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Dietary consumption of meat, fat, animal products and advanced glycation end-products and the risk of barrett's esophagus

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Abstract

Background—Advanced glycation end-products (AGEs) are found in high quantity in high-fat foods and meat cooked at high temperature. AGEs have been shown to contribute to chronic inflammation and oxidative stress in humans.

Aim—To investigate the associations between consumption of meat, fat and AGEs, and risk of Barrett's esophagus (BE).

Methods—We conducted a case-control study using data from the patients who were scheduled for elective esophagogastroduodenoscopy (EGD) and from a random sample of patients who were identified at primary care clinics. Daily consumption of meat, fat and Nε-(carboxymethyl) lysine (CML), a major type of AGEs, was derived from the food frequency questionnaire (FFQ). Multivariate logistic regression models were used to estimate the odds ratio (OR) and its 95% confidence interval (CI) for BE.

Results—A total of 151 cases with BE and 777 controls without BE completed the FFQ. The multivariate OR (95% CI) for BE was 1.91 (1.07–3.38) for total meat, 1.80 (1.02–3.16) for saturated fat, and 1.63 (0.96–2.76) for CML-AGE, when the highest tertile of intake was compared with the lowest. The association for total meat was attenuated to 1.61 (0.82–3.16), and that for saturated fat to 1.54 (0.81–2.94) after adjusting for CML-AGE.

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Conclusions—Higher consumption of total meat, saturated fat or possibly CML-AGE was associated with an increased risk of BE. CML-AGE may partly explain the association between total meat and saturated fat consumption and risk of BE.

Keywords

diet; barrette's esophagus; risk factor; epidemiology

INTRODUCTION

Barrett's esophagus (BE) is a premalignant condition that carries a small but significant risk of esophageal adenocarcinoma. BE is estimated to affect approximately 10% of patients with frequent gastroesophageal reflux disease (GERD) symptoms and approximately 1% of the general adult population. Consumption of high-fat meals and meat has been associated with an increased risk of esophageal adenocarcinoma in a few studies.[1]

Only two population-based case-control studies have examined the association between intake of meat and fatty foods with the risk of BE. [2,3] In one study, higher consumption of omega-3-fatty-acids and polyunsaturated fatty acid (PUFA) was inversely associated with risk of having BE, whereas total meat consumption was inversely related to the presence of longsegment BE.[2] The other study did not observe a consistent association between consumption of meat and fat and risk of BE.[3] Clearly, more studies are needed to examine this association given its potential implications for BE prevention.

Advanced glycation end-products (AGEs) are compounds that created through nonenzymatic reaction between reducing sugars and free amino groups in proteins, lipids or nucleic acids.[4] Animal-derived foods that are high in fat and protein are generally rich in AGEs and are also prone to new AGEs formation during the cooking process.[5] AGEs can induce oxidative stress and chronic inflammation through binding with the receptor for AGEs (RAGE) that is present in a wide range of differentiated adult cells including epithelial, immune and endothelial cells.[6] Several studies have shown that high circulating levels of AGEs are associated with increased risk of diabetes, heart diseases, and renal failure in humans.[7–10] Oxidative stress and chronic inflammation have also been implicated in the development of BE and in the progression from BE to EAC.[11] It is therefore plausible that AGEs play a role in BE etiology. N^{ε}-(carboxymethyl) lysine (CML) is the major type of dietary AGEs. Recently, the amounts of CML-AGE in 549 commonly consumed foods were quantified using a validated immunoassay.[5,12] However, there has been no study evaluating dietary intake of CML-AGE and risk of BE.

In this hospital-based case-control study, we examined the association between dietary consumption of total meat, total fat and fat subtypes and the risk of BE. We also estimated the daily CML-AGE intake values using the published food AGEs database and examined the association between CML-AGE and risk of BE.[5] We hypothesized that higher consumption of total meat, total and saturated fat, or CML-AGE was associated with increased risk of BE. In addition, we examined the association between other animal products, including dairy products and egg, and the risk of BE.

METHODS

Study design and study population

We obtained the cases and controls for this analysis from two cross-sectional studies in subjects seeking health care at the Michael E. DeBakey Veterans Affairs Medical Center (MEDVAMC) in Houston, Texas from February 1, 2008 to July 31, 2011. One of the cross-sectional studies was conducted among consecutive eligible patients (see criteria below) who underwent an elective esophagogastroduodenoscopy (EGD). The other was conducted in patients who were randomly identified from primary care facilities in the MEDVAMC and were eligible for a screening colonoscopy; furthermore, they agreed to undergo an EGD at the same time as their colonoscopy. This study was approved by the Institutional Review Boards at both Baylor College of Medicine and the MEDVAMC.

