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Circulating Inflammatory Cytokines and Adipokines are Associated With Barrett's Esophagus: a Case–Control Study

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Abstract

Background & Aims—Obesity is associated with Barrett's esophagus (BE) and with changes in circulating levels of adipokines (leptin and adiponectin) and cytokines. Although studies have reported that adipokines and inflammatory cytokines are necessary for the development of BE, their role is controversial.

Methods—We performed a case–control study; cases (n=141) were patients who underwent esophagogastroduodenoscopy and were found to have BE, based on endoscopy and histology, and controls (n=139) were primary care patients eligible for screening colonoscopies who agreed to undergo esophagogastroduodenoscopy. We examined the association between BE and circulating levels of adipokines and cytokines (interleukin [IL]1 β , 6, 8, 10, and 12p70; tumor necrosis factor [TNF] α ; and interferon [IFN] γ). Cases and controls were compared, calculating odds ratios (ORs) and 95% confidence intervals (CIs) and using unadjusted and multiple logistic regression, adjusting for age, sex, race, waist–hip ratio, use of proton pump inhibitors and non-steroidal anti-inflammatory drugs, and *Helicobacter pylori* infection.

Results—The adjusted ORs for BE were 2.62 (95% CI, 1.0–6.8), 5.18 (95% CI, 1.7–15.7), and 8.02 (95% CI, 2.79–23.07) for the highest quintile vs the lowest quintile of levels of IL12p70, IL8, and leptin, respectively, but the OR not significant for IL6 (2.39; 95% CI, 0.84–6.79). The adjusted OR for BE was 0.14 for highest quintile of IL10 compared with lowest quintile (95% CI, 0.05–0.35) and 0.03 for IL1 β median vs none detected (95% CI, 0.006–0.13). Higher levels of IL8 and leptin and lower levels of IL10 and IL1 β were associated with the presence of long- (3 cm) and short-segment BE. There were no differences between cases and controls in levels of IFN γ , TNF α , adiponectin, or insulin.

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Disclosures: None

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Conclusions—Based on a case-control study, BE is associated with circulating inflammatory cytokines and leptin and low levels of anti-inflammatory cytokines. These findings could partly explain the effect of obesity on BE.

Keywords

Leptin; adiponectin; insulin; obesity; GERD; adipokines; NSAID

Introduction

Barrett's esophagus (BE) is the precancerous lesion for esophageal adenocarcinoma, which is the fastest-increasing malignancy in white men in the United States.^{1, 2} BE affects 6% to 12% of persons with chronic gastroesophageal reflux disease (GERD)³ and offers a potential target for prevention of esophageal adenocarcinoma. Unfortunately, few predictive factors of BE are known, limiting our understanding of disease mechanism, targeted recognition by clinicians, and preventive efforts.

Obesity has been identified as a risk factor for GERD symptoms and esophageal adenocarcinoma, although the association with the latter seems to be independent of the degree of GERD symptoms.^{4, 5} Obesity, especially abdominal obesity, is also associated with BE;⁶⁻⁹ but the mechanism is unclear, and several hypotheses have been proposed. Obesity is strongly associated with inflammation, presumably due to an increase in visceral fat and other tissues, such as the liver secreting proinflammatory cytokines (e.g., interleukin-6). Although animal models have suggested that the presence of proinflammatory cytokines is necessary for the development of BE¹⁰, their role in humans is controversial. Chronic inflammation is associated with epithelial metaplasia, present in BE, and also increases cancer risk, presumably by favoring tumor progression.¹¹

Adipose tissue is known to produce hormones known as "adipokines," such as adiponectin and leptin, which may regulate inflammation and cell proliferation.^{12, 13} Obesity is associated with changes in the circulating levels of these adipokines. Leptin is secreted proportionally to fat mass, and it has been proposed as a pathophysiologic mediator of BE formation.¹⁴⁻¹⁶ Moreover, leptin's intracellular signaling pathway is similar to that of inflammatory cytokines in several models including in-vitro models of BE.^{17, 18} Adiponectin is a protein secreted by adipocytes in the visceral adipose tissue in inverse proportion to fat mass,¹² and it has an anti-inflammatory effect.¹⁹ The role of adiponectin in BE remains controversial. Some reports have found an inverse association between circulating adiponectin and BE, while others have failed to show this association.^{20, 21} The insulin signaling pathway has been postulated to have a role in the development of BE although this has not been confirmed.^{22, 23} The role of these "proximal" events (to obesity) and the risk of BE is unclear.

In this study, we examined the associations between the presence and length of BE and the levels of circulating adipokines [leptin, adiponectin], insulin as well as cytokines [interleukin (IL)-1 β , 6, 8, 10, 12p70, tumor necrosis factor (TNF)- α , and interferon (IFN)- γ]. Our a priori hypothesis was that inflammatory cytokines and adipokines would be associated with the development of BE.

