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Smoking and Barrett's Esophagus in Women who Undergo Upper Endoscopy

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Abstract

Background—Cigarette use is associated with esophageal adenocarcinoma, and cross-sectional studies suggest an association between smoking and Barrett's esophagus.

Aims—We sought to examine prospectively the influence of smoking on the risk for Barrett's esophagus.

Methods—This was a prospective cohort study among 20,863 women within the Nurses' Health Study who underwent upper gastrointestinal endoscopy for any reason between 1980 and 2006. We assessed the association between smoking and pathologically-confirmed Barrett's esophagus (n=377). Self-reported data on smoking and potential confounding variables were collected from biennial questionnaires.

Results—Compared to women who never smoked, former smokers who used 1-24 cigarettes/day had a multivariate odds ratio for Barrett's esophagus of 1.25 (95% CI 0.99-1.59), former smokers who used ≥25 cigarettes/day had a multivariate odds ratio of 1.52 (95% CI 1.04-2.22), current smokers who used 1-24 cigarettes/day had a multivariate odds ratio of 0.89 (95% CI 0.54-1.45), and current smokers who used ≥25 cigarettes/day had a multivariate odds ratio of 0.92 (95% CI 0.34-2.54). The risk for Barrett's esophagus increased significantly with increasing pack-years smoked among former (P = 0.008), but not current smokers (p=0.99), especially when considering exposure ≥25 years prior to index endoscopy. Results were similar among women reporting regular heartburn/acid-reflux one or more times a week, and were not accounted for by changes in weight.

Conclusions—Heavy, remote smoking is associated with an increased risk for Barrett's esophagus. This finding suggests a long latency period between exposure and development of the disease, even after discontinuation of smoking.

Keywords

Barrett's esophagus; smoking; cigarettes; gastroesophageal reflux; GERD

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INTRODUCTION

Barrett's esophagus is a metaplastic condition resulting from exposure of the esophageal epithelium to refluxed gastric contents, particularly acid and possibly bile.(1, 2) It has been hypothesized that a portion of denuded squamous mucosa is repopulated by columnar cells originating either from pluripotent cells in the basal epithelium(3, 4) or circulating stem cells derived from bone marrow.(5) Barrett's esophagus is found in 3% to 25% of patients undergoing upper gastrointestinal endoscopy (6-9) and 0.3% among the general population. (10) Barrett's esophagus has a male to female ratio of approximately 2:1, (9, 11-13) which likely explains the limited data available about this condition in women.

Barrett's esophagus is also a precursor for esophageal adenocarcinoma, and both conditions appear to have an increasing incidence in recent decades.(14-18) Progression of Barrett's esophagus to malignancy occurs at a rate of approximately 0.4% to 0.5% per patient-year. (11, 19-25) While cigarette smoking is strongly associated with squamous cell carcinoma of the esophagus(26), several studies have also demonstrated an association between smoking and esophageal adenocarcinoma.(27-32) It is unclear if this association is mediated by carcinogenic effects of smoking on previously established Barrett's mucosa, or if smoking itself increases one's risk for developing Barrett's metaplasia.

Indeed, some(33-38), but not all(8, 39-42), previous studies have suggested an association between smoking and Barrett's esophagus. These studies, however, have all been limited by their cross-sectional or retrospective case-control designs, and have had predominantly male populations. Furthermore, several studies failed to make a distinction between current and former smokers.(34, 36, 42, 43) We therefore sought to further clarify the relationship between smoking and Barrett's esophagus in women using data collected prospectively as part of the Nurses' Health Study, a large, ongoing cohort study in which detailed information on smoking and other health-related factors have been collected over 30 years.

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 Smoking and Other Exposures

Smoking status was first assessed in 1976 and updated every two years thereafter. Participants were asked "Do you currently smoke cigarettes?" Current smokers were further asked for the number of cigarettes smoked per day, with potential responses including 1-4, 5-14, 15-24, 25-34, 35-44, and 45+. In 1976 women were asked their age when they started to smoke, initial amount smoked, age upon quitting and quantity last smoked for former smokers. Cumulative dose was calculated in pack-years of smoking by multiplying the number of packs smoked per day (a pack contains 20 cigarettes) by the number of years in which that amount was smoked.

