Published in final edited form as:
Gut. 2009 November ; 58(11): 1460–1466. doi:10.1136/gut.2008.174508.

Body Mass Index and Barrett's Oesophagus in Women

Brian C. Jacobson, MD, MPH, **Andrew T. Chan, MD, MPH**, **Edward L. Giovannucci, MD, ScD**, and **Charles S. Fuchs, MD, MPH**
From the Section of Gastroenterology, Department of Medicine, Boston Medical Center (Dr. Jacobson); the Boston University School of Medicine (Dr. Jacobson); the Gastrointestinal Unit, Department of Medicine, Massachusetts General Hospital (Dr. Chan); The Department of Epidemiology and the Department of Nutrition, Harvard School of Public Health (Dr. Giovannucci); Cancer Epidemiology Program, Dana-Farber and Harvard Cancer Center (Drs. Chan and Fuchs); the Department of Medical Oncology, Dana-Farber Cancer Institute (Dr. Fuchs); and the Channing Laboratory, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School (Drs. Chan, Giovannucci, and Fuchs); all in Boston, MA, United States.

Abstract

Objective—Excess body mass is associated with symptoms of gastroesophageal reflux disease, and cross-sectional studies suggest an association between body mass index (BMI) and Barrett's oesophagus. We sought to prospectively examine the influence of BMI and other anthropomorphic measures on the risk for Barrett's oesophagus among women.

Design—Prospective cohort study.

Setting—Nurses' Health Study.

Participants—15,861 women without a history of cancer, who underwent upper gastrointestinal endoscopy for any reason between 1986 and 2004.

Main outcome measures—261 cases of pathologically confirmed specialised intestinal metaplasia within the oesophagus (Barrett's oesophagus). Self-reported data on weight were collected from biennial questionnaires. Self-reported height was collected in 1976, and self-reported waist and hip circumferences were collected in 1986.

Results—Compared to women with BMI 20–24.9 kg/m^2, women with BMI 25–29.9 had a multivariate odds ratio for Barrett's oesophagus of 0.92 (95% CI 0.66–1.27), women with BMI >30 had a multivariate odds ratio of 1.52 (95% CI 1.02–2.28), and women with BMI <20 had a multivariate odds ratio of 0.92 (95% CI 0.65–1.31). Results were similar when controlling for symptoms of gastroesophageal reflux, and among the entire Nurses' Health Study cohort (n=93,609) regardless of a history of endoscopy. In contrast, waist-to-hip ratio, waist circumference, and height did not appear to be associated with Barrett's oesophagus.

Conclusions—Obese, but not overweight, women appear to be at increased risk for Barrett's oesophagus.

Keywords

Barrett's oesophagus; body mass index; obesity

Address for correspondence and reprint requests: Brian C. Jacobson, MD, MPH, Boston University Medical Center, 88 East Concord Street, Room 7721, Boston, MA 02118, Phone: 617-638-6525, Fax: 617-638-6529, Email: brian.jacobson@bmc.org.

None of the authors have any conflicts of interest to report.

INTRODUCTION

Barrett's oesophagus is a metaplastic condition resulting from exposure of the oesophagus to refluxed gastric contents, particularly acid and possibly bile.[1, 2] It is postulated that denuded squamous mucosa is repopulated by columnar cells originating from pluripotent cells in the basal epithelium[3, 4] or circulating stem cells derived from bone marrow.[5] The prevalence of Barrett's oesophagus among patients undergoing upper gastrointestinal endoscopy in the United States is between 3 and 25%[6, 7, 8, 9] and 0.3% among the general population.[10] Barrett's oesophagus appears to have a male predominance, with a male to female ratio of 1.7–2.0:1[9, 11, 12, 13] and this may explain the paucity of data about women with this condition.

The prevalence of Barrett's oesophagus among patients with heartburn is higher than those without, supporting the role of acid-reflux in this disease.[9, 14, 15] In addition, factors associated with Barrett's oesophagus include increased duration of reflux symptoms, increased exposure of the oesophagus to refluxed gastric contents, hiatus hernia, and a defective lower oesophageal sphincter.[16, 17, 18] Barrett's oesophagus is also a precursor lesion for oesophageal adenocarcinoma, with an incidence of 0.4 to 0.5% per patient-year.[11, 19, 20, 21, 22, 23, 24, 25]

Increased body mass index (BMI) has been associated with an excess risk of gastroesophageal reflux disease (GORD), including symptoms of heartburn, erosive oesophagitis, and oesophageal adenocarcinoma.[26, 27, 28, 29, 30, 31, 32, 33] The rising prevalence of overweight and obesity in the United States[34] may therefore explain some of the increased incidence of Barrett's oesophagus[35, 36] and oesophageal adenocarcinoma, one of the few cancers whose incidence has been increasing steadily over the past several years.[37, 38, 39, 40]

Indeed, previous studies have suggested an association between BMI and Barrett's oesophagus. These studies, however, have been limited by their cross-sectional or retrospective case-control designs, and have had predominantly male populations.[8, 41, 42, 43, 44, 45] We sought to further clarify the relationship between excess body mass and Barrett's oesophagus in women using data collected prospectively as part of the Nurses' Health Study, a large, ongoing cohort study in which detailed information on weight and other health-related factors have been collected over 30 years. To further understand any association between BMI and Barrett's oesophagus, we also sought to explore the relative importance of body mass itself, body fat distribution (e.g. waist circumference and waist-to-hip ratio), and height (a marker of growth factor exposure).

METHODS

Study Population

The Nurses' Health Study cohort was established in 1976 when 121,700 female registered nurses, 30 to 55 years of age, completed a questionnaire about risk factors for cancer and cardiovascular disease. With an overall response rate exceeding 90%, participants have received follow-up questionnaires every two years to obtain information about personal habits (including detailed dietary information every four years), medical diagnoses and medication use.

Assessment of BMI and Other Exposures

We determined BMI - the weight in kilograms divided by the square of the height in meters- from measurements of height provided by participants in 1976 and from measurements of weight reported in 1976 and updated every two years thereafter. Waist and hip measurements were self-reported in 1986, and subsequently validated among a sample of 140 Nurses' Health Study cohort members.[46] Trained technicians visited these 140 participants twice, approximately 6 months apart, to measure weight and waist and hip circumferences. The correlation between self-report and the average of the technicians' two measurements was 0.97

for weight, 0.87 for waist circumference, 0.81 for hip circumference, and 0.66 for waist-to-hip ratio.