Methods

Study Population and Design

This is a case-control study nested within a cross-sectional study at the Michael E. DeBakey VA Medical Center (MEDVAMC) in Houston, TX. This research was approved by the

Institutional Review Boards for the MEDVAMC and Baylor College of Medicine on January 8, 2008. We recruited all consecutive eligible patients scheduled for an elective esophagogastroduodenoscopy (EGD) at MEDVAMC between February 15, 2008, and July 31, 2011; BE cases were identified from this group while the rest of this group was included in this analysis. For the control group, we recruited eligible patients who were scheduled for an elective visit for any reason to 1 of 7 selected primary care clinics at the same hospital between September 1, 2008, and December 31, 2010; we invited only patients who were eligible for screening colonoscopy to participate in this study, including an EGD at the same time as their colonoscopy. The study eligibility criteria were 1) age between 40–80 years (and 50–80 for the control group because eligibility for colorectal screening starts in most people at age 50); 2) no previous gastroesophageal surgery; 3) no previous gastroesophageal cancer; 4) no active lung, liver, colon, breast, or stomach cancer; 5) no anticoagulants; 6) no significant liver disease, indicated by platelet count below 70,000, ascites, or known gastroesophageal varices; and 7) no history of major stroke or mental condition. These criteria were meant to include subjects with intact esophagus and stomach, no major recent changes in weight, no contraindications to obtaining informed study consent, completing the study questionnaires, or obtaining mucosal biopsies.

Data Collection

Participants were interviewed before the study EGD and answered a computer-assisted survey ascertaining information on lifetime alcohol use and smoking, frequency and severity of GERD symptoms, use of histamine 2 receptor antagonists (H2RA), proton pump inhibitors (PPI), and nonsteroidal anti-inflammatory drugs (NSAID). The standardized instrument used to assess symptoms of GERD was the validated gastroesophageal reflux questionnaire (GERQ).^{24, 25}

All study participants underwent an EGD, with systematic recording of suspected BE, based on the Prague CM classification,²⁶ and targeted biopsies from these areas, using Jumbo biopsy forceps. Definitive BE was considered in the presence of specialized small-intestinal epithelium in the histopathological examination of samples obtained from suspected BE areas. BE ≥ 3 cm either on the C or M score was considered long segment BE. Patients from the primary care clinic with no suspected or definitive BE served as controls in this analysis. *H. pylori*-positive status was defined, based on organisms seen on histopathology of any of 7 gastric biopsies obtained in the study EGD, or previously positive gastric biopsy or serum antibodies or treatment for *H. pylori*. All authors had access to the study data and reviewed and approved the final manuscript. See supplemental material for more details.

Data Analysis

We conducted an analysis considering all patients with definitive BE and controls without endoscopic or definitive BE. The main exposure variables were serum levels of cytokines (IL-1 β , IL-12p70, IFN- γ , IL-6, IL-8, IL-10, TNF- α), insulin, leptin and adiponectin, examined in quintiles (The first quintile representing the lowest fifth of the data (1–20%); the second quintile represents the second fifth (21%–40%) etc.) as well as median levels; the cutoffs are based on the distribution of these biomarkers in entire study population. The 2 groups were compared in unadjusted as well as adjusted analyses. Similar exploratory analyses were conducted for long- (≥ 3 cm) and short-(<3 cm) segment BE compared with controls. The GERD variable was categorized as weekly or more frequent symptoms for 0 years 1–<5 years, and ≥ 5 years. Body mass index (BMI) was categorized as <20, 20–24.9, 25–29.9, and ≥ 30 kg/m², and waist circumference was measured in centimeters. We also adjusted for age, sex, race, tobacco smoking and alcohol use, *H. pylori* status, and medication use (H2RA, PPI, aspirin, and NSAID). No adjustments for multiple comparisons were made because we had a priori decided to test only these biomarkers.

Chi-square tests were used for categorical variables and Wilcoxon's test for nonparametric continuous variables. Logistic-regression models were used for multivariable adjustment, including the following variables: age, sex, race, waist-hip ratio, current PPI use, NSAID use, and *H. pylori*. Only variables with *p* value <0.2 were retained in the final models. Parameter estimates and standard errors from the model were used to calculate odds ratios and their accompanying 95% confidence intervals (CI).

After EGD, all patients with BE and controls recruited from the primary care clinics without BE were identified. Within these 2 control groups, we created a random ordering of eligible patients who had blood samples collected, physical measurements, and completed surveys on smoking, drinking, and GERD, using the *Ranuni* function in SAS. We then chose patients with BE and controls for comparison, starting from the beginning of the list. Subjects with only endoscopic but not histologic evidence of BE as well as subjects recruited from endoscopy without BE ('endoscopy controls') were excluded from the analysis.

Results

A flow diagram (Figure 1) shows the enrollment for this study. Approximately 2948 subjects were eligible for the study, of whom 1942 underwent EGD (583 PCP subjects and 1359 EGD subjects). We randomly chose 624 subjects to undergo biomarker assay. We excluded 302 endoscopy controls and 42 visible BE only (9 from PCP, 33 from EGD) which resulted in 141 cases with BE (11 were from PCP) and 139 controls included in this analysis. There were 39 prevalent or existing BE cases, and the rest were new cases. Only 11 patients had low grade dysplasia.

Comparison of the 141 patients with BE and 139 controls showed the minimum detectable difference between the median values in each group were 0.13 pg/mL, 1.7 pg/mL, 0.9 pg/mL, 0.35 pg/mL, 1.05 pg/mL, 1.15 pg/mL, 6.15 ng/mL, 142 pg/mL, 1.95 pg/mL for IFN- γ , IL-10, IL-12, IL-6, IL-8, TNF- α , leptin, insulin and adiponectin, respectively, with a power of 80%, and an alpha of 0.05.