Weight, menopausal status, use of postmenopausal hormones, and history of cancer were assessed in 1976 and updated every two years thereafter. We determined body mass index (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

updated every two years. Dietary information was first obtained using a semi-quantitative food frequency questionnaire in 1980, updated in 1984, 1986, and subsequently every four years thereafter. 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. Regular use of histamine type 2 receptor antagonists was asked in 1982, 1994, and every two years thereafter. Regular use of proton pump inhibitors was asked in 2000 and every two years thereafter. In 2002, Nurses' Health Study participants were asked if they "ever regularly had heartburn/acid-reflux one or more times a week." Those who answered in the affirmative were classified as having a history of frequent gastroesophageal reflux disease (GERD) symptoms. Cigarette use, caloric intake, alcohol use, physical activity, menopausal status, and GERD symptoms in this cohort have been validated previously.(44-50)

Ascertainment of Cases

In 2002, 2004 and 2006 Nurses' Health Study participants were asked if they had ever undergone upper gastrointestinal endoscopy or been diagnosed with Barrett's esophagus. We requested written permission to acquire endoscopy and pathology records from women reporting Barrett's esophagus. A study physician (BCJ), blinded to exposure information, reviewed records to extract information on the initial date of diagnosis of Barrett's esophagus, the length of columnar-lined esophagus seen at endoscopy, and the presence or absence of specialized intestinal metaplasia (SIM) documented in biopsies taken from the esophagus. Our primary case definition included only women with esophageal SIM of any length. Secondary case definitions included 1) women with SIM and at least 1cm of columnar-lined esophagus, and 2) any woman with an esophageal biopsy demonstrating SIM, columnar epithelium, or a pathology report simply stating "Barrett's esophagus" without a microscopic description. When calculating mean length of SIM, reports describing only "tongue(s)" of Barrett's esophagus or "irregular z-lines" were considered to be 0.5cm in length.

To verify that failure to report Barrett's esophagus 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 esophagus. After one mailing attempt, we obtained records from 95 women. In none of these instances did the endoscopist suspect Barrett's esophagus.

Statistical Analysis

To minimize bias, our primary study population was restricted to those women who reported undergoing upper endoscopy between 1980 and 2006 (n=23,394). We excluded women with cancer (except non-melanoma skin cancer) prior to their index endoscopy (n=1,731) and those with missing smoking information (n=196). To avoid misclassification bias, we excluded women who reported Barrett's esophagus, but for whom review of records failed to support a diagnosis of at least columnar-lined esophagus (n=604).

Women were categorized according to smoking status (never, former, current) and ever smokers were further categorized by number of cigarettes smoked per day: 1-24 vs ≥25. This cut-point was selected a priori based on the closest estimate we had to stratify women into those who smoked more or less than a pack a day. Categories of pack-years analyzed included 0 (never smokers), 1-10, 11-25, 26-50, and >50. These cut-points were chosen a priori in keeping with prior Nurses' Health Study smoking research.(51) To determine the long-term effect of smoking, we calculated pack-years at age 30 based upon responses to the 1976 questionnaire, and also assessed the risk of increasing pack-years based upon the

period of cigarette consumption (<25 years and ≥25 years prior to index endoscopy). The 25 year cut-off was also chosen a priori in keeping with prior Nurses' Health Study smoking research.(51) We also analyzed the risk for Barrett's esophagus based upon the duration of smoking and the number of years since discontinuation of smoking. In the latter case, we also controlled for pack-years of smoking in the multivariate model.

