Published in final edited form as:

J Clin Gastroenterol. 2015 April ; 49(4): 282–288. doi:10.1097/MCG.0000000000000119.

Metabolic syndrome increases risk of Barrett's esophagus in the absence of gastroesophageal reflux: An analysis of SEER-Medicare data

Jennifer Drahos, PhD, MPH¹, Winnie Ricker, MS², Ruth Parsons, BA², Ruth M. Pfeiffer, PhD¹, Joan L. Warren, PhD³, and Michael B. Cook, PhD¹

¹ Division of Cancer Epidemiology and Genetics, National Cancer Institute, National Institutes of Health, Bethesda, MD ² Information Management Services, Rockville, Maryland ³ Division of Cancer Control and Population Sciences, National Cancer Institute, National Institutes of Health, Bethesda, MD

Abstract

GOALS: Evaluate the association between metabolic syndrome (MetS) and risk of Barrett's esophagus (BE) using the Surveillance, Epidemiology, and End Results (SEER)-Medicare linked database compared with two control groups—Medicare population controls and endoscopy controls.

BACKGROUND: Barrett's esophagus principally arises as an adaptation to the proinflammatory state induced by gastroesophageal reflux disease (GERD). The relationship between obesity and BE is presumed to be mediated by GERD. However, evidence suggests central adiposity also increases risk of BE independent of GERD. Central adiposity is one risk factor defining metabolic syndrome, which confers a systemic proinflammatory state—a potential GERD-independent mechanism by which obesity could increase risk of BE.

STUDY: MetS was defined as diagnosis of at least three of the following conditions: obesity, elevated triglycerides, high blood pressure, and elevated fasting glucose. Multivariable logistic regression was used to estimate adjusted odds ratios (ORs) and 95% confidence intervals (95% CIs).

RESULTS: In 2,198 incident BE cases, prior MetS was significantly associated with BE [OR 1.20; 95%CI 1.07, 1.36] compared with population controls. However, GERD status modified the association; among those without prior GERD, MetS increased risk of BE by 34%, however no association was observed among those with a prior GERD diagnosis (*p*-value for effect

Corresponding author: Jennifer Drahos Division of Cancer Epidemiology and Genetics National Cancer Institute, NIH, DHHS 9609 Medical Center Drive, Rm 7-E226, MSC 9774 Bethesda, MD 20892-9774 Phone: 240-276-7330 Fax: 240-276-7838 jennifer.drahos@nih.gov.

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the National Institutes of Health.

There are no financial disclosures from any of the authors.

There are no competing interests to disclose.

modification <0.001). MetS was not associated with risk of BE compared with endoscopy controls.

CONCLUSIONS: MetS increased risk of BE compared with population controls, an association driven by and confined to the non-GERD stratum. MetS may mediate an association between central adiposity and BE for those without GERD.

Keywords

Barrett's esophagus; metabolic syndrome; obesity; gastroesophageal reflux; SEER-Medicare

INTRODUCTION

Barrett's esophagus is a precancerous condition that is considered to arise as a complication of gastroesophageal reflux disease (GERD) ¹ and substantially increases the risk of developing esophageal adenocarcinoma ². For reasons not fully understood, the incidence of esophageal adenocarcinoma has increased rapidly in the U.S. ³. Diagnosis of Barrett's esophagus and follow-up surveillance could provide a point of intervention. Elucidated risk factors for Barrett's esophagus include tobacco smoking ⁴, GERD ⁵, and obesity, however the mechanism of the latter remains unclear.

Though the mechanical effect of obesity is widely accepted—by which adiposity amplifies intragastric pressure and disturbs normal sphincter function, culminating in a higher propensity for GERD and increased risk of Barrett's esophagus ⁶—evidence also suggests that increasing central adiposity increases risk of Barrett's esophagus independent of GERD symptoms ^{7, 8}. While the interpretation of these studies could be questioned since GERD symptoms have only moderate sensitivity (51.4%) for acid reflux exposure ⁹, the facts that GERD symptoms are highly specific (>95%) for ^{10, 11}, and correlate with ¹², acid reflux exposure support the existence of a GERD-independent mechanism of central adiposity in the pathogenesis of Barrett's esophagus.

Adipose tissue, particularly central adiposity, secretes bioactive adipokines resulting in a chronic systemic inflammatory state^{13, 14}. Therefore it has been posited that a mechanistic link between obesity and increased risk of Barrett's esophagus, or esophageal adenocarcinoma, may be related to the proinflammatory effects of excess adipose tissue—namely, metabolic syndrome¹⁵⁻¹⁷.

Metabolic syndrome confers a chronic systemic inflammatory state¹⁸⁻²¹, which may increase the risk of Barrett's esophagus^{22, 23}, and could represent a potential indirect mechanism by which increasing adiposity is associated with Barrett's esophagus. Metabolic syndrome is a cluster of metabolic disorders that includes obesity, high blood pressure, insulin resistance, and dyslipidemia ²⁴. Initially described as a risk factor for cardiovascular disease, metabolic syndrome is also associated with increased risk of certain cancers including colon, liver, breast, ovarian, and endometrial ²⁵. Studies evaluating the association between metabolic syndrome and Barrett's esophagus are sparse. Cross-sectional data suggested that the prevalence of metabolic syndrome in Barrett's esophagus cases far exceeded population estimates ²³, however prevalence among those referred for endoscopy

did not substantially differ between patients diagnosed with Barrett's esophagus or not²². Thus, whether metabolic syndrome has an etiologic role in development of Barrett's esophagus remains unclear.