Patients with BE were 1.6 years older, more likely to have had at least weekly GERD symptoms for a longer time, and to be white than controls. BE patients were less likely to be *H. pylori* positive and were more likely to use PPIs. BMI was not different between groups, but BE patients had larger W/H ratio than controls as reported in our previous publication, indicating a greater degree of central obesity.²⁷ There was no significant difference in smoking or drinking status, level of physical activity or NSAID use between cases and controls (Table 1).

Inflammatory Cytokines

Circulating levels of the proinflammatory cytokines IL-6, IL-12p70 and IL-8 were significantly higher in BE patients than in controls (Table 2A). On the other hand, circulating levels of IL-1 β and the anti-inflammatory cytokine IL-10 were significantly lower in BE patients than in controls. There was no significant difference in IFN- γ or TNF- α levels between groups. After we adjusted for age, gender, race, W/H ratio, PPI and NSAID use, and *H. pylori* status, these associations remained significant for IL-10, IL-8 and IL-1 β and trended towards significance for IL-12p70 and IL-6 (Table 3). Similar results were found when subgroup analyses were performed in white men only comparing BE cases with controls, except for IL-6, which did not reach significance and IL-12p70 that became significant (Table 2B).

Leptin, Adiponectin, and Insulin

Circulating leptin levels were significantly higher in BE patients than in controls. After we adjusted for age, gender, race, W/H ratio, PPI and NSAIDS use and *H. pylori* status, leptin continued to be a significant predictor for BE. Total adiponectin serum levels showed a trend that did not reach statistical significance, while circulating insulin levels (excluding patients with diabetes) were not different between the 2 groups (Table 3A). A secondary analysis for leptin was performed excluding women, given that gender is known to greatly affect circulating leptin levels, and found similar results (data not shown). Analyses including only white men also showed similar results (Table 3B). See supplemental material for more results.

Discussion

We report the relationship between circulating adipokines and inflammatory cytokines and BE. In agreement with our a priori hypothesis, we showed that BE is associated with an increase in proinflammatory cytokines and leptin and a decrease in anti-inflammatory cytokines. There was an increase in the pro-inflammatory cytokines IL-12p70, IL-6 and IL-8, along with a decrease in circulating levels of the anti-inflammatory cytokine IL-10 in BE compared with controls. Most of these associations remained significant after adjusting for other confounders, suggesting a key role for cytokines and inflammation in the development of BE.

The genesis of our hypotheses is related to the observed link between abdominal obesity and BE²⁸. There could be several plausible mechanisms explaining the role of obesity in increasing the risk of BE. First, abdominal obesity can cause direct mechanical pressure on the stomach, increasing the intragastric pressure and leading to increased frequency of relaxation of the lower esophageal sphincter, with subsequent reflux of acid and, possibly, bile.²⁹ A second mechanism may specifically relate to visceral obesity and its potential role in inflammation. Visceral fat is strongly associated with circulating levels of proinflammatory cytokines, including IL-6,^{30, 31} and use of anti-inflammatory agents has recently been associated with a decreased risk of BE.³² Therefore, our current study has focused on mechanisms that are more proximal to obesity and their association with BE.

Here we also report an increase in circulating levels of the pro-inflammatory cytokine IL-12 p70 and a decrease in the levels of the anti-inflammatory cytokine IL-10 in the setting of BE. In previous studies the expression of the IL-12B C-allele, which is associated with increased IL-12p70 expression, was more frequently observed in BE than in GERD patients.³³ In the same study, the IL-10 21082 GG genotype, which is associated with higher IL-10 levels, was associated with a decreased risk of BE when linked with the IL-12B C-allele, indicating IL-10-dependent down-regulation of IL-12p70 expression. On the other hand, another study found an association of the IL-10+1082 2/2 genotype (associated with higher levels of IL-10) in patients with BE and patients with esophageal adenocarcinoma compared with patients with esophagitis.³⁴ Animal and histopathological studies suggest that increased expression of IL-10 is associated with the development of BE.^{35, 36}

Interleukin-1 β (IL-1 β) is a proinflammatory cytokine that plays a role in the pathogenesis of several inflammatory conditions.³⁷ Proinflammatory genotypes of IL-1 β are associated, especially in the presence of *H. pylori* infection, with severe corpus gastritis with gastric atrophy and low gastric-acid secretion, thus potentially “protecting” against GERD.³⁸ However, the association between circulating IL-1 β and GERD/BE has not been examined before our study. We found an inverse association between circulating levels of IL-1 β and BE. All the data indicating a potential role of this cytokine in the setting of BE comes from in-vitro and immunostaining studies looking at the local esophageal effect of IL-1 β .

Furthermore, this cytokine circulates at very low levels and, in our study, levels were below the lower limit of detection in a significant number of subjects. We hypothesize that this inverse association between serum IL-1 β levels and BE could be explained by a lack of correlation between circulating and tissue levels. Further studies looking at the association between circulating levels and tissue action of IL-1 β will be needed to test this hypothesis.

In-vitro studies have suggested a role for TNF α on BE progression to adenocarcinoma potentially through upregulation of β -catenin-mediated transcription of *c-myc*.³⁹ Also, expression of IFN γ in the esophageal mucosa of BE patients is increased compared with controls.⁴⁰ However, we are not aware of other reports of circulating levels of these markers in this setting. In our study we did not detect an association between TNF α levels and BE suggesting that if they play a role, they do so at the tissue level. Whether circulating levels of TNF α and IFN γ are good markers of tissue level or tissue action was not evaluated in this study.