Cases and controls

All study participants had to be 40–80 years of age (and 50–80 years for primary care patients). We did not include the patients who had the following conditions: 1) previous gastro-esophageal surgery; 2) previous/current neoplastic epithelial diseases; 3) taking anticoagulants; 4) platelet count < 70,000, ascites, or known gastro-esophageal varices; or 5) history of major stroke or severe mental conditions.

Case subjects were defined as subjects with definite BE as confirmed by the presence of intestinalized columnar epithelium (confirmed by Alcian-PAS stain) in at least one biopsy sample obtained from tubular esophagus of suspected BE. Control subjects were enrolled from the elective EGD (endoscopy controls) or primary care patients who underwent EGD at the time of their screening colonoscopy (colonoscopy controls) and they were found to have no suspected BE. The controls were recruited from the patients presenting for elective endoscopy who had a clinical reason for an EGD. On the other hand, the control group that was recruited from primary care clinics had no clinical indication for an EGD. Participants with only suspected BE, i.e., those identified by EGD but not confirmed on histopathology, were excluded from this analysis. We further excluded the participants who did not respond to the Block Food Frequency Questionnaire (FFQ), and those with the reported daily energy intake < 800 Kcal and > 5000 Kcal because their responses to FFQs were considered to be unreliable.[13]

Study measurements

We interviewed all study participants before the EGD to collect data on age, sex, ethnicity, cigarette smoking, alcohol consumption, physical activity, medication use including proton pump inhibitors (PPI) and aspirin, and onset, frequency and severity of GERD symptoms (heartburn or acid regurgitation). Height and weight were measured by a research coordinator prior to the EGD and were used to calculate body mass index (BMI) as well as waist and hip circumference to calculate waist-to-hip ratio (WHR).

We used the 110-item Block FFQ (version 2005) to ascertain diet during the previous year. Participants were asked to report their usual frequency and portion size of the consumption of various foods. Each food item had nine options for frequency (ranging from “never or less than once per month” to “2+ times per day”) and three options for portion size (small, medium, and large). Pictures were provided to enhance accuracy of quantification of portion size. The raw data of FFQ were processed at the NutritionQuest service. The USDA MyPyramid Equivalents Database (MPED) version 1.0[14] was merged with the FFQ data to calculate ounce equivalent for total meat (including fish, chicken, and red meat) and egg (1 egg equals 1 oz meat), cup equivalent for dairy products (including milk, cheese, and yogurt) and fruits and vegetables (1 cup = 237 mL).

CML-AGE value assignment

The published food CML-AGE database for 549 food items representing foods and culinary techniques typical for the Northeastern American multiethnic urban population has been generated using a validated immunoassay.[5,12] We used this published dataset to assign the CML-AGE values (Kunit (KU))/100g solid food or 100 ml liquid) to a total of 216 food items evaluated in the Block FFQ. The CML-AGE values were directly available for 137 food items, and computed for another 52 food items from the same foods that were cooked or processed under different conditions. For example, the value for "cheese" was the average of the CML-AGE values for all types of the cheese[5] assuming that each type of cheese was consumed equally in quantity and frequency. For mixed foods such as breakfast egg sandwich and low fat luncheon meat, the CML-AGE values of different meal components were use to generate an average value for this mixed meal. For two mixed food items (Posole and Guysava) that are not consumed frequently in our study population, the CML-AGE value was set as missing. The CML-AGE values for additional 25 food items were estimated from similar food items for which the CML-AGE value has been measured.[5] For example, because the CML-AGE value was not available for each of fruits or vegetables, we used the mean for known values of fruits or uncooked vegetables to substitute the missing values. We used the CML-AGE value of a donut to substitute for frybread. The daily intake value of CML-AGE was calculated for each study subject without knowing the case-control status.

Statistics

We compared the demographic and lifestyle factors between cases and the combined group of controls using χ^2 or two sample Student's t tests as appropriate. Daily average consumption of foods or nutrients was energy adjusted using the density method.[15] Correlations between intake of CML-AGE and other nutrients or foods among controls were evaluated by Spearman's rank correlation coefficients.

