Published in final edited form as:

Nutr Cancer. 2009 ; 61(5): 607–616. doi:10.1080/01635580902846585.

Effects of dietary fiber, fats, and meat intakes on the risk of Barrett's Esophagus

Ai Kubo¹, Gladys Block², Charles P. Quesenberry Jr.¹, Patricia Buffler², and Douglas A. Corley^{1,3}

¹ Northern California Kaiser Permanente; Division of Research

² University of California, Berkeley; School of Public Health

³ University of California, San Francisco; Department of Medicine and Comprehensive Cancer Center

Abstract

Animal and human models suggest associations between fat intake, fiber intake and the risk of esophageal adenocarcinoma. We evaluated whether these factors may act early in the carcinogenic pathway as a risk factor for Barrett's esophagus, a potentially premalignant precursor to esophageal adenocarcinoma using a case-control design within the Kaiser Permanente, Northern California population. Incident Barrett's esophagus cases (n=296) were matched to persons with gastroesophageal reflux disease (GERD) (n=308), and to population controls (n=309). Higher intakes of omega-3-fatty-acids (cases vs. population controls; OR=0.46, 95% CI 0.22–0.97, 4th vs. 1st quartiles of intake), polyunsaturated fat, total fiber (OR=0.34, 95% CI 0.15–0.76), and fiber from fruits and vegetables (OR=0.47 95% CI 0.25–0.88) were associated with a lower risk of Barrett's esophagus. Higher meat intakes were associated with a lower risk of long-segment Barrett's esophagus (OR=0.25, 95% CI 0.09–0.72). In contrast, higher trans-fat intakes were associated with increased risk (OR=1.11; 95% CI 1.03–1.21 per gram/day). Total fat intake, barbecued foods, and fiber intake from sources other than fruits and vegetables were not associated with Barrett's esophagus. Future studies to evaluate whether dietary interventions might influence the risk of Barrett's esophagus or esophageal adenocarcinoma in high risk persons are needed.

Background

Barrett's esophagus (BE) is a metaplastic transformation of the esophageal squamous epithelium into specialized intestinal columnar epithelium(1) as a result of chronic gastroesophageal reflux (GERD) injury. Barrett's esophagus predisposes to esophageal adenocarcinoma, a cancer with one of the fastest rising incidence rates in the United States and an exceptionally poor prognosis.(2–6) Currently, there are limited therapeutic options to either prevent or treat this highly lethal cancer, making the identification of modifiable risk factors for primary prevention programs an urgent need. The treatment or prevention of Barrett's esophagus presents the potential for early risk interventions, thus the evaluation of modifiable risk factors for Barrett's esophagus may provide information on early events in the carcinogenic pathway for esophageal adenocarcinoma and is of considerable clinical interest.

Diet is one potential environmental factor that may influence the risk of developing esophageal adenocarcinoma. Previous studies have reported adverse associations between dietary fat,(7–

10) animal protein,(8) processed meat,(11) and cholesterol(8) with the risk of esophageal adenocarcinoma, whereas dietary fiber,(7,8,10,12) antioxidants,(13) fruits and vegetables(9, 14,15) are associated with a reduced risk. It has also been hypothesized that barbecued or charbroiled meat, a major source of polycyclic aromatic hydrocarbons (PAHs), may be associated with increased risk.(16) It is unknown, however, whether these dietary elements may decrease the risk of Barrett's esophagus itself, or may, instead, decrease the risk of Barrett's esophagus progressing to esophageal adenocarcinoma.

Minimal human data are available regarding the associations between diet and Barrett's esophagus. A recent study reported that high dietary animal fat (beef) increased the incidence of Barrett's esophagus in rats, and hypothesized that animal fat changed the bile-acid composition and increased the concentration of taurine conjugates in the bile juice.(17) Another study reported an increase in the carcinogenetic process of Barrett's esophagus among rats fed a higher fat diet along with a carcinogen.(18) In humans, fruits and/or vegetables(19,20) as well as a dietary pattern rich in fruits and vegetables(21) are observed to be inversely associated with the risk, while a "Western" style dietary pattern high in fast food and processed meat products may be adversely associated.(21) However, it is still unclear what components of these diets actually play role in changing the risk of Barrett's esophagus. For instance, fiber in fruits and vegetables may be the active 'protective' components, while higher contents of certain fats or meat in the "Western" diet may increase the carcinogenesis process, as suggested from the animal studies.

Thus far, no previous study has examined the effects of diet apart from fruits and vegetables or antioxidants on Barrett's esophagus. We thus examined the associations between intakes of various nutrients including fats and fiber, as well as meat intake, cooking methods of meat and the risk of Barrett's esophagus using a case-control design that compared patients with a new diagnosis of Barrett's esophagus to population controls and, separately, to patients with gastroesophageal reflux disease (GERD). The latter group permits evaluation of risk factors for Barrett's esophagus among persons with GERD.

Materials and Methods

Study Population

Details of the study design have been described previously.(22) Briefly, this was a case-control study conducted within the Kaiser Permanente, Northern California (KPNC) population, an integrated health services delivery organization. The KPNC membership contains approximately 3.3 million persons whose demographics closely approximate the underlying census population of Northern California.(23,24) Potentially eligible subjects for this study were all adult (ages 18–79 years) KPNC members who were continuously enrolled for at least 2 years prior to their index period, met the case or control definitions outlined below, and were able to understand spoken and written English. The index date for cases was the date of Barrett's esophagus diagnosis. The index date for controls was the midpoint of each 2–3 month selection interval for the cases. The membership population and GERD comparison groups were frequency matched to the cases by gender (given the high proportion of males among Barrett's esophagus patients), age at the index date, and geographic region (each subject's home facility).