Leptin is an adipokine secreted proportionally to the amount of fat.¹⁴ However, the role of leptin in BE is not clear. Thompson et al. showed an association between BE and leptin levels in women but not in men,⁴¹ while others have reported an association in men but not in women.⁴² Our results showed a clear association of higher circulating levels of leptin with BE that was independent of gender, race and abdominal obesity, suggesting a role for leptin in the setting of BE. The leptin receptor, member of the cytokine receptor superfamily, is known to activate several pathways that are normally activated by cytokines, such as the JNK pathway.^{43, 44} This link between proinflammatory cytokines and leptin has been illustrated well in animal models, showing that administration of proinflammatory cytokines increased levels of both circulating leptin and leptin mRNA in adipose tissue and that peripheral leptin administration causes inflammation in target organs.⁴⁵ Although the mechanism for this relationship between BE, inflammation and leptin cannot be elucidated from this study, it is intriguing to think that leptin may be one of the links between obesity and inflammation.

Adiponectin is the most abundant peptide secreted from fat cells.⁴⁶ Adiponectin levels are inversely related to body fat, especially visceral fat;⁴⁷ and lower levels have also been strongly associated with insulin-resistance syndrome.^{48–50} Low adiponectin levels have also been associated with an increased risk of several different types of cancer. Adiponectin receptors are expressed in the esophageal mucosa, and adiponectin has been shown to induce apoptosis in a cell line of esophageal cancer.⁵¹ In a previous report, low levels of circulating adiponectin were associated with BE, although this association was driven by gender (men had lower adiponectin levels) and abdominal obesity in one study;²⁰ and it lost significance after adjusting for these factors. The same group later reported that only the low-molecular weight adiponectin fraction but not total adiponectin levels were associated with a decreased risk of BE.⁵² In our study, there was a statistically non-significant trend for BE cases to have lower levels of total adiponectin in agreement with the findings reported previously.^{20,52} Larger studies decreasing the chance of a type II error, measuring adiponectin sub-fractions and accounting for the effects of gender and abdominal obesity will be needed to establish the role of adiponectin in the setting of BE.

Strengths of our study include that it is the largest study to date to examine this topic, controlled for several covariates such as gender, race and adiposity. However, it also has limitations. Our results may not be applicable to a female population. While these markers may predict the presence of Barrett's esophagus, the cross-sectional nature of the study prevents us from determining the causality of these associations, or whether they can predict BE progression. Longitudinal studies addressing natural history can help clarify these questions. Only circulating levels of these biomarkers were measured, and these may not

represent tissue expression or action; only total adiponectin levels were measured given that our assay does not distinguish between low, medium, or high molecular weight forms. Lastly, an increase in inflammatory markers is not specific to obesity and it may be related to other conditions often associated with obesity such as sleep apnea, metabolic syndrome and arthritis that we did not control for.

In summary, this study shows a significant association between increased circulating cytokine and leptin levels and BE. These markers may serve as prognostic factors in subjects at risk. This also adds to the burden of evidence supporting a role for inflammation in the development of this condition and may help tailor treatment strategies for BE that specifically target inflammation.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

BE	Barrett's Esophagus
BMI	Body Mass Index
CI	Confidence Intervals
CM	Circumferential Maximal
EGD	Esophagogastroduodenoscopy
GERD	Gastroesophageal Reflux Disease
H. pylori	Helicobacter pylori
H2RA	Histamine 2 Receptor Antagonists
IFN-γ	Interferon
IL	Interleukin
JNK	Jun N-terminal Protein Kinases
MEDVAMC	Michael E. DeBakey Veteran Affairs Medical Center
mRNA	messenger Ribonucleic Acid
NIH	National Institutes of Health
NSAIDs	Non-Steroidal Anti-Inflammatory Drugs
OR	Odds Ratios
PCP	Primary Care Providers
pg/mL	picograms per millilitre
PPI	Proton Pump Inhibitors

TNF Tumor Necrosis Factor
W/H Waist/Hip ratio

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Figure 1.
Enrollment Flow Diagram

Table 1

Baseline Characteristics of Definitive BE Patients and Controls without BE.

	Cases n=141	Controls n=139	p-value
Age, mean (sd)	62.8 (6.7)	61.2 (7.6)	0.02
Ethnicity			
Black	12 (8.5%)	45 (32.4%)	<0.001
White	126 (89.4%)	90 (64.7%)	
Other	3 (2.1%)	4 (2.9%)	
Gender			
Male	137 (97.2%)	135 (97.1%)	0.98
Female	4 (2.8%)	4 (2.9%)	
BMI (kg/m ²)	30.3 (5.7)	31.6 (6.7)	0.08
W/H Ratio	0.97 (0.05)	0.96 (0.07)	0.02
Tobacco Smoking			
Never	30 (23.0%)	33 (25.0%)	0.93
Former	37 (28.5%)	37 (28.0%)	
Current	63 (48.5%)	62 (47.0%)	
Missing	11	7	
Alcohol Drinking			
Never	13 (9.9%)	6 (4.6%)	0.08
Former	68 (51.9%)	84 (64.1%)	
Current	50 (38.2%)	41 (31.3%)	
Missing	10	8	
Duration of at least weekly GERD symptoms			
None	50 (38.5%)	78 (59.1%)	0.002
< 5 Years	6 (4.6%)	7 (5.3%)	
5 or More Years	74 (56.9%)	47 (35.6%)	
Missing	11	7	
<i>H. pylori</i>			
Positive	17 (13.1%)	37 (28.5%)	0.003
Negative	113 (86.9%)	93 (71.5%)	
Missing	11	9	
PPI Use			
Yes	96 (72.7%)	39 (29.5%)	<0.001
No	36 (27.3%)	93 (70.5%)	
Missing	9	7	
NSAID Use			
Yes	82 (62.6%)	83 (62.9%)	0.96
No	49 (37.4%)	49 (37.1%)	