Using Surveillance, Epidemiology, and End Results (SEER)–Medicare data we evaluated whether metabolic syndrome is associated with Barrett's esophagus and whether this relationship is modified by GERD. To provide comparison with previous studies that used endoscopy Barrett's esophagus-negative controls, we used the two distinct control groups of general Medicare beneficiaries and individuals who underwent endoscopy but were Barrett's esophagus-negative.

MATERIALS AND METHODS

Data Source

Data for the study were obtained from the linked SEER-Medicare database. The population-based SEER registries collect demographic and clinical information for each patient living in defined geographic areas and represent 28% of the U.S. population. The Medicare data, collected by the Center for Medicare and Medicaid Services (CMS), include claims for each beneficiary with fee-for-service coverage, with information about all inpatient hospitalizations, outpatient and physician services. All files include specific dates of service and codes for specific diagnoses and procedures using the International Classification of Disease, ninth revision (ICD-9-CM) codes or Health Care Procedure Codes (HCPCS). The database is comprised of multiple files that were created during an electronic linkage of the SEER and Medicare data, as has been previously described²⁶. The SEER-Medicare files include two cohorts of people—persons with cancer and a random 5% sample of Medicare beneficiaries residing in the SEER areas which includes billing claims for almost one million Medicare enrollees.

Study Population

We utilized the 5% random sample of Medicare beneficiaries residing in any of the SEER regions to select our study population. To ensure complete claims data, only persons enrolled in Medicare Parts A and B continuously for at least 2.5 years before diagnosis/selection were eligible for inclusion. We further excluded those enrolled because of disabilities or end-stage renal disease, before age 64.5 years, enrolled in a health maintenance organization (HMO), missing registry data, and persons with esophageal cancer prior to selection.

All relevant claims files were used in the analysis, which included the Enrollment Data base (EDB), outpatient, carrier claims, and Medicare Provider Analysis and Review (MEDPAR) data. Cases were defined as Medicare beneficiaries with a Barrett's esophagus billing claim through 2009. Barrett's esophagus diagnosis was captured by ICD-9-CM code 530.85, which was introduced by CMS in 2003 and specifically identifies patients with Barrett's esophagus. In addition, a Barrett's esophagus diagnosis required an endoscopy code within the period three months prior- to one-month post-date of Barrett's esophagus diagnosis. Barrett's esophagus patients identified with ICD-9-CM code 530.85 were excluded if he or

she had a prior diagnosis with ICD-9-CM 530.2, a previously used, non-specific code for Barrett's esophagus.

Two control groups were selected from the 5% random sample described above—general Medicare beneficiary controls (population controls) and endoscopy Barrett's esophagus-negative controls (endoscopy-negative controls). Population controls could not have an endoscopy in the window of 2.5 years prior to selection, whereas endoscopy controls were required to have a claim with an endoscopy code during this period. All controls had to be free of Barrett's esophagus. Each control group was frequency-matched to Barrett's esophagus cases to the extent possible at a ratio of 3:1 using the variables age (± 1 year), sex, diagnosis date (based on month and year of endoscopy), and SEER registry. Population controls were matched on their date of selection as a control. The number of Medicare beneficiaries and Barrett's esophagus cases after each exclusion criteria is provided in Supplementary Data (Tables 1a and 1b).

Definition of Metabolic syndrome and covariate selection

Metabolic syndrome was defined as suggested by The U.S. National Cholesterol Education Program Adult Treatment Panel III²⁷ which requires the presence of at least three of the following conditions: elevated waist circumference/central obesity, elevated triglycerides, lowered high-density lipoprotein cholesterol, high blood pressure, and elevated fasting glucose. Obesity served as a surrogate variable for elevated waist circumference, since no specific ICD-9-CM code exists for elevated waist circumference and body mass is not captured in Medicare claims. Reduced high-density lipoprotein cholesterol was not assessed due to the absence of a specific ICD-9-CM for this condition. Type II diabetes diagnoses were included in the definition of elevated fasting glucose. This definition has been used previously to identify those within the SEER-Medicare database as suffering from metabolic syndrome²⁸. The metabolic conditions are referred to as obesity, elevated triglycerides, high blood pressure, and elevated fasting glucose. Each exposure was assessed as the presence or absence of a corresponding ICD-9-CM code (Supplementary Table 6).

Tobacco smoking and GERD are demonstrated to be associated with Barrett's esophagus and were included in our models. Exposure to GERD was assessed as the presence or absence of ICD-9CM codes that included diagnoses of esophageal reflux, reflux esophagitis, and heartburn (Supplementary Table 6). The exposure window began 2.5 years prior to diagnosis for cases, prior to endoscopy for endoscopy-negative controls, and prior to pseudo-diagnosis date for population controls. Components of metabolic syndrome, as well as all covariates, were captured during a 2-year exposure period which ended 6 months prior to study entry, allowing a six-month period for exposure lag.