Case Definition

Cases were KPNC members (ages 18–79 years) assigned a new diagnosis of Barrett's esophagus between the years 2002 and 2005. First, potentially eligible cases were identified using the International Classification of Disease, 9th revision (ICD-9) code 530.2, which at KPNC is uniquely coded on reporting sheets as "Barrett's esophagitis". A board-certified gastroenterologist (DAC) then reviewed the endoscopy and pathology of records of potentially

eligible cases to determine if they met the stated Barrett's esophagus definition. Subsequently, all pathologic slides underwent a separate review by an independent gastrointestinal pathologist to evaluate for the presence of intestinal metaplasia. The following patients were excluded: patients with only gastric-type metaplasia of the esophagus; patients with columnar metaplasia without features of intestinal metaplasia on all pathologic evaluations; patients without a biopsy of esophageal origin; and patients with a prior Barrett's esophagus diagnosis.

Population Controls

Population controls were randomly selected from at risk members of the entire Northern California Kaiser membership roster at the time the Barrett's esophagus cases were identified. Controls carrying a prior diagnosis of Barrett's esophagus by ICD-9 code 530.2 in the database were excluded.

GERD Comparison Group

GERD controls were adult KPNC members who had a diagnosis of GERD (International Classification of Disease, version 9 codes 530.11 reflux esophagitis or 530.81 gastroesophageal reflux); a prescription sufficient for at least 90 days use of histamine-2 receptor antagonists or proton pump inhibitors (medications used for treating GERD symptoms) in the previous year (documented from electronic pharmacy records); no prior known diagnosis of Barrett's esophagus prior to the period of case selection by electronic coding; and performance of an esophagogastroduodenoscopy (in proximity to the index date of the case group) that did not demonstrate esophageal columnar metaplasia of any type (all reports were manually reviewed by a study gastroenterologist). A prior study that contrasted a similar strategy with interviews for GERD symptoms demonstrated that this method is highly specific for a GERD diagnosis. (25)

Exposure Measurements

All study subjects completed: 1.) an in-person interview (most commonly at the subject's home) of GERD symptoms, medication use, medical history, tobacco use and alcohol use, 2.) phlebotomy, and 3.) anthropometric measurements. We assessed subjects' nutritional intake using a validated 110-item food frequency questionnaire (FFQ; the Block 98).(26–29) This FFQ estimates average daily nutrient intake, including various types of fat, fiber, and protein based on questions about frequency and portion size of a given food and usual eating habits over the year before the index date. The FFQ results show good correlations with multiple-day dietary records in a wide variety of population subgroups, in assessing past dietary habit,(30) and strong correlations with serum measures for lipids and antioxidants.(31,32) The original dietary data were translated to daily intakes of specific nutrients using Dietary Data Systems (Berkeley, CA. www.nutritionquest.com). We excluded subjects with over 20 missing food items or with extremely high or low total caloric intakes. The food questionnaire also asked a question regarding the "doneness" of meat (i.e., rareness of cooked meat) and, separate from the questionnaire, the interviewer asked "How often do you eat barbecued or smoked foods?" Quartile categories used distributions from the population control group.

Statistical Analysis

After exclusion of subjects who did not complete the food frequency questionnaire (n=28) or who had extreme responses in the questionnaire (skipped items>20 n=5; extreme caloric intakes n=7), 296 Barrett's esophagus cases, 308 GERD controls, and 309 population controls were included in the analyses. Unconditional logistic regression was used to calculate odds ratios (ORs) as an estimate of the relative risk, and corresponding 95% confidence intervals (CIs).(33) All analyses were performed comparing cases vs. population controls *and* cases vs. GERD controls. The control groups were frequency matched to cases (at the time of case

diagnosis) by gender (given the high proportion of males among Barrett's esophagus patients), age at the index date (by 5 year age groups), and by geographic region (each subject's home facility). We evaluated the following additional variables as potential confounders: ethnicity (classified as white vs. non-white due to small sample sizes in the ethnic subgroups), smoking (ever vs. never, current vs. never), body mass index (BMI=kg/m²), abdominal obesity (waist circumference), recent alcohol use (number of drinks/week), aspirin or nonsteroidal anti-inflammatory drug (NSAID) use, a comorbidity index (the DxCg score, which creates a predictive comorbidity score based on demographic data, medical coding, and pharmacy utilization), (34,35) education, income, serum *Helicobacter Pylori* (*H. Pylori*) antibody status, regular vitamin supplement intake, and total caloric intake per day. Potential confounding factors were included in the final model if their inclusion altered the β coefficient by >10%. The final model was adjusted for the frequency matched variables (age, sex and geographic region) in addition to race, use of dietary supplements, and energy intake, which are known to be associated with Barrett's esophagus and/or diet.

Data were first analyzed by quartile (the lowest quartile as referent). We also evaluated intake as a continuous variable for each nutrient, to maximize the power to detect trends. All analyses were performed using SAS statistical software (Cary, NC). The study and analyses were approved by KPNC institutional review board.

RESULTS

Baseline characteristics

Baseline characteristics of the study subjects are presented in Table 1. The demographic characteristics were fairly evenly distributed among the three groups, although cases tended to have a slightly higher proportion of ever smokers compared to the other groups. The average intakes of energy and total fat were comparable among the three groups, though population control subjects tended to have somewhat higher intakes of fruits and vegetables. Among the cases, the length of the Barrett's segment was <3 centimeters in 111 subjects (38%), ≥ 3 centimeters in 139 subjects (47%), and not reported in 46 subjects (15%).