	Cases n=141	Controls n=139	p-value
Missing	10	7	

BMI = body mass index; W/H = waist-to-height; GERD = gastroesophageal reflux disorder; H. pylori = *Helicobacter pylori*; PPI = proton pump inhibitor; NSAID = nonsteroidal anti-inflammatory drug

Table 2A

Comparison of Cytokine Levels between BE Patients and Controls and Relative Risk of BE.

	Cases (n=141)	Controls (n=139)	Unadjusted OR (95% CI)	Adjusted OR (95% CI)
IFN- γ				
Median (IQR)	0.40 (0.23–0.67)	0.40 (0.24–0.67)		
Q 1 (Lowest–0.1800)	27 (19.2%)	18 (12.9%)	Ref	Ref
Q 2 (0.1800–0.3113)	21 (14.9%)	30 (21.6%)	0.47 (0.21–1.06)	0.44 (0.16–1.19)
Q 3 (0.3113–0.4698)	34 (24.1%)	34 (24.5%)	0.67 (0.31–1.43)	0.78 (0.31–1.95)
Q 4 (0.4698–0.7906)	34 (24.1%)	33 (23.7%)	0.69 (0.320–1.48)	0.62 (0.25–1.53)
Q 5 (0.7906–Highest)	25 (17.7%)	24 (17.3%)	0.69 (0.31–1.57)	0.65 (0.24–1.76)
<i>p</i> Values *			0.85	0.49
IL-10				
Median (IQR)	1.08 (0.52–1.97)	6.52 [#] (0.85–16.21)		
Q 1 (Lowest–0.5541)	36 (25.5%)	14 (10.1%)	Ref	Ref
Q 2 (0.5541–0.9910)	28 (19.9%)	28 (20.3%)	0.39 (0.17–0.87)	0.44 (0.17–1.11)
Q 3 (0.9910–1.7926)	38 (27.0%)	14 (10.1%)	1.06 (0.44–2.52)	1.34 (0.48–3.73)
Q 4 (1.7926–10.1456)	24 (17.0%)	30 (21.7%)	0.31 (0.14–0.71)	0.36 (0.14–0.93)
Q 5 (10.1456–Highest)	15 (10.6%)	52 (37.7%)	0.11 (0.05–0.27)	0.14 (0.05–0.35)
<i>p</i> Values *			<0.001	<0.001
IL-12 p70				
Median (IQR)	1.10 (0.34–3.28)	0.54 [#] (0.30–1.63)		
Q 1 (Lowest–0.2557)	26 (18.4%)	30 (21.8%)	Ref	Ref
Q 2 (0.2557–0.5393)	25 (17.7%)	38 (27.5%)	0.76 (0.37–1.57)	0.78 (0.32–1.88)
Q 3 (0.5393–1.2830)	26 (18.4%)	31 (22.5%)	0.97 (0.46–2.03)	1.15 (0.47–2.81)
Q 4 (1.2830–4.7748)	34 (24.2%)	21 (15.2%)	1.87 (0.88–3.98)	2.17 (0.88–5.37)
Q 5 (4.7748–Highest)	30 (21.3%)	18 (13.0%)	1.82 (0.84–3.97)	2.62 (1.00–6.82)
<i>p</i> Values *			0.02	0.06
IL-1 β				
Median (IQR)	0.09 (0.01–0.21)	0.14 [#] (0.10–0.27)		
None detected	46 (32.6%)	2 (1.4%)	Ref	Ref
Below median	42 (29.8%)	75 (54.0%)	0.02 (0.01–0.11)	0.02 (0.005–0.10)
At or above median	53 (37.6%)	62 (44.6%)	0.04 (0.01–0.16)	0.03 (0.006–0.13)
<i>p</i> Values *			<0.001	<0.001
IL-6				
Median (IQR)	1.01 (0.58–1.81)	0.85 [#] (0.50–1.48)		
Q 1 (Lowest–0.5407)	32 (22.7%)	41 (29.5%)	Ref	Ref
Q 2 (0.5407–0.8446)	21 (14.9%)	27 (19.4%)	0.99 (0.48–2.08)	1.43 (0.50–1.08)
Q 3 (0.8446–1.2860)	34 (24.1%)	29 (20.9%)	1.50 (0.76–2.96)	1.31 (0.51–3.41)