Modified Charlson Comorbidity Score

A modified Charlson comorbidity score was calculated based on the clinical comorbidity index developed by Charlson²⁹, updated by Deyo³⁰ and expanded by Klabunde *et al*³¹. The modified Charlson comorbidity score incorporates both inpatient and outpatient Medicare claims data and included diagnosis codes related to myocardial infarction, congestive heart failure, peripheral vascular diseases, cerebrovascular disease, COPD,

dementia, cirrhodites, ulcers, paralysis, chronic renal failure, and liver disease³². Diabetes was not included in the comorbidity score since it is a condition defining metabolic syndrome. Our Charlson comorbidity score was a weighted-score based on diagnoses during the same time-frame as the exposure window of 2 years starting 2.5 years prior to diagnosis for cases, 2.5 years prior to endoscopy for endoscopy-negative controls, and 2.5 years prior to pseudo-diagnosis date for population controls. The Charlson comorbidity weighted-score was categorized into none (0), low (1), moderate (2), and high (3+).

Statistical Analyses

To characterize the case and control analytic groups, we calculated frequencies and percentages for categorical variables, and the means and standard deviations for continuous variables. Variables included age (categorical: 65–69, 70–74, 75–79, 80–84, 85+), sex, race (white, black, Hispanic, Asian, other, unknown), SEER registry, Medicaid dual enrollment (ever/never), comorbidities (categorical: 0, 1, 2, 3+), and GERD (yes/no). The Medicaid dual enrollment indicates the months for which a beneficiary is eligible for Medicaid. This variable was included as a proxy of lower socioeconomic status. Demographic features were compared between cases and controls in univariate analyses using t-tests for continuous variables and chi-square or Fisher's exact tests for categorical variables.

Multivariable logistic regression models were used to calculate adjusted odds ratios (OR) and 95% confidence intervals (95% CI) of the association between metabolic syndrome and Barrett's esophagus³³. Wald chi-square tests were used to determine the significance of variables. A two-sided *P*-value of <0.05 was considered statistically significant. The models included variables whose inclusion altered the log odds ratio estimates for metabolic syndrome by >10% (smoking), factors with a known or probable association with Barrett's esophagus (GERD; comorbidities; race; low SES [Medicaid dual enrollment]), and the main matching variables (age, sex, and SEER registry)³⁴. We assessed effect-modification by multivariable logistic regression models that included an interaction term of GERD and metabolic syndrome as well as through stratified analyses by GERD, since GERD may be associated with metabolic syndrome^{35, 36}.

RESULTS

Study Population and Baseline Characteristics

A total of 2,198 Barrett's esophagus patients were identified among 250,754 study eligible Medicare beneficiaries in the SEER-Medicare database. The median age of Barrett's esophagus diagnosis was 76.6 years, 52.3% of the patients were male, and 91.5% were white (Table 1). Barrett's esophagus cases had significantly more moderate (10.3%) and high (8.3%) comorbidities compared with population controls (7.2% and 5.2%), but significantly fewer moderate and high comorbidities compared with endoscopy controls (11.6% and 13.1%).

Risk Factors and Metabolic Conditions Associated with Barrett's esophagus

The proportion of GERD positive patients was higher in Barrett's esophagus cases (43.4%) compared with population controls (16.4%) and endoscopy controls (39.0%). All individual

conditions of metabolic syndrome were positively associated with Barrett's esophagus when compared with population controls (Table 1). In the univariate comparison, metabolic syndrome as defined by NCEP-ATP III definition as three or more of the above conditions was significantly higher in those that developed Barrett's esophagus (29.1%) than population controls (23.8%). However, in the unadjusted comparisons the overall prevalence of metabolic syndrome was significantly higher in endoscopy controls (33.8%) than Barrett's esophagus cases (29.1%).

Multivariable logistic regression analysis

Adjusted odds ratios comparing Barrett's esophagus cases with population controls and endoscopy controls are presented in Table 2. Barrett's esophagus cases were significantly more likely to have prior diagnosis of three or more components of metabolic syndrome compared with population controls (OR: 1.20, 95%CI: 1.07, 1.36). Elevated fasting glucose, high blood pressure, and elevated triglycerides were each significantly associated with increased risk of Barrett's esophagus.

There was no association between metabolic syndrome and Barrett's esophagus compared with endoscopy controls (OR: 0.93, 95%CI: 0.83, 1.04). In addition, there were no associations between individual components of metabolic syndrome and risk of Barrett's esophagus compared with endoscopy-negative controls, except for elevated triglycerides (OR 1.19, 95%CI: 1.07, 1.33).

Stratification by GERD status

Given the importance of GERD in the etiology of Barrett's esophagus, we evaluated GERD as a potential effect-modifier. In stratified models, among those without GERD, metabolic syndrome was associated with an odds ratio of 1.34 (95%CI: 1.16, 1.54) comparing Barrett's esophagus cases with population controls (Table 3). Each metabolic condition was significantly associated with increased risk of Barrett's esophagus. Further stratification by sex did not alter the results (Supplementary Data: Table 2). However, among those with a history of GERD no association between metabolic syndrome and Barrett's esophagus was observed (OR: 0.91, 95%CI: 0.74, 1.12). Corroborating these results, the Wald *p*-value for effect modification was significant (*p*=0.0002). Akin to the main analysis comparing Barrett's esophagus with endoscopy-negative controls, there were no statistically significant associations observed in either GERD stratum (Supplementary Data: Table 3).