Fats and Cholesterol

There was an inverse association between intakes of polyunsaturated fat, omega 3, and the risk of Barrett's esophagus, and the associations were stronger for long-segment Barrett's esophagus. For instance, those who consumed the highest amount of omega 3 fatty-acid were at less than half the risk of developing any Barrett's esophagus (OR=0.46; 95% CI 0.22–0.97, 4th vs. 1st quartiles), and at three times lower the risk of having long-segment Barrett's esophagus (OR=0.36; 95% CI 0.14–0.90). Poly-unsaturated fats had trends for inverse associations with any Barrett's esophagus (Table 2). On the other hand, trans-fat, often found in highly processed food, was significantly associated with an increased risk of Barrett's esophagus when examined continuously (OR=1.11; 95% CI 1.03–1.21, any Barrett's esophagus; OR=1.15; 95% CI 1.04–1.27, for long-segment BE, per gram/day). Saturated fat, mainly found in animal products, was associated with increased risk of long-segment Barrett's esophagus (OR=1.05; 95% CI 1.01–1.09, per gram/day). There were no consistent associations between total fat or cholesterol and the risk of Barrett's esophagus (Table 2).

Fiber

Total fiber was significantly inversely associated with the risk of any Barrett's esophagus (OR=0.34; 95% CI 0.15–0.76, 4th vs. 1st quartiles) and long-segment Barrett's esophagus (OR=0.20 95% CI 0.07–0.56). When the sources of fiber were examined separately, fruits and vegetables were the only sources associated with significant reduction of the risk (OR=0.47;

95% CI 0.25–0.88, for any Barrett's; OR=0.30; 95% CI 0.13–0.69, for long-segment): fiber from beans and grains were not significantly associated with Barrett's esophagus (Table 3).

Protein, meat, and meat cooking methods

There was a strong trend for a lower risk of Barrett's esophagus among persons with higher meat intakes, with a significant association among persons with long-segment Barrett's esophagus (Table 4): those in the highest quartile of meat consumption (median: 3.3 servings/day) were at four times lower risk of Barrett's esophagus (OR=0.25 95% CI 0.09–0.72) compared to subjects in the lowest quartile (median 0.9 servings/day). The inverse association between higher meat intake and any Barrett's esophagus was of borderline significance (OR=0.46 95% CI 0.21–1.01). The associations between total protein and dairy intakes were not consistent (Table 3).

There was no significant association between the risk of Barrett's esophagus and frequent consumption of barbecued foods (OR=0.84; 95% CI 0.53–1.35, 1+/week vs. <1/month) (Table 4) or well-cooked meats (OR=1.30; 95% CI 0.62–2.72).

Supplemental Analyses

Dietary factors and GERD

We evaluated whether the associations between fiber and meat intake may be present solely through increasing GERD symptoms, a strong risk factor for Barrett's esophagus. First, we evaluated whether adjustment for at least weekly GERD symptoms changed the association between each risk factor and Barrett's esophagus (cases vs. population controls). If the association were markedly diminished, this would suggest some of the association may be mediated through GERD. Adjustment for GERD only somewhat weakened the observed associations; for instance, the effect estimate for total fiber was attenuated from (OR=0.34; 95% CI 0.15–0.76, 4th vs. 1st quartiles) to (OR=0.58 95% CI (0.21–1.61). Similarly, the inverse association between meat intake and long-segment Barrett's esophagus was slightly weakened from [OR=0.25 95% CI (0.09–0.72), 4th vs. 1st quartile comparison] to [OR=0.33, 95% CI (0.08–1.30)].

Second, we evaluated mediation through GERD by comparing cases to GERD controls who lacked Barrett's esophagus on endoscopy. These analyses effectively helped “match” for a GERD-type diagnosis and for health-care seeking behaviors leading to an endoscopy; they thus help identify risk factors for Barrett's esophagus among people with GERD. For these comparisons, strong inverse trends persisted for omega 3 and polyunsaturated fatty-acids, though the confidence intervals were wider and included 1.0 (data not shown). Total fiber was significantly inversely associated with Barrett's esophagus [OR=0.40; 95% CI (0.17–0.91)], though fiber from fruits and vegetables was not significantly associated. Meat and protein intakes were also inversely associated, with results that were of borderline significance: individuals in the highest quartile of meat or protein consumption were at about half the risk of developing any Barrett's esophagus [OR=0.49 95% CI(0.23–1.07); OR=0.42; 95% CI (0.17–1.05), respectively]. Taken in total, these analyses adjusting for GERD decreased the precision of the estimates but strong inverse trends persisted. These suggest that the associations found are unlikely to be predominantly mediated through GERD.

Analyses of confounding and interaction

There was no evidence of strong confounding by smoking, BMI, abdominal obesity, recent alcohol use, aspirin or NSAID use, education, income, serum H. *Pylori* antibody status, or comorbidity. Inclusion of fruits and vegetables, which are closely related to intakes of many of the nutrients examined in these analyses, did attenuate many of the results. For instance, the

associations for fiber, meat, omega 3 fatty-acid, and unsaturated fats, were markedly attenuated by including a fruit and vegetable variable in the model. However, these results were expected because plant-based food items are the main sources of fiber and unsaturated fats, and omega 3 mainly comes from fish, nuts, seeds, beans, and olive oil.

There was no evidence of interaction with age, gender, race, vitamin supplement intake, or education. The only effect modification was observed for the lengths of Barrett's esophagus, as described above: in general, stronger and more significant associations were observed between the dietary factors evaluated above and the risk of long-segment Barrett's (≥ 3 centimeters), compared to short-segment type (< 3 centimeters).

DISCUSSION

This is the first community-based study that evaluated the associations between dietary fats, fiber and animal products and the risk of Barrett's esophagus. Our data suggested that plant-based fats (e.g., polyunsaturated fat), omega 3 fatty-acids, fiber (particularly fiber from fruits and vegetables), and meat intakes were inversely associated with the risk of Barrett's esophagus, while trans-fat may be adversely associated with the disease. There was no association between cooking methods of meat (charbroiled or well-done) and the risk of Barrett's esophagus.

