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Dietary antioxidants, fruits and vegetables, and the risk of Barrett's esophagus

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Abstract

OBJECTIVE—The present study evaluated the associations between antioxidants, fruit and vegetable intakes and the risk of Barrett's esophagus, a potential precursor to esophageal adenocarcinoma.

METHODS—We conducted a case-control study within the Kaiser Permanente Northern California population. Incident Barrett's esophagus cases (n=296) were matched to persons with gastroesophageal reflux disease (GERD) (GERD controls, n=308) and to population controls (n=309). Nutrient intake was measured using a validated 110-item food frequency questionnaire. The antioxidant results were stratified by dietary vs. total intake of antioxidants.

RESULTS—Comparing cases to population controls, dietary intake of vitamin C and beta-carotene were inversely associated with the risk of Barrett's esophagus [4th vs. 1st quartile, adjusted odds ratio [OR]=0.48 95% confidence interval [CI] (0.26–0.90); OR=0.56 95% CI(0.32–0.99), respectively], and the inverse association was strongest for vitamin E [OR=0.25 95% CI (0.11–0.59)]. The inverse trends for antioxidant index (total and dietary) and fruit and vegetable intake were statistically significant, while most total intakes were not associated with reduced risk. The use of antioxidant supplements did not influence the risk of Barrett's esophagus, and antioxidants and fruits and vegetables were inversely associated with a GERD diagnosis.

CONCLUSION—Dietary antioxidants, fruit and vegetable are inversely associated with the risk of Barrett's esophagus, while no association was observed for supplement intake. Our results suggest that fruits and vegetables themselves or associated undetected confounders may influence early events in the carcinogenesis of esophageal adenocarcinoma.

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Ai Kubo contributed to the reviews of the existing literature, statistical analyses, and the preparation of the manuscript.

T.R. Levin & Greg Rumore conducted medical and pathology review.

Charles Quesenberry and Gladys Block contributed to the statistical methods of the nutritional analysis.

Patricia Buffler helped design the study.

Douglas Corley is a principal investigator of the case-control study, and contributed to the statistical analyses and the preparation of the manuscript.

Potential competing interests: None

Keywords

epidemiology; nutrition; antioxidants; fruits and vegetables; Barrett's esophagus

BACKGROUND

The incidence of esophageal adenocarcinoma has increased by greater than 500% in the last three decades, more rapidly than any other malignancy in the United States.^{1–6} Barrett's esophagus is a metaplastic transformation of the esophageal squamous epithelium into specialized intestinal columnar epithelium, and is a strong risk factor for esophageal adenocarcinoma.^{1, 7–9} The risk factors for Barrett's esophagus are not well understood, and may represent early events in the carcinogenic pathway for esophageal adenocarcinoma. Since patients with Barrett's esophagus have a 30–40 fold increased risk of esophageal adenocarcinoma, there is a compelling rationale for characterizing its potentially modifiable risk factors.¹⁰ Diet may be a modifiable risk factor, though its associations with Barrett's esophagus have not been reported.

Antioxidants such as vitamin C, vitamin E, selenium and carotenoids may be anti-carcinogens, possibly through their ability to reduce DNA damage by scavenging reactive oxygen species.¹¹ A recent meta-analysis of epidemiological studies reported that antioxidants such as vitamin C, E, and beta-carotene are inversely associated with the risk of esophageal adenocarcinoma.¹² Higher serum selenium levels may also be associated with a lower risk of progression from Barrett's esophagus to esophageal adenocarcinoma, although data are somewhat discordant.^{13–15}

On the other hand, others postulate that fruit and vegetable are more important in the etiology of esophageal adenocarcinoma than antioxidants themselves. Fruit and vegetable contain not only high levels of antioxidants, but also numerous other known and unknown nutrients and compounds that may interact in a particular way to affect human health. A few case-control studies have reported an inverse association between fruit and vegetable intake and the risk of esophageal adenocarcinoma.^{16–20} Another large scale US case-control study, while not examining the effect of fruit and vegetable, reported that antioxidants from dietary source were inversely associated with the risk of esophageal adenocarcinoma, while no association was found for antioxidants taken as a dietary supplement.²¹ In vitro experiments suggest that some oxidizing agents cause DNA damage and enhance cancer cell replication.^{22, 23} Since esophageal populations of Barrett's esophagus cells are frequently clonal, such agents could theoretically both initiate and promote clonal growth of cells such as Barrett's esophagus.²⁴ An animal model of Barrett's esophagus and esophageal adenocarcinoma also supported a role for antioxidants in the carcinogenic pathway: supplementation with the antioxidant vitamin E decreased the cancer risk for the animals whereas iron (an oxidizing agent) increased the risk.^{15, 25}

Little human data exist on the associations between diet and Barrett's esophagus.²⁵ The evaluation of an esophageal adenocarcinoma precursor (such as Barrett's esophagus) may reduce biases seen in case-control studies of esophageal adenocarcinoma, since this malignancy may alter diet or body weight. In addition, examination of the earlier stages of carcinogenesis permits an evaluation of whether diet acts early in the carcinogenic sequence by increasing the incidence of a precursor, Barrett's esophagus. A recent study from Ireland reported an inverse association between fruits and vegetables intake and the risk of Barrett's esophagus,²⁶ and another hospital-based study reported an inverse association between vitamin C intake and Barrett's esophagus,²⁷ though both study used only population-controls as a comparison group. Another study that examined the plasma concentration of antioxidants and

the risk of Barrett's esophagus reported that Barrett's esophagus patients had lower levels of plasma antioxidants such as selenium and vitamin C compared to controls.²⁸ However, plasma biomarkers do not provide definitive information on patterns of food consumption (such as fruit and vegetable), and cannot separate dietary vs. supplement intake; these factors are all important in planning potential nutritional interventions.²⁹

We conducted the first U.S. case-control study within a community-based population to examine the association between antioxidant intake (both dietary and supplemental) and the risk for a new diagnosis of Barrett's esophagus.

