Published in final edited form as:
Am J Gastroenterol. 2008 December ; 103(12): 2997–3004. doi:10.1111/j.1572-0241.2008.02156.x.

Iron Intake and Body Iron Stores as Risk Factors for Barrett's Esophagus: A Community-Based Study

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Abstract

OBJECTIVE—High iron stores are a proposed modifiable risk factor for esophageal adenocarcinoma, but minimal human data exist. We evaluated whether iron intake and iron stores were associated with Barrett's esophagus, a metaplastic change that is a strong risk factor for esophageal adenocarcinoma.

METHODS—We conducted a case-control study within the Kaiser Permanente Northern California population. We identified all persons with a new diagnosis of Barrett's esophagus (cases); they were matched to persons with GERD (without Barrett's esophagus) and to population controls. Subjects completed examinations, dietary questionnaires, and testing for serum iron stores (ferritin and transferrin saturation). Analyses used unconditional logistic regression.

RESULTS—We evaluated 319 cases, 312 GERD patients, and 313 population controls. Compared with population controls, Barrett's esophagus patients had lower dietary iron intakes (4th *vs* 1st quartiles, odds ratio [OR] = 0.37, 95% confidence interval [CI] 0.17–0.80), similar total iron intakes (including supplement use), and lower iron stores (4th *vs* 1st quartiles, ferritin OR = 0.24, 95% CI 0.14–0.40;% transferrin saturation OR = 0.66, 95% CI 0.41–1.04; *P* value trend <0.01 and 0.03, respectively). Similar associations were observed in comparisons with GERD controls and among subjects without clear sources of blood loss on endoscopy.

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CONFLICT OF INTEREST

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Financial support: United States National Institutes of Health RO1 DK63616 and K08 DK02697.

Potential competing interests: The sponsor reviewed the study design, but had no role in the collection, analysis, or interpretation of the data, in the writing of the report, or in the decision to submit the report for publication.

CONCLUSIONS—Patients with Barrett's esophagus had lower dietary iron intakes and lower serum iron stores than controls in our population. These findings do not provide support for the current hypothesis that high iron stores or a high iron intake are risk factors for Barrett's esophagus, a potential early event in the carcinogenic sequence for esophageal adenocarcinoma.

BACKGROUND

The incidence of esophageal adenocarcinoma is rising more rapidly than that of any other malignancy in many countries, but relatively little population-based information is available about the carcinogenic sequence leading to cancer development (1–4). Barrett's esophagus, a potential aberrant healing response after esophageal injury that results in a metaplastic change in the esophageal lining from its usual squamous epithelium to a specialized columnar epithelium, is believed to be an early event in the carcinogenesis of esophageal adenocarcinoma (5). Persons with Barrett's esophagus have a 30- to 40-fold increased risk of esophageal adenocarcinoma; thus, there is a compelling rationale for characterizing its associated risk factors (5). Cancer risk factors could act by either increasing risk factors for Barrett's esophagus itself (*e.g.*, increasing the risk of gastroesophageal reflux disease "GERD"), increasing the risk of developing Barrett's esophagus among persons with such conditions (*e.g.*, increasing the risk of someone with GERD developing Barrett's esophagus), or by enhancing the risk of malignant transformation from Barrett's esophagus to adenocarcinoma. Knowledge of when putative risk factors act is crucial for timing potential interventions. One proposed modifiable risk factor for both Barrett's esophagus and esophageal adenocarcinoma, supported by experimental models, is a high iron intake or elevated iron stores, but little human data exist (6,7).