Our results extend the prior findings of associations between diet and Barrett's esophagus as well as esophageal adenocarcinoma. The inverse associations observed for plant-based nutrients such as fiber and unsaturated fat corroborate the previous studies that reported beneficial effects of fruits and vegetables,(19,20) a dietary pattern rich in plant-based foods,(21) and dietary antioxidants(20) on Barrett's esophagus. They also confirm results of previous studies that examined the associations between these nutrients/food groups and esophageal adenocarcinoma.(7–10,12–15) However, few of the previous studies further evaluated whether the beneficial effects came from the fruits and vegetables themselves, or due to lack of certain foods or nutrients (e.g., fat or meat) associated with diet rich in fruits and vegetables. Further, few examined different types of fat or fiber separately: a Swedish study reported that intake of total fiber, especially cereal fiber was inversely associated with risk of esophageal adenocarcinoma,(36) and a US case-control study reported an adverse association between total and saturated fats and the risk of esophageal adenocarcinoma.(8) Other studies reported the effects of total fat or total fibers only, and to our knowledge, no previous study has examined the effect of trans-fat or omega 3 fatty-acid on the risk of Barrett's esophagus or esophageal adenocarcinoma.

While previous animal studies suggested an adverse effect of fat (total or animal) on Barrett's esophagus,(17,18) our data suggest that instead, trans-fat, which often comes from partially hydrogenated unsaturated plant fats (generally vegetable oils) created by processed food, fast food, snack food, fried food and baked goods industries(37) may be the component that is adversely associated; a model for trans-fat adjusted for saturated fat still provided a strong adverse association between trans-fat and Barrett's esophagus (data not shown). Trans-fats and saturated fats have been found to increase the risks of various chronic diseases including coronary heart disease and diabetes,(38,39) by raising LDL ("bad" cholesterol), lowering HDL ("good" cholesterol) and by increasing systemic inflammation such as tumor necrosis factor α receptors 1 and 2.(40) A previous study reported that the epithelial expression of tumor necrosis factor- α (TNF- α) increases with progression along the metaplasia-dysplasia-carcinoma sequence, suggesting an important role of TNF- α in the carcinogenesis process from Barrett's esophagus into esophageal adenocarcinoma.(41)

The reported adverse effects of animal-based fat or diet lacking plant products naturally leads us to suspect that consumption of animal products would also have a positive association with the risk of Barrett's esophagus: however, our results showed unexpected *inverse* associations between meat and long-segment Barrett's esophagus, even after adjustment for fruits and vegetables intake. In addition, we observed a significant inverse association between omega 3 fatty-acid and Barrett's esophagus. Although this fatty-acid could come from plant products as mentioned before, the main source is fatty fish. A previous study demonstrated that Barrett's esophagus patients who were randomly assigned omega 3 fatty-acid eicosapentaenoic acid (a metabolically active omega 3 fatty-acid) experienced a significant reduction in COX-2 protein concentrations, suggesting a potential chemopreventive effect of omega 3 fatty-acid or regular consumption of oily fish.(42,43)

The strong inverse association we found between fiber and Barrett's esophagus corroborates results from other previous studies of esophageal adenocarcinoma and suggests, if causal, that fiber may act early in the carcinogenic process for esophageal adenocarcinoma.(7,8,10,12) The present study also suggested that fiber from fruits and vegetables was the main source of the significant inverse association with the risk of Barrett's esophagus. Considering our results and previous evidence, it is difficult to isolate the effect of the specific nutrients or food items. Fiber itself may absorb carcinogens from food items that pass through the esophagus tract, (12) or may reduce the risk of Barrett's esophagus by decreasing the risk of hiatal hernia.(44) However, we cannot exclude the possibility that high fiber is a proxy for certain dietary or lifestyle factors. In conjunction with our previous study that showed that a "Western" dietary pattern rich in fast foods and processed meat products was adversely associated with the risk of Barrett's esophagus, while a diet rich in fruits and vegetables was inversely associated, (21) the present analysis further suggests that it may be a diet that is rich in whole food items, including fruits, vegetables, fish and meat that is beneficial, while a diet that is high in processed foods or fast foods and low in whole foods may be associated with a higher risk. Although we did not observe confounding by various demographic and lifestyle factors, it is difficult to segregate dietary habits from overall lifestyle and health consciousness which may not be fully measured by questionnaires.

There are numerous strengths of this study. First, to our knowledge, this is the first community-based study to investigate the effect of dietary fats and fibers on the risk of Barrett's esophagus, a metaplastic precursor to esophageal adenocarcinoma. This research complements prior studies of dietary components as risk factors for esophageal adenocarcinoma by determining that diet may be associated with early changes in the carcinogenic pathway (e.g. Barrett's esophagus). Studies of cancer patients may be biased due to recall bias or behavioral/biological changes such as changes in weight or diet, due to the diagnosis or treatments for the cancer itself. By using only patients with a new diagnosis of Barrett's esophagus and by identifying all patients with a new diagnosis within this well defined population, we were able to evaluate whether diet acts early in the carcinogenic sequence, with less opportunity for bias.

Second, the study subjects came from a diverse, broad population base that closely approximates the region's census demographics; thus, the results can more readily be generalized to similar large populations. Third, the availability of two comparison groups permitted us to evaluate the effect of diet in the general population, as well as whether diet is a risk factor for Barrett's esophagus among persons with GERD.

There are several potential limitations of these analyses. Case-control studies cannot definitively establish cause and effect(33) and observational studies in general are subject to confounding by other unmeasured variables. Although analyses that evaluated several potential confounders provided little evidence of confounding, we cannot exclude the possibility that some measured or unmeasured factors might have influenced the results. Second, the main

exposure variables were measured just after a Barrett's esophagus diagnosis. Although it is possible that the presence of Barrett's esophagus or GERD may have influenced the subjects' diet, we addressed this issue by evaluating GERD patients as a separate group, and the participants were asked to estimate their dietary intake in the year prior to their Barrett's diagnosis. The food frequency questionnaire is also highly correlated with historical food intake,(30) minimizing the potential recall bias. Potential random measurement error of dietary data from food frequency questionnaire is an important issue in nutritional epidemiology, though such measurement error would most likely bias the results towards the null unless there is random error in several covariates. Third, the presence of non-responders may lead to bias; however, the electronic data suggested that non-responders were, on average, somewhat healthier than the responders, with lower comorbidity scores. This finding would suggest that the effect of non-response, if any, may bias the results towards the null (making the population controls more similar to the cases), and more difficult to detect a difference of causal significance. Lastly, although adjustment for GERD symptoms or a GERD diagnosis did not eliminate the associations seen, these are imperfect measures of true gastroesophageal reflux. Thus, we cannot exclude that some of the associations seen are mediated through diet altering gastroesophageal reflux, which, in turn, may have altered the risk of Barrett's esophagus.