Materials and Methods

Study Population

The details of the study design have been described previously.³⁰ This case-control study was conducted within the Kaiser Permanente, Northern California (NCKP) population, an integrated health services delivery organization. NCKP contains approximately 3.3 million persons; the membership has demographics that closely approximate the underlying census population of Northern California.^{31, 32} Eligible subjects were all adult (ages 18–79 years) NCKP 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 questionnaires asked participants to report exposures in the year prior to the index date.

Case Definition

Cases were NCKP patients (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 NCKP 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 any pathologic evaluation; 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 NCKP 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.³³

Exposure Measurements

All study subjects completed: an in-person interview (most commonly at the subject's home) of GERD symptoms, medication use, medical history, tobacco use and alcohol use; phlebotomy; and anthropometric measurements.

We assessed subjects' nutritional intake using a validated 110-item food frequency questionnaire (Block 98).^{34–37} This FFQ estimates average daily nutrient intake, including antioxidants, fruit and vegetable based on questions about frequency and portion size of a given food and usual eating habits over the year before the index date. The questionnaire has good correlations with multiple-day dietary records in a wide variety of population subgroups, in assessing past dietary habit,³⁸ correlates with serum measures for lipids and antioxidants,^{39, 40} and provides information on the source of micronutrients (i.e., dietary vs. supplemental). Subjects indicated use of dietary supplements by answering the questions regarding the type, amount, frequency, and duration of various vitamins, minerals, and commonly used multivitamins. The original dietary data were translated to daily intakes of specific nutrients using Block Dietary Data Systems (Berkeley, CA).

Quartile categories used distributions from the population control group. An antioxidant composite variable (antioxidant index) was created to obtain a combined measure of dietary and supplemental antioxidant intake from vitamins C, E, beta-carotene, and selenium. We evaluated each subject's total antioxidant intake using an "antioxidant index" that summed the decile category of each nutrient for each subject. For example, a subject with an antioxidant intake in the first decile for each of the four micronutrients had an antioxidant index equal to four, while a subject in the tenth decile for each micronutrient had an antioxidant index equal to 40. We excluded subjects with over 20 missing food items or with extremely high or low total caloric intakes.

Statistical Analysis

296 Barrett's esophagus cases, 308 GERD controls, and 309 population controls were included in the analyses, after exclusion of subjects who did not complete the food frequency questionnaire (n=28) or who had extreme responses in the questionnaire as described previously (skipped items >20 n=5; extreme caloric intakes n=7).

Unconditional logistic regression was used to calculate odds ratios (ORs) as an estimate of the relative risk, and corresponding 95% confidence intervals (CIs).⁴¹ 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),^{42, 43} education, income, and total caloric intake per day. Confounders were included in the final model if their inclusion altered the β coefficient by >10%. Since each antioxidant is likely to be collinear with one another, we did

not control for other antioxidants in the final model. The final model was adjusted for the frequency matched variables (age, sex and geographic region), in addition to race, supplement use status, and energy intake, which are known to be associated with Barrett's esophagus and/or diet.

The results for antioxidant intakes were stratified by dietary intake and total intake to separately evaluate the influence of antioxidants from different sources. For total intake (combined supplemental and dietary intake), only individuals who reported the use of the specific supplement for >2 years were included. Subjects with ≤ 2 years of supplement use before diagnosis were excluded to avoid potential bias: those who were diagnosed with Barrett's esophagus or GERD, or those who are more symptomatic may have started to use supplement soon after the diagnosis or appearance of the symptoms. For dietary intake analyses, all subjects were included.

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. Given the extremely non-normal distribution of intake and the possibility that the change in risk may not be linear, the continuous values were transformed using the natural log. The antioxidant index and fruit/vegetable intake patterns, which were more normally distributed, are reported without log transformation.

We also examined whether use of dietary antioxidant supplements had an effect if one's baseline dietary intakes were low. For this analysis, among subjects in the lowest quartile of *dietary* antioxidant intake, we evaluated whether the risks of Barrett's esophagus differed between long-term supplement users of each micronutrient (either as a multivitamin or a specific supplement) vs. supplement non-users.

All studies were analyzed using SAS statistical software (Cary, NC). The study and analyses were approved by the institutional review board.

RESULTS

Baseline Characteristics

The 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 slightly higher proportion of ever smokers compared to the other groups, and population controls were more likely to have higher education and income. The unadjusted average intakes of total antioxidants (combination of dietary and supplemental), energy, and fat were comparable between the three groups, though population control subjects tended to have somewhat higher unadjusted intakes of individual micronutrients and fruit and vegetable. Among the long-term supplement users, 83% used a multivitamin at least once a week (majority of them including minerals), approximately 50% took vitamin C and/or vitamin E, 7% took beta-carotene, and none used a selenium supplement. Multivitamins such as antioxidant complex or stress tabs were assumed to provide vitamin C, E, and beta-carotene, and those that contained minerals provide selenium. As described above, 148 (16%) subjects were excluded from the total antioxidant analyses (but not the dietary analyses) because of their short-term vitamin use (141 subjects) or missing supplement information (7 subjects).

Vitamin C—When cases were compared to population controls, there was a strong inverse association between dietary intake of vitamin C and the risk of Barrett's esophagus: subjects in the 4th quartile of *dietary* vitamin C intake (median intake=179mg/day) had a 50% lower risk of Barrett's esophagus than those in the first quartile (median=46mg/day) [0.48 95%CI

(0.26–0.90)](Table 2). On the other hand, there was no association between total intake (dietary plus supplemental) of vitamin C and the risk of Barrett's esophagus (Table 2).

When cases were compared to GERD controls, the associations were similar for dietary intake: the highest quartile of dietary vitamin C intake was associated with over a 50% reduction in the risk [OR=0.44 95%CI(0.24–0.83)], while for total intake, the associations were inconsistent and not statistically significant (Table 3).

Vitamin E—When cases were compared to population controls, dietary vitamin E had a strong inverse association with the risk of Barrett's esophagus [OR=0.25, 95% CI (0.11–0.59), median=18 vs. 5.2 ug/day](Table 2). In contrast, there was no significant association between total vitamin E intake and Barrett's esophagus.

Intake of vitamin E did not appear to have strong and consistent association when cases were compared to GERD controls (Table 3).