Smoking status, menopausal status, use of postmenopausal hormones, and history of cancer or diabetes were assessed in 1976 by self-report and updated every two years thereafter. Dietary information was first obtained using a semi-quantitative food frequency questionnaire in 1980, updated in 1984, 1986, and subsequently every four years thereafter. The Nurses' Health Study food frequency questionnaire has ranged in size over the years from 61 to over 120 items. This permitted calculations of daily caloric intake and alcohol use. Physical activity was assessed in 1980, 1986, 1988, 1992, 1994, 1996, and 2000. Each activity reported was measured in metabolic equivalent task (MET)-hours per week. One MET represents the energy expended during one hour of rest. In 1982, 1994 and every two years thereafter, participants were asked to indicate if they used histamine type 2 receptor antagonists "regularly in the past 2 years." Regular use of proton pump inhibitors was asked in 2000, 2002 and 2004. In 2002, Nurses' Health Study participants were asked if they "ever regularly had heartburn/acid-reflux one or more times a week." Caloric intake, alcohol use, physical activity, menopausal status, and GORD symptoms in this cohort have been validated previously.[27, 46, 47, 48, 49, 50]

Ascertainment of Cases

In 2002 and 2004 Nurses' Health Study participants were asked if they had ever undergone upper gastrointestinal endoscopy or been diagnosed with Barrett's oesophagus. We requested written permission to acquire endoscopy and pathology records from women reporting Barrett's oesophagus. A study physician, blinded to exposure information, reviewed records to extract information on the initial date of diagnosis of Barrett's oesophagus, the length of columnar-lined oesophagus seen at endoscopy, and the presence or absence of specialised intestinal metaplasia (SIM) documented in biopsies taken from the oesophagus. Our primary case definition included only women with oesophageal SIM of any length. Secondary case definitions included 1) women with SIM and at least 1cm of columnar-lined oesophagus, and 2) any woman with an oesophageal biopsy demonstrating SIM, columnar epithelium, or a pathology report simply stating "Barrett's oesophagus" without a microscopic description.

To verify that failure to report Barrett's oesophagus was a reliable indication that a participant did not have the condition, we requested written permission to acquire records from 200 randomly-selected women who reported an upper endoscopy but not Barrett's oesophagus. After one mailing attempt, we obtained records from 95 women. In none of these instances did the endoscopist suspect Barrett's oesophagus.

Statistical Analysis

To avoid detection or selection bias, our primary study population was restricted to those women who reported undergoing upper endoscopy during the study period (n=19,005), as only those who underwent endoscopy could be accurately classified as either having or not having Barrett's oesophagus. We excluded women with cancer (except non-melanoma skin cancer) prior to their index endoscopy (n=1,293), women who never provided height or weight (n=140), and those with a BMI <15 kg/m^2 (n=1,333). We excluded women whose endoscopy occurred prior to 1987 as waist and hip measurements were ascertained in 1986 (n=3). To avoid misclassification bias, we excluded women who reported Barrett's oesophagus, but for whom review of records failed to support a diagnosis of at least columnar-lined oesophagus (n=375).

Women were categorized according to categories of BMI (<20, 20–24.9, 25–29.9, and >30 kg/m^2) calculated by taking an updated cumulative average of BMI between 1976 and all available questionnaires up to the 2-year cycle prior to the index endoscopy. We used age- and multivariate-adjusted unconditional logistic regression to obtain odds ratios (OR) and 95%

confidence intervals for the risk of Barrett's oesophagus. Women with a BMI of 20–24.9 kg/m^2 served as the reference population. Multivariate models controlled for year of endoscopy in addition to the covariates described above. We performed several secondary analyses, all planned a priori, to verify the robustness of our findings. These included an analysis controlling for frequent GORD symptoms in 2002, an analysis restricted to women reporting frequent GORD symptoms, and an analysis using the entire NHS cohort regardless of history of endoscopy. In this last case, as we had no date of index endoscopy for most cohort members, we modeled data from our dietary baseline (1980) or the earliest relevant questionnaire.

We also conducted a stratified analysis to determine whether the risk associated with excess weight was modified by the use of acid-blocking medications. We performed a test for interaction by entering into the multivariate model the cross-product term of BMI and acid-blocker use, each as a categorical variable. To examine the effect of weight change on the risk of Barrett's oesophagus, we categorized women according to their difference in weight between 1976 and their index endoscopy. We calculated the ORs for Barrett's oesophagus among women categorized by quartiles of height, waist-to-hip ratio, and waist circumference. When calculating mean length of Barrett's oesophagus, reports describing only "tongue(s)" of Barrett's oesophagus, a "short-segment" Barrett's oesophagus, or an "irregular z-line" were considered to be 0.5cm in length. Finally, we assessed for an association between BMI and length of Barrett's oesophagus using Pearson's correlation coefficient.

Analyses were performed with SAS, version 9.1 (SAS Institute, Cary, North Carolina). All P values are two-sided. The current study was approved by the institutional review boards of Brigham and Women's Hospital and Boston University Medical Center.

RESULTS

Baseline Characteristics

Among 15,861 eligible women, we documented 261 pathologically confirmed cases of SIM, and an additional 80 cases with either columnar epithelium within the oesophagus or simply a pathologist's diagnosis of "Barrett's oesophagus" without documentation of SIM. Among the cases with SIM, 20 (8%) were diagnosed prior to 1994, 92 (35%) were diagnosed between 1994 and 1999, and 149 (57%) were diagnosed between 2000 and 2004. As a percentage of endoscopies during each timeframe, SIM was present in 0.6% of endoscopies prior to 1994, 1.6% of endoscopies between 1994 and 1999, and 2.2% of endoscopies between 2000 and 2004. Length was described to some extent by the endoscopist in 330/341 (97%) instances of columnar-lined oesophagus. Among those with segments <1 cm, the endoscopist had described only an "irregular z-line", a "short-segment Barrett's oesophagus", or "tongue(s)" of Barrett's oesophagus. The mean (SD) length of columnar-lined esophagus was 1.9 (2.6) cm, with 74 (22%) having a segment length >3 cm. There appeared to be no association between BMI and length of Barrett's oesophagus (r=0.06; p=0.32).