Adjustment for the modified Charlson comorbidity score did not significantly alter the results and we retained the score in our adjustment models to provide the most conservative estimates. Models unadjusted for the modified Charlson comorbidity score are presented in the Supplementary Data: Tables 4 and 5.

DISCUSSION

In this analysis of SEER-Medicare data, we find evidence for an association between metabolic syndrome and risk of Barrett's esophagus when compared with population controls. The individual components of metabolic syndrome that were driving this association were elevated fasting glucose, high blood pressure and elevated triglycerides.

GERD was an effect-modifier, whereby the associations were restricted to the stratum without GERD symptoms. Neither metabolic syndrome, nor its individual components, was associated with Barrett's esophagus amongst those with a history of GERD. We thus propose the provocative hypothesis that the direct, proinflammatory effects of GERD cause esophageal tissues to reach a saturated inflammatory state, in which the effects of metabolic syndrome have little or no additional effect negating any relationship to be observed. Conversely, in those without symptomatic GERD, systemic inflammation conferred by metabolic syndrome increases risk of Barrett's esophagus.

GERD symptoms and metabolic syndrome are both biomarkers of a proinflammatory state. Acid reflux in the lower esophagus induces secretion of numerous proinflammatory cytokines including IL-8, IL-6, IL-1 β , NFK β , and TNF- α ³⁷⁻³⁹. The chronic acid and inflammation induced by GERD damages the native stratified squamous epithelium⁴⁰ and, without repair, cells become necrotic, slough off and may be replaced with the metaplasia Barrett's esophagus. Barrett's esophagus can be viewed as a successful adaption to this chronic inflammatory exposure of GERD capable of increasing mucosal defense, however this adaptive epithelium may ultimately give rise to adenocarcinoma of the esophagus^{41,42}. Similar to GERD, metabolic syndrome is a constellation of phenotypes each of which contributes to a chronic inflammation state, and many of the same proinflammatory cytokines are elevated in the blood of individuals with metabolic syndrome including IL-6, IL-1 β , and TNF- α ^{18, 20, 21}. The chronic, systemic inflammation represented by metabolic syndrome is important in the etiology of cancer²⁵ and our findings suggest these processes may also contribute to the pathogenesis of Barrett's esophagus in the absence of symptomatic GERD. One conjecture is that the systemic inflammation of metabolic syndrome perhaps increases esophageal inflammation to a threshold beyond the capacity of normal cell function.

A previous study by Healy *et. al.*²² presented tentative evidence for an association between metabolic syndrome and Barrett's esophagus (n=118, 31% exposed) when compared with validated GERD controls (n=113, 20% exposed; $P=0.05$). Although our analysis comparing Barrett's esophagus to endoscopy controls does not substantiate this observation, our control group may be suboptimal for several reasons. First, Medicare data may fail to capture some index Barrett's esophagus diagnoses since the diagnosis code is not required for justification of the initial, diagnostic endoscopy and does not provide additional payment. In contrast, Healy *et al.* ensured GERD controls did not have Barrett's esophagus, thus maximizing their power to detect an association. Second, our endoscopy control group could be heterogeneous insofar as we are unable to discern the indications for endoscopy, which could include many non-GERD symptoms. Consequently the endoscopy controls may not be comparable to the GERD controls in the prior study. Therefore our results utilizing the endoscopy controls should be interpreted with caution.

Our data suggests that obesity, as part of metabolic syndrome increases the risk of Barrett's esophagus, independent of GERD. Other studies have also focused on clarifying the biological mechanisms of the association by elucidating the role of the obesity-related cytokines leptin and adiponectin. Adiponectin and leptin are key regulators of insulin sensitivity^{43, 44}. Serum levels of leptin and adiponectin may partially account for the

relationship between obesity and Barrett's esophagus⁴⁵, although studies have yielded inconsistent and sex-specific results^{46, 47}. We did not observe sex-specific results by GERD in our study (Supplementary Table 2). While outside the purview of this study, it is plausible that alterations in these cytokines are part of the constellation of metabolic syndrome and increase risk of Barrett's esophagus.

The strengths of this study include the population-based ascertainment of Medicare beneficiaries randomly selected from locations within the SEER registries. We were able to prospectively evaluate the presence of metabolic syndrome and identify incident cases of Barrett's esophagus within the Medicare data. Our case selection criteria were stringent and required record of both an endoscopy and diagnosis of Barrett's esophagus. Our population was also sufficient in size to enable stratification by GERD and sex. Importantly, to our knowledge this is the first population-based study to evaluate the association of metabolic syndrome and the risk of Barrett's esophagus.