Beta-carotene—When cases were compared to population controls, subjects in the highest quartile of dietary beta-carotene intake had a 44% lower risk of Barrett's esophagus compared to those in the lowest quartile [OR=0.56 95%CI(0.32–0.99), median=6.1 vs. 1.2mg/day:]. The total intake was also inversely associated, though the confidence interval included 1.0. Compared with GERD controls, the inverse associations were weaker and inconsistent (Table 3).

Selenium—Dietary selenium intake was inversely associated with the risk of Barrett's esophagus with a borderline significance. On the other hand, the highest intake of total selenium was strongly associated with reduced risk of Barrett's esophagus [OR=0.29 95%CI(0.09–0.94), median 214 vs. 66ug/day](Table 2).

When cases were compared with GERD controls, the results for the categorical analysis for dietary intake were similar to the population control comparison, though the results for continuous analysis was statistically significant [OR=0.78 95%CI(0.61–0.99)] (Table 3). No association was observed for total intake.

Antioxidant Index—The overall standing of antioxidant intake was measured as an antioxidant index. Our results demonstrated strong associations of overall *dietary* antioxidant intake as an index: individuals in the highest category of antioxidant index had a substantially lower risk of Barrett's esophagus compared to those in the lowest category [OR=0.30 95%CI (0.13–0.71)], with a significant trend across the categories ($p=0.004$). The antioxidant index for total intake also had an inverse association ($p=0.01$). For cases vs. GERD controls, no significant association was observed for dietary or total antioxidant intake (Table 3).

The effects of fruits and vegetables—There was a strong inverse association between consumption of fruits and vegetables and the risk of Barrett's esophagus (Table 4). Individuals with the highest intake of fruits and vegetables (median intake=8.3 servings/day) had a 73% lower risk of developing Barrett's esophagus compared to those in the lowest category (median=2.0 servings/day) [4th vs. 1st quartile OR=0.27 95%CI (0.15–0.50)]. The analyses of continuous variables demonstrated that each additional serving/day of fruit/vegetable intake was associated with a 14% reduction in risk [OR=0.86 95%CI(0.80–0.93)]. When GERD controls were compared, the protective effects were weaker and statistically non-significant. When fruits and vegetables are analyzed separately, consumption of vegetables had a slightly stronger effect than fruits alone (data not shown). Inclusion of long-term vitamin use in the model did not change the effect estimates substantially (data not shown).

Effect of Supplement use—The long-term use of dietary supplements did not influence the risk of Barrett's esophagus, even among persons with low dietary intakes (Table 5). For example, among subjects within the lowest quartile of dietary vitamin C intake, vitamin C supplement users had a slightly higher, though non-significant, risk of Barrett's esophagus compared to nonusers (OR=1.32, 95% CI 0.70–2.47). Similar results were observed for vitamin E and beta-carotene (Table 5), as well as for comparisons between cases vs. GERD controls (data not shown.)

Additional analysis comparing the risks for different levels (low, medium, high) of total antioxidant intake among supplement users to non-users showed similar associations: all OR were above 1 for each micronutrient, indicating that supplement intake had little effect on the risk of Barrett's esophagus (data not shown).

Supplemental analyses

Stratification by supplement users vs. non-users—Since those who are long-term supplement users may be fundamentally different from non-users, we conducted an additional analysis stratifying the results by supplement user status. The results were similar to what we found in the present analyses: dietary intakes for most antioxidants were associated with lower risk of Barrett's esophagus among both supplement users and non-users, while no association was seen for total intake (data not shown).

Effects of antioxidants on GERD

We also evaluated associations between antioxidants (and fruits and vegetables) and a GERD diagnosis by contrasting intakes between the GERD group (who lacked Barrett's esophagus) and population controls. There were inverse associations between dietary vitamin C, E, and beta-carotene and the risk of GERD [4th vs. 1st quartile: OR=0.51 95% CI(0.29–0.90); OR=0.46 95% CI(0.21–0.99); OR=0.49 95% CI(0.28–0.85), respectively.] There was no association between the total intake of any antioxidant and the risk of GERD. Each daily serving of a fruits or vegetable was associated with a 10% reduction in the risk of a GERD diagnosis [OR=0.90 95% CI(0.85–0.97), per serving].

Analysis of confounders—The evaluation of additional potential confounders did not demonstrate any evidence of confounding by smoking (ever vs. never or current vs. never), body mass index (BMI=kg/m²), recent alcohol use (number of drinks/week), aspirin or nonsteroidal anti-inflammatory drug (NSAID) use, a comorbidity index (the DxCG score), education, and income. A fully adjusted model for the highest quartile of vitamin E dietary intake (containing all these factors plus age, gender, geographic region, supplement use status, and ethnicity) (OR=0.27, 95% CI (0.11–0.67)) was similar to a model that contained only age, gender, ethnicity, supplement use status, geographic region, and total caloric intake (OR=0.27, 95% CI (0.12–0.65)). For both antioxidants and the fruits and vegetables analyses, when other dietary factors such as folic acid, cholesterol, isoflavone, meat, cereal fiber, and protein were included in the model one by one, the results did not change substantially.

DISCUSSION

This is the first United States population-based case-control study that examined the association between intake of antioxidants and the risk of Barrett's esophagus. The study demonstrated that antioxidant intake was inversely associated with the risk of developing Barrett's esophagus, and that the effects appear to come mainly from dietary sources, rather than from supplemental sources. There was a low threshold level for dietary intake beyond which higher intakes of micronutrients were not associated with a further reduction in the risk. Consumption of fruits and vegetables was strongly associated with a lower risk of Barrett's esophagus, which

is also strongly associated with antioxidant intake. These associations were weaker and inconsistent when GERD controls were compared with cases, suggesting that although diet may influence the occurrence of GERD, among persons with GERD, diet does not substantially influence the risk of Barrett's esophagus.