In summary, in a community-based population, we found that omega 3 fatty-acid, fiber, and meat intake were inversely associated with the risk of Barrett's esophagus, while trans-fat intake may be adversely associated with risk. Combining our results with previous reports, a dietary pattern that is rich in whole foods, including animal products, may be inversely associated with risk, whereas a diet high in processed foods and fast foods is adversely associated with risk. Future studies are needed to evaluate the role of GERD on the etiological pathway and whether dietary interventions may influence the risk of Barrett's esophagus or esophageal adenocarcinoma in high risk persons (such as persons with GERD).

References

1. Reid BJ, Barrett MT, Galipeau PC, Sanchez CA, Neshat K, et al. Barrett's esophagus: ordering the events that lead to cancer. *Eur J Cancer Prev* 1996;5(Suppl 2):57–65. [PubMed: 9061296]
2. Blot WJ, Devesa SS, Fraumeni JF Jr. Continuing climb in rates of esophageal adenocarcinoma: an update. *Jama* 1993;270(11):1320. [PubMed: 8360967]
3. Blot WJ, Devesa SS, Kneller RW, Fraumeni JF Jr. Rising incidence of adenocarcinoma of the esophagus and gastric cardia. *Jama* 1991;265(10):1287–9. [PubMed: 1995976]
4. Blot WJ, McLaughlin JK. The changing epidemiology of esophageal cancer. *Semin Oncol* 1999;26(5 Suppl 15):2–8. [PubMed: 10566604]
5. Kubo A, Corley DA. Marked regional variation in adenocarcinomas of the esophagus and the gastric cardia in the United States. *Cancer* 2002;95(10):2096–102. [PubMed: 12412162]
6. Lagergren J. Adenocarcinoma of oesophagus: what exactly is the size of the problem and who is at risk? *Gut* 2005;54(Suppl 1):i1–5. [PubMed: 15711002]
7. 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(2):123–32. [PubMed: 8481491]
8. Mayne ST, Risch HA, Dubrow R, Chow WH, Gammon MD, et al. Nutrient intake and risk of subtypes of esophageal and gastric cancer. *Cancer Epidemiol Biomarkers Prev* 2001;10(10):1055–62. [PubMed: 11588131]
9. Tzonou A, Lipworth L, Garidou A, Signorello LB, Laggiou P, et al. Diet and risk of esophageal cancer by histologic type in a low-risk population. *Int J Cancer* 1996;68(3):300–4. [PubMed: 8903470]
10. Zhang ZF, Kurtz RC, Yu GP, Sun M, Gargon N, et al. Adenocarcinomas of the esophagus and gastric cardia: the role of diet. *Nutr Cancer* 1997;27(3):298–309. [PubMed: 9101561]
11. Gonzalez CA, Pera G, Agudo A, Bueno-de-Mesquita HB, Ceroti M, et al. Fruit and vegetable intake and the risk of stomach and oesophagus adenocarcinoma in the European Prospective Investigation