Increased body iron levels have been associated with an increased risk of both hepatic and nonhepatic malignancies, presumably through increased oxidative stress, although data conflict (8–13). The investigation of a potential link between iron, Barrett's esophagus and esophageal adenocarcinoma is appealing for several reasons (14). First, iron supplementation before reflux-induced esophageal injury substantially increased the risk of esophageal metaplasia and esophageal adenocarcinoma in animal models (6,7). The cells in these models demonstrated oxidative damage, and the risk was decreased by supplementation with vitamin E, which also suggested that the balance between oxidizing agents (such as iron) and antioxidants (such as vitamin E) may influence cancer risk (6,15). Second, *in vitro* experiments indicate iron may induce genetic damage, and that cancer cell division is enhanced in the presence of iron (16,17). Barrett's esophagus cells are frequently clonal populations; thus, iron could theoretically act as both an initiator and promoter of clonal growth (18). Third, the incidences of Barrett's esophagus and esophageal adenocarcinoma are substantially higher among males and among whites, though no clear explanation for this demographic pattern exists to date (19); iron levels offer a potential explanation, as the groups at highest risk of cancer also have the highest average iron saturation levels in the population (20–24). However, the only study we could identify of this hypothesis in humans demonstrated an inverse association between iron intake and the risk of esophageal adenocarcinoma (no data on iron stores were available) (25), and studies of iron stores in cancer case-control studies are complicated by blood loss from the cancer; iron stores measured at the time of cancer diagnosis (and specimen ascertainment) may thus not reflect the body iron stores at the initiation of the carcinogenic pathway. Evaluations of patients with a new diagnosis of Barrett's esophagus and of iron intake (which may be correlated with iron stores, but not necessarily associated with iron loss) are less susceptible to this type of bias.

We conducted a case-control study to evaluate whether iron stores and iron intake were associated with the risk of a new diagnosis of Barrett's esophagus in a community-based population.

DESIGN AND METHODS

Study Population

We conducted a nested case-control study among the 3.3 million members of the Kaiser Permanente, Northern California (KPNC) population, an integrated health services delivery organization. The membership demographics closely approximate the underlying census population of Northern California (26). Eligible subjects were all adult (ages 18–79 yr) members who were continuously enrolled for at least 2 yr prior to their index period and able to understand spoken and written English; details of recruitment have been previously reported (27). 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 population and GERD comparison groups were frequency matched to the cases (prior to interview, at the time of case selection) by sex, age at the index date, and geographic region (each subject's home facility).

Case Definition

Cases were eligible members who received a new diagnosis of Barrett's esophagus between October, 2002 and September, 2005. Newly diagnosed patients 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 single board-certified gastroenterologist (DAC) then reviewed the endoscopy and pathology records. Subjects were included if the endoscopist clearly described a visible length of columnar-type epithelium proximal to the gastroesophageal junction/gastric folds, this area was biopsied, and the biopsies showed specialized intestinal epithelium (5). Patients were also excluded if they had a prior Barrett's esophagus diagnosis, if no pathology evaluations demonstrated intestinal metaplasia, or if, to minimize misclassification, the biopsies were only from an irregular squamocolumnar junction (*i.e.*, an "irregular z-line"). Pathology slides underwent a separate manual review by a gastrointestinal pathologist (GJR).

Population Controls

Population controls were randomly selected from at risk (no prior Barrett's esophagus) members using risk set sampling (28). This method randomly selected subjects (matched by age, gender, and home medical center) who were without an electronic diagnosis of Barrett's esophagus when their matched cases were diagnosed. Population controls included persons who had and who had not undergone prior endoscopic procedures.

GERD Comparison Group

GERD comparison group members were randomly selected from among persons with all of the following characteristics prior to the index date: a GERD-related diagnosis (ICD-9 codes 530.11 [reflux esophagitis] or 530.81 [gastroesophageal reflux]); a prescription sufficient for at least 90 days supply of a histamine-2 receptor antagonist or a proton pump inhibitor (medications used for treating GERD symptoms) in the previous year (from electronic pharmacy records); no prior Barrett's esophagus diagnosis; and performance of an esophagogastroduodenoscopy (in proximity to the index date) that did not demonstrate Barrett's esophagus by endoscopy or by pathology (among persons who also had biopsies done for any reason, all reports were manually reviewed).