Among eligible women, 24% were overweight (BMI 25–29.9 kg/m^2) and 9% were obese (BMI >30 kg/m^2). Compared with lean women (BMI <25kg/m^2), overweight and obese women (BMI >25kg/m^2) were less likely to be current smokers (p<0.001), to use post-menopausal hormones (p<0.001), or to participate in regular vigorous exercise (p<0.001). Overweight and obese women consumed more calories (p=0.006), although less alcohol (p<0.001), and were more likely to have diabetes mellitus (p<0.001), experience symptoms of GORD (p<0.001), and use acid-blocking medications (p<0.001; Table 1).

BMI and Risk for Barrett's Oesophagus

We observed a significantly increased risk for Barrett's oesophagus among obese, but not overweight, women (Table 2). Compared with women having a BMI of 20 to 24.9 kg/m^2, those with BMI 25–29.9 kg/m^2 had a multivariate OR for Barrett's oesophagus of 0.92 (95% CI 0.66–1.27), while those with BMI >30 kg/m^2 had a multivariate OR of 1.52 (95% CI 1.02–2.28). Our findings were similar between age-adjusted univariate and multivariate models, suggesting minimal confounding by the other covariates tested (Table 2). The multivariate models presented yielded the same results as more complicated models controlling for a cumulative average of aspirin and non-steroidal anti-inflammatory drug use (data not shown).

We observed similar risks for Barrett's oesophagus when using a less-stringent definition of Barrett's oesophagus, requiring only the presence of columnar histology in an oesophageal biopsy (Table 2). When restricting the definition of Barrett's oesophagus to SIM of at least 1cm length, the risk-estimates were similar, but the association between obesity and Barrett's oesophagus was no longer statistically significant, likely owing to a smaller sample size (OR 1.75; 95% CI 0.97–3.14).

To minimize detection or selection biases, our primary analysis restricted eligibility to participants who had undergone upper endoscopy. Nonetheless, we conducted a secondary analysis that included all participants in the Nurses' Health Study, regardless of having an upper endoscopy (n=93,609). In this analysis, compared with women having a BMI of 20–24.9, the multivariate OR for Barrett's oesophagus among obese women (BMI >30 kg/m^2) was 1.55 (95% CI 1.04–2.29; Table 2). In all these analyses, excess risk for Barrett's oesophagus was only experienced by women with BMI >30 kg/m^2; women with BMI 25–29.9 kg/m^2 appeared to have the same risk as the reference population.

Controlling for frequent GORD symptoms did not materially alter the observed risks for Barrett's oesophagus, although the association between obesity and Barrett's oesophagus was no longer statistically significant. Compared with women having a BMI of 20 to 24.9 kg/m^2, those with BMI 25–29.9 kg/m^2 had a multivariate OR of 0.89 (95% CI 0.64–1.24), while those with BMI >30 kg/m^2 had a multivariate OR for Barrett's oesophagus of 1.46 (95% CI 0.98–2.20). These findings were similar in an analysis restricted only to women who reported frequent GORD symptoms in 2002 and had undergone upper endoscopy (n= 9,436 total; 224 cases; Table 2).

To further define the risk for Barrett's oesophagus among women with GORD symptoms, we stratified women according to whether or not they reported regular use of acid-blocking medications prior to their endoscopy. Among participants who reported regular use of acid-blocking medications prior to their index endoscopy, obese women had a non-significant multivariate OR for Barrett's oesophagus of 1.94 (95% CI 0.94–4.01) compared to those having a BMI of 20 to 24.9 kg/m^2. Formal testing revealed no evidence for an interaction between BMI and acid-blocker use (P value = 0.82).

We found no association between weight change and Barrett's oesophagus (Table 3). Compared to women whose weight remained stable between 1976 and their index endoscopy, women who gained over 50 pounds had a multivariate OR for Barrett's oesophagus of 1.08 (95% CI 0.64–1.83). This was similar when restricting the analysis to women with BMI <25kg/m^2 in 1976 (Table 3).

Waist Circumference, Waist-to-Hip Ratio, and Height

To evaluate whether other anthropomorphic measurements are also associated with Barrett's oesophagus, we categorized participants according to quartiles of waist-to-hip ratio, waist circumference and height. We observed no significant association between these measures and

Barrett's oesophagus (Table 4). Simultaneous inclusion of both BMI and waist-to-hip ratio in the same model failed to appreciably attenuate the ORs for either variable (data not shown). A secondary analysis using clinically-meaningful measures of waist circumference and waist-to-hip ratios[51] also failed to demonstrate any significant association between these measures and Barrett's oesophagus. For example, compared to those women with a waist circumference of <80cm, the multivariate odds ratios for those with waist circumference of 80cm and 88cm were 0.93 (95%CI 0.62–1.39) and 0.99 (95% CI 0.63–1.55) respectively.

DISCUSSION

We found a positive association between obesity and Barrett's oesophagus among a large cohort of women who underwent upper endoscopy for any reason. The observed risk was similar when restricting our analyses to women with frequent GORD symptoms and those who regularly took acid-blocking medications prior to their index endoscopy. Controlling for other known or suspected risk factors for Barrett's oesophagus did not alter these findings. This risk for Barrett's oesophagus appears limited to obesity, as overweight women had a risk similar to women with BMI 20–24.9 kg/m^2. Waist-to-hip ratio, waist circumference, and height did not appear to be strongly associated with Barrett's oesophagus in this cohort. We also noted an increasing temporal trend in the percentage of endoscopies during which Barrett's oesophagus was diagnosed. However we were unable to determine whether this was due to an increased prevalence of disease or an increased awareness by endoscopists.