	Cases (n=141)	Controls (n=139)	Unadjusted OR (95% CI)	Adjusted OR (95% CI)
Q 4 (1.2860–2.2980)	29 (20.6%)	25 (18.0%)	1.49 (0.73–3.01)	1.90 (0.66–5.51)
Q 5 (2.2980–Highest)	25 (17.7%)	17 (12.2%)	1.88 (0.87–4.07)	2.39 (0.84–6.79)
<i>p</i> Values *			0.06	0.40
IL-8				
Median (IQR)	3.26 (2.15–5.15)	2.16 [#] (1.60–3.27)		
Q 1 (Lowest-1.9126)	30 (21.3%)	54 (38.8%)	Ref	Ref
Q 2 (1.9126–2.8590)	26 (18.4%)	40 (28.8%)	1.17 (0.60–2.28)	1.48 (0.68–3.16)
Q 3 (2.8590–4.3168)	38 (27.0%)	24 (17.3%)	2.85 (1.45–5.62)	3.31 (1.61–8.47)
Q 4 (4.3168–7.0980)	31 (22.0%)	14 (10.1%)	3.99 (1.84–8.63)	4.35 (1.75–10.80)
Q 5 (7.0980–Highest)	16 (11.3%)	7 (5.0%)	4.11 (1.52–11.12)	5.18 (1.70–15.75)
<i>p</i> Values *			<0.001	<0.001
TNF-α				
Median (IQR)	5.30 (3.48–7.11)	5.73 (2.38–8.84)		
Q 1 (Lowest-3.2150)	33 (23.4%)	49 (35.3%)	Ref	Ref
Q 2 (3.2150–5.0911)	37 (26.2%)	16 (11.5%)	3.43 (1.65–7.15)	3.36 (1.40–8.07)
Q 3 (5.0911–6.9340)	32 (22.7%)	11 (7.9%)	4.32 (1.91–9.76)	6.08 (2.22–16.68)
Q 4 (6.9340–8.9145)	20 (14.2%)	32 (23.0%)	0.93 (0.46–1.89)	1.05 (0.46–2.44)
Q 5 (8.9145–Highest)	19 (13.5%)	31 (22.3%)	0.91 (0.44–1.87)	1.16 (0.49–2.74)
<i>p</i> Values *			0.52	<0.001

Median levels for all biomarkers are shown in pg/mL.

* Goodness-of-fit to marginal frequencies was tested by χ^2 (rightmost column); Kendall's tau-b (p for trend, in second-right column) for the unadjusted analyses and logistic-regression models adjusting for age, sex, race, waist-hip ratio, current use of proton pump inhibitors, use of nonsteroidal anti-inflammatory drugs, and *H. pylori* for the adjusted analyses.

[#] indicates a *p* value <0.05, using the Mann-Whitney U statistic.

IFN-γ = interferon; IL = interleukin; TNF-α – tumor-necrosing factor alpha

Table 2B

Comparison of Cytokine Levels Between BE Patients and Controls and Relative Risk of BE in White Men only (n=209).

	Cases (n=122)	Controls (n=87)	Unadjusted OR (95% CI)	Adjusted OR (95% CI)
IFN- γ				
Median (IQR)	0.41 (0.23–0.69)	0.41 (0.24–0.70)		
Q 1 (Lowest–0.1800)	24 (19.7%)	12 (13.8%)	Ref	Ref
Q 2 (0.1800–0.3113)	16 (13.1%)	14 (16.1%)	0.57 (0.21–1.55)	0.38 (0.11–1.30)
Q 3 (0.3113–0.4698)	29 (23.8%)	21 (24.1%)	0.69 (0.28–1.69)	0.78 (0.26–2.33)
Q 4 (0.4698–0.7906)	30 (24.6%)	23 (26.5%)	0.65 (0.27–1.57)	0.54 (0.18–1.58)
Q 5 (0.7906–Highest)	23 (18.8%)	17 (19.5%)	0.68 (0.27–1.72)	0.47 (0.15–1.46)
<i>p</i> Values *			0.57	0.84
IL-10				
Median (IQR)	1.08 (0.52–1.97)	6.52 (0.81–15.24)		
Q 1 (Lowest–0.5541)	32 (26.2%)	9 (10.3%)	Ref	Ref
Q 2 (0.5541–0.9910)	25 (20.5%)	18 (20.7%)	0.39 (0.15–1.02)	0.570 (0.19–1.70)
Q 3 (0.9910–1.7926)	31 (25.4%)	11 (12.6%)	0.79 (0.29–2.18)	1.285 (0.40–4.12)
Q 4 (1.7926–10.1456)	21 (17.2%)	15 (17.2%)	0.39 (0.15–1.06)	0.62 (0.20–1.95)
Q 5 (10.1456–Highest)	13 (10.7%)	34 (39.1%)	0.11 (0.04–0.29)	0.13 (0.04–0.40)
<i>p</i> Values *			<0.001	<0.001
IL-12 p70				
Median (IQR)	1.09 (0.33–3.52)	0.53 (0.30–1.08)		
Q 1 (Lowest–0.2557)	22 (18.1%)	20 (23.0%)	Ref	Ref
Q 2 (0.2557–0.5393)	21 (17.2%)	24 (27.6%)	0.80 (0.34–1.85)	0.99 (0.35–2.83)
Q 3 (0.5393–1.2830)	25 (20.5%)	24 (27.6%)	0.95 (0.42–2.16)	1.33 (0.48–3.70)
Q 4 (1.2830–4.7748)	27 (22.1%)	10 (11.5%)	2.46 (0.95–6.32)	4.21 (1.33–13.26)
Q 5 (4.7748–Highest)	27 (22.1%)	9 (10.3%)	2.73 (1.04–7.18)	4.00 (1.24–12.90)
<i>p</i> Values *			0.003	0.02
IL-1 β				
Median (IQR)	0.08 (0.01–0.21)	0.14 [#] (0.10–0.27)		
None detected	42 (34.5%)	1 (1.1%)	Ref	Ref
Below median	33 (27.0%)	48 (55.2%)	0.02 (0.00–0.13)	0.01 (0.00–0.12)
At or above median	47 (38.5%)	38 (43.7%)	0.03 (0.00–0.22)	0.02 (0.00–0.19)
<i>p</i> Values *			0.001	<0.001
IL-6				
Median (IQR)	0.98 (0.55–1.77)	0.87 (0.51–1.67)		
Q 1 (Lowest–0.5407)	29 (23.8%)	25 (28.7%)	Ref	Ref
Q 2 (0.5407–0.8446)	20 (16.4%)	16 (18.4%)	1.08 (0.46–2.52)	1.15 (0.47–2.82)
Q 3 (0.8446–1.2860)	30 (24.6%)	18 (20.7%)	1.44 (0.65–3.17)	1.45 (0.65–3.26)

