (0.75–1.96)	1.47 (0.93–2.32)	1.18 (0.74–1.89)	0.55	1.00 (0.89–1.13)	
Trans fat								
Cases (n)	26	43	45	47	54			
Energy adjusted, HR (95%CI)	1.00 (Ref)	1.65 (1.02–2.69)	1.73 (1.07–2.81)	1.80 (1.11–2.92)	2.06 (1.28–3.30)	0.01	1.56 (1.17–2.08)	
Multivariate adjusted, HR (95%CI)	1.00 (Ref)	1.55 (0.94–2.56)	1.52 (0.91–2.52)	1.52 (0.91–2.55)	1.68 (1.00–2.81)	0.13	1.34 (0.97–1.85)	
Omega-3 fatty acid								
Cases (n)	38	38	44	51	44			
Energy adjusted, HR (95%CI)	1.00 (Ref)	1.00 (0.64–1.56)	1.15 (0.75–1.78)	1.35 (0.88–2.05)	1.18 (0.77–1.83)	0.25	1.42 (0.45–4.47)	
Multivariate adjusted, HR (95%CI)	1.00 (Ref)	0.97 (0.62–1.53)	1.05 (0.67–1.63)	1.14 (0.74–1.77)	0.85 (0.53–1.35)	0.54	0.46 (0.13–1.59)	
Gastric cardia adenocarcinoma								
Saturated fat								
Cases (n)	72	86	92	99	105			
Energy adjusted, HR (95%CI)	1.00 (Ref)	1.17 (0.85–1.60)	1.22 (0.89–1.66)	1.30 (0.96–1.76)	1.41 (1.04–1.90)	0.02	1.11 (1.04–1.17)	
Multivariate adjusted, HR (95%CI)	1.00 (Ref)	1.06 (0.76–1.46)	1.04 (0.74–1.46)	1.04 (0.72–1.48)	1.02 (0.70–1.50)	1.00	1.05 (0.97–1.13)	
Monounsaturated fat								
Cases (n)	77	73	87	99	118			
Energy adjusted, HR (95%CI)	1.00 (Ref)	0.91 (0.66–1.25)	1.05 (0.77–1.42)	1.15 (0.85–1.55)	1.37 (1.02–1.83)	0.01	1.09 (1.03–1.16)	
Multivariate adjusted, HR (95%CI)	1.00 (Ref)	0.84 (0.60–1.17)	0.93 (0.66–1.30)	0.96 (0.68–1.37)	1.03 (0.71–1.51)	0.59	1.03 (0.95–1.12)	
Polyunsaturated fat								
Cases (n)	84	88	101	92	89			
Energy adjusted, HR (95%CI)	1.00 (Ref)	1.01 (0.75–1.36)	1.15 (0.86–1.54)	1.05 (0.78–1.42)	1.09 (0.81–1.47)	0.56	1.07 (0.99–1.17)	
Multivariate adjusted, HR (95%CI)	1.00 (Ref)	0.97 (0.71–1.31)	1.08 (0.80–1.45)	0.96 (0.70–1.31)	0.95 (0.69–1.30)	0.69	1.04 (0.95–1.13)	