Previous studies have documented an association between BMI and GORD. The risk for GORD symptoms rises progressively with increasing BMI, even among normal weight individuals.[27] Erosive oesophagitis and oesophageal adenocarcinoma have also been prospectively associated with BMI.[31, 33, 52] Various mechanisms have been proposed to explain these associations, including increased numbers of transient lower oesophageal sphincter relaxations[53], increased gastro-oesophageal pressure gradients[54], an increased prevalence of hiatus hernia[55], and excess production of endogenous oestrogen.[28, 49]

It is therefore reasonable to consider that the observed risk between BMI and Barrett's oesophagus is primarily mediated through increased gastroesophageal reflux. However, the epidemiology of GORD suggests a more complex story. While men and women report GORD symptoms with equal frequency [56], men are approximately twice as likely as women to have Barrett's oesophagus [57], and five to eight times as likely to develop oesophageal adenocarcinoma.[58]

In the present study, our results were similar even after accounting for GORD symptoms and the previous use of acid-blocking medications, suggesting obesity may play a role in Barrett's metaplasia beyond the promotion of GORD. This conclusion differs from that of a recent meta-analysis of previously unpublished data culled from studies designed to answer various questions about either esophageal adenocarcinoma or Barrett's oesophagus.[59] The authors found no association between BMI and Barrett's oesophagus when Barrett's cases were compared to controls with esophagitis or positive esophageal pH monitoring. In our study, we attempted to address this by performing a secondary analysis limiting the entire cohort to those with frequent GORD symptoms. In this case, the association between obesity (defined by a cumulative average BMI, assessed prospectively over many years) and Barrett's oesophagus remained, and was consistent with the risk observed among the entire endoscopy cohort and the entire Nurses' Health Study population.

The difference between our study and the meta-analysis may reflect the choice of control population. For example, if esophagitis itself is associated with obesity, the use of patients with esophagitis as controls may yield a null result, even though obesity could be associated with

both esophagitis and Barrett's oesophagus.[60] However, we also acknowledge that GORD symptoms were assessed among the entire Nurses' Health Study population in 2002 only. We therefore relied on participants' recollection of prior symptoms throughout their life, making our GORD symptom analyses cross-sectional in design. Nonetheless, we prospectively examined the association between obesity and Barrett's oesophagus among regular users of acid-suppressing medications, finding a multivariate OR for Barrett's oesophagus of 1.94 (95% CI 0.94–4.01). While not statistically significant, the risk estimate suggests that obesity itself is independently associated with Barrett's oesophagus.

It is intriguing to consider gender differences in body fat distribution when studying the association between BMI and Barrett's oesophagus. For example, overweight and obese men tend to have more centralised, visceral fat, while women deposit more body fat in their subcutaneous tissues. This may partly explain why measures of fat distribution appeared more strongly associated with Barrett's oesophagus than BMI among predominantly male populations[41,43,61], while BMI itself may be more important among women. Visceral fat, as observed to a greater extent among men than women, is more active in the production of leptin and adiponectin, two adipokines that have been implicated in the pathogenesis of Barrett's oesophagus.[62, 63, 64, 65] This may also help clarify why both overweight and obese men experience excess risk for Barrett's oesophagus[41,43], while we observed excess risk only among obese women.

The strengths of our study include its prospective collection of exposure variables (thereby avoiding the potential biases inherent in cross-sectional and retrospective analyses), repeated assessments of BMI, detailed data on potential confounders, and a large number of cases. Nevertheless, we acknowledge certain limitations. We relied on self-reported measures of height, weight, and waist and hip circumference. However, these measures have been validated previously in our cohort.{Rimm, 1990 #75} Furthermore, our use of an updated cumulative average of BMI as our primary exposure limits the effects of year-to-year variation and inconsistencies in reporting accuracy. Waist and hip measurements were assessed only in 1986, and therefore were not updated. However, as all participants had their index endoscopy after 1986, we were able to maintain a prospective design.

Our definition of Barrett's oesophagus was based upon review of endoscopy and pathology reports, but did not include central review of pathology specimens, potentially resulting in misclassification bias. However, in a recent study of BMI and Barrett's oesophagus [41], independent pathologist review confirmed SIM in 91% of 616 cases identified in a manner similar to ours.[70] We also employed three different definitions of Barrett's oesophagus to verify that our findings were robust. The first, requiring the presence of SIM, is the standard definition of Barrett's oesophagus used in the United States.[71] The second definition required the presence of at least 1 cm of columnar epithelium with documented SIM. This should have increased the specificity of our definition by excluding cases of intestinal metaplasia of the gastroesophageal junction, a potentially distinct entity.[72] The third definition of Barrett's oesophagus required only the presence of columnar histology, as currently used by the British Society of Gastroenterology.[73]

In some of our secondary analyses, the association between obesity and Barrett's oesophagus was no longer statistically significant. However, the odds ratios in all cases were similar to our primary analysis, suggesting loss of significance reflected smaller numbers of participants.

In summary, we found that obese, but not overweight, women are at increased risk for Barrett's oesophagus. This risk did not appear to be explained solely by body fat distribution. These findings differ from observations among predominantly male cohorts wherein central adiposity may account for much of the risk. As the predominant pattern of body fat distribution differs

between men and women, (i.e. central versus peripheral, respectively) this may account for the skewed male to female preponderance of Barrett's oesophagus. Further studies are needed to determine if significant weight loss can decrease the risk for Barrett's oesophagus.

ACKNOWLEDGEMENT

The sponsors had no role in the design and conduct of the study; collection, management, analyses, and interpretation of the data; or preparation, review, or approval of the manuscript.

FUNDING

This work was supported by the National Cancer Institute [CA087969]; and the National Institutes of Diabetes and Digestive and Kidney Diseases [DK070706 to BCJ].