Potential confounding variables were taken from the questionnaire cycle two years prior to the index endoscopy. We used age- and multivariate-adjusted unconditional logistic regression to obtain odds ratios (OR) and 95% confidence intervals (CI) for the risk of Barrett's esophagus. Never-smokers were the reference population in all analyses, except where indicated. Multivariate models controlled for age (5-year categories), year of endoscopy, BMI (<20, 20-24.9, 25-29.9, and ≥30 kg/m^2), physical activity (<1.7, 1.7 to 4.5, 4.6 to 10.5, 10.6 to 22.1, and >22.1 METS per week), daily caloric intake/day (quartiles), alcohol consumption (0, 0.1 to 4.9, 5.0 to 15.0, and >15g/day), and postmenopausal hormone use (premenopausal, never, past, current).

The attributable risk of Barrett's esophagus due to ever smoking was calculated with multivariate relative risks (in this case, odds ratios) with the use of the formula 1- (1 ÷ RR), where RR is the relative risk.(52) We performed several secondary analyses, all planned a priori, to verify the robustness of our findings. These included an analysis controlling for GERD symptoms, an analysis restricted to women with a history of frequent GERD symptoms, and an analysis using the entire Nurses' Health Study cohort regardless of history of endoscopy. In this last case, as the vast majority of cohort members had never undergone endoscopy, we modeled data from our dietary baseline (1980) questionnaire.

A post-hoc analysis was performed to examine whether risks associated with former smoking related to changes in weight after discontinuation of cigarette use. We categorized former smokers according to their difference in weight between the year they stopped smoking and their index endoscopy.

Tests for trend across categories of interest were calculated by treating the median value for each category as an ordinal variable in the multivariate mode. 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

Among 20,863 eligible women, we documented 377 pathologically confirmed cases of SIM (1.8%), and an additional 92 cases with either columnar epithelium within the esophagus or simply a pathologist's diagnosis of "Barrett's esophagus" without documentation of SIM. Among all women with documented SIM for whom length was described by the endoscopist (n=369), the mean (SD) length was 1.9 (2.5) cm, with 80 (22%) having a segment length ≥3 cm.

Among eligible women, 46% were former smokers and 10% were current smokers at the time of their index endoscopy. Compared with never and former smokers, current smokers were slightly younger, and less likely to report GERD symptoms, regularly use acid-suppression medications, perform regular vigorous exercise, or use post-menopausal hormones. Ever smokers reported more daily alcohol use than never smokers (Table 1).

Compared to women who never smoked, ever smokers had a multivariate OR for Barrett's esophagus of 1.20 (1.02-1.41). However, we observed a significantly increased risk for Barrett's esophagus among former, but not current, smokers (Table 2). Compared with

women who never smoked, former smokers had a multivariate OR for Barrett's esophagus of 1.28 (95% CI 1.02-1.61), while current smokers had a multivariate OR of 0.89 (95% CI 0.57-1.39). To determine the burden of Barrett's esophagus due to cigarette use, we calculated the population attributable risk of ever smoking. Approximately 17% of the increased risk for Barrett's esophagus among smokers could be accounted for by their cigarette use. Given that 44% of the U.S. population are past or current smokers(53), approximately 7% of Barrett's esophagus in the U.S. could be attributable to smoking (assuming causality).

When smoking categories were expanded by numbers of cigarettes smoked per day, there appeared to be a dose-response that was largely restricted to former smokers. Compared to never smokers, former smokers reporting 1-25 cigarettes/day experienced a multivariate OR for Barrett's esophagus of 1.25 (95% CI, 0.99-1.59), whereas former smokers reporting ≥25 cigarettes/day had an OR of 1.52 (95% CI 1.04-2.22; p value for trend = 0.03; Table 2). We observed similar risks for Barrett's esophagus when restricting the case definition to SIM of at least 1cm length, and when using a less-stringent definition of Barrett's esophagus, requiring only the presence of columnar histology in an esophageal biopsy (Table 2). Our findings were not altered after excluding those women who had or developed low or high grade dysplasia at some point in their history (n=26; data not shown).

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 endoscopy (n=113,224). In this analysis, compared to women who never smoked, former smokers who used 1-24 cigarettes/day had a multivariate odds ratio for Barrett's esophagus of 1.18 (95% CI 0.89-1.56), former smokers who used ≥25 cigarettes/day had a multivariate odds ratio of 1.61 (95% CI 1.03-2.52), current smokers who used 1-24 cigarettes/day had a multivariate odds ratio of 0.90 (95% CI 0.66-1.25), and current smokers who used ≥25 cigarettes/day had a multivariate odds ratio of 1.29 (95% CI 0.87-1.90).