This study complements previous analyses that reported an association between antioxidant intake^{18, 21, 44, 45} or fruits and vegetables^{16, 17, 20, 26, 46} and esophageal adenocarcinoma. Most of these studies reported a lower risk of esophageal adenocarcinoma among subjects with higher antioxidant intakes, but very few investigated the sources of antioxidants. Our study demonstrates that dietary factors affect the early stage of carcinogenesis process, and corroborates the previous study reporting stronger beneficial effect of dietary sources of antioxidants compared to supplemental intake on the risk of esophageal adenocarcinoma.²¹ The inverse association between fruits and vegetables and the risk of Barrett's esophagus agrees with the previous population-based case-control study in Ireland.²⁶ Our results further suggest that antioxidants may only be surrogates for fruit and vegetable intake, and that antioxidant supplements do not modify the risk of Barrett's esophagus among persons with low intakes of fruits and vegetables. This finding supports the recommendation from World Cancer Research Fund and American Institute for Cancer Research that individuals should try meeting nutritional needs through diet alone, and dietary supplements are not recommended for cancer prevention.⁴⁷ The same report also warned that high-doses of supplement use, particularly beta-carotene, can increase the risk of certain cancers;⁴⁷ it is conceivable that other antioxidants may also have paradoxical toxicities at higher doses. If true, this finding may partially explain the null effects of total intake observed in this study.

The discrepancy between dietary and total intake, as well as the lack of effect of supplement intake among those with low dietary intakes, indicate that the beneficial effects of fruits and vegetables cannot be fully explained by the intake of antioxidants per se. In addition, the observed inverse associations for fruits and vegetables persisted even after controlling for other factors such as obesity, intakes of total energy, folic acid, total fat, saturated fat, trans fat, cholesterol, meat, isoflavone, or fiber (data not shown), demonstrating that the effect of fruit and vegetable intake was independent of other dietary factors that affect various health outcomes. There are likely to be other unmeasured compounds in fruit and vegetable that affect the early events in carcinogenesis, or there may be complex interactions among various known and unknown compounds and nutrients affecting the etiology of Barrett's esophagus.

Our results also suggest that the effect of diet on esophageal adenocarcinoma may be at least partially mediated by changes in the risk of GERD and Barrett's esophagus. The strong inverse associations observed in case vs. population control comparison weakened when GERD controls were used as referent. This may be due to a few different reasons. First, the diet-Barrett's esophagus association may be at least partially mediated by GERD: our supplemental analyses showed strong inverse associations between vitamin C, E, and beta-carotene and a diagnosis of GERD. Diet may modify the risk of developing GERD, which in turn affect the risk of Barrett's esophagus. Second, GERD controls may be similar to cases in many ways, thus overmatched with the cases. For instance, both cases and the GERD controls had upper GI symptoms requiring an endoscopy: individuals who undergo endoscopy may be fundamentally different from those who don't in many ways including dietary choices. Both GERD group and cases may have lower intakes of antioxidants and fruits and vegetables compared to population controls, making the two groups similar to each other (i.e., weakening the associations that were seen in the comparison of population controls.) Third, there may be differences in dietary effects depending on the severity or frequency of the GERD symptoms. However, our supplemental analysis adjusting for weekly GERD symptoms did not change the point estimate substantially: for instance, the effect of high dietary vitamin E intake [OR=0.27, 95% CI (0.12–0.65)] was almost identical to the odds ratio adjusted for weekly

GERD symptoms [OR=0.25 95% CI (0.08–0.82)]. Further research is needed to examine these effects to better understand the role of GERD in diet and Barrett's esophagus association.

There are several strengths of this analysis. First, the subjects came from a diverse population base that closely approximates the region's census demographics; thus, the results can likely be generalized to similar large populations. Second, this is the first study to use only patients with an incident diagnosis of Barrett's esophagus and the study identified all patients with an incident diagnosis within the population. The use of prevalent cases or referral cases may select for patients with a different clinical course or patients compliant with follow-up; prevalent cases may also have initiated changes in diet or other behaviors after their Barrett's esophagus diagnosis.⁴⁸ The use of cases with an incident diagnosis thus minimizes selection bias and provides the most valid evaluation of the entire population of Barrett's esophagus patients. Third, the availability of a GERD comparison group provided information on the risk of Barrett's esophagus among patients with GERD. Finally, the data were of high quality. Measurements used trained personnel, a systematic protocol, an established laboratory, validated questionnaires, and direct review of the endoscopy and pathology results.

There are several potential limitations of this analysis. First, case-control studies cannot definitively establish cause and effect.⁴¹ Barrett's esophagus could have developed years before the diagnosis and the effects of dietary factors that influence its development could have begun long prior to the diagnosis. Although a prospective cohort study would be a better design to detect the temporality of these events, the cost of such a study may be prohibitive. Second, observational studies are subject to confounding by other unmeasured variables. Although analyses that evaluated all the measured potential confounders provided little evidence of confounding, we cannot exclude the possibility that some measured or unmeasured factors might have influenced the results. Third, estimation of one's dietary intake using the food frequency questionnaire may not be accurate and lead to misclassifications of antioxidant index: the lack of association seen for supplement intake could have been due to such non-differential misclassification bias, although it is not clear that subjects recall dietary intake more accurately than supplemental intake. Lastly, the presence of non-responders may lead to bias. However, electronic data suggested that non-responders were similar to responders on major demographic variables and were slightly healthier than the responders (slightly lower comorbidity scores), which would tend to bias the results towards the null (if at all).

In summary, in a non-referral population, we found inverse associations between dietary antioxidants, fruit and vegetable intake, and a new diagnosis of Barrett's esophagus. Higher doses of antioxidants from vitamin supplements did not reduce the risk beyond dietary intake, and the inverse effects were also seen with fruit and vegetable intake. Future avenues of research could include an intervention study to evaluate whether changes in diet can modify the risk of esophageal adenocarcinoma. A recent intervention study that assigned low-fat, high fruit and vegetable diet and weight loss for Barrett's esophagus patients reported no significant difference in biomarkers of cellular proliferation in the intervention group,⁴⁹ suggesting that diet may not influence the later stage of esophageal adenocarcinoma sequence (i.e., Barrett's esophagus → esophageal adenocarcinoma). To examine whether diet modifies the earlier stages of the esophageal adenocarcinoma pathway (normal mucosa → GERD → Barrett's esophagus), a similar study could examine the effects of diet high in fruits and vegetables for subjects at higher risk of Barrett's esophagus (i.e., obese individuals or persons with GERD).