REFERENCES

1. Caldwell MT, Lawlor P, Byrne PJ, Walsh TN, Hennessy TP. Ambulatory oesophageal bile reflux monitoring in Barrett's oesophagus. British Journal of Surgery 1995;82:657–660. [PubMed: 7613943]
2. Vaezi MF, Richter JE. Role of acid and duodenogastroesophageal reflux in gastroesophageal reflux disease. Gastroenterology 1996;111:1192–1199. [PubMed: 8898632]
3. Jankowski J, Wright N, Meltzer S, Triadafilopoulos G, Geboes K, Casson A, et al. Molecular evolution of the metaplasia-dysplasia-adenocarcinoma sequence in the esophagus. Am J Pathol 1999;154:965–973. [PubMed: 10233832]
4. Boch J, Shields H, Antonioli D, Zwas F, Sawhney R, Trier J. Distribution of cytokeratin markers in Barrett's specialized columnar epithelium. Gastroenterology 1997;112:760–765. [PubMed: 9041237]
5. Okamoto R, Yajima T, Yamazaki M, Kanai T, Mukai M, Okamoto S, et al. Damaged epithelia regenerated by bone marrow-derived cells in the human gastrointestinal tract. Nature Med 2002;8:1011–1017. [PubMed: 12195435]
6. Cameron A. Epidemiology of columnar-lined esophagus and adenocarcinoma. Gastroenterol Clin North Am 1997;26:487–494. [PubMed: 9309399]
7. Winters C, Spurling T, Cohbanian S, Curtis D, Esposito R, Hacker J, et al. Barrett's esophagus: a prevalent, occult complication of gastroesophageal reflux disease. Gastroenterology 1987;92:118–124. [PubMed: 3781178]
8. Gerson L, Shetler K, Triadafilopoulos G. Prevalence of Barrett's esophagus in asymptomatic individuals. Gastroenterology 2002;123:461–467. [PubMed: 12145799]
9. Rex DK, Cummings OW, Shaw M, Cumings MD, Wong RKH, Vasudeva RS, et al. Screening for Barrett's esophagus in colonoscopy patients with and without heartburn. Gastroenterology 2003;125:1670–1677. [PubMed: 14724819]
10. Cameron A, Zinsmeister A, Ballard D, Carney J. Prevalence of columnar-lined (Barrett's) esophagus: comparison of population-based and autopsy findings. Gastroenterology 1990;99:918–922. [PubMed: 2394347]
11. O'Connor J, Falk GW, Richter JE. The incidence of adenocarcinoma and dysplasia in Barrett's esophagus. Am J Gastroenterol 1999;94:2037–2042. [PubMed: 10445525]
12. Spechler S, Zeroogian J, Antonioli D, Wang H, Goyal R. Prevalence of metaplasia at the gastro-oesophageal junction. Lancet 1994;344:1533–1536. [PubMed: 7983953]
13. Caygill C, Reed P, McIntyre A, Hill M. The UK national barrett's oesophagus registry: a study between two centres. Eur J Cancer Prev 1998;7:161–163. [PubMed: 9818779]
14. Shaheen N, Ransohoff D. Gastroesophageal reflux, Barrett esophagus, and esophageal cancer. JAMA 2002;287:1972–1981. [PubMed: 11960540]
15. Spechler S. Barrett's esophagus. N Engl J Med 2002;346:836–842. [PubMed: 11893796]
16. Campos GMR, DeMeester SR, Peters JH, Oberg S, Crookes PF, Hagen JA, et al. Predictive factors of Barrett esophagus: multivariate analysis of 502 patients with gastroesophageal reflux disease. Arch Surg 2001;136:1267–1273. [PubMed: 11695971]

17. Eisen GM, Sandler RS, Murray S, Gottfried M. The relationship between gastroesophageal reflux disease and its complications with Barrett's esophagus. Am J Gastroenterol 1997;92:27–31. [PubMed: 8995932]
18. Lieberman DA, Oehlke M, Helfand M. Risk factors for Barrett's esophagus in community-based practice. Am J Gastroenterol 1997;92:1293–1297. [PubMed: 9260792]
19. Spechler SJ, Robbins AH, Rubins HB, Vincent ME, Heeren T, Doos WG, et al. Adenocarcinoma and Barrett's esophagus: an overrated risk? Gastroenterology 1984;87:927–933. [PubMed: 6468881]
20. Cameron A, Ott B, Payne W. The incidence of adenocarcinoma in columnar-lined (Barrett's) esophagus. N Engl J Med 1985;313:857–859. [PubMed: 4033716]
21. Spechler S, Lee E, Ahnen D, Goyal R, Hirano I, Ramirez F, et al. Long-term outcome of medical and surgical therapies for gastroesophageal reflux disease: follow-up of a randomized controlled trial. JAMA 2001;285:2331–2338. [PubMed: 11343480]
22. Corey K, Schmitz S, Shaheen N. Does a surgical antrireflux procedure decrease the incidence of esophageal adenocarcinoma in Barrett's esophagus? A meta-analysis. Am J Gastroenterol 2003;98:2390–2394. [PubMed: 14638338]
23. Shaheen N, Crosby M, Bozymski E, Sandler R. Is there publication bias in the reporting of cancer risk in Barrett's esophagus? Gastroenterology 2000;119:333–338. [PubMed: 10930368]
24. Murray L, Watson P, Johnston B, SLoan J, Mainie I, Gavin A. Risk of adenocarcinoma in Barrett's esophagus: population based study. BMJ 2003;327:534–535. [PubMed: 12958113]
25. Conio M, Blanchi S, Lapertosa G, Ferraris R, Sablich R, Marchi S, et al. Long-term endoscopic surveillance of patients with Barrett's esophagus Incidence of dysplasia and adenocarcinoma: A prospective study. Am J Gastroenterol 2003;98:1931–1939. [PubMed: 14499768]
26. Hampel H, Abraham N, El-Serag H. Meta-analysis: Obesity and the risk for gastroesophageal reflux disease and its complications. Ann Intern Med 2005;143:199–211. [PubMed: 16061918]
27. Jacobson BC, Somers SC, Fuchs CS, Kelly CP, Camargo CA Jr. Body-mass index and symptoms of gastroesophageal reflux in women. N Engl J Med 2006;354:2340–2348. [PubMed: 16738270]
28. Nilsson M, Johnsen R, Ye W, Hveem K, Lagergren J. Obesity and Estrogen as Risk Factors for Gastroesophageal Reflux Symptoms. JAMA 2003;290:66–72. [PubMed: 12837713]
29. Nilsson M, Lundegardh G, Carling L, Ye W, Lagergren J. Body mass and reflux esophagitis: an oestrogen-dependent association? Scand J Gastroenterol 2002;37:626–630. [PubMed: 12126237]
30. Corley DA, Kubo A, Zhao W. Abdominal Obesity and the Risk of Esophageal and Gastric Cardia Carcinomas. Cancer Epidemiol Biomarkers Prev 2008;17:352–358. [PubMed: 18268119]
31. Reeves G, Pirie K, Beral V, Green J, Spencer E, Bull D. Cancer incidence and mortality in relation to body mass index in the Million Women Study: cohort study. BMJ 2007;335:1134–1139. [PubMed: 17986716]
32. Lagergren J, Bergstrom R, Nyren O. Association between body mass and adenocarcinoma of the esophagus and gastric cardia. Ann Intern Med 1999;130:883–890. [PubMed: 10375336]
33. Merry A, Schouten L, Goldbohm R, van den BrandtP. Body mass index, height and risk of adenocarcinoma of the oesophagus and gastric cardia: a prospective cohort study. Gut 2007;56:1503–1511. [PubMed: 17337464]
34. Ogden C, Carroll M, Curtin L, McDowell M, Tabak C, Flegal K. Prevalence of overweight and obesity in the United States, 1999–2004. JAMA 2006;295:1549–1555. [PubMed: 16595758]
35. Prach AT, MacDonald TA, Hopwood DA, Johnston DA. Increasing incidence of Barrett's oesophagus: education, enthusiasm, or epidemiology? Lancet 1997;350:f933.
36. van Soest E, Dieleman J, Siersema P, Sturkenboom M, Kuipers E. Increasing incidence of Barrett's oesophagus in the general population. Gut 2005;54:1062–1066. [PubMed: 15857935]
37. Devesa S, Blot WJ, Fraumeni JF. Changing patterns in the incidence of esophageal and gastric carcinoma in the United States. Cancer 1998;83:2049–2053. [PubMed: 9827707]
38. Blot WJ, Devesa SS, Kneller RW, Fraumeni JF. Rising incidence of adenocarcinoma of the esophagus and gastric cardia. JAMA 1991;265:1287–1289. [PubMed: 1995976]
39. Daly J, Karnell L, Menck H. National cancer data base report on esophageal carcinoma. Cancer 1996;78:1820–1828. [PubMed: 8859198]