Among participants who underwent upper endoscopy (primary study population), we repeated our analyses after further controlling for frequent GERD symptoms. Consistent with previous findings from predominantly male populations, women who reported frequent GERD symptoms had a multivariate OR for Barrett's esophagus of 3.83 (2.92-5.02). Nonetheless, adding the presence of frequent GERD symptoms to our multivariate model did not materially alter the influence of smoking on the risk of Barrett's esophagus. Compared to women who never smoked, former smokers who used 1-24 cigarettes/day had a multivariate OR for Barrett's esophagus of 1.21 (95% CI 0.95-1.53), former smokers who used ≥25 cigarettes/day had a multivariate OR of 1.46 (95% CI 1.00-2.14), current smokers who used 1-24 cigarettes/day had a multivariate OR of 0.93 (95% CI 0.57-1.52), and current smokers who used ≥25 cigarettes/day had a multivariate OR of 1.00 (95% CI 0.36-2.76).

We also performed an analysis controlling for regular use of proton pump inhibitors and histamine type 2 receptor antagonists in the years prior to the index endoscopy. In this case, compared to women who never smoked, former smokers who used 1-24 cigarettes/day had a multivariate OR for Barrett's esophagus of 1.23 (95% CI 0.97-1.56), former smokers who used ≥25 cigarettes/day had a multivariate OR of 1.50 (95% CI 1.03-2.20), current smokers who used 1-24 cigarettes/day had a multivariate OR of 0.90 (95% CI 0.55-1.47), and current smokers who used ≥25 cigarettes/day had a multivariate OR of 0.91 (95% CI 0.33-2.50). Not surprisingly, in this prospective analysis, regular use of these medications was associated with an increased risk of finding Barrett's esophagus at subsequent endoscopy, with a multivariate OR of 2.64 (95% CI 2.08-3.34).

Findings were similar in an analysis restricted only to women who reported a history of frequent GERD symptoms and had undergone upper endoscopy (n=11,359 total; 297 cases). Compared to women who never smoked, former smokers who used 1-24 cigarettes/day had a multivariate OR for Barrett's esophagus of 1.23 (95% CI 0.94-1.61), former smokers who used ≥25 cigarettes/day had a multivariate OR of 1.49 (95% CI 0.98-2.27), current smokers who used 1-24 cigarettes/day had a multivariate OR of 0.85 (95% CI 0.47-1.54), and current smokers who used ≥25 cigarettes/day had a multivariate OR of 1.02 (95% CI 0.32-3.29).

The risk for Barrett's esophagus increased non-significantly with increasing numbers of pack-years smoked (P value for trend = 0.05; Table 3). This trend was statistically significant only among former smokers (P value for trend = 0.008). We had too few cases of Barrett's esophagus among current smokers to stratify by pack-year categories. However, when pack years were modeled as a continuous variable, this trend was not significant (P value for trend = 0.99). Because the risk for Barrett's esophagus appeared related to previous cigarette exposure, we examined the differential effects of cigarette consumption within the past 25 years or consumption beyond that time. Since we observed a significant linear trend between pack-years of smoking and Barrett's esophagus only among former smokers, we excluded current smokers from the analysis. In the regression models, we included values for pack-years of smoking within each period simultaneously. When restricted to cigarette consumption 25 years or more in the past, we observed a significant trend in risk with increasing categories of pack-years (P value for trend = 0.01; Table 4). However, for cigarette consumption less than 25 years in the past, we did not observe an association between pack-years and risk for Barrett's esophagus (P value for trend = 0.35).