We used unconditional multivariate logistic regression models to calculate odds ratios (ORs) and their 95% confidence intervals (CIs) for BE while controlling for potential confounders. Tertiles of each food and nutrient intake were generated based on the distributions of the intake in the combined control group. The lowest tertile was used as the reference category. Covariates included age, sex, ethnicity, smoking status (never, former and current), alcohol consumption (never, former, and current), aspirin use in the previous three months (yes versus no), PPI use any time in the past (yes versus no), frequency of GERD symptom (never, ≤ 1 month, 1–2 times per week, and daily), WHR (tertiles), physical activity (low, moderate, and high according to metabolic equivalent of task (MET) for recreational activity), and dark green vegetables (tertiles). The first basic model (model 1) contained the fixed variables of age and energy intake (all continuous). The second model (model 2) contained additional variables described above. These variables changed the parameter estimate for total meat, saturated fat or CML-AGE by >10% or were potential risk factors for BE. Approximately 80% of study subjects who ever had GERD symptoms reported severity of heartburn or regurgitation in the past year as "never, mild, moderate, severe, or very severe". We found that adjustment for severity of GERD symptoms did not change the BE risk estimate for total meat, saturated fat or CML-AGE, and these variables therefore were not included in the final model. In addition, we found that severity of GERD symptoms was not significantly associated with the intake of total meat, saturated fat and CML-AGE in the endoscopy or colonoscopy controls. The only exception was the study subjects consumed more total meat had a higher frequency of several or very severe heartburn in the endoscopy controls ($P = 0.02$). Model 3 further incorporated the term of CML-AGE to examine its confounding or mediating effect on any positive associations observed for total meat and fat. For CML-AGE, saturated fat was adjusted in model 3. Trends for the association between foods/nutrients (tertiles) and risk of BE were assessed by using the Wald tests.

Stratified analyses were performed according to abdominal obesity (WHR < 0.95 for men and < 0.80 for women versus WHR ≥ 0.95 for men and ≥ 0.80 for women)[16] or presence of GERD symptoms (never or ≤ 1 per month versus > 1 per month). The interaction terms by

WHR or frequency of GERD symptoms were generated using the categorical variables of total meat, saturated fat, and CML-AGE. The interaction effect was tested by likelihood ratio test. Lastly, we examined in a sensitivity analysis the same associations comparing all BE cases with each control group separately (endoscopy or colonoscopy). The cutoff points used to define the tertiles were derived separately according to the distribution of the foods/nutrients in each control group.

All analyses were conducted using STATA 12.0 (Stata Corporation, College Station, TX). A *P* value less than 0.05 indicated statistical significance.

RESULTS

We recruited 1,859 subjects comprising of 237 cases with definite BE, 122 cases with suspected (endoscopic finding only) BE, and 1,500 controls with no BE (1,021 endoscopy controls and 479 colonoscopy controls). We excluded 122 with suspected BE and 697 participants who did not complete the FFQ. The response rates to the Block FFQ were 70% for cases, 56% for endoscopy controls and 62% for colonoscopy controls. Those who did not complete the FFQ were two years older on average, significantly more likely to be African American, current smokers, and had lower self-reported physical activity than those who completed the FFQ. We further excluded 112 individuals with daily energy intake of < 800 or > 5000 Kcal. Therefore, our present analysis was based on 928 study participants: 151 cases with definitive BE (82 had short [<3 cm] and 49 had long segment) and 777 combined controls (521 endoscopy controls and 256 colonoscopy controls).

Colonoscopy controls were significantly older, more likely to be African American men, and to have a higher BMI, and to report lower physical activity and less PPI or aspirin use and less frequent and severe GERD symptoms than endoscopy controls. However, as shown below, the differences between two control groups did not affect the direction of the examined association between diet and risk of BE when we examined them separately. We therefore presented the results derived from comparing the BE cases with two control groups combined.

The characteristics of cases and controls have been reported previously.[17] Briefly, cases were significantly more likely to be older, Caucasian, have a higher average WHR or report more frequent PPI use and GERD symptoms while more controls reported more frequent use of aspirin.

The mean CML-AGE intake was 6871 (standard deviation: 2137; median: 6647) and 6803 (standard deviation: 2198; median: 6565) KU/1000 Kcal among cases and controls, respectively ($P = 0.73$). The distribution of energy-adjusted CML-AGE was skewed slightly to the left, with very few people having a value of greater than 12,000 KU (18 controls, and 4 cases). Among the controls, the consumption of CML-AGE had statistically significant positive correlation with that of total meat (r = 0.61), total fat (r = 0.54), saturated fat (r = 0.53), protein (r = 0.51), egg (r = 0.27), and cholesterol (r = 0.56), and inverse correlation with dark green vegetables consumption (r = − 0.05, $P = 0.13$).