Exposure Measurements

All study subjects completed (most commonly at the subject's home): an in-person interview that included questions about GERD symptoms and medication use (both historically and in the year prior to diagnosis); a medical history; a validated food frequency questionnaire (the

Block 1998 full-length, 110 food items) (29–32); phlebotomy; and anthropometric measurements. Subjects reported exposures (including dietary exposures) for the year prior to the index date. Micronutrient values were calculated using NutritionQuest (33).

Assessments of serum ferritin and iron saturation levels, two indirect measures of total body iron stores, utilized standard assays at a regional commercial clinical laboratory (34–36). The serum ferritin, which is in equilibrium with tissue ferritin, may be the most accurate serologic estimate of the body's total iron stores (34,35,37,38). Transferrin is an iron transport protein; the transferrin saturation (the ratio of the serum iron concentration to transferrin's iron binding capacity) also correlates with body iron stores (34–36). Blood samples were stored on ice, centrifuged the day drawn, and processed at a regional commercial reference laboratory using standard assays. Reproducibility was confirmed using serial specimens in a test subject and samples were run in mixed batches of cases and controls.

Confounding and Effect Modification

We evaluated as potential confounders: body mass index, *Helicobacter pylori* antibody status, ethnicity (classified as whites *vs* non-whites), smoking status (at least 20 packs of cigarettes over lifetime *vs* never smoked), alcohol use, aspirin, or nonsteroidal antiinflammatory drug (NSAID) use, a comorbidity index (the DxCg score, a predictive comorbidity score based on demographic data, medical coding, and pharmacy utilization) (39,40), caloric intake, waist circumference, high-sensitivity c-reactive protein, antioxidant intake (using an index of vitamin C, vitamin E, beta-carotene, and selenium), proton pump inhibitor use (for >1 yr) and ingestion of well-cooked meat. We evaluated for the presence of effect modification (*e.g.*, whereby the associations varied across variables such as age or ethnicity) using cross product terms in the logistic regression model and by comparing stratum-specific odds ratios (41). We evaluated for differences between participants *versus* eligible nonparticipants (nonresponse bias) by comparing selected variables available in electronic databases (BMI, smoking status, ethnicity, age, sex, DxCg score, GERD diagnosis).

Statistical Analysis

The study utilized standard analytic techniques for evaluating frequency-matched case-control studies including the use of unconditional logistic regression (28,41–43). Confounding was considered present if inclusion of a variable altered the odds ratio for the main association by >10% (41). The number of predictor variables evaluated was substantially fewer than the recommended maximum of 10 per outcome (44,45). The ferritin levels and transferrin saturations had extremely non-normal distributions; these were converted using log transformation for some analyses. For the dietary analyses, we excluded 12 subjects who had either over 20 missing food items reported or extreme total caloric intakes (>6000 kcal/day or <400 kcal/day).

The study and analyses were reviewed and approved by the Kaiser Permanente institutional review board. Analyses used the STATA statistical package (version 8, STATA Corporation, College Station, TX).

RESULTS

Study Population

We interviewed 953 subjects; serologic data for iron stores were available for 944 subjects (99% of interviewed subjects): 319 cases, 312 GERD patients, and 313 population controls. Selected characteristics of the study population are provided in Table 1. Among the cases, the length of the Barrett's segment was <3 cm in 118 subjects (37%), ≥3 cm in 150 subjects (47%), and the length was not reported in 51 subjects (16%).

Dietary Iron Intake

The risk of Barrett's esophagus decreased as dietary iron intake increased (Table 2). Compared with population controls, the risk of Barrett's esophagus was 63% lower among subjects in the 4th *versus* 1st quartiles of iron intake (OR 0.37, 95% CI 0.17–0.80; cases *vs* population controls). The inverse association was stronger among subjects with longer segments of Barrett's esophagus (≥3 cm) (OR = 0.23, 95% CI 0.09–0.62) than among subjects with shorter segments (OR = 0.59, 95% CI 0.20–1.77). Compared with GERD controls, a similar association was seen (OR = 0.42, 95% CI 0.20–0.91; cases *vs* GERD controls).