To further explore the effect of distant cigarette use, we assessed the association between pack-years smoked by age 30 and Barrett's esophagus. Compared to women who never smoked, women who had accumulated 1 to 10 pack-years of smoking by age 30 had a multivariate OR for Barrett's esophagus of 1.15 (95% CI 0.90-1.45), while women with >10 pack-years of smoking by age 30 had a multivariate OR for Barrett's esophagus of 1.61 (1.17-2.20). We also considered the influence of smoking duration, finding no association among current smokers. However, the association was significant among former smokers (P value for trend = 0.04) with a slight increase in risk for each additional year of smoking (OR 1.01, 95% CI 1.00-1.02).

Smoking cessation was not observed to decrease the risk of Barrett's esophagus. In fact, there was a non-significant trend for increased risk the longer time elapsed after cessation of smoking. Compared to current smokers, women who stopped smoking < 5 years prior to endoscopy had a multivariate OR for Barrett's esophagus of 1.49 (95% CI 0.78-2.84), women who stopped smoking 5-9 years prior to endoscopy had a multivariate OR for Barrett's esophagus of 1.43 (95% CI 0.77-2.64), women who stopped smoking 10-20 years prior to endoscopy had a multivariate OR for Barrett's esophagus of 1.70 (95% CI 1.01-2.89), and women who stopped smoking >20 years prior to endoscopy had a multivariate OR for Barrett's esophagus of 1.79 (95% CI 1.05-3.06; P value for trend =0.08).

We considered the possibility that the association between former cigarette use and Barrett's esophagus could reflect weight gain associated with smoking cessation. We therefore controlled for weight change between 1976 and the questionnaire immediately prior to participants' index endoscopy. This caused no significant change in our results. Compared to never smokers, former smokers had a multivariate OR for Barrett's esophagus of 1.27 (95% CI 1.02-1.60) and current smokers had a multivariate OR of 0.90 (95% CI 0.58-1.40). We also examined the effect of weight change among former smokers assessing weight change between the year the participant completely discontinued smoking and the questionnaire immediately prior to their index endoscopy. Compared to former smokers who

did not materially alter their body weight (+/- ≤5 pounds), former smokers who gained 6 to 15 pounds had a multivariate OR for Barrett's esophagus of 0.93 (95% CI 0.51-1.67), those who gained 16 to 30 pounds had an OR of 1.46 (95% CI 0.84-2.54), those who gained more than 30 pounds had an OR of 1.12 (95% CI 0.60-2.10), and those who lost more than 5 pounds had an OR of 1.00 (95% CI 0.49-2.07).

DISCUSSION

In this large prospective cohort study, cigarette smoking conferred a significant elevation in the risk of Barrett's esophagus among women who underwent upper endoscopy for any reason. The risk appeared to be restricted to former smokers, among whom, risk increased with increasing cigarettes smoked per day, pack-years, and smoking duration. The observed risk was similar when restricting our analyses to women with frequent GERD symptoms who underwent upper endoscopy, and among the entire Nurses' Health Study cohort, regardless of reporting upper endoscopy. Controlling for other known or suspected risk factors for Barrett's esophagus did not alter these findings. Remote cigarette use appeared to be more important than recent use, including smoking early in life (i.e. prior to age 30). The observed association did not appear to be explained by weight gain after smoking cessation.

Previous retrospective case-control and cross-sectional studies have reported conflicting results when examining the relationship between cigarette smoking and Barrett's esophagus. While some found no clear association(8, 39-42), others have reported an increased risk. (33-38) Our finding that primarily former smokers appear to experience increased risk may help clarify the findings of several prior investigators. For example, in a recent case-control study from Washington state, Edelstein and colleagues also noted that former, but not current smokers, had an increased risk for Barrett's esophagus (adjusted OR 2.4; 95% CI 1.5-3.8).(33) In another study, these same investigators found a significantly elevated risk for Barrett's esophagus among both former and current smokers, but the risk for long-segment Barrett's esophagus was significant only among former smokers.(37)

Likewise, in a recent large, population-based, case-control study using data from Kaiser Permanente in Northern California, Kubo and colleagues found no overall association between current smoking and Barrett's esophagus using both population-level controls and controls with GERD diagnoses.(54) However, they observed an adjusted OR of 1.35 (95% CI 0.94-1.94) for the risk of Barrett's esophagus among former smokers compared to population controls. This risk-estimate is very similar to ours when considering all former smokers. The authors did not further categorize smokers by daily exposure as we did, and thus may have missed finding a more significant association.