- into Cancer and Nutrition (EPIC-EURGAST). *Int J Cancer* 2006;118(10):2559–66. [PubMed: 16380980]
12. Brown LM, Swanson CA, Gridley G, Swanson GM, Schoenberg JB, et al. Adenocarcinoma of the esophagus: role of obesity and diet. *J Natl Cancer Inst* 1995;87(2):104–9. [PubMed: 7707381]
 13. Kubo A, Corley DA. Meta-Analysis of Antioxidant Intake and the Risk of Esophageal and Gastric Cardia Adenocarcinoma. *Am J Gastroenterol*. 2007
 14. Cheng KK, Sharp L, McKinney PA, Logan RF, Chilvers CE, et al. A case-control study of oesophageal adenocarcinoma in women: a preventable disease. *Br J Cancer* 2000;83(1):127–32. [PubMed: 10883680]
 15. Terry P, Lagergren J, Hansen H, Wolk A, Nyren O. Fruit and vegetable consumption in the prevention of oesophageal and cardia cancers. *Eur J Cancer Prev* 2001;10(4):365–9. [PubMed: 11535879]
 16. Ward MH, Sinha R, Heineman EF, Rothman N, Markin R, et al. Risk of adenocarcinoma of the stomach and esophagus with meat cooking method and doneness preference. *Int J Cancer* 1997;71(1):14–9. [PubMed: 9096659]
 17. Chen KH, Mukaisho K, Sugihara H, Araki Y, Yamamoto G, et al. High animal-fat intake changes the bile-acid composition of bile juice and enhances the development of Barrett's esophagus and esophageal adenocarcinoma in a rat duodenal-contents reflux model. *Cancer Sci* 2007;98(11):1683–8. [PubMed: 17868414]
 18. Clark GW, Smyrk TC, Mirvish SS, Anselmino M, Yamashita Y, et al. Effect of gastroduodenal juice and dietary fat on the development of Barrett's esophagus and esophageal neoplasia: an experimental rat model. *Ann Surg Oncol* 1994;1(3):252–61. [PubMed: 7842295]
 19. Anderson LA, Watson RG, Murphy SJ, Johnston BT, Comber H, et al. Risk factors for Barrett's oesophagus and oesophageal adenocarcinoma: results from the FINBAR study. *World J Gastroenterol* 2007;13(10):1585–94. [PubMed: 17461453]
 20. Kubo A, Levin TR, Block G, Rumore GJ, Quesenberry CP Jr, et al. Dietary Antioxidants, Fruits, and Vegetables and the Risk of Barrett's Esophagus. *Am J Gastroenterol*. 2008
 21. Kubo A, Levin TR, Block G, Rumore GJ, Quesenberry CP Jr, et al. Dietary Patterns and the Risk of Barrett's Esophagus. *Am J Epidemiol* 2008;167(7):839–46. [PubMed: 18218607]
 22. Corley DA, Kubo A, Levin TR, Block G, Habel L, et al. Abdominal Obesity and Body Mass Index as Risk Factors for Barrett's Esophagus. *Gastroenterology* 2007;133(1):34–41. [PubMed: 17631128]
 23. Hiatt RA, Friedman GD. The frequency of kidney and urinary tract diseases in a defined population. *Kidney Int* 1982;22(1):63–8. [PubMed: 6181284]
 24. Krieger N. Overcoming the absence of socioeconomic data in medical records: validation and application of a census-based methodology. *Am J Public Health* 1992;82(5):703–10. [PubMed: 1566949]
 25. Ofman JJ, Ryu S, Borenstein J, Kania S, Lee J, et al. Identifying patients with gastroesophageal reflux disease in a managed care organization. *Am J Health Syst Pharm* 2001;58(17):1607–13. [PubMed: 11556654]
 26. Block G, Hartman AM. Issues in reproducibility and validity of dietary studies. *Am J Clin Nutr* 1989;50(5 Suppl):1133–8. [PubMed: 2683721]discussion 1231–5
 27. Block G, Hartman AM, Dresser CM, Carroll MD, Gannon J, et al. A data-based approach to diet questionnaire design and testing. *Am J Epidemiol* 1986;124(3):453–69. [PubMed: 3740045]
 28. Block G, Thompson FE, Hartman AM, Larkin FA, Guire KE. Comparison of two dietary questionnaires validated against multiple dietary records collected during a 1-year period. *J Am Diet Assoc* 1992;92(6):686–93. [PubMed: 1607564]
 29. Block G, Woods M, Potosky A, Clifford C. Validation of a self-administered diet history questionnaire using multiple diet records. *J Clin Epidemiol* 1990;43(12):1327–35. [PubMed: 2254769]
 30. Sobell J, Block G, Koslowe P, Tobin J, Andres R. Validation of a retrospective questionnaire assessing diet 10–15 years ago. *Am J Epidemiol* 1989;130(1):173–87. [PubMed: 2741904]
 31. Coates RJ, Eley JW, Block G, Gunter EW, Sowell AL, et al. An evaluation of a food frequency questionnaire for assessing dietary intake of specific carotenoids and vitamin E among low-income black women. *Am J Epidemiol* 1991;134(6):658–71. [PubMed: 1951269]

32. Willett W, Stampfer M, Chu NF, Spiegelman D, Holmes M, et al. Assessment of questionnaire validity for measuring total fat intake using plasma lipid levels as criteria. *Am J Epidemiol* 2001;154(12): 1107–12. [PubMed: 11744515]
33. Rothman, K.; Greenland, S. *Modern Epidemiology*. Vol. 2. Philadelphia, PA: Lippincott Williams & Wilkins; 1998.
34. Zhao Y, Ash A, Ellis R, Ayanian J, Pope GC, et al. Predicting Pharmacy Costs and Other Medical Costs Using Diagnoses and Drug Claims. *Medical Care* 2005;43(1):34–43. [PubMed: 15626932]
35. Zhao Y, Ash A, Haughton J, McMillan B. Identifying Future High Cost Cases: Through Predictive Modeling. *Dis Manage Health Outcomes* 2003;11(6):389–397.
36. Terry P, Lagergren J, Ye W, Wolk A, Nyren O. Inverse association between intake of cereal fiber and risk of gastric cardia cancer. *Gastroenterology* 2001;120(2):387–91. [PubMed: 11159879]
37. Health HSoP. In with the Good. The Nutrition Source- Fats and Cholesterol: Out with the Bad.
38. Ascherio A, Katan MB, Zock PL, Stampfer MJ, Willett WC. Trans fatty acids and coronary heart disease. *N Engl J Med* 1999;340(25):1994–8. [PubMed: 10379026]
39. Salmeron J, Hu FB, Manson JE, Stampfer MJ, Colditz GA, et al. Dietary fat intake and risk of type 2 diabetes in women. *Am J Clin Nutr* 2001;73(6):1019–26. [PubMed: 11382654]
40. Mozaffarian D, Pischon T, Hankinson SE, Rifai N, Joshipura K, et al. Dietary intake of trans fatty acids and systemic inflammation in women. *Am J Clin Nutr* 2004;79(4):606–12. [PubMed: 15051604]
41. Tselepis C, Perry I, Dawson C, Hardy R, Darnton SJ, et al. Tumour necrosis factor-alpha in Barrett's oesophagus: a potential novel mechanism of action. *Oncogene* 2002;21(39):6071–81. [PubMed: 12203119]
42. Mehta SP, Boddy AP, Cook J, Sams V, Lund EK, et al. Effect of n-3 polyunsaturated fatty acids on Barrett's epithelium in the human lower esophagus. *Am J Clin Nutr* 2008;87(4):949–56. [PubMed: 18400718]
43. Corley DA, Kerlikowske K, Verma R, Buffler P. Protective association of aspirin/NSAIDs and esophageal cancer: a systematic review and meta-analysis. *Gastroenterology* 2003;124(1):47–56. [PubMed: 12512029]
44. Burkitt DP. Hiatus hernia: is it preventable? *Am J Clin Nutr* 1981;34(3):428–31. [PubMed: 6259926]