Table 1 shows that higher total meat or saturated fat consumption (3rd compared with 1st tertile) was significantly associated with an increased risk of BE. However, the adjustment of CML-AGE attenuated the OR from 1.91 (95% CI: 1.07–3.38) to 1.61 (95% CI: 0.82–3.16) for total meat, and from 1.80 (95% CI: 1.02–3.16) to 1.54 (95% CI: 0.81–2.94) for saturated fat. Dietary intake of CML-AGE was associated with a non-significant increase in BE risk (OR = 1.63, 95% CI: 0.96–2.76) (model 2), and this association was attenuated when saturated fat (tertile) was included in the model (model 3) (OR = 1.45, 95% CI: 0.79–

2.67). Consumption of other animal products, total and other subtypes of fat was not associated with BE (supplemental table 1 and 2).

The association between total meat (continuous scale) and risk of BE was observed for both short (n = 82) (OR = 1.12, 95% CI 0.84–1.49) and long segment (n = 49) (OR = 1.14, 95% CI: 0.81–1.62) BE (model 2). The positive association between saturated fat intake (continuous scale) and risk of BE was observed for short segment BE (OR = 1.09, 95% CI: 0.99–1.19), but not for long segment BE (OR = 1.00, 95%: 0.89–1.13) (model 2). However, neither of these associations was statistically significant.

In the stratified analyses by WHR or frequency of GERD symptoms, highest tertile of CML-AGE intake was associated with a statistically significant increased risk of BE among those with a high WHR (OR = 2.08, 95% CI: 1.07–4.06, *P* trend = 0.03) or among those with frequent GERD symptoms (OR = 1.93, 95% CI: 1.00–3.73, *P* trend = 0.05). We did not find evidence of an association among those with a low WHR or with no or less frequent GERD symptoms. The *P* value for interaction by WHR and frequency of GER was 0.13 and 0.18 respectively (Table 2). There was no potential interaction by WHR or frequency of GERD symptoms for saturated fat or total meat and BE (supplemental table 3 and 4).

The main findings were robust in the sensitivity analyses. There was no difference in the direction of associations between food/nutrient consumption and risk of BE according to the source of the control group. However, the magnitude of the association was stronger when the colonoscopy control group was used. For instance, when the 3rd compared with the 1st tertile, the OR (95% CI) was 1.42 (0.81–2.47) and 2.02 (0.93–4.40) for CML-AGE; 1.71 (0.95–3.07) and 2.64 (1.14–6.11) for saturated fat; 1.57 (0.92–2.70) and 2.41 (1.01–5.74) for total meat, when controls were from the endoscopic clinic and colonoscopy clinic, respectively (model 2).

DISCUSSION

In this hospital-based case-control study, we found a positive association between higher dietary consumption of total meat or saturated fat and an increased risk of having BE, which may be partially mediated by CML-AGE. Furthermore, the association between CML-AGE and BE was observed in the study subjects with a higher WHR. However, the effect modification by WHR was not statistically significant. Intake of total fat, other fat subtypes, or dairy products was not associated with the risk of BE in our study population.

Only two studies have investigated the consumption of meat and fat in association with the risk of BE.[2,3] One was a case-control study conducted in a Kaiser Permanente, Northern California (KPNC) population of 296 incident cases with BE compared with 308 persons with GERD disease and 309 population controls. The investigators found similar to our study that saturated fat was associated with an increased risk of long-segment BE (OR=1.05; 95% CI 1.01–1.09, per gram/day). However, contrary to our study, they found that higher meat consumption was associated with a lower risk of BE, especially long segment BE (OR = 0.25, 95% CI = 0.09–0.72).[2] In our analysis, there were 82 cases with short segment BE and 49 with long segment BE. The stratified analyses showed a non-significant increased risk associated with total meat in both types of BE. In an all-Ireland the Factors INfluencing the Barrett's Adenocarcinoma Relationship (FINBAR) study of 220 BE patients and 256 controls, intakes of total fat, saturated fat and fat subtypes were not associated with risk of BE; but higher consumption of processed meat and saturated fat was associated with an increased risk of esophageal adenocarcinoma.[3] In addition, intake of omega-3-fatty-acids or PUFA had an inverse association with risk of BE while intake of trans fat had a positive association with BE in the KPNC study.[2] However, neither FINBAR nor our study confirmed this finding. The discrepancy of the study findings is likely due to different study population and study design including diet ascertainment.