STUDY HIGHLIGHTS

What is current knowledge:

-Antioxidant intake is associated with esophageal adenocarcinoma

-It is unknown if diet affects Barrett's esophagus development

-It is unclear if supplements affect cancer development

What is new here:

-Dietary antioxidants were inversely associated with Barrett's esophagus compared to population controls, but not to GERD controls

-Supplement intake was not associated with a reduced risk of Barrett's esophagus

-Fruit and vegetable intake is more important than total anti-oxidant intake

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References

1. Pohl H, Welch HG. The role of overdiagnosis and reclassification in the marked increase of esophageal adenocarcinoma incidence. *J Natl Cancer Inst* 2005;97:142–6. [PubMed: 15657344]
2. Blot WJ, Devesa SS, Fraumeni JF Jr. Continuing climb in rates of esophageal adenocarcinoma: an update. *Jama* 1993;270:1320. [PubMed: 8360967]
3. Blot WJ, Devesa SS, Kneller RW, Fraumeni JF Jr. Rising incidence of adenocarcinoma of the esophagus and gastric cardia. *Jama* 1991;265:1287–9. [PubMed: 1995976]
4. Blot WJ, McLaughlin JK. The changing epidemiology of esophageal cancer. *Semin Oncol* 1999;26:2–8. [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;95:2096–102. [PubMed: 12412162]
6. Kubo A, Corley DA. Marked multi-ethnic variation of esophageal and gastric cardia carcinomas within the United States. *Am J Gastroenterol* 2004;99:582–8. [PubMed: 15089886]
7. Reid BJ, Barrett MT, Galipeau PC, Sanchez CA, Neshat K, Cowan DS, Levine DS. Barrett's esophagus: ordering the events that lead to cancer. *Eur J Cancer Prev* 1996;5(Suppl 2):57–65. [PubMed: 9061296]
8. Cameron AJ, Lomboy CT, Pera M, Carpenter HA. Adenocarcinoma of the esophagogastric junction and Barrett's esophagus. *Gastroenterology* 1995;109:1541–6. [PubMed: 7557137]
9. Pera M, Cameron AJ, Trastek VF, Carpenter HA, Zinsmeister AR. Increasing incidence of adenocarcinoma of the esophagus and esophagogastric junction. *Gastroenterology* 1993;104:510–3. [PubMed: 8425693]
10. Sharma P, McQuaid K, Dent J, Fennerty MB, Sampliner R, Spechler S, Cameron A, Corley D, Falk G, Goldblum J, Hunter J, Jankowski J, Lundell L, Reid B, Shaheen NJ, Sonnenberg A, Wang K, Weinstein W. A critical review of the diagnosis and management of Barrett's esophagus: the AGA Chicago Workshop. *Gastroenterology* 2004;127:310–30. [PubMed: 15236196]
11. Clarkson PM, Thompson HS. Antioxidants: what role do they play in physical activity and health? *Am J Clin Nutr* 2000;72:637S–46S. [PubMed: 10919970]
12. Kubo A, Corley DA. Meta-Analysis of Antioxidant Intake and the Risk of Esophageal and Gastric Cardia Adenocarcinoma. *Am J Gastroenterol*. 2007
13. Moe GL, Kristal AR, Levine DS, Vaughan TL, Reid BJ. Waist-to-hip ratio, weight gain, and dietary and serum selenium are associated with DNA content flow cytometry in Barrett's esophagus. *Nutr Cancer* 2000;36:7–13. [PubMed: 10798210]
14. Rudolph RE, Vaughan TL, Kristal AR, Blount PL, Levine DS, Galipeau PC, Prevo LJ, Sanchez CA, Rabinovitch PS, Reid BJ. Serum selenium levels in relation to markers of neoplastic progression among persons with Barrett's esophagus. *J Natl Cancer Inst* 2003;95:750–7. [PubMed: 12759393]