Total Iron Intake

There was no significant association between total iron intake (dietary iron plus iron supplements or iron-containing multivitamins, among subjects using supplements for >2 yr) and the risk of Barrett's esophagus (cases *vs* population controls, 4th *vs* 1st quartiles of total iron intake OR 0.84, 95% CI 0.49–1.45; test for trend across quartiles p = 0.65) (Table 2). Similarly, compared with the GERD controls, no clear association was seen between iron intake and the risk of Barrett's esophagus (4th *vs* 1st quartiles of total iron intake OR 0.87, 95% CI 0.52–1.45; test for trend $P = 0.80$).

Serum Iron Stores

There was an inverse association between serum iron stores and the risk of Barrett's esophagus (Table 3). Compared with population controls, the risk of Barrett's esophagus was 76% lower among subjects in the 4th *versus* 1st quartile of serum ferritin (OR 0.24, 95% CI 0.14–0.40) and 44% lower among subjects in the 4th *versus* 1st quartiles of serum transferrin saturation (OR = 0.66, 95% CI 0.41–1.04). There were significant dose trends for decreasing risk of Barrett's with increasing serum iron stores (test for trend $P < 0.01$ for ferritin and $P = 0.03$ for transferrin saturation). Similar to dietary iron intake, the inverse association between ferritin and Barrett's esophagus was stronger for subjects with longer segments of Barrett's esophagus (OR =0.14, 95% CI 0.07–0.29) than for subjects with shorter segments (OR = 0.35, 95% CI 0.17–0.72); the associations with iron saturation did not differ markedly by the length of Barrett's esophagus (longer segment OR = 0.66, 95% CI 0.38–1.15 *vs* shorter segment OR = 0.70, 95% CI 0.36–1.35). Compared with GERD patients, higher ferritin levels were also associated with a decreased risk for Barrett's esophagus (Table 3).

Confounding

Confounding was considered present if inclusion of a variable altered the odds ratio for the main association by >10% (41). Potential confounders that did not alter the associations were not included in the final logistic models, with the exceptions of ethnicity and smoking, given their known associations with both iron status and the risk of esophageal adenocarcinoma. The main frequency-matched variables (age, gender) were also included in all analyses; there was no evidence of residual confounding by these variables. There was also no residual confounding of the estimates by geographic region, another frequency matched variable; it was not included in analyses given its multiple values created imprecision among analyses of small groups. The evaluation of potential confounders did not demonstrate any evidence of confounding by body mass index, waist circumference, smoking status, alcohol use, aspirin use, nonsteroidal antiinflammatory agents, *H. pylori* antibody status, socioeconomic status (measured by educational level and income), caloric intake, daily proton pump inhibitor use for at least 1 yr, or comorbidity (DxCg score). The odds ratio from a fully adjusted model for the highest quartile of ferritin (containing all these factors plus age, sex, and ethnicity) (OR = 0.18, 95% CI 0.09, 0.34) was similar to the odds ratio from a model that contained only the bivariate association between case status and ferritin status (OR = 0.29, 95% CI 0.18, 0.47). Similar results were seen for dietary iron intake.

Supplemental Analyses

Systemic inflammation may influence serum measures of iron stores (46); thus, we evaluated whether adjusting for a sensitive marker of systemic inflammation (high-sensitivity c-reactive protein) altered the observed associations. There was no evidence that inflammation biased the results. The association between Barrett's esophagus and the highest quartile of ferritin without c-reactive protein in the model (OR 0.24, 95% CI 0.14–0.40) was almost identical to a model that included c-reactive protein (OR = 0.23, 95% CI 0.14, 0.39).

We also evaluated dietary components that could alter the risk of Barrett's esophagus or influence iron stores. There was no evidence of confounding by intake of antioxidant micronutrients (vitamin C, vitamin E, beta-carotene, selenium) or by the ingestion of well-done meats. Similar associations were also seen among those above *versus* below the median total protein intake.