Table 1

Characteristics of study groups

	Cases	GERD controls	Population controls
	Mean/# (SD/%)	Mean/# (SD/%)	Mean/# (SD/%)
Number of subjects	296	308	309
Age	62.3 (± 10.7)	61.7 (± 10.8)	62.3 (± 10.3)
Race			
White	255 (86%)	247 (80%)	262 (85%)
Black	5 (2)	20 (7)	16 (5)
Hispanic	24 (8)	20 (6)	12 (4)
Asian	4 (1)	8 (3)	9 (3)
Others	8 (3)	13 (4)	10 (3)
Gender			
Male	218 (74)	211 (68)	208 (67)
Female	77 (26)	97 (32)	101 (33)
Education			
High school or less	77 (26)	77 (25)	85 (29)
Some college	134 (45)	126 (41)	105 (34)
College and beyond	85 (29)	118 (38)	132 (43)
Income			
<50k	125 (46)	108 (41)	104 (36)
50–75	61 (22)	59 (22)	67 (23)
75k+	87 (32)	96 (37)	119 (41)
Smoking status (Ever smokers)	197 (67)	182 (59)	173 (56)
Alcohol			
None	77 (26)	109 (36)	78 (25)
Light (≤ 1 /week)	153 (52)	131 (42)	157 (51)
Moderate (1–2/week)	27 (9)	27 (9)	48 (15)
Heavy (2+/week)	39 (13)	41 (13)	26 (8)
Body mass index (kg/m^2)	29.4 (± 5.8)	28.9 (± 5.3)	29.5 (± 5.8)
Dietary intake			
Energy (kcal)	1805 (± 857)	1827 (± 770)	1839 (± 794)
Total fat (g)	79.2 (± 46.4)	77.9 (± 37.9)	81.1 (± 42.5)
Total fiber (g)	15.9 (± 8.6)	16.2 (± 8.3)	18.1 (± 9.4)
Meat (servings/day)	2.0 (± 1.3)	2.0 (± 1.2)	2.1 (± 1.4)
Fruit and vegetable (servings/day)	4.1 (± 2.4)	4.3 (± 2.6)	5.0 (± 2.9)
Vitamin supplement use			
>2 years	163 (55)	157 (51)	163 (53)
≤ 2 years	59 (20)	45 (15)	37 (12)
Never	74 (25)	106 (34)	102 (33)

Table 2

Odds Ratios and 95% CI for Associations of Dietary Fat with Barrett's esophagus: cases vs. population controls

	Median intake ¹	# Case/control	OR (95% CI) ² Any Barrett's	OR (95% CI) ² Long-segment only
Total Fat (g/day)				
Quartile 1	39.6	81/77	1.0 (ref)	1.0 (ref)
Quartile 2	60.3	72/77	1.00 (0.53–1.88)	1.86 (0.84–4.15)
Quartile 3	85.2	69/77	1.07 (0.45–2.52)	1.07 (0.33–3.46)
Quartile 4	131.4	74/78	0.49 (0.20–1.20)	0.52 (0.18–1.53)
OR per unit increase (gram)			1.00 (0.99–1.01)	1.01 (0.99–1.02)
Saturated Fat (g/day)				
Quartile 1	10.6	77/77	1.0 (ref)	1.0 (ref)
Quartile 2	17.8	65/77	1.16 (0.64–2.12)	1.66 (0.77–3.60)
Quartile 3	23.4	73/75	1.55 (0.71–3.36)	3.33 (1.07–10.3)
Quartile 4	36.1	81/80	1.05 (0.47–2.34)	1.11 (0.42–2.93)
OR per unit increase (gram)			1.02 (0.99–1.05)	1.05 (1.01–1.09)
Monounsaturated fat (g/day)				
Quartile 1	14.3	84/77	1.0 (ref)	1.0 (ref)
Quartile 2	23.0	68/76	0.83 (0.45–1.54)	1.32 (0.60–2.86)
Quartile 3	31.9	72/78	0.89 (0.40–1.94)	1.08 (0.38–3.08)
Quartile 4	50.5	72/78	0.54 (0.23–1.28)	0.50 (0.18–1.44)
OR per unit increase (gram)			0.99 (0.97–1.02)	1.01 (0.98–1.05)
Polyunsaturated Fat (g/day)				
Quartile 1	9.3	85/76	1.0 (ref)	1.0 (ref)
Quartile 2	14.9	84/77	1.12 (0.64–1.96)	1.35 (0.68–2.64)
Quartile 3	22.5	66/78	0.56 (0.26–1.22)	0.38 (0.14–1.02)
Quartile 4	34.7	61/78	0.49 (0.22–1.11)	0.47 (0.17–1.27)
OR per unit increase (gram)			0.97 (0.94–0.99)	0.98 (0.94–1.01)
Trans Fat (g/day)				
Quartile 1	2.2	63/77	1.0 (ref)	1.0 (ref)
Quartile 2	3.8	79/76	1.83 (1.05–3.18)	2.28 (1.13–4.61)
Quartile 3	5.6	59/78	1.38 (0.73–2.63)	1.27 (0.56–3.00)
Quartile 4	8.9	95/78	1.54 (0.76–3.10)	1.21 (0.52–2.84)
OR per unit increase (gram)			1.11 (1.03–1.21)	1.15 (1.04–1.27)
Omega3 (g/day)				
Quartile 1	0.83	88/76	1.0 (ref)	1.0 (ref)
Quartile 2	1.32	83/78	0.88 (0.51–1.52)	0.85 (0.44–1.65)
Quartile 3	2.16	63/77	0.70 (0.36–1.38)	0.46 (0.19–1.11)
Quartile 4	3.02	62/78	0.46 (0.22–0.97)	0.36 (0.14–0.90)
OR per unit increase (gram)			0.75 (0.59–0.97)	0.68 (0.49–0.97)
Cholesterol (mg/day)				
Quartile 1	51	79/77	1.0 (ref)	1.0 (ref)
Quartile 2	86	68/77	1.06 (0.61–1.83)	1.44 (0.71–2.91)
Quartile 3	237	81/77	1.89 (0.99–3.59)	1.63 (0.69–3.85)
Quartile 4	370	68/78	0.70 (0.34–1.44)	0.73 (0.31–1.72)
OR per unit increase (mg)			1.00 (1.00–1.01)	1.00 (0.99–1.01)

¹ Only dietary intake was included in the analyses. The quartile cutoff points and median intakes are from the distribution of all population controls.² Model was adjusted for age, sex, race (white vs. non-white), long-term vitamin use (>2 years), and energy.