15. Chen X, Mikhail SS, Ding YW, Yang G, Bondoc F, Yang CS. Effects of vitamin E and selenium supplementation on esophageal adenocarcinogenesis in a surgical model with rats. *Carcinogenesis* 2000;21:1531–6. [PubMed: 10910955]
16. Brown LM, Swanson CA, Gridley G, Swanson GM, Schoenberg JB, Greenberg RS, Silverman DT, Pottern LM, Hayes RB, Schwartz AG, et al. Adenocarcinoma of the esophagus: role of obesity and diet. *J Natl Cancer Inst* 1995;87:104–9. [PubMed: 7707381]
17. 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;10:365–9. [PubMed: 11535879]
18. 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;68:300–4. [PubMed: 8903470]
19. Chen H, Ward MH, Graubard BI, Heineman EF, Markin RM, Potischman NA, Russell RM, Weisenburger DD, Tucker KL. Dietary patterns and adenocarcinoma of the esophagus and distal stomach. *Am J Clin Nutr* 2002;75:137–44. [PubMed: 11756071]
20. 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]
21. Mayne ST, Navarro SA. Diet, obesity and reflux in the etiology of adenocarcinomas of the esophagus and gastric cardia in humans. *J Nutr* 2002;132:3467S–3470S. [PubMed: 12421872]
22. Luo Y, Henle ES, Linn S. Oxidative damage to DNA constituents by iron-mediated fenton reactions. The deoxycytidine family. *J Biol Chem* 1996;271:21167–76. [PubMed: 8702887]
23. Hann HW, Stahlhut MW, Hann CL. Effect of iron and desferoxamine on cell growth and in vitro ferritin synthesis in human hepatoma cell lines. *Hepatology* 1990;11:566–9. [PubMed: 2158479]
24. Barrett MT, Sanchez CA, Prevo LJ, Wong DJ, Galipeau PC, Paulson TG, Rabinovitch PS, Reid BJ. Evolution of neoplastic cell lineages in Barrett oesophagus. *Nat Genet* 1999;22:106–9. [PubMed: 10319873]
25. Chen X, Yang G, Ding WY, Bondoc F, Curtis SK, Yang CS. An esophagogastrroduodenal anastomosis model for esophageal adenocarcinogenesis in rats and enhancement by iron overload. *Carcinogenesis* 1999;20:1801–8. [PubMed: 10469627]
26. Anderson LA, Watson RG, Murphy SJ, Johnston BT, Comber H, Mc Guigan J, Reynolds JV, Murray LJ. Risk factors for Barrett's oesophagus and oesophageal adenocarcinoma: results from the FINBAR study. *World J Gastroenterol* 2007;13:1585–94. [PubMed: 17461453]
27. Veugelers PJ, Porter GA, Guernsey DL, Casson AG. Obesity and lifestyle risk factors for gastroesophageal reflux disease, Barrett esophagus and esophageal adenocarcinoma. *Dis Esophagus* 2006;19:321–8. [PubMed: 16984526]
28. Clements DM, Oleesky DA, Smith SC, Wheatley H, Hullin DA, Havard TJ, Bowrey DJ. A study to determine plasma antioxidant concentrations in patients with Barrett's oesophagus. *J Clin Pathol* 2005;58:490–2. [PubMed: 15858119]
29. Pollard J, Wild CP, White KL, Greenwood DC, Cade JE, Kirk SF. Comparison of plasma biomarkers with dietary assessment methods for fruit and vegetable intake. *Eur J Clin Nutr* 2003;57:988–98. [PubMed: 12879094]
30. Corley DA, Kubo A, Levin TR, Block G, Habel L, Zhao W, Leighton P, Quesenberry C, Rumore GJ, Buffler PA. Abdominal Obesity and Body Mass Index as Risk Factors for Barrett's Esophagus. *Gastroenterology* 2007;133:34–41. [PubMed: 17631128]
31. Hiatt RA, Friedman GD. The frequency of kidney and urinary tract diseases in a defined population. *Kidney Int* 1982;22:63–8. [PubMed: 6181284]
32. Krieger N. Overcoming the absence of socioeconomic data in medical records: validation and application of a census-based methodology. *Am J Public Health* 1992;82:703–10. [PubMed: 1566949]
33. Ofman JJ, Ryu S, Borenstein J, Kania S, Lee J, Grogg A, Farup C, Weingarten S. Identifying patients with gastroesophageal reflux disease in a managed care organization. *Am J Health Syst Pharm* 2001;58:1607–13. [PubMed: 11556654]
34. Block G, Hartman AM. Issues in reproducibility and validity of dietary studies. *Am J Clin Nutr* 1989;50:1133–8. [PubMed: 2683721]discussion 1231–5

35. Block G, Hartman AM, Dresser CM, Carroll MD, Gannon J, Gardner L. A data-based approach to diet questionnaire design and testing. *Am J Epidemiol* 1986;124:453–69. [PubMed: 3740045]
36. 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;92:686–93. [PubMed: 1607564]
37. Block G, Woods M, Potosky A, Clifford C. Validation of a self-administered diet history questionnaire using multiple diet records. *J Clin Epidemiol* 1990;43:1327–35. [PubMed: 2254769]
38. 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;130:173–87. [PubMed: 2741904]
39. Coates RJ, Eley JW, Block G, Gunter EW, Sowell AL, Grossman C, Greenberg RS. 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;134:658–71. [PubMed: 1951269]
40. Willett W, Stampfer M, Chu NF, Spiegelman D, Holmes M, Rimm E. Assessment of questionnaire validity for measuring total fat intake using plasma lipid levels as criteria. *Am J Epidemiol* 2001;154:1107–12. [PubMed: 11744515]
41. Rothman, KJ.; Greenland, S. *Modern Epidemiology*. Lippincott-Raven; 1998.
42. Zhao Y, Ash A, Ellis R, Ayanian J, Pope GC, Bowen B, Weyuker L. Predicting Pharmacy Costs and Other Medical Costs Using Diagnoses and Drug Claims. *Medical Care* 2005;43:34–43. [PubMed: 15626932]
43. Zhao Y, Ellis RP, Ash AS, Calabrese D, Ayanian JZ, Slaughter JP, Weyuker L, Bowen B. Measuring population health risks using inpatient diagnoses and outpatient pharmacy data. *Health Serv Res* 2001;36:180–93. [PubMed: 16148968]
44. Terry P, Lagergren J, Ye W, Nyren O, Wolk A. Antioxidants and cancers of the esophagus and gastric cardia. *Int J Cancer* 2000;87:750–4. [PubMed: 10925371]
45. Bollschweiler E, Wolfgarten E, Nowroth T, Rosendahl U, Monig SP, Holscher AH. Vitamin intake and risk of subtypes of esophageal cancer in Germany. *J Cancer Res Clin Oncol* 2002;128:575–80. [PubMed: 12384802]
46. Gonzalez CA, Pera G, Agudo A, Bueno-de-Mesquita HB, Ceroti M, Boeing H, Schulz M, Del Giudice G, Plebani M, Carneiro F, Berrino F, Sacerdote C, Tumino R, Panico S, Berglund G, Siman H, Hallmans G, Stenling R, Martinez C, Dorronsoro M, Barricarte A, Navarro C, Quiros JR, Allen N, Key TJ, Bingham S, Day NE, Linseisen J, Nagel G, Overvad K, Jensen MK, Olsen A, Tjonneland A, Buchner FL, Peeters PH, Numans ME, Clavel-Chapelon F, Boutron-Ruault MC, Roukos D, Trichopoulou A, Psaltopoulou T, Lund E, Casagrande C, Slimani N, Jenab M, Riboli E. 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;118:2559–66. [PubMed: 16380980]
47. Food, Nutrition, Physical Activity, and the Prevention of Cancer: a Global Perspective. Washington DC: World Cancer Research Fund/American Institute for Cancer Research; 2007.
48. Morrison, AS. *Screening in Chronic Disease*. Oxford University Press; 1992.
49. Kristal AR, Blount PL, Schenk JM, Sanchez CA, Rabinovitch PS, Odze RD, Standley J, Vaughan TL, Reid BJ. Low-fat, high fruit and vegetable diets and weight loss do not affect biomarkers of cellular proliferation in Barrett esophagus. *Cancer Epidemiol Biomarkers Prev* 2005;14:2377–83. [PubMed: 16214920]

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)
Total intake (dietary+supplemental)			
Energy (kcal)	1805 (857)	1827 (770)	1839 (794)
Vitamin C (mg/day)	210.6	198.3	214.9
Vitamin E (ug/day)	35.2	34.8	37.7
Beta Carotene (mg/day)	4.3	4.3	4.7
Selenium (ug/day)	86.5	90.0	90.0
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)

	Cases	GERD controls	Population controls
	Mean/# (SD/%)	Mean/# (SD/%)	Mean/# (SD/%)
Never	74 (25)	106 (34)	102 (33)

*
Some items do not add up to the total numbers of subjects included in the dietary analyses due to missing data.