40. Botterweck AA, Schouten LJ, Volovics A, Dorant E, van den Brandt PA. Trends in incidence of adenocarcinoma of the oesophagus and gastric cardia in ten European countries. Int J Epidemiol 2000;29:645–654. [PubMed: 10922340]
41. Corley DA, Kubo A, Levin T, Block G, Habel L, Zhao W, et al. Abdominal obesity and body mass index as risk factors for Barrett's esophagus. Gastroenterology 2007;133:34–41. [PubMed: 17631128]
42. Stein DJ, El-Serag H, Kuczynski J, Kramer JR, Sampliner R. The associaiton of body mass index with Barrett's esophagus. Aliment Pharmacol Ther 2005;22:1005–1010. [PubMed: 16268976]
43. Edelstein Z, Farrow DC, Bronner M, Rosen S, Vaughan TL. Central adiposity and risk of Barrett's esophagus. Gastroenterology 2007;133:403–411. [PubMed: 17681161]
44. El-Serag H, Graham D, Satia J, Rabeneck L. Obesity is an independent risk factor for GERD symptoms and erosive esophagitis. Am J Gastroenterol 2005;100:1243–1250. [PubMed: 15929752]
45. Smith KJ, O'Brien SM, Smithers BM, Gotley DC, Webb PM, Green AC, et al. Interactions among smoking, obesity, and symptoms of acid reflux in Barrett's esophagus. Cancer Epidemiol Biomarkers Prev 2005;14:2481–2486. [PubMed: 16284367]
46. Rimm EB, Stampfer MJ, Colditz GA, Chute CG, Litin LB, Willett WC. Validity of self-reported waist and hip circumferences in men and women. Epidemiology 1990;1:466–473. [PubMed: 2090285]
47. Wolf AM, Hunter DJ, Colditz GA, Manson JE, Stampfer MJ, Corsano KA, et al. Reproducibility and validity of a self-administered physical activity questionnaire. Int J Epidemiol 1994;23:991–999. [PubMed: 7860180]
48. Willett WC, Sampson L, S MJ. Reproducibility and validity of a semiquantitative food frequency questionnaire. Am J Epidemiol 1985;122:51–65. [PubMed: 4014201]
49. Jacobson B, Moy B, Colditz GA, Fuchs CS. Postmenopausal hormone use and symptoms of gastroesophageal reflux. Arch Intern Med 2008;168:1798–1804. [PubMed: 18779468]
50. Colditz G, Stampfer M, Willett W, Stason W, Rosner B, Hennekens CH. Reproducibility and validity of self-reported menopausal status in a prospective cohort study. Am J Epidemiol 1987;126:319–325. [PubMed: 3605058]
51. Lean M, Han T, Morrison C. Waist circumference as a measure for indicating need for weight management. BMJ 1995;311:158–161. [PubMed: 7613427]
52. Ruhl CR, Everhart JE. Overweight, but not high dietary fat intake, increases risk of gastroesophageal reflux disease hospitalization: The NHANES I epidemiologic followup study. Ann Epidemiol 1999;9:424–435. [PubMed: 10501410]
53. Wu J, Mui L, Cheung C, Chan Y, Sung J. Obesity in associated with increased transient lower esophageal sphincter relaxation. Gastroenterology 2007;132:883–889. [PubMed: 17324403]
54. Pandolfino J, El-Serag H, Zhang Q, Shah N, Ghosh S, Kahrilas P. Obesity: a challenge to esophagogastric junction integrity. Gastroenterology 2006;130:639–649. [PubMed: 16530504]
55. Wilson L, Ma W, Hirshowitz B. Association of obesity with hiatal hernia and esophagitis. Am J Gastroenterol 1999;94:2840–2844. [PubMed: 10520831]
56. Locke GR, Talley NJ, Fett SL, Zinsmeister AR, Melton LJ. Prevalence and clinical spectrum of gastroesophageal reflux: a population-based study in Olmsted County, Minnesota. Gastroenterology 1997;112:1448–1456. [PubMed: 9136821]
57. Cook M, Wild C, Forman D. A Systematic Review and Meta-Analysis of the Sex Ratio for Barrett's Esophagus, Erosive Reflux Disease, and Nonerosive Reflux Disease. Am J Epidemiol 2005;162:1050–1060. [PubMed: 16221805]
58. El-Serag HB, Mason AC, Petersen N, Key CR. Epidemiological differences between adenocarcinoma of the oesophagus and adenocarcinoma of the gastric cardia in the USA. Gut 2002;50:368–372. [PubMed: 11839716]
59. Cook M, Greenwood D, Hardie L, Wild C, Forman D. 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]
60. Moayyedi P. Barrett's esophagus and obesity: the missing part of the puzzle. Am J Gastroenterol 2008;103:301–303. [PubMed: 18289199]