	Cases (n=122)	Controls (n=87)	Unadjusted OR (95% CI)	Adjusted OR (95% CI)
Q 4 (1.2860–2.2980)	22 (18.0%)	12 (13.8%)	1.58 (0.65–3.82)	1.29 (0.56–3.00)
Q 5 (2.2980–Highest)	21 (17.2%)	16 (18.4%)	1.13 (0.49–2.63)	2.67 (1.05–6.74)
<i>p</i> Values *			0.47	0.820
IL-8				
Median (IQR)	3.16 (2.05–4.50)	2.16 [#] (1.47–3.19)		
Q 1 (Lowest-1.9126)	28 (23.0%)	36 (41.4%)	Ref	Ref
Q 2 (1.9126–2.8590)	22 (18.0%)	23 (26.4%)	1.23 (0.57–2.64)	1.74 (0.69–4.38)
Q 3 (2.8590–4.3168)	34 (27.9%)	15 (17.2%)	2.91 (1.33–6.38)	3.65 (1.37–9.72)
Q 4 (4.3168–7.0980)	26 (21.3%)	7 (8.1%)	4.78 (1.81–12.59)	5.38 (1.74–16.66)
Q 5 (7.0980–Highest)	12 (9.8%)	6 (6.9%)	2.57 (0.86–7.71)	2.83 (0.76–10.51)
<i>p</i> Values *			<0.001	0.003
TNF-α				
Median (IQR)	5.01 (3.43–7.15)	7.05 (2.49–8.91)		
Q 1 (Lowest-3.2150)	29 (23.8%)	30 (34.5%)	Ref	Ref
Q 2 (3.2150–5.0911)	33 (27.0%)	7 (8.0%)	4.88 (1.86–12.76)	6.92 (2.12–22.67)
Q 3 (5.0911–6.9340)	25 (20.5%)	6 (6.9%)	4.31 (1.54–12.04)	8.93 (2.44–32.78)
Q 4 (6.9340–8.9145)	18 (14.8%)	22 (25.3%)	0.85 (0.38–1.89)	1.01 (0.38–2.66)
Q 5 (8.9145–Highest)	17 (13.9%)	22 (25.3%)	0.80 (0.36–1.80)	1.25 (0.46–3.34)
<i>p</i> Values *			0.26	<0.001

Median levels for all biomarkers are shown in pg/mL.

* Goodness-of-fit to marginal frequencies was tested by χ^2 ; *p* values were calculated using Kendall's tau-b (*p* for trend) for the unadjusted analyses and logistic-regression models, adjusting for age, sex, race, waist-hip ratio, current use of proton pump inhibitors, use of nonsteroidal anti-inflammatory drugs, and *H. pylori* for the adjusted analyses.

[#] indicates a *p* value <0.05 using the Mann-Whitney U statistic.

IFN-γ = interferon; IL = interleukin; TNF-α – tumor-necrosing factor alpha

Table 3A

Comparison of Leptin, Adiponectin and Insulin Levels Between BE Patients and Controls and Relative Risk of BE.