However, within a large case-control study from Australia, Smith and colleagues found that both current and former smokers had a 2- to 3-fold increased risk for Barrett's esophagus. (38) These authors failed to find a significant trend in increasing risk with increasing pack-years when using population-based controls. They did see increased risk with increasing pack-years when using non-Barrett's esophagitis patients as controls. Moreover, they found the risk for Barrett's esophagus relatively unchanged after smoking cessation, and suggested that the effects of smoking are thus persistent and perhaps irreversible. In all of these prior studies, the retrospective design could not control for recall bias that may have altered participants' ability to accurately represent their remote smoking history. By capturing smoking data prospectively since 1976, our study distinguishes itself in its ability to accurately account for long term cigarette exposure.

We acknowledge that it is counter-intuitive to claim that former, but not current, smoking carries increased risk for Barrett's esophagus, even if this finding is consistent with some

previous investigations.(33, 54) One must consider that, while former smoking is associated with Barrett's esophagus, current smoking might somehow be protective, countering the effects of previous cigarette exposure, and providing a current smoker the same risk as a never smoker. It appears, for example, that cigarette smoking is protective against ulcerative colitis, with current smokers experiencing a pooled OR of 0.41 (95% CI 0.34-0.48) compared to non-smokers in one meta-analysis.(55) Cessation of smoking is also associated with flares of ulcerative colitis(56), while nicotine is superior to placebo in the treatment of acute ulcerative colitis.(57)

It is also conceivable that cigarettes have become “safer” over the decades, as filters were added or various chemical components were changed. If a key noxious compound is no longer present in cigarettes, this could appear as increased risk among former but not current smokers who only began smoking in more recent years. We have too few current smokers to stratify them by when they began smoking, so this group remains heterogeneous regarding the decade in which they first became exposed to cigarettes. We also note that never and former smokers were more likely than current smokers to report symptoms of heartburn/acid-reflux and regular use of acid blocking medications (Table 1). Therefore, smokers who experience more severe GERD symptoms, and are thus at higher risk of developing Barrett's esophagus, may quit smoking (becoming classified as former smokers) in hopes of alleviating symptoms. However, our findings persisted among a cohort of women who all reported a history of regular GERD symptoms at least weekly, therefore controlling for the effects of GERD and permitting independent assessment of the effect of smoking.

Our findings also suggest, however, that there is a prolonged latency between cigarette exposure and the development of Barrett's esophagus. This would indicate that smoking confers risk independently of gastroesophageal reflux, a finding consistent with our secondary analyses that controlled for GERD symptoms and the use of acid-blocking agents. Smoking has been associated with DNA damage in esophageal squamous epithelium.(58) This could indicate that carcinogens from cigarette smoke might cause irreversible genetic damage in the normal esophageal mucosa, but many years are required for completion of metaplastic events after initiation. Such a model exists in the association between cigarette smoking and colorectal cancer(59) and suggests areas for future research.

We also considered that weight-gain associated with smoking cessation could be confounding the association between former smoking and Barrett's esophagus. However, all of our multivariate analyses controlled for body mass index. Furthermore, we performed an analysis controlling for changes in weight between 1976 and the questionnaire cycle prior to participants’ index endoscopy, and found no significant difference in our risk-estimates. Finally, we examined the association between weight change and Barrett's esophagus among former smokers, using former smokers with stable weight as our reference population. This revealed no evidence that weight gain accounts for the association between smoking and Barrett's esophagus.