The potential role of fat intake in the pathogenesis of BE is supported by at least two animal studies.[18,19] In one study, the incidence of BE and dysplasia was higher in reflux rats fed with high chow-fat diet than in reflux rats fed with low soybean-oil diet.[18] The other study performed esophagoduodenostomy with gastric preservation on 165 sprague-dawley rats to expose the esophagus to the reflux of gastroduodenal juice. The rats then were treated with the carcinogen methyl-n-amylnitrosamine and fed diets of differing fat and calorie content for 20 weeks. Addition of a carcinogen increased the tumor yield due to reflux. This carcinogenic process was promoted by a diet with a high fat content. Diet alone did not influence the incidence of neoplasm in the absence of the carcinogens.[19] Nevertheless, in our study, the positive association between saturated fat intake and risk of BE was seen regardless of GERD symptoms.

Furthermore, we found that the associations between total meat or saturated fat and BE were partially explained by dietary intake of CML-AGE. Dietary CML-AGE is found in high quantity in high-fat animal foods and contributes significantly to the body's AGE pool.[20] The involvement of CML-AGE in the association between total meat or saturated fat and BE implies that the biological function of CML-AGE, such as inducing oxidative stress and chronic inflammation, may play a role in BE development. CML-AGE can be harmful by cross-linking with amino acids. It also binds to RAGE, which triggers a vicious cycle of chronic inflammation and generation of reactive oxidative species.[21] Chronic inflammation and oxidative stress have been implicated in BE development.[22] Although there has been no experimental study investigating the effect of CML-AGE on the esophagus, RAGE has been shown to take part in Zn modulated inflammation signaling by binding to S100A8 in rat esophagus.[23,24] Loss of RAGE expression may play an important role in the progression of esophageal squamous cell carcinoma.[25] Further investigation on AGEs/RAGE induced chronic inflammation and oxidative stress and its role in BE development may provide novel insight into BE etiology.

Our study carries several limitations. First, we have attempted to assess the dietary intake of CML-AGE in the study population using a published CML-AGE database. However, an accurate assessment of dietary exposure to CML-AGE requires a detailed assessment of cooking practice, which was not queried in the Block FFQ. The resulting information bias was however likely to be non-differential, and thus drove the association toward the null. Second, the characteristics of the two control groups used in this study were not entirely the same in terms of age, BMI, frequency of GERD symptoms, and PPI use. The association between total meat or saturated fat was stronger when the colonoscopy control group was used indicating that using the controls with a clinical indication for EGD might have driven the risk estimate toward the null. However, the risk estimates derived from two controls groups were in the same direction, thus affirming the internal validity of the findings. Third, 30% to 44% of participants did not respond to the FFQ among cases and the two control groups. Non-respondents were older, had a higher BMI, and were more likely to be current smoker. However, because we did not know the non-respondents' eating habits, this non-response bias can distort the risk estimate in either direction. Fourth, the study population comprised of mostly men, the findings may not be generalized to women. Lastly, we examined multiple nutrients in this study, and the positive findings may have been due to type 1 error. Similarly, the insignificant positive findings may have been due to the type 2 error because of small sample size. The observed associations, in particular those for the stratified analyses, need to be interpreted with caution and confirmed in future studies.

The strengths of our study included the novel evaluation of CML-AGE and its association with BE, the uniform use of strict and well-validated definition of cases and controls, the low possibility of recall bias given that the self-administrated FFQ was completed before knowing the BE status, and adjustment of multiple potential confounders including PPI and aspirin use, GERD symptoms and physical activity in risk estimate.

This study complements our prior study on plant-based foods for BE,[17] and suggests that higher consumption of plant-based foods and lower consumption of meat may be the dietary recommendation for preventing BE.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Associations between consumption of total meats, saturated fat, and CML-AGE and risk of Barrett's esophagus (151 cases and 777 controls)