While the SEER-Medicare provided a novel data source for our analysis, several limitations inherent to the data constrain the interpretation and generalizability of our results. First, our findings are restricted to those aged 65 years and older. Second, our definition of metabolic syndrome relied on medical billing which insufficiently captured obesity and smoking. Capture efficiency, however, should not differ by group—thus any imprecision caused underascertainment of risk factors is expected to bias results towards the null. Lastly, residual confounding resulting from inefficient identification of symptomatic GERD or due to the presence of asymptomatic acid reflux in our population could drive the association. However, low capture of symptomatic GERD is an unlikely explanation, since GERD prevalence in our Barrett's esophagus population (43%) is similar to those previously reported by detailed clinical studies at 33–44%^{48, 49} (Drs. Shyam Menon and Nigel Trudgill, unpublished data). Asymptomatic acid reflux is plausible and is a problem with self-report of GERD symptoms as a proxy of acid reflux exposure. But, since the severity of acid reflux is positively associated with both GERD symptoms¹² and risk of Barrett's esophagus⁵⁰⁻⁵², adjustment for symptomatic reflux should somewhat protect against this route of residual confounding. Symptomatic reflux is more likely to be diagnosed and would account for more severe and clinically relevant exposure. Nevertheless, residual confounding by asymptomatic acid reflux cannot be ruled out and further investigation of these hypotheses in other populations with a full range of ages and improved exposure ascertainment is necessary.

While not without limitations, our results and hypothesized paradigm are provocative. Despite the evidence that Barrett's esophagus is associated with GERD and proposed to be an protective adaptation to such^{42, 53}, typical GERD symptoms are the primary reason for endoscopy in only 33–44% of patients diagnosed with Barrett's esophagus^{48, 49} (Drs. Shyam Menon and Nigel Trudgill, unpublished data) and 20% do not have any detectable acid reflux when monitored by 24-hour pH-metry^{54, 55}. Our findings suggest that a systemic inflammatory state, represented by metabolic syndrome, could increase risk for Barrett's esophagus and thus represent an indirect causal pathway of obesity.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

ACKNOWLEDGMENTS

This work was supported by the Intramural Program of the National Cancer Institute at the National Institutes of Health and Department of Health and Human Services.

The authors would like to thank Dr. Brad Kendall and Dr. David Whitman for their critical review and valuable contributions during manuscript preparation.

References

1. DeMeester TR. Clinical biology of the Barrett's metaplasia, dysplasia to carcinoma sequence. *Surg Oncol.* 2001; 10:91–102. [PubMed: 11750228]
2. Sharma P, Falk GW, Weston AP, et al. Dysplasia and cancer in a large multicenter cohort of patients with Barrett's esophagus. *Clin Gastroenterol Hepatol.* 2006; 4:566–72. [PubMed: 16630761]
3. Surveillance, Epidemiology, and End Results (SEER) Program (www.seer.cancer.gov) SEER*Stat Database: Incidence - SEER 18 Regs Research National Cancer Institute, DCCPS, Surveillance Research Program, Surveillance Systems Branch, released April 2012, based on the November 2011 submission, May 2012
4. Cook MB, Shaheen NJ, Anderson LA, et al. Cigarette smoking increases risk of Barrett's esophagus: an analysis of the Barrett's and Esophageal Adenocarcinoma Consortium. *Gastroenterology.* 2012; 142:744–53. [PubMed: 22245667]
5. Taylor JB, Rubenstein JH. Meta-analyses of the effect of symptoms of gastroesophageal reflux on the risk of Barrett's esophagus. *Am J Gastroenterol.* 2010; 105:1729. 1730-7; quiz 1738. [PubMed: 20485283]
6. Cook MB, Greenwood DC, Hardie LJ, et al. A systematic review and meta-analysis of the risk of increasing adiposity on Barrett's esophagus. *Am J Gastroenterol.* 2008; 103:292–300. [PubMed: 17986313]
7. Corley DA, Kubo A, Levin TR, et al. Abdominal obesity and body mass index as risk factors for Barrett's esophagus. *Gastroenterology.* 2007; 133:34–41. quiz 311. [PubMed: 17631128]
8. Kubo A, Cook MB, Shaheen NJ, et al. Sex-specific associations between body mass index, waist circumference and the risk of Barrett's oesophagus: a pooled analysis from the international BEACON consortium. *Gut.* 2013; 62:1684–91. [PubMed: 23355549]
9. Zerbib F, Roman S, Ropert A, et al. Esophageal pH-impedance monitoring and symptom analysis in GERD: a study in patients off and on therapy. *Am J Gastroenterol.* 2006; 101:1956–63. [PubMed: 16848801]
10. Manterola C, Munoz S, Grande L, et al. Initial validation of a questionnaire for detecting gastroesophageal reflux disease in epidemiological settings. *J Clin Epidemiol.* 2002; 55:1041–5. [PubMed: 12464381]
11. Fuchs KH, DeMeester TR, Albertucci M. Specificity and sensitivity of objective diagnosis of gastroesophageal reflux disease. *Surgery.* 1987; 102:575–80. [PubMed: 3660234]
12. Bredenoord AJ, Weusten BL, Curvers WL, et al. Determinants of perception of heartburn and regurgitation. *Gut.* 2006; 55:313–8. [PubMed: 16120760]
13. Festa A, D'Agostino R Jr. Williams K, et al. The relation of body fat mass and distribution to markers of chronic inflammation. *Int J Obes Relat Metab Disord.* 2001; 25:1407–15. [PubMed: 11673759]
14. Tsigos C, Kyrou I, Chala E, et al. Circulating tumor necrosis factor alpha concentrations are higher in abdominal versus peripheral obesity. *Metabolism.* 1999; 48:1332–5. [PubMed: 10535400]