	Cases (n=141)	Controls (n=139)	Unadjusted OR (95% CI)	Adjusted OR (95% CI)
Leptin				
Median (IQR)	12,902 (4,615–42,997)	5,232 (2,634–3,808)		
Q 1 (Lowest–3154)	24 (17.0%)	39 (28.1%)	Ref	Ref
Q 2 (3154–5377)	17 (12.1%)	34 (24.5%)	0.81 (0.38–1.76)	1.12 (0.43–2.90)
Q 3 (5377–12629)	26 (18.4%)	28 (20.1%)	1.51 (0.72–3.15)	2.53 (0.99–6.43)
Q 4 (12629–33904)	35 (24.8%)	22 (15.8%)	2.59 (1.237–5.401)	3.96 (1.56–10.01)
Q 5 (33904–Highest)	39 (27.7%)	16 (11.5%)	3.96 (1.84–8.58)	8.02 (2.79–23.07)
<i>p</i> Values *			<0.001	<0.001
Adiponectin				
Median (IQR)	7.02 (3.79–11.75)	5.71 (3.32–9.16)		
Q 1 (Lowest–3.20)	21 (19.4%)	32 (23.0%)	Ref	Ref
Q 2 (3.20–5.258)	18 (16.7%)	30 (21.6%)	0.91 (0.41–2.04)	1.11 (0.42–2.93)
Q 3 (5.258–8.203)	25 (23.2%)	31 (22.3%)	1.23 (0.57–2.63)	1.77 (0.69–4.54)
Q 4 (8.203–12.713)	23 (21.3%)	27 (19.4%)	1.30 (0.59–2.84)	2.62 (0.99–6.91)
Q 5 (12.713–Highest)	21 (19.4%)	19 (13.7%)	1.68 (0.74–3.86)	1.49 (0.54–4.11)
<i>p</i> Values *			0.15	0.65
Insulin (non-diabetics)				
Median (IQR)	470.4 (270.2–887.0)	440.02 (209.3–716.9)		
Q 1 (Lowest–210)	21 (17.4%)	28 (25.3%)	Ref	Ref
Q 2 (210–390)	27 (22.3%)	23 (20.7%)	1.57 (0.71–3.46)	1.43 (0.57–3.64)
Q 3 (390–579)	21 (17.4%)	23 (20.7%)	1.217 (0.537–2.76)	1.02 (0.38–2.75)
Q 4 (579–921)	23 (19.0%)	20 (18.0%)	1.53 (0.67–3.50)	0.79 (0.30–2.07)
Q 5 (921–Highest)	29 (24.0%)	17 (15.3%)	2.275 (0.998–5.18)	2.06 (0.78–5.46)
<i>p</i> Values *			0.081	0.363

Median levels for all biomarkers are shown in pg/mL.

* Goodness-of-fit to marginal frequencies was tested by χ^2 (*p* values in rightmost column); Kendall's tau-b (*p* for trend) in second-right column, for the unadjusted analyses and logistic-regression models, adjusting for age, sex, race, waist-hip ratio, current use of proton pump inhibitors, use of nonsteroidal anti-inflammatory drugs, and *H. pylori* for the adjusted analyses.

indicates a *p* value <0.05 using the Mann-Whitney U statistic.

Table 3B

Comparison of Leptin, Adiponectin and Insulin Levels between BE Patients and Controls and Relative Risk of BE in White Men Only.

	Cases (n=122)	Controls (n=87)	Unadjusted OR (95% CI)	Adjusted OR (95% CI)
Leptin				
Median (IQR)	13,091 (4,668–43,675)	4,979 (3,155–11,382)		
Q 1 (Lowest–3154)	20 (16.4%)	21 (24.1%)	Ref	Ref
Q 2 (3154–5377)	15 (12.3%)	27 (31.0%)	0.58 (0.24–1.41)	0.65 (0.22–1.91)
Q 3 (5377–12629)	22 (18.0%)	20 (23.0%)	1.16 (0.49–2.73)	1.66 (0.57–4.87)
Q 4 (12629–33904)	31 (25.4%)	11 (12.6%)	2.96 (1.18–7.43)	4.42 (1.48–13.18)
Q 5 (33904–Highest)	34 (27.9%)	8 (9.2%)	4.46 (1.67–11.94)	10.99 (2.90–41.61)
<i>p</i> Values *			<0.001	<0.001
Adiponectin				
Median (IQR)	7.42 (3.8–12.2)	5.61 (3.3–9.2)		
Q 1 (Lowest–3.20)	16 (17.4%)	20 (23.0%)	Ref	Ref
Q 2 (3.20–5.258)	15 (16.3%)	20 (23.0%)	0.94 (0.37–2.40)	1.34 (0.44–4.08)
Q 3 (5.258–8.203)	20 (21.7%)	17 (19.5%)	1.47 (0.59–3.70)	1.71 (0.57–5.09)
Q 4 (8.203–12.713)	20 (21.7%)	16 (18.4%)	1.56 (0.62–3.96)	3.27 (1.06–10.05)
Q 5 (12.713–Highest)	21 (22.8%)	14 (16.1%)	1.88 (0.73–4.82)	2.30 (0.72–7.33)
<i>p</i> Values *			0.10	0.54
Insulin (non-diabetics)				
Median (IQR)	473.1 (275.0–872.8)	450.2 (217.8–823.1)		
Q 1 (Lowest–210)	18 (17.1%)	17 (24.3%)	Ref	Ref
Q 2 (210–390)	21 (20.0%)	14 (20.0%)	1.42 (0.55–3.65)	1.48 (0.48–4.54)
Q 3 (390–579)	20 (19.0%)	15 (21.4%)	1.26 (0.49–3.23)	1.13 (0.36–3.48)
Q 4 (579–921)	22 (21.0%)	13 (18.6%)	1.60 (0.62–4.15)	1.17 (0.38–3.62)
Q 5 (921–Highest)	24 (22.9%)	11 (15.7%)	2.06 (0.78–5.46)	2.23 (0.68–7.30)
<i>p</i> Values *			0.15	0.67

Median levels for all biomarkers are shown in pg/mL.

* Goodness-of-fit to marginal frequencies was tested by χ^2 ; *p* values were calculated using Kendall's tau-b (*p* for trend) for the unadjusted analyses and logistic-regression models, adjusting for age, sex, race, waist-hip ratio, current use of proton pump inhibitors, use of nonsteroidal anti-inflammatory drugs, and *H. pylori* for the adjusted analyses.

indicates a *p* value <0.05 using the Mann-Whitney U statistic.