We evaluated whether persons who used supplements differed from persons who did not use supplements by analyzing dietary iron intake and iron stores only in the 432 persons who did not use any multivitamin or iron supplements. For subjects not taking supplements, dietary iron intake would equal total iron intake. The inverse association between Barrett's esophagus and dietary iron intake was of a similar direction, though somewhat weaker and the confidence interval included 1.0, for subjects not taking supplements (OR = 0.56, 95% CI 0.17–1.87; 4th *vs* 1st quartiles, cases *vs* population controls) *versus* subjects taking supplements for > 2 yr (iron supplements or multivitamins) (OR = 0.31, 95% CI 0.10–0.95). The odds ratios for the 4th *versus* 1st quartiles of ferritin were similar between supplement nonusers (OR = 0.24, 95% CI 0.11–0.52) and supplement users (OR = 0.21, 95% CI 0.09–0.46) (47).

We then evaluated for reverse causation, whereby the lower iron stores in the Barrett's esophagus patients were from conditions that may cause gastrointestinal blood loss. Results for ferritin analyses restricted to cases with esophagitis, hiatal hernias, esophageal strictures, or masses seen on their index endoscopy (OR 0.22, 95% CI 0.14–0.40; ferritin 4th *versus* 1st quartiles) were similar to analyses restricted to cases without these findings (OR 0.25, 95% CI 0.12, 0.52). To evaluate for menstrual sources of blood loss, we stratified by sex; similar associations were found in analyses restricted to male subjects for both dietary iron intake and serum ferritin levels.

DISCUSSION

To our knowledge, this is the first study of the association between iron intake, iron stores, and the risk of Barrett's esophagus. Patients with Barrett's esophagus had lower dietary iron intakes, comparable total iron intakes, and lower iron stores than the control populations.

This study extends the findings of prior human and animal models. A carcinogenic role for iron has been supported by its ability to induce oxidative DNA damage and an increased risk for some cancer types among persons with higher iron stores (8–13). Several experimental animal studies found that iron supplementation markedly increased the risk of esophageal adenocarcinoma (6,7,48), and that this risk was decreased by antioxidant intake. In contrast, a prior human dietary study suggested that persons with esophageal adenocarcinoma had lower than average dietary iron intakes (25). Similarly, the current study suggests that, among a large community-based sample, persons with Barrett's esophagus also have lower than average dietary iron intakes, in analyses using both population and GERD control groups. Concordant with this finding, this study also found lower than average iron stores in subjects with Barrett's esophagus.

There are several potential reasons for the disparate results between this study and the animal models. First, the animal models utilized marked intestinal rearrangements to create bile reflux; these models are unlikely to exactly replicate the conditions that create Barrett's esophagus in humans. Second, iron may enhance the risk of neoplastic transformation from Barrett's esophagus to esophageal adenocarcinoma, but may not increase the risk of Barrett's esophagus itself. Third, acid suppressing medications (commonly used among patients with Barrett's esophagus) may theoretically decrease iron absorption, leading to lower iron stores in our subjects with Barrett's esophagus, though this has not been clearly demonstrated to occur, did not alter the associations seen when acid inhibition was included in the logistic models for this study, and it should not influence iron intake (49,50). Fourth, there may be a true protective association between iron and the risk of Barrett's esophagus. Gastric adenocarcinomas have also demonstrated an inverse association between dietary iron intake and cancer risk (51), and a recent long-term cohort study found trends for lower iron intakes and lower serum iron levels among persons who ultimately developed colon cancer many years later (52).

The results for total iron intake differed somewhat from dietary iron intake, though neither total nor dietary intake was associated with a risk estimate for Barrett's esophagus >1.0, as might be expected if iron intake was harmful. Total intake represents dietary intake plus intake from supplements, and both diet and supplement use may be associated with other health behaviors or risk factors. Thus, both total intake and dietary intake are susceptible to confounding, though inclusion of several potential confounding factors (smoking, comorbidity score, other dietary components, etc.) did not markedly diminish the associations described.