15. Hoyo C, Cook MB, Kamangar F, et al. Body mass index in relation to oesophageal and oesophagogastric junction adenocarcinomas: a pooled analysis from the International BEACON Consortium. *Int J Epidemiol.* 2012
16. Ryan AM, Duong M, Healy L, et al. Obesity, metabolic syndrome and esophageal adenocarcinoma: epidemiology, etiology and new targets. *Cancer Epidemiol.* 2011; 35:309–19. [PubMed: 21470937]
17. van Kruijsdijk RC, van der Wall E, Visseren FL. Obesity and cancer: the role of dysfunctional adipose tissue. *Cancer Epidemiology, Biomarkers and Prevention.* 2009; 18:2569–78.
18. Pradhan AD, Manson JE, Rifai N, et al. C-reactive protein, interleukin 6, and risk of developing type 2 diabetes mellitus. *JAMA.* 2001; 286:327–34. [PubMed: 11466099]
19. Nishida M, Moriyama T, Sugita Y, et al. Interleukin-10 associates with adiponectin predominantly in subjects with metabolic syndrome. *Circ J.* 2007; 71:1234–8. [PubMed: 17652887]
20. Despres JP, Lemieux I. Abdominal obesity and metabolic syndrome. *Nature.* 2006; 444:881–7. [PubMed: 17167477]
21. Berg AH, Scherer PE. Adipose tissue, inflammation, and cardiovascular disease. *Circ Res.* 2005; 96:939–49. [PubMed: 15890981]
22. Healy LA, Ryan AM, Pidgeon G, et al. Lack of differential pattern in central adiposity and metabolic syndrome in Barrett's esophagus and gastroesophageal reflux disease. *Dis Esophagus.* 2010; 23:386–91. [PubMed: 20353443]
23. Ryan AM, Healy LA, Power DG, et al. Barrett esophagus: prevalence of central adiposity, metabolic syndrome, and a proinflammatory state. *Ann Surg.* 2008; 247:909–15. [PubMed: 18520215]
24. Cowey S, Hardy RW. The metabolic syndrome: A high-risk state for cancer? *Am J Pathol.* 2006; 169:1505–22. [PubMed: 17071576]
25. Esposito K, Chiodini P, Colao A, et al. Metabolic Syndrome and Risk of Cancer: A systematic review and meta-analysis. *Diabetes Care.* 2012; 35:2402–11. [PubMed: 23093685]
26. Engels EA, Pfeiffer RM, Ricker W, et al. Use of Surveillance, Epidemiology, and End Results-Medicare Data to Conduct Case-Control Studies of Cancer Among the US Elderly. *Am J Epidemiol.* 2011; 174:860–70. [PubMed: 21821540]
27. Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report. *Circulation.* 2002; 106:3143–421. [PubMed: 12485966]
28. Welzel TM, Graubard BI, Zeuzem S, et al. Metabolic syndrome increases the risk of primary liver cancer in the United States: a study in the SEER-Medicare database. *Hepatology.* 2011; 54:463–71. [PubMed: 21538440]
29. Charlson ME, Pompei P, Ales KL, et al. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis.* 1987; 40:373–83. [PubMed: 3558716]
30. Deyo RA, Cherkin DC, Ciol MA. Adapting a clinical comorbidity index for use with ICD-9-CM administrative databases. *J Clin Epidemiol.* 1992; 45:613–9. [PubMed: 1607900]
31. Klabunde CN, Legler JM, Warren JL, et al. A refined comorbidity measurement algorithm for claims-based studies of breast, prostate, colorectal, and lung cancer patients. *Ann Epidemiol.* 2007; 17:584–90. [PubMed: 17531502]
32. SEER-Medicare: Calculation of Comorbidity Weights: National Cancer Institute, Health Services and Economics, Cancer Control and Population Sciences, December 2010
33. Hosmer, DW.; Lemeshow, S. *Applied logistic regression.* Wiley; New York: 2000.
34. Rothman, KJ.; Greenland, S.; Lash, TL. *Modern epidemiology.* Wolters Kluwer Health/Lippincott Williams & Wilkins; Philadelphia: 2008.
35. Kallel L, Bibani N, Fekih M, et al. Metabolic syndrome is associated with gastroesophageal reflux disease based on a 24-hour ambulatory pH monitoring. *Dis Esophagus.* 2011; 24:153–9. [PubMed: 20946134]
36. Lee YC, Yen AM, Tai JJ, et al. The effect of metabolic risk factors on the natural course of gastro-oesophageal reflux disease. *Gut.* 2009; 58:174–81. [PubMed: 18936105]