Table 3

Odds Ratios and 95% CI for Associations of Dietary fiber and Barrett's esophagus risk cases vs. population controls

	Median intake ¹	# Case/control	OR (95% CI) ² Any Barrett's	OR (95% CI) ² Long-segment only
Total Fiber (g/day)				
Quartile 1	8.6	91/77	1.0 (ref)	1.0 (ref)
Quartile 2	13.9	76/77	0.70 (0.40–1.24)	0.71 (0.36–1.38)
Quartile 3	18.8	82/76	0.86 (0.47–1.58)	0.79 (0.38–1.65)
Quartile 4	29.7	47/79	0.34 (0.15–0.76)	0.20 (0.07–0.56)
OR per unit increase (gram)			0.95 (0.93–0.98)	0.95 (0.91–0.99)
Fiber from grains (g/day)				
Quartile 1	3.1	87/77	1.0 (ref)	1.0 (ref)
Quartile 2	5.0	60/77	0.72 (0.43–1.22)	0.72 (0.37–1.41)
Quartile 3	7.0	93/77	1.13 (0.66–1.93)	1.03 (0.53–1.99)
Quartile 4	12.3	56/78	0.73 (0.36–1.45)	0.63 (0.27–1.51)
OR per unit increase (gram)			0.98 (0.94–1.03)	1.00 (0.95–1.05)
Fiber from fruits and vegetables (g/day)				
Quartile 1	3.2	103/77	1.0 (ref)	1.0 (ref)
Quartile 2	5.4	67/77	0.65 (0.39–1.07)	0.51 (0.28–0.94)
Quartile 3	8.3	76/77	0.63 (0.36–1.09)	0.44 (0.23–0.86)
Quartile 4	13.2	50/78	0.47 (0.25–0.88)	0.30 (0.13–0.69)
OR per unit increase (gram)			0.93 (0.89–0.97)	0.88 (0.82–0.94)
Fiber from beans (g/day)				
Quartile 1	0.74	94/74	1.0 (ref)	1.0 (ref)
Quartile 2	1.56	72/80	0.72 (0.43–1.21)	0.70 (0.37–1.32)
Quartile 3	2.94	70/77	0.69 (0.39–1.22)	0.68 (0.33–1.40)
Quartile 4	5.99	60/78	0.69 (0.36–1.33)	0.66 (0.30–1.44)
OR per unit increase (gram)			0.94 (0.87–1.02)	0.98 (0.89–1.07)

¹ Only dietary intake was included in the analyses. The quartile cutoff points and median intakes are from the distribution of all population controls. Quartiles are specific to each type of fiber.

² Model was adjusted for age, sex, race (white vs. non-white), long-term vitamin use (>2 years), and energy.

Table 4

Odds Ratios and 95% CI for Associations of Dietary protein, dairy, meat, and methods of cooking meat and Barrett's esophagus risk cases vs. population controls

	Median intake ¹	# Case/control	OR (95% CI) ² Any Barrett's	OR (95% CI) ² Long-segment only
Protein (g/day)				
Quartile 1	37.4	93/76	1.0 (ref)	1.0 (ref)
Quartile 2	52.1	63/78	0.65 (0.35–1.23)	0.82 (0.38–1.76)
Quartile 3	71.6	78/77	0.75 (0.34–1.65)	0.49 (0.18–1.37)
Quartile 4	103.4	62/78	0.47 (0.19–1.12)	0.36 (0.12–1.05)
OR per unit increase (gram)			0.99 (0.98–1.00)	0.98 (0.97–1.00)
Dairy (servings/day)				
Quartile 1	0.2	84/70	1.0 (ref)	1.0 (ref)
Quartile 2	0.7	59/75	0.72 (0.43–1.21)	0.65 (0.33–1.25)
Quartile 3	1.1	62/78	0.59 (0.34–1.00)	0.55 (0.28–1.07)
Quartile 4	2.2	91/86	0.95 (0.56–1.60)	0.85 (0.45–1.63)
OR per unit increase (serving)			1.14 (0.96–1.36)	1.14 (0.91–1.41)
Meat (servings/day)				
Quartile 1	0.9	85/73	1.0 (ref)	1.0 (ref)
Quartile 2	1.5	80/81	0.88 (0.51–1.52)	1.10 (0.55–2.18)
Quartile 3	2.1	61/73	0.83 (0.40–1.70)	0.64 (0.25–1.63)
Quartile 4	3.3	70/82	0.46 (0.21–1.01)	0.25 (0.09–0.72)
OR per unit increase (serving)			0.83 (0.66–1.04)	0.72 (0.52–0.99)
Meat doneness preference				
Rare		43/46	1.0 (ref)	1.0 (ref)
Welldone		71/63	1.30 (0.62–2.72)	1.41 (0.77–2.56)
Barbecued food				
<1/month		149/144	1.0 (ref)	1.0 (ref)
1+ /week		72/75	0.84 (0.53–1.35)	1.26 (0.64–1.99)

¹ Only dietary intake was included in the analyses. The quartile cutoff points and median intakes are from the distribution of all population controls.

² Model was adjusted for age, sex, race (white vs. non-white), long-term vitamin use (>2 years), and energy.