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 a new diagnosis of Barrett's esophagus and the study identified all patients with a new diagnosis within the population. The use of prevalent cases or cases at referral centers may select for patients with a different clinical course or patients compliant with follow-up; prevalent cases may also have initiated changes in diet, supplement intake, or other behaviors after their Barrett's esophagus diagnosis that could influence iron intake, iron absorption (through the use of proton pump inhibitors), or iron stores (53). The use of incident cases 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, a risk factor for Barrett's esophagus. 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 (28). This is particularly true when risk factors for Barrett's esophagus (*i.e.*, gastroesophageal reflux disease) may also cause esophagitis and low levels of blood loss; however, we also found that low dietary intake (which would not be clearly related to GERD) was also associated with an increased risk of Barrett's esophagus. In addition, analyses that excluded subjects with esophagitis and other disorders at the time of the index endoscopy were similar to analyses that included such patients and similar findings were found in comparisons with GERD patients (who have similar conditions as Barrett's esophagus patients). Second, observational studies are subject to confounding by other factors. Although analyses that evaluated multiple variables provided little evidence of confounding, we cannot exclude incomplete control of confounding. Knowledge of case status could bias subjects or interviewers through differences in recall or questioning; however, the recruitment materials did not specifically mention Barrett's esophagus and the interviewers were blinded to the case or control status. Thus, the true case assignment was not known to the subjects providing the

data or to the interviewers extracting the data, making this type of bias less likely. Third, incomplete recruitment of subjects may lead to bias; however, the electronic data suggested that nonresponders were, on average, somewhat healthier than the responders, with lower comorbidity scores. Fourth, because an endoscopy is required for the diagnosis of Barrett's esophagus, the cases do not represent all patients with Barrett's esophagus. In addition, a small proportion of the general population sample may have had undetected Barrett's esophagus. The effects of nonresponse and undetected Barrett's esophagus in the population controls may bias the results toward the null (making the population controls more similar to the cases).

In summary, in a community-based population, patients with Barrett's esophagus had lower dietary iron intakes and lower serum iron stores than either population controls or GERD patients. Although we cannot exclude the possibility that prior GERD-induced changes may have contributed to iron loss (and thus lower iron stores) among the Barrett's esophagus cases, the finding that patients with Barrett's esophagus also had lower iron intakes is concordant with the lower iron stores and suggests this finding is less likely due solely to confounding. At the minimum, these findings do not support the hypothesis that iron acts as a risk factor for Barrett's esophagus, a potential early event in the carcinogenic sequence that leads to esophageal adenocarcinoma; in contrast, they suggest higher iron intakes may even have a protective association. Future studies are needed to confirm these results in other populations and to evaluate whether iron stores and iron intake influence the risk of Barrett's esophagus progressing to esophageal adenocarcinoma.

STUDY HIGHLIGHTS

What Is Current Knowledge

- Animal experiments suggest iron intake markedly increases the risk of esophageal adenocarcinoma.
- Iron is a proposed modifiable risk factor for Barrett's esophagus and esophageal adenocarcinoma.

What Is New Here

- This study, in contrast, found patients with Barrett's esophagus had lower dietary iron intakes and lower body iron stores than population controls.

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Table 1

Characteristics of Study Groups

	Cases Number or Mean (% or Standard Deviation)	GERD Controls Number or Mean (% or Standard Deviation)	Population Controls Number or Mean (% Standard Deviation)
Number of subjects	319	312	313
Age (yr)			
20–39	9 (3)	12 (4)	9 (3)
40–59	120 (38)	113 (36)	104 (33)
60–79	190 (59)	187 (60)	200 (64)
Race			
White	277 (87)	250 (80)	265 (85)
Black	4 (1)	20 (6)	16 (5)
Hispanic	25 (8)	20 (6)	13 (4)
Asian/Pacific Islander	4 (1)	11 (4)	11 (4)
Others	7 (2)	9 (3)	7 (2)
Unknown	2 (1)	2 (1)	1 (0)
Sex			
Male	233 (73)	215 (69)	212 (68)
Smoking status (ever smoked)	211 (66)	184 (59)	174 (56)
Mean serum ferritin (ng/mL)	116 (±132)	129 (±134)	156 (±137)
Mean body mass index (kg/m^2)	30 (±6)	29 (±5)	30 (±6)