37. O’Riordan JM, Abdel-latif MM, Ravi N, et al. Proinflammatory cytokine and nuclear factor kappa-B expression along the inflammation-metaplasia-dysplasia-adenocarcinoma sequence in the esophagus. *Am J Gastroenterol.* 2005; 100:1257–64. [PubMed: 15929754]
38. Dvorakova K, Payne CM, Ramsey L, et al. Increased expression and secretion of interleukin-6 in patients with Barrett’s esophagus. *Clin Cancer Res.* 2004; 10:2020–8. [PubMed: 15041721]
39. Allen K, Jaeschke H, Copple BL. Bile acids induce inflammatory genes in hepatocytes: a novel mechanism of inflammation during obstructive cholestasis. *Am J Pathol.* 2011; 178:175–86. [PubMed: 21224055]
40. Spechler SJ. Clinical practice. Barrett’s Esophagus. *N Engl J Med.* 2002; 346:836–42. [PubMed: 11893796]
41. Sharma, P.; Sampliner, RE. Barrett’s esophagus and esophageal adenocarcinoma. Blackwell Pub.; Malden, Mass.: 2006.
42. Reid BJ, Li X, Galipeau PC, et al. Barrett’s oesophagus and oesophageal adenocarcinoma: time for a new synthesis. *Nat Rev Cancer.* 2010; 10:87–101. [PubMed: 20094044]
43. Chen SJ, Yen CH, Huang YC, et al. Relationships between Inflammation, Adiponectin, and Oxidative Stress in Metabolic Syndrome. *PLoS One.* 2012; 7:e45693. [PubMed: 23029185]
44. Kennedy A, Gettys TW, Watson P, et al. The metabolic significance of leptin in humans: gender-based differences in relationship to adiposity, insulin sensitivity, and energy expenditure. *J Clin Endocrinol Metab.* 1997; 82:1293–300. [PubMed: 9100610]
45. Thompson OM, Beresford SA, Kirk EA, et al. Serum leptin and adiponectin levels and risk of Barrett’s esophagus and intestinal metaplasia of the gastroesophageal junction. *Obesity (Silver Spring).* 2010; 18:2204–11. [PubMed: 20111023]
46. Kendall BJ, Macdonald GA, Hayward NK, et al. Leptin and the risk of Barrett’s oesophagus. *Gut.* 2008; 57:448–54. [PubMed: 18178609]
47. Mokrowiecka A, Daniel P, Jasinska A, et al. Serum Adiponectin, Resistin, Leptin Concentration and Central Adiposity Parameters in Barrett’s Esophagus Patients with and without Intestinal Metaplasia in Comparison to Healthy Controls and Patients with GERD. *Hepatogastroenterology.* 2012;59. [PubMed: 22260822]
48. Omer ZB, Ananthakrishnan AN, Nattinger KJ, et al. Aspirin protects against Barrett’s esophagus in a multivariate logistic regression analysis. *Clin Gastroenterol Hepatol.* 2012; 10:722–7. [PubMed: 22426086]
49. Menon S, Jayasena H, Nightingale P, et al. Influence of age and sex on endoscopic findings of gastroesophageal reflux disease: an endoscopy database study. *Eur J Gastroenterol Hepatol.* 23:389–95. [PubMed: 21448069]
50. Smith KJ, O’Brien SM, Smithers BM, et al. Interactions among smoking, obesity, and symptoms of acid reflux in Barrett’s esophagus. *Cancer Epidemiol Biomarkers Prev.* 2005; 14:2481–6. [PubMed: 16284367]
51. Lieberman DA, Oehlke M, Helfand M. Risk factors for Barrett’s esophagus in community-based practice. GORGE consortium. Gastroenterology Outcomes Research Group in Endoscopy. *Am J Gastroenterol.* 1997; 92:1293–7. [PubMed: 9260792]
52. Eisen GM, Sandler RS, Murray S, et al. The relationship between gastroesophageal reflux disease and its complications with Barrett’s esophagus. *Am J Gastroenterol.* 1997; 92:27–31. [PubMed: 8995932]
53. Orlando, RC. Mucosal Defense in Barrett’s Esophagus. *Barrett’s Esophagus and Esophageal Adenocarcinoma*: Blackwell Publishing Ltd; 2007. p. 60-72.
54. Gutschow CA, Bludau M, Vallbohmer D, et al. NERD, GERD, and Barrett’s esophagus: role of acid and non-acid reflux revisited with combined pH-impedance monitoring. *Dig Dis Sci.* 2008; 53:3076–81. [PubMed: 18438712]
55. Wolfgarten E, Putz B, Holscher AH, et al. Duodeno-gastric-esophageal reflux—what is pathologic? Comparison of patients with Barrett’s esophagus and age-matched volunteers. *J Gastrointest Surg.* 2007; 11:479–86. [PubMed: 17436133]

Table 1

Demographic characteristics of Barrett's esophagus cases, population controls and endoscopy-negative controls