Table 2
Barrett's esophagus risk and antioxidant use, total vs. dietary intakes; cases vs. population controls

Median intake		Total intake ¹		Dietary Intake ²	
Total/Dietary ⁷		# Case/control		# Case/control	
Vitamin C (mg/day) ⁵		OR (95% CI) ³		OR (95% CI) ⁴	
Quartile 1	91/43	57/46	1	114/77	1
Quartile 2	206/79	35/46	0.58 (0.30–1.09)	71/77	0.51 (0.31–0.85)
Quartile 3	597/124	39/47	1.01 (0.56–1.83)	56/77	0.49 (0.27–0.86)
Quartile 4	1305/184	42/46	0.85 (0.45–1.58)	55/78	0.48 (0.26–0.90)
OR per unit increase ⁶			0.97 (0.80–1.00)		0.76 (0.64–0.91)
Vitamin E (ug/day)					
Quartile 1	13/5.4	57/46	1	101/78	1
Quartile 2	35/8.5	49/46	0.99 (0.54–1.81)	77/81	0.57 (0.31–1.05)
Quartile 3	183/12	53/47	0.81 (0.46–1.42)	67/74	0.56 (0.28–1.15)
Quartile 4	334/19	34/46	0.67 (0.36–1.24)	51/76	0.25 (0.11–0.59)
OR per unit increase ⁶			0.87 (0.72–1.05)		0.66 (0.52–0.83)
Beta carotene (mg/day)					
Quartile 1	2.1/1.8	69/46	1	108/77	1
Quartile 2	3.6/2.8	49/46	0.54 (0.29–0.99)	58/77	0.55 (0.33–0.93)
Quartile 3	5.2/4.8	30/47	0.46 (0.24–0.89)	64/77	0.59 (0.34–0.98)
Quartile 4	9.5/6.8	45/46	0.57 (0.29–1.14)	66/78	0.56 (0.32–0.99)
OR per unit increase ⁶			0.82 (0.67–1.00)		0.83 (0.70–0.99)
Selenium (ug/day)					
Quartile 1	60/46	41/33	1	99/77	1
Quartile 2	88/67	25/32	0.66 (0.28–1.55)	64/78	0.55 (0.31–0.98)
Quartile 3	111/89	38/33	1.52 (0.55–4.22)	62/76	0.65 (0.32–1.32)
Quartile 4	195/133	21/33	0.29 (0.09–0.94)	71/78	0.58 (0.26–1.30)
OR per unit increase ⁶			0.76 (0.55–1.05)		0.81 (0.64–1.03)

	Median intake	Total intake ¹		Dietary Intake ²	
	Total/Dietary ⁷	# Case/control	OR (95% CI) ³	# Case/control	OR (95% CI) ⁴
Antioxidant index					
Quartile 1		59/39	1	101/75	1
Quartile 2		42/40	0.54 (0.26–1.11)	72/81	0.48 (0.27–0.87)
Quartile 3		28/38	0.54 (0.24–1.20)	74/77	0.56 (0.28–1.10)
Quartile 4		34/46	0.35 (0.16–0.79)	49/76	0.30 (0.13–0.71)
Test for trend			0.01		0.004

¹ Long-term supplement users only. Excluded individuals who took supplement (vitamin C, E, beta-carotene, selenium, or multivitamin) 2 years or less.

² Includes all study population.

³ Model was adjusted for age, sex, race (white vs. non-white), geographic region, and energy.

⁴ The model was adjusted for the variable mentioned above plus long-term vitamin supplement use.

⁵ The cutoff points for all quartiles were made from the distribution of all population controls

⁶ The unit is the natural log of the measured unit for each nutrient.

⁷ The median intake was based on population controls: total intake was among those who used supplement for the particular micronutrients >2 years, while all subjects were included for dietary intake.

Table 3
Barrett's esophagus risk and antioxidant use, stratified by use of vitamin supplements; cases vs. GERD controls

Median intake		Total intake ¹		Dietary Intake ²	
Total/Dietary ⁷		# Case/control		# Case/control	
Vitamin C (mg/day) ⁵		OR (95% CI) ³		OR (95% CI) ⁴	
Quartile 1	91/43	57/35	1	114/109	1
Quartile 2	206/79	35/49	0.46 (0.23–0.89)	71/72	0.52 (0.31–0.87)
Quartile 3	597/124	39/49	0.85 (0.46–1.57)	56/71	0.44 (0.25–0.79)
Quartile 4	1305/184	42/42	0.67 (0.36–1.24)	55/56	0.44 (0.24–0.83)
OR per unit increase ⁶			0.92 (0.76–1.11)		0.83 (0.60–1.14)
Vitamin E (ug/day)					
Quartile 1	13/5.4	57/44	1	101/99	1
Quartile 2	35/8.5	49/42	1.11 (0.59–2.09)	77/77	0.79 (0.45–1.39)
Quartile 3	183/12	53/42	0.88 (0.49–1.56)	67/73	1.17 (0.60–2.30)
Quartile 4	334/19	34/47	0.55 (0.30–1.01)	51/59	0.53 (0.23–1.25)
OR per unit increase ⁶			0.84 (0.70–1.02)		0.86 (0.68–1.08)
Beta carotene (mg/day)					
Quartile 1	2.1/1.8	69/63	1	108/97	1
Quartile 2	3.6/2.8	49/37	1.24 (0.68–2.27)	58/65	0.83 (0.50–1.38)
Quartile 3	5.2/4.8	30/27	1.26 (0.67–2.38)	64/90	0.59 (0.35–0.98)
Quartile 4	9.5/6.8	45/48	0.88 (0.48–1.61)	66/56	1.02 (0.57–1.81)
OR per unit increase ⁶			0.97 (0.81–1.17)		0.90 (0.76–1.07)
Selenium (ug/day)					
Quartile 1	60/46	41/36	1	99/75	1
Quartile 2	88/67	25/22	0.69 (0.28–1.74)	64/81	0.50 (0.28–0.91)
Quartile 3	111/89	38/38	0.89 (0.33–2.37)	62/75	0.62 (0.30–1.26)
Quartile 4	195/133	21/28	0.42 (0.12–1.41)	71/77	0.50 (0.22–1.15)
OR per unit increase ⁶			0.73 (0.52–1.03)		0.78 (0.61–0.99)