Table 2

Iron Intake and Barrett's Esophagus, Comparisons With Population Controls and Patients With Gastroesophageal Reflux Disease (GERD)

	Median Values*	Number Barrett's Esophagus/ GERD Population	Barrett's Esophagus *versus* Population Controls	Barrett's Esophagus *versus* GERD Patients
Dietary Iron Intake	Milligrams		OR (95% CI)†	OR (95% CI)†
Quartile 1	7.7	90/69/74	1.00 (reference)	1.00 (reference)
Quartile 2	10.7	70/82/78	0.71 (0.41–1.21)	0.67 (0.39–1.15)
Quartile 3	14.4	77/83/77	0.85 (0.44–1.62)	0.64 (0.34–1.19)
Quartile 4	21.9	58/70/76	0.37 (0.17–0.80)	0.42 (0.20–0.91)
P value for trend			0.03	0.04
Total Iron Intake‡	Milligrams			
Quartile 1	9.3	82/89/76	1.00 (reference)	1.00 (reference)
Quartile 2	16.5	73/79/75	0.98 (0.60–1.60)	1.23 (0.75–2.00)
Quartile 3	27.5	64/52/78	0.80 (0.50–1.29)	1.36 (0.84–2.23)
Quartile 4	36.6	76/84/76	0.84 (0.49–1.45)	0.87 (0.52–1.45)
P value for trend			0.65	0.80

*Quartiles were derived from the absolute iron intake (not log transformed) distribution among the population controls; median values are the median of each quartile for the population controls.

†Adjusted for sex, age, ethnicity, calorie intake, and smoking status.

‡Dietary intake plus intake from supplements. Totals exclude supplement intake from subjects with ≤2 yr of iron supplement use.

Table 3

Serum Iron Stores and Barrett's Esophagus, Comparisons With Population Controls and Patients With Gastroesophageal Reflux Disease (GERD)

	Median Values*	Number Barrett's Esophagus/ GERD/ Population	Barrett's Esophagus *versus* Population Controls	Barrett's Esophagus *versus* GERD Patients
Ferritin	(ng/mL)		OR (95% CI)†	OR (95% CI)†
Quartile 1	38	135/113/77	1.00 (reference)	1.00 (reference)
Quartile 2	81	86/87/78	0.60 (0.39–0.91)	0.81 (0.55–1.20)
Quartile 3	163	58/58/78	0.37 (0.23–0.59)	0.78 (0.49–1.22)
Quartile 4	291	40/52/78	0.24 (0.14–0.40)	0.60 (0.36–0.98)
P value for trend			<0.01	0.04
Ferritin (natural log)‡			0.58 (0.48–0.70)	0.83 (0.70–0.99)
Iron Saturation	(%)			
Quartile 1	13	97/92/71	1.00 (reference)	1.00 (reference)
Quartile 2	19	82/65/77	0.76 (0.49–1.20)	1.18 (0.76–1.83)
Quartile 3	24	56/68/79	0.49 (0.30–0.79)	0.75 (0.47–1.19)
Quartile 4	30	83/87/86	0.66 (0.41–1.04)	0.85 (0.55–1.31)
P value for trend			0.03	0.19
Iron saturation (natural log)§			0.69 (0.49–0.97)	0.73 (0.53–1.01)

*Quartiles are derived from the distribution among the population controls; median values are the median of each quartile for the population controls.

†Adjusted for sex, age, ethnicity, and smoking status.

‡Analyzed as a continuous variable. Ferritin had a non-normal distribution and was transformed using the natural log.

§Analyzed as a continuous variable. Iron saturation had a non-normal distribution and was transformed using the natural log.