The strengths of our study include its prospective design, repeated assessments of smoking, detailed data on potential confounders, and a large number of cases. Nevertheless, we recognize certain limitations. We relied on self-reported measures of smoking. However, these measures have been validated previously in this cohort(44) and significantly predict other diseases including coronary heart disease(60), stroke(61), pulmonary embolism(62), lung(63), colorectal(64), bladder(65), and ovarian cancers(66), and overall mortality.(67) We acknowledge the relatively small number of current smokers in our study, and this may have limited our ability to fully characterize the association between ongoing cigarette use and Barrett's esophagus. Furthermore, our study population was limited to women, and our

results may not necessarily apply to men. However, as described above, our findings do support those of some prior large studies which included predominantly male populations.

Our definition of Barrett's esophagus was based upon review of endoscopy and pathology reports, but did not include review of pathology specimens, potentially resulting in misclassification bias. However, in a recent study of BMI and Barrett's esophagus(68), independent pathology review confirmed SIM in 91% of 616 cases identified in a manner similar to ours.(69) We also employed three different definitions of Barrett's esophagus to verify that our findings were robust. The first, requiring the presence of SIM, is the standard definition of Barrett's esophagus used in the United States.(70) 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.(71) The third definition of Barrett's esophagus required only the presence of columnar histology, as currently used by the British Society of Gastroenterology.(72) Finally, we are reassured that misclassification in defining Barrett's esophagus should have biased our results toward the null hypothesis.

In summary, we found that former, but not necessarily current, cigarette use is independently associated with an increased risk for Barrett's esophagus. Heavier, remote smoking conveys the highest risk, and this risk persists despite smoking cessation. This may indicate that the association between smoking and esophageal adenocarcinoma may be mediated, in part, through an increased risk for Barrett's esophagus. These findings also raise questions about the genesis of Barrett's metaplasia. Namely, are there particular agents that promote future susceptibility to esophageal damage from gastroesophageal reflux, and is such susceptibility reversible? Furthermore, our findings have clinical implications; specifically, former smokers may represent an at-risk population that may derive benefit from screening upper endoscopy.(73)

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Abbreviations

BMI	body mass index
GERD	gastroesophageal reflux disease
SIM	specialized intestinal metaplasia
MET	metabolic equivalent task
CI	confidence interval
OR	odds ratio

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Table 1

Smoking Status and other Characteristics of 20,863 Nurses Who Underwent Upper Gastrointestinal Endoscopy.

Characteristic	Smoking Status		
	Never	Former	Current
Participants, n	9,214	9,620	2,029
Age	64 (8)	64 (8)	61 (8)
Body mass index*	23 (6)	23 (6)	22 (6)
Regular vigorous exercise, %†	37	39	29
Calories consumed/d	1757 (526)	1728 (516)	1727 (515)
Alcohol use, g/d	3 (7)	6 (9)	7 (12)
Postmenopausal, %‡	94	95	92
Never used hormones,%	26	25	32
Past use of hormones,%	27	29	28
Current use of hormones,%	47	46	40
Heartburn/acid-reflux symptoms, %//	54	57	49
Regular use of acid-suppression medication, %§	15	16	13

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).

*Body mass index = weight in kilograms divided by the square of the height in meters.

†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 estrogen or estrogen 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

Relative Risk for Barrett's Esophagus According to Smoking Status

	Smoking Status				
	Never	**Former (1-24 cigarettes per day)**	**Former (25+ cigarettes per day**	**Current (1-24 cigarettes per day)**	**Current (25+ cigarettes per day)**
Specialized Intestinal Metaplasia Cases/women, n/n	152 / 9177	159 / 7562	37 / 1524	20 / 1573	4 / 335
Age-adjusted OR (95% CI)	1.00 (reference)	1.23 (0.98-1.54)	1.43 (0.99-2.06)	0.80 (0.50-1.28)	0.78 (0.29-2.11)
Multivariate OR (95% CI)	1.00 (reference)	1.25 (0.99-1.59)	1.52 (1.04-2.22)	0.89 (0.54-1.45)	0.92 (0.34-2.54)
Specialized Intestinal Metaplasia ≥ 1cm Cases/women, n/n	58 / 9083	62 / 7624	16 / 1540	10 / 1583	2 / 337
Age-adjusted OR (95% CI)	1.00 (reference)	1.25 (0.88-1.80)	1.61 (0.93-2.81)	1.01 (0.51-1.98)	0.97 (0.23-3.97)
Multivariate OR (95% CI)	1.00 (reference)	1.24 (0.85-1.83)	1.70 (0.95-3.05)	1.04 (0.50-2.13)	1.12 (0.27-4.70)
Columnar Histology with or without Specialized Intestinal Metaplasia Cases/women, n/n	189 / 9214	194 / 7756	47 / 1571	27 / 1600	5 / 340
Age-adjusted OR (95% CI)	1.00 (reference)	1.21 (0.99-1.48)	1.46 (1.06-2.02)	0.86 (0.57-1.29)	0.78 (0.31-1.88)
Multivariate OR (95% CI)	1.00 (reference)	1.21 (0.98-1.50)	1.51 (1.08-2.11)	0.94 (0.61-1.43)	0.87 (0.35-2.16)