61. El-Serag H, Kvapil P, Hacken-Bitar J, Kramer JR. Abdominal obesity and the risk of Barrett's esophagus. Am J Gastroenterol 2005;100:2151–2156. [PubMed: 16181362]
62. Francois F, Roper J, Goodman AJ, Pei Z, Ghumman M, Mourad M, et al. The association of gastric leptin with oesophageal inflammation and metaplasia. Gut 2008;57:16–24. [PubMed: 17761783]
63. Kendall BJ, Macdonald GA, Hayward NK, Prins JB, Brown I, Walker N, et al. Leptin and the risk of Barrett's oesophagus. Gut 2008;57:448–454. [PubMed: 18178609]
64. Ogunwobi O, Mutungi G, Beales IL. Leptin stimulates proliferation and inhibits apoptosis in Barrett's esophageal adenocarcinoma cells by cyclooxygenase-2-dependent, prostaglandin-E2-mediated transactivation of the epidermal growth factor receptor and c-Jun NH2-terminal kinase activation. Endocrinology 2006;147:4505–4516. [PubMed: 16740977]
65. Rubenstein JH, Dahlkemper A, Kao JY, Zhang M, Morgenstern H, McMahon L, et al. A pilot study of the association of low plasma adiponectin and Barrett's esophagus. Am J Gastroenterol 2008;103:1358–1364. [PubMed: 18510610]
66. Li TY, Rana JS, Manson JE, Willett WC, Stampfer MJ, Colditz GA, et al. Obesity as compared with physical activity in predicting risk of coronary heart disease in women. Circulation 2006;113:499–506. [PubMed: 16449729]
67. Giovannucci E, Colditz GA, Stampfer MJ, Willett WC. Physical activity, obesity, and risk of colorectal adenoma in women (United States). Cancer Causes Control 1996;7:253–263. [PubMed: 8740738]
68. Michaud DS, Giovannucci E, Willett WC, Colditz GA, Stampfer MJ, Fuchs CS. Physical activity, obesity, height, and the risk of pancreatic cancer. JAMA 2001;286:921–929. [PubMed: 11509056]
69. Huang Z, Willett WC, Colditz GA, Hunter DJ, Manson JE, Rosner B, et al. Waist circumference, waist:hip ratio, and risk of breast cancer in the Nurses' Health Study. Am J Epidemiol 1999;150:1316–1324. [PubMed: 10604774]
70. Corley DA, Kubo A, DeBoer J, Rumore G. Diagnosing Barrett's esophagus: reliability of clinical and pathological diagnoses. Gastrointest Endosc. in press
71. Wang K, Sampliner R. Updated Guidelines 2008 for the diagnosis, surveillance, and therapy of Barrett's esophagus. Am J Gastroenterol 2008;103:788–797. [PubMed: 18341497]
72. Spechler SJ. The role of gastric carditis in metaplasia and neoplasia at the gastroesophageal junction. Gastroenterology 1999;117:218–228. [PubMed: 10381931]
73. Playford RJ. New British Society of Gastroenterology (BSG) guidelines for the diagnosis and management of Barrett's oesophagus. Gut 2006;55:f442.

Table 1

Characteristics of the Study Cohort*

Characteristic	Body Mass Index (kg/m^2)			
	<20	20–24.9	25–29.9	30+
Participants, n	3275	7312	3793	1481
Age	62 (8)	63 (8)	63 (8)	62 (7)
Smoking status, %				
Never	42	44	46	47
Former	45	46	46	47
Current	13	10	8	6
Regular vigorous exercise, %†	38	40	35	28
Calories consumed/d	1730 (525)	1737 (509)	1754 (535)	1777 (535)
Alcohol use, g/d	5 (9)	5 (9)	4 (8)	2 (6)
Postmenopausal, %‡	93	93	94	94
Never used hormones,%	25	24	29	36
Past use of hormones,%	23	25	26	26
Current use of hormones,%	52	51	45	39
Diabetes, %	3	3	8	15
Heartburn/acid-reflux symptoms, %‖	55	59	64	65
Regular use of acid-suppression medication, %§	14	15	20	22

*Values were calculated from the most recent questionnaire before index endoscopy except heartburn/acid-reflux symptoms (asked only in 2002) and body mass index which represents a cumulative average between 1976 and the most recent questionnaire before endoscopy. Continuous variables are given as means (SD).

†Regular vigorous exercise was defined as vigorous physical activity (enough to work up a sweat) for 1 or more days per week or for 10.6 or more metabolic equivalents per week.

‡Hormones are defined as postmenopausal oestrogen or oestrogen and progesterone preparations. Percentage of never, past, and current use was calculated among postmenopausal women only.

‖Heartburn/acid-reflux symptoms experienced regularly, 1 or more times a week

§Acid-suppression medications included histamine type-2 receptor antagonists or proton-pump inhibitors used regularly.