	Median intake	Total intake ¹		Dietary Intake ²	
	Total/Dietary ⁷	# Case/control	OR (95% CI) ³	# Case/control	OR (95% CI) ⁴
Antioxidant index					
Quartile 1		59/41	1	101/90	1
Quartile 2		42/43	0.66 (0.32–1.34)	72/95	0.71 (0.41–1.23)
Quartile 3		28/36	0.60 (0.28–1.30)	74/67	0.90 (0.48–1.71)
Quartile 4		34/37	0.49 (0.22–1.10)	49/56	0.72 (0.30–1.71)
Test for trend			0.10		0.44

¹ Long-term supplement users only. Excluded individuals who took supplement (vitamin C, E, beta-carotene, selenium, or multivitamin) 2 years or less.

² Includes all study population.

³ Model was adjusted for age, sex, race (white vs. non-white), geographic region, and energy.

⁴ The model was adjusted for the variable mentioned above plus long-term vitamin supplement use.

⁵ The cutoff points for all quartiles were made from the distribution of all population controls

⁶ The unit is the natural log of the measured unit for each nutrient.

⁷ The median intake was based on population controls: total intake was among those who used supplement for the particular micronutrients >2 years, while all subjects were included for dietary intake.

Table 4

Results of multivariate logistic regression: the effect of fruit and vegetable intake and the risk of Barrett's esophagus

	Median Intake (servings/day)	N BE/Population/GERD	BE vs. Population OR (95% CI) ^I	BE vs. GERD OR (95% CI) ^I
Quartile 1	2.0	111/101/74	1	1
Quartile 2	3.6	68/82/79	0.55 (0.35–0.87)	0.80 (0.51–1.24)
Quartile 3	5.3	76/73/77	0.59 (0.36–0.97)	0.96 (0.60–1.54)
Quartile 4	8.3	41/52/79	0.27 (0.15–0.50)	0.64 (0.35–1.15)
Test for trend			<0.01	0.45
OR per unit increase (serving/day)			0.86 (0.80–0.93)	0.97 (0.91–1.05)

^I Model was adjusted for age, sex, race (white vs. non-white), geographic region, and energy.

Table 5

Supplement use and the risk of Barrett's esophagus, among subjects within the lowest quartile of each dietary antioxidant intake; cases vs. population controls.

	# Case/control	Median Intake	OR (95% CI) ³
Vitamin C (mg/day)			
No supplement use ²	48/36	150	1
Supplement use ¹	66/41	610	1.26 (0.68–2.33)
Vitamin E (ug/day)			
No supplement use	39/33	25	1
Supplement use	59/43	170	1.20 (0.63–2.28)
Beta carotene (mg/day)			
No supplement use	43/42	1.3	1
Supplement use	65/34	3.5	1.77 (0.94–3.34)
Selenium (ug/day)			
No supplement use	60/51	52	1
Supplement use	39/27	73	1.13 (0.93–1.37)

¹ Supplement users are defined as those who have been using a supplement containing each specific micronutrient for >2 years.

² Non-users are those who did not use any of the supplements mentioned above.

³ Model was adjusted for age, sex, race (white vs. non-white), geographic region, and calorie intake. Each odds ratio represents the change in the risk of Barrett's esophagus associated with supplement use, for a supplement containing the micronutrient of interest. For example, among subjects within the lowest quartile of dietary vitamin C intake, persons taking a multivitamin containing vitamin C or a specific vitamin C supplement had a similar risk of Barrett's esophagus compared with nonusers (OR=1.26, 95%CI 0.68–2.33).

Table 6

Evaluation of the effect of supplement use on the risk of Barrett's esophagus comparing different total intake among supplement users vs. non-users; cases vs. population controls.

	Median intake	# Case/control	OR (95% CI) ³
Vitamin C	(mg/day)		
Supplement Non-users ¹	88	123/132	1
Users low ²	140	57/55	1.10 (0.69–1.75)
Users medium	370	55/51	1.36 (0.84–2.21)
Users high	1140	56/52	1.37 (0.85–2.20)
Vitamin E	(ug/day)		
Supplement Non-users	10	123/132	1
Users low	27	64/51	1.51 (0.94–2.42)
Users medium	84	61/55	1.30 (0.81–2.07)
Users high	305	39/55	0.88 (0.53–1.46)
Carotene	(mg/day)		
Supplement Non-users	2400	123/132	1
Users low	2473	55/46	1.30 (0.79–2.14)
Users medium	4316	48/54	1.08 (0.66–1.75)
Users high	9301	37/45	1.02 (0.60–1.74)

¹ Non-users are those who do not use any of the supplements mentioned above.

² Supplement users are defined as those who have been using a supplement containing each specific micronutrient for three or more years.

³ Model was adjusted for age, sex, race (white vs. non-white), and calorie intake. Each odds ratio represents the change in the risk of Barrett's esophagus associated with the levels of supplement use, for a supplement containing the micronutrient of interest. For example, compared to the non-users of vitamin C supplement, highest vitamin C supplement users had a slightly higher risk of Barrett's esophagus as nonusers (OR=1.37 95%CI 0.85–2.20).