Multivariate ORs are adjusted for year of endoscopy; age (5-year categories); body mass index (weight in kilograms divided by the square of the height in meters; <20, 20-24.9, 25-29.9, ≥30); 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); daily caloric intake/day (quartiles); alcohol consumption (0, 0.1 to 4.9, 5.0 to 15.0, and >15g/day); and postmenopausal hormone use (premenopausal, never, past, current).

OR = odds ratio; CI = confidence interval

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Table 3

Relative Risk for Barrett's Esophagus According to Pack-years of Cigarette Use

	Pack Years of Cigarette Smoking					
Smoking Status*	**0**	**1-10**	**11-25**	**26-50**	**>50**	**P Value for Trend**
Ever Smokers						
Cases/Total	152 / 9177	70 / 3897	63 / 3029	56 / 3085	29 / 1230	
Multivariate OR (95% CI)	1.00 (reference)	1.09 (0.81-1.48)	1.26 (0.92-1.73)	1.23 (0.89-1.69)	1.45 (0.95-2.22)	0.05
Former Smokers						
Cases/Total	152 / 9177	69 / 3775	58 / 2725	48 / 2177	18 / 618	
Multivariate OR (95% CI)	1.00 (reference)	1.12 (0.83-1.52)	1.25 (0.91-1.73)	1.44 (1.02-2.02)	1.70 (1.00-2.89)	0.008

Multivariate ORs are adjusted for year of endoscopy; age (5-year categories); body mass index (weight in kilograms divided by the square of the height in meters; <20, 20-24.9, 25-29.9, ≥30); 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); daily caloric intake/day (quartiles); alcohol consumption (0, 0.1 to 4.9, 5.0 to 15.0, and >15g/day); and postmenopausal hormone use (premenopausal, never, past, current).

OR = odds ratio; CI = confidence interval

* Due to a limited number of current smokers, stable modeling stratified by pack-year categories could not be accomplished for this group of smokers. However, a p-value of 0.99 was obtained modeling pack-years as a continuous variable for current smokers.

Table 4

Relative Risk for Barrett's Esophagus Among Former Smokers According to Period of Cigarette Consumption.

	Pack Years of Cigarette Use				
Period of Smoking	**0**	**1-5**	**6-10**	**>10**	**P Value for Trend**
≥25 Years Prior to Endoscopy					
Cases/Total	152 / 7551	37 / 1943	19 / 1216	83 / 4237	
Multivariate OR (95% CI)	1.00 (reference)	1.18 (0.83-1.67)	1.11 (0.71-1.73)	1.46 (1.10-1.95)	0.01
< 25 Years Prior to Endoscopy					
Cases/Total	214 / 12688	24 / 1309	6 / 602	7 / 427	
Multivariate OR (95% CI)	1.00 (reference)	1.00 (0.65-1.53)	0.74 (0.38-1.45)	0.77 (0.33-1.81)	0.35

Multivariate ORs are adjusted for year of endoscopy; age (5-year categories); body mass index (weight in kilograms divided by the square of the height in meters; <20, 20-24.9, 25-29.9, ≥30); 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); 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 pack years smoked from both time periods.

OR = odds ratio; CI = confidence interval

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