Table 2

Odds Ratios for Barrett's Oesophagus According to Body Mass Index

	Body Mass Index (kg/m^2)			
	<20	**20–24.99**	**25–29.99**	**≥30**
Specialised Intestinal Metaplasia Cases/women, n/n	50/3,261	117/7,275	58/3,774	36/1,471
Age-adjusted OR (95% CI)	0.98 (0.70–1.36)	1.0	0.94 (0.68–1.29)	1.56 (1.07–2.27)
Multivariate OR (95% CI)	0.92 (0.65–1.31)	1.0	0.92 (0.66–1.27)	1.52 (1.02–2.28)
Specialised Intestinal Metaplasia ≥ 1cm Cases/women, n/n	21/3,246	51/7,246	20/3,755	17/1,462
Age-adjusted OR (95% CI)	0.93 (0.56–1.55)	1.0	0.74 (0.44–1.25)	1.65 (0.95–2.87)
Multivariate OR (95% CI)	0.89 (0.52–1.50)	1.0	0.76 (0.45–1.29)	1.75 (0.97–3.14)
Columnar Histology with or without Specialised Intestinal Metaplasia Cases/women, n/n	64/3,275	154/7,312	77/3,793	46/1,481
Age-adjusted OR (95% CI)	0.95 (0.71–1.27)	1.0	0.95 (0.72–1.25)	1.51 (1.08–2.11)
Multivariate OR (95% CI)	0.90 (0.66–1.23)	1.0	0.93 (0.70–1.24)	1.49 (1.04–2.13)
Specialised Intestinal Metaplasia among Women with Frequent GORD Symptoms* Cases/women, n/n	37/1,806	100/4,271	51/2,411	36/948
Age-adjusted OR (95% CI)	0.90 (0.61–1.31)	1.0	0.89 (0.63–1.25)	1.67 (1.13–2.47)
Multivariate OR (95% CI)	0.92 (0.62–1.37)	1.0	0.89 (0.62–1.26)	1.66 (1.09–2.51)
Specialised Intestinal Metaplasia among the Entire NHS Cohort Regardless of Endoscopy† Cases/women, n/n	29/9,407	143/52,084	54/21,785	39/10,333
Age-adjusted OR (95% CI)	1.11 (0.75–1.66)	1.0	0.92 (0.67–1.26)	1.39 (0.98–1.98)
Multivariate OR (95% CI)	1.16 (0.76–1.78)	1.0	1.05 (0.75–1.47)	1.55 (1.04–2.29)

*Control population included women who underwent upper gastrointestinal endoscopy AND reported symptoms of heartburn/acid-reflux at least weekly.

†Control population included all women in the Nurses Health Study regardless of having undergone upper gastrointestinal endoscopy.

Multivariate ORs are adjusted for year of endoscopy; age (5-year categories); physical activity (<1.7, 1.7 to 4.5, 4.6 to 10.5, 10.6 to 22.1, and >22.1 metabolic equivalent task score per week); smoking history (never, former, current); daily caloric intake/day (quartiles); alcohol consumption (0, 0.1 to 4.9, 5.0 to 15.0, and >15g/day); postmenopausal hormone use (premenopausal, never, past, current); and a history of diabetes. GORD = gastroesophageal reflux disease; NHS = Nurses' Health Study

Table 3

Odds Ratios for Barrett's Oesophagus Based on Change in Weight Between 1976 and the Index Endoscopy

Entire Upper Gastrointestinal Endoscopy Cohort					
	Lost > 5 lbs	**Stable Weight**	**Gained 5–24.9 lbs**	**Gained 25–49.9 lbs**	**Gained 50+ lbs**
Cases/Women, (n/n)	19/1375	46/2942	92/6038	67/3773	26/1224
Multivariate OR (95% CI)	0.80 (0.46–1.39)	1.0	0.91 (0.63–1.31)	0.95 (0.64–1.41)	1.08 (0.64–1.83)
Participants of the Upper Gastrointestinal Endoscopy Cohort with BMI <25 kg/m^2 in 1976					
	Lost > 5 lbs	**Stable Weight**	**Gained 5–24.9 lbs**	**Gained 25–49.9 lbs**	**Gained 50+ lbs**
Cases/Women, (n/n)	6/624	35/2132	71/4617	41/2612	18/624
Multivariate OR (95% CI)	0.53 (0.22–1.29)	1.0	0.86 (0.57–1.32)	0.75 (0.46–1.22)	1.21 (0.65–2.26)

Multivariate ORs are adjusted for year of endoscopy; age (5-year categories); physical activity (<1.7, 1.7 to 4.5, 4.6 to 10.5, 10.6 to 22.1, and >22.1 metabolic equivalent task score per week); smoking history (never, former, current); daily caloric intake/day (quartiles); alcohol consumption (0, 0.1 to 4.9, 5.0 to 15.0, and >15g/day); postmenopausal hormone use (premenopausal, never, past, current); and history of diabetes. Analysis of the entire upper gastrointestinal endoscopy cohort also controlled for body mass index at baseline.

Table 4

Odds Ratios for Barrett's Oesophagus based upon waist to hip ratio, waist circumference, and height

	Waist-to-Hip Ratio Quartiles			
	≤0.73	**0.74–0.77**	**0.78–0.81**	**0.82+**
Cases/Women (n/n)	30/2007	32/2383	35/1972	50/2525
Age-Adjusted OR (95% CI)	1.0	0.85 (0.52–1.41)	1.11 (0.68–1.82	1.21 (0.76–1.91)
Multivariate OR (95% CI)	1.0	0.87 (0.52–1.47)	1.21 (0.73–2.03)	1.37 (0.84–2.23)
	Waist Circumference Quartiles			
	≤68.6 cm	**68.7–77.4 cm**	**77.5–86.3cm**	**86.4+ cm**
Cases/Women (n/n)	34/2228	38/2118	37/2299	40/2295
Age-Adjusted OR (95% CI)	1.0	1.11 (0.69–1.77)	0.96 (0.60–1.53)	1.03 (0.65–1.64)
Multivariate OR (95% CI)	1.0	1.05 (0.65–1.71)	0.92 (0.56–1.51)	1.05 (0.63–1.74)
	Height Quartiles			
	≤159 cm	**160–165 cm**	**166–169 cm**	**170+ cm**
Cases/Women (n/n)	58/3646	80/4704	65/4390	58/3041
Age-Adjusted OR (95% CI)	1.0	1.08 (0.77–1.52)	0.95 (0.66–1.35)	1.23 (0.85–1.78)
Multivariate OR (95% CI)	1.0	1.10 (0.78–1.56)	0.94 (0.65–1.35)	1.20 (0.83–1.75)

Multivariate ORs are adjusted for year of endoscopy; age (5-year categories); physical activity (<1.7, 1.7 to 4.5, 4.6 to 10.5, 10.6 to 22.1, and >22.1 metabolic equivalent task score per week); smoking history (never, former, current); daily caloric intake/day (quartiles); alcohol consumption (0, 0.1 to 4.9, 5.0 to 15.0, and >15g/day); postmenopausal hormone use (premenopausal, never, past, current); and a history of diabetes. Waist-to-hip ratio and waist circumference multivariate models were also adjusted for height.