Food groups (per 1000 Kcal)	Tertile 1	Tertile 2	Tertile 3	*P* value[§]
Total meat (oz)				
Median (Range)	1.36 (0.01–1.78)	2.14 (1.79–2.49)	2.98 (2.49–8.16)	
Case/control	39/259	57/259	55/259	
OR[*] (95% CI)	1.00	1.43 (0.91–2.24)	1.35 (0.86–2.13)	0.21
OR[†] (95% CI)	1.00	1.88 (1.09–3.24)	1.91 (1.07–3.38)	0.03
OR[‡] (95% CI)	1.00	1.75 (0.98–3.12)	1.61 (0.82–3.16)	0.17
Continuous[‡]			1.25 (0.99–1.58)	0.06
Saturated fat (gram)				
Median (Range)	10.5 (4.0–12.0)	13.2 (12.0–14.4)	16.0 (14.4–24.7)	
Case/control	35/259	51/259	65/259	
OR[*] (95% CI)	1.00	1.49 (0.93–2.40)	1.78 (1.13–2.81)	0.01
OR[†] (95% CI)	1.00	1.55 (0.86–2.77)	1.80 (1.02–3.16)	0.06
OR[‡] (95% CI)	1.00	1.47 (0.80–2.71)	1.54 (0.81–2.94)	0.22
Continuous[†]			1.06 (0.98–1.14)	0.13
CML-AGE (kU)				
Median (Range)	7428 (2209–25841)	11617 (4935–35821)	15375 (6595–47653)	
case/control	49/259	43/259	59/259	
OR[*] (95% CI)	1.00	0.89 (0.56–1.40)	1.19 (0.78–1.82)	0.41
OR[†] (95% CI)	1.00	1.15 (0.67–1.98)	1.63 (0.96–2.76)	0.07
OR[‡] (95% CI)	1.00	1.08 (0.61–1.90)	1.45 (0.79–2.67)	0.23
Continuous			1.00 (0.99–1.00)	0.26

CI, confidence interval; CML-AGE, N^{ε}-(carboxymethyl) lysine (CML); OR, odds ratio.

[*]Model 1: OR was adjusted for age and energy intake.

[†]Model 2: OR was adjusted for age, energy intake, sex, ethnicity, smoking status, alcohol consumption, waist to hip ratio (tertile), recent use of aspirin, ever or never use of proton pump inhibitor, frequency of GER symptoms, physical activity (low, moderate, and high according to metabolic equivalent of task), and dark-green vegetables (quintiles).

[‡]Model 3: OR was adjusted for CML-AGE in addition. For CML-AGE, OR was adjusted for saturated fat in addition.

[§]*P* value for trend across tertiles. Tertile was determined according to the distribution of the intake among the combined controls.

Table 2

Associations between CML-AGE and risk of Barrett's esophagus by waist to hip ratio and frequency of GER symptoms (151 cases and 777 controls).

	No Abdominal Obesity			Abdominal Obesity*		
CML	Case/Control	OR† (95% CI)	OR‡ (95% CI)	Case/Control	OR† (95% CI)	OR‡ (95% CI)
Tertile 1	20/102	1.00	1.00	29/150	1.00	1.00
Tertile 2	16/103	1.68 (0.63–4.47)	1.38 (0.50–3.84)	27/150	1.04 (0.52–2.10)	0.97 (0.45–2.08)
Tertile 3	14/95	1.20 (0.42–3.42)	0.92 (0.29–2.92)	45/154	2.08 (1.07–4.06)	1.88 (0.86–4.11)
P-trend§		0.67	0.92		0.03	0.09
		No or infrequent GER symptoms (≤ 1 per month)		**Frequent GER symptoms(> 1/month)**		
Tertile 1	15/117	1.00	1.00	34/131	1.00	1.00
Tertile 2	10/97	1.24 (0.39–3.96)	0.70 (0.19–2.53)	31/148	1.28 (0.68–2.43)	1.25 (0.63–2.47)
Tertile 3	20/129	1.38 (0.51–3.76)	0.67 (0.20–2.17)	35/117	1.93 (1.00–3.73)	2.10 (0.97–4.54)
P-trend§		0.53	0.52		0.05	0.06

CI, confidence interval; CML-AGE, N^{ε}-(carboxymethyl) lysine (CML); OR, odds ratio.

P value for interaction by WHR was 0.13, and by frequency of GERD symptom was 0.18.

*Abdominal obesity is defined as a waist-hip ratio above 0.95 for men and above 0.80 for women.

†Model 1: OR was adjusted for age, energy intake, sex, ethnicity, smoking status, alcohol consumption, waist to hip ratio (tertile), recent use of aspirin, ever or never use of proton pump inhibitor, frequency of GER symptoms, physical activity (low, moderate, and high according to metabolic equivalent of task), and dark green vegetables (tertiles).

‡Model 2: OR for CML-AGE was adjusted for saturated fat.

§*P* value for trend across tertiles. Tertile was determined according to the distribution of the intake among the combined controls.