	BE Cases N= 2,198		Population Controls N= 6,594			Endoscopy-negative controls N= 5,972		
	N	%	N	%	P Value	N	%	P Value
Mean Age (SD) **	76.6 (6.6)		76.7 (6.7)			76.7 (6.5)		
Male Sex **	1150	52.3%	3450	52.3%	1.00	3036	45.8%	<0.01
Race								
White	2010	91.5%	5672	86.0%	<0.01	4955	83.0%	<0.01
Black	42	1.9%	343	5.4%		448	7.5%	
Asian	51	2.3%	231	3.7%		290	4.9%	
Hispanic	46	2.1%	140	2.1%		121	2.0%	
Native American	11	0.5%	24	0.4%		16	0.3%	
Unknown/Other	38	1.7%	184	2.1%		142	2.3%	
Charlson Comorbidity Score								
None (0)	1316	59.9%	4578	69.4%	<0.01	3162	53.0%	<0.01
Low (1)	473	21.5%	1201	18.2%		1337	22.4%	
Moderate (2)	226	10.3%	473	7.2%		690	11.6%	
High (3+)	183	8.3%	342	5.2%		783	13.1%	
Medicaid Dual Enrollment	234	10.7%	805	12.2%	0.05	933	15.6%	<0.01
Smoking	252	11.5%	514	7.8%	< 0.01	741	12.4%	0.25
Gastroesophageal Reflux	954	43.4%	1081	16.4%	< 0.01	2327	39.0%	<0.01
Metabolic conditions								
Obesity	133	6.1%	295	4.5%	< 0.01	399	6.7%	0.34
Elevated fasting glucose	835	38.0%	2106	31.9%	< 0.01	2578	43.2%	<0.01
High blood pressure	1802	82.0%	4838	73.4%	< 0.01	5027	84.2%	0.09
Elevated triglycerides	1492	67.4%	3737	56.7%	< 0.01	3824	64.0%	<0.01
Metabolic syndrome *	642	29.1%	1567	23.8%	< 0.01	2018	33.8%	< 0.01

P-value for control groups compared to cases

Bold indicates statistically significant $P < 0.05$

** Matching factors, incomplete matching on sex for endoscopy controls

* NCEP-ATP III definition of 3 or more metabolic conditions

Table 2

Association between metabolic syndrome and Barrett's esophagus compared with population controls and endoscopy-negative controls

	BE vs. Population Controls		BE vs. Endoscopy-negative controls	
	Adjusted OR (95% CI)	P Value	Adjusted OR (95% CI)	P Value
Metabolic syndrome*	1.20 (1.07, 1.36)	<0.01	0.93 (0.83, 1.04)	0.20
Metabolic conditions				
Obesity	1.19 (0.95, 1.49)	0.13	0.98 (0.80, 1.21)	0.89
Elevated fasting glucose	1.24 (1.11, 1.38)	<0.01	0.93 (0.83, 1.03)	0.18
High blood pressure	1.37 (1.20, 1.56)	<0.01	0.98 (0.85, 1.12)	0.75
Elevated triglycerides	1.36 (1.22, 1.51)	<0.01	1.19 (1.07, 1.33)	<0.01
Number of conditions				
1	1.53 (1.27, 1.85)	<0.01	1.12 (0.91, 1.37)	0.28
2	1.87 (1.56, 2.24)	<0.01	1.26 (1.04, 1.53)	0.02
3	1.87 (1.54, 2.27)	<0.01	1.09 (0.89, 1.33)	0.41
4	2.57 (1.80, 3.68)	<0.01	1.20 (0.86, 1.68)	0.28

All models were adjusted for age, sex, race, registry, smoking, Medicaid dual enrollment, modified Charlson score, gastroesophageal reflux
P-value for control groups compared to cases

Bold indicates statistically significant *P*<0.05

* NCEP-ATP III definition of 3 or more metabolic conditions

Association between metabolic syndrome and Barrett's esophagus compared with population controls and stratified by gastroesophageal reflux (GERD) status

Table 3

	NO GERD					GERD						
	BE N= 1,244 (56.6%)		Population Controls N=5,513 (83.6%)		P Value	BE N= 954 (43.4%)		Population Controls N=1,081 (16.4%)		P Value		
	N	%	N	%		Adjusted OR (95% CI)	N	%	N		%	
Metabolic syndrome *	365	29.4	1243	22.5	1.34 (1.16, 1.54)	<0.01	277	29	340	30.7	0.91 (0.74, 1.12)	0.37
<i>p-value of effect modification</i>					<i>p= 0.0002</i>							
Metabolic conditions												
Obesity	67	5.4	234	4.2	1.18 (0.88, 1.57)	0.27	66	6.9	61	5.6	1.12 (0.77, 1.64)	0.55
Elevated fasting glucose	489	39.3	1696	30.8	1.40 (1.23, 1.60)	<0.01	346	36.3	410	37.9	0.95 (0.79, 1.15)	0.62
High blood pressure	991	79.7	3925	71.2	1.46 (1.25, 1.71)	<0.01	811	85.0	913	84.5	1.12 (0.87, 1.45)	0.38
Elevated triglycerides	824	66.2	3009	54.6	1.52 (1.34, 1.74)	<0.01	658	69.0	728	67.3	1.03 (0.85, 1.26)	0.75
Number of conditions												
1	262	21.1	1377	25	1.46 (1.16, 1.84)	<0.01	224	23.5	236	21.8	1.46 (0.98, 2.17)	0.06
2	489	39.3	1833	33.2	2.02 (1.63, 2.50)	<0.01	396	41.5	440	40.7	1.36 (0.93, 1.99)	0.11
3	329	26.4	1151	20.9	2.14 (1.70, 2.68)	<0.01	243	25.5	300	27.8	1.23 (0.82, 1.83)	0.32
4	36	2.9	92	1.7	2.66 (1.71, 4.13)	<0.01	34	3.6	24	2.2	1.91 (0.99, 3.67)	0.05

All models were adjusted for age, sex, race, registry, smoking, Medicaid dual enrollment, modified Charlson score

Bold indicates statistically significant $P<0.05$

* NCEP-ATP III definition of 3 or more metabolic conditions