Energy adjustment model	Quintile of intake ²					P _{trend} [†]	Fat intake as a continuous variable [‡]
	1	2	3	4	5		
<i>Trans fat</i>							
Cases (n)	81	85	87	86	115		
Energy adjusted, HR (95%CI)	1.00 (Ref)	1.01 (0.74–1.36)	1.00 (0.74–1.35)	0.96 (0.71–1.31)	1.30 (0.97–1.73)	0.07	1.21 (0.97–1.50)
Multivariate adjusted, HR (95%CI)	1.00 (Ref)	0.91 (0.66–1.25)	0.86 (0.62–1.19)	0.79 (0.57–1.11)	1.03 (0.74–1.43)	0.68	1.04 (0.81–1.33)
<i>Omega-3 fatty acid</i>							
Cases (n)	90	100	97	72	95		
Energy adjusted, HR (95%CI)	1.00 (Ref)	1.10 (0.83–1.46)	1.07 (0.80–1.42)	0.82 (0.60–1.11)	1.17 (0.88–1.56)	0.70	1.66 (0.74–3.73)
Multivariate adjusted, HR (95%CI)	1.00 (Ref)	1.07 (0.80–1.43)	1.03 (0.76–1.38)	0.77 (0.56–1.07)	1.08 (0.79–1.47)	0.91	1.41 (0.59–3.38)
Gastric non-cardia adenocarcinoma							
<i>Saturated fat</i>							
Cases (n)	92	88	107	104	110		
Energy adjusted, HR (95%CI)	1.00 (Ref)	0.96 (0.71–1.28)	1.15 (0.87–1.52)	1.12 (0.84–1.48)	1.19 (0.90–1.57)	0.13	1.04 (0.98–1.10)
Multivariate adjusted, HR (95%CI)	1.00 (Ref)	0.99 (0.73–1.35)	1.22 (0.89–1.66)	1.19 (0.85–1.66)	1.26 (0.88–1.79)	0.14	1.04 (0.97–1.12)
<i>Monounsaturated fat</i>							
Cases (n)	101	86	105	106	103		
Energy adjusted, HR (95%CI)	1.00 (Ref)	0.84 (0.63–1.12)	1.01 (0.76–1.32)	0.99 (0.76–1.31)	0.97 (0.73–1.28)	0.82	1.01 (0.96–1.07)
Multivariate adjusted, HR (95%CI)	1.00 (Ref)	0.84 (0.62–1.13)	0.99 (0.73–1.34)	0.96 (0.69–1.33)	0.89 (0.62–1.28)	0.78	1.00 (0.92–1.08)
<i>Polysaturated fat</i>							
Cases (n)	97	120	83	108	93		
Energy adjusted, HR (95%CI)	1.00 (Ref)	1.21 (0.93–1.59)	0.83 (0.62–1.12)	1.08 (0.82–1.42)	0.95 (0.72–1.27)	0.50	0.97 (0.90–1.05)
Multivariate adjusted, HR (95%CI)	1.00 (Ref)	1.25 (0.95–1.65)	0.86 (0.64–1.17)	1.11 (0.83–1.49)	0.95 (0.70–1.28)	0.45	0.96 (0.88–1.05)
<i>Trans fat</i>							
Cases (n)	87	103	98	103	110		
Energy adjusted, HR (95%CI)	1.00 (Ref)	1.16 (0.87–1.55)	1.09 (0.81–1.45)	1.12 (0.84–1.49)	1.17 (0.88–1.55)	0.41	1.13 (0.92–1.38)
Multivariate adjusted, HR (95%CI)	1.00 (Ref)	1.18 (0.88–1.59)	1.09 (0.80–1.49)	1.10 (0.80–1.51)	1.11 (0.81–1.54)	0.77	1.08 (0.86–1.36)
<i>Omega-3 fatty acid</i>							
Cases (n)	102	98	97	103	101		
Energy adjusted, HR (95%CI)	1.00 (Ref)	0.95 (0.72–1.25)	0.93 (0.71–1.23)	1.00 (0.76–1.32)	1.02 (0.78–1.35)	0.73	1.40 (0.65–2.99)
Multivariate adjusted, HR (95%CI)	1.00 (Ref)	1.00 (0.75–1.33)	0.99 (0.74–1.32)	1.07 (0.80–1.43)	1.07 (0.79–1.44)	0.56	1.52 (0.69–3.35)

Cox proportional hazards regression was used to estimate hazard ratios (HR) and 95% confidence intervals (95%CI).

¹The results are shown for the density model which contains the percentage of non-alcohol energy contributed by fat intake. Energy adjusted Cox regression models adjusted for age, sex and non-alcohol energy intake. Multivariate Cox proportional hazards regression models adjusted for age, sex, non-alcohol energy intake, body mass index, education, ethnicity, alcohol, cigarette smoking, diabetes, physical activity, fruit and vegetable intake, and red meat intake.

²Median values (percentage of non-alcohol energy): saturated fat, Q1 (5.9), Q2 (7.9), Q3 (9.4), Q4 (11.0), Q5 (13.5); monounsaturated fat, Q1 (7.5), Q2 (10.0), Q3 (11.7), Q4 (13.3), Q5 (15.6); polyunsaturated fat, Q1 (4.6), Q2 (5.9), Q3 (6.9), Q4 (8.0), Q5 (9.9); trans fat, Q1 (1.2), Q2 (1.7), Q3 (2.0), Q4 (2.5), Q5 (3.2); omega-3 fatty acid, Q1 (0.5), Q2 (0.6), Q3 (0.7), Q4 (0.8), Q5 (1.0).

[#]Two-sided Wald χ^2 test for linear trend using median intake in each quintile.

^{*}Hazard ratios presented for a twofold increase in percent non-alcohol energy from fat.