Published in final edited form as:
Gastroenterology. 2012 April ; 142(4): 744–753. doi:10.1053/j.gastro.2011.12.049.

Cigarette Smoking Increases Risk of Barrett's Esophagus: an Analysis of the Barrett's and Esophageal Adenocarcinoma Consortium

Michael B. Cook, Ph.D.[1], **Nicholas J. Shaheen, M.D., M.P.H.**[2], **Lesley A. Anderson, Ph.D., M.P.H.**[3], **Carol Giffen, Ph.D.**[4], **Wong-Ho Chow, Ph.D.**[1], **Thomas L. Vaughan, M.D., M.P.H.**[5], **David C. Whiteman, M.B.B.S., Ph.D.**[6], and **Douglas A. Corley, M.D., Ph.D.**[7]

[1]Division of Cancer Epidemiology and Genetics, NCI [2]University of North Carolina, Chapel Hill, North Carolina [3]Centre for Public Health, Queen's University, Belfast, Northern Ireland [4]Information Management Services, Bethesda, MD [5]Program in Epidemiology, Fred Hutchinson Cancer Research Center, Seattle, WA [6]Queensland Institute of Medical Research, Brisbane, Australia [7]Division of Research and Oakland Medical Center, Kaiser Permanente, CA

Abstract

Background & Aims—Cigarette smoking has been implicated in the etiology of esophageal adenocarcinoma, but it is not clear if smoking is a risk factor for Barrett's esophagus (BE). We investigated whether tobacco smoking and other factors increase risk for BE.

Methods—We analyzed data from 5 case-control studies included in the international Barrett's and Esophageal Adenocarcinoma Consortium. We compared data from subjects with BE (n=1059) with those from subjects with gastroesophageal reflux disease (GERD controls, n=1332) and population-based controls (n=1143), using multivariable logistic regression models to test

Correspondence to: Michael Blaise Cook, PhD, Hormonal and Reproductive Epidemiology Branch, Division of Cancer Epidemiology and Genetics, National Cancer Institute, NIH, DHHS, 6120 Executive Blvd, EPS/Suite 550/Room 5014, Bethesda, MD 20852-7234, USA, phone: 301-496-1613, fax: 301-402-0916, michael.cook@nih.gov.

No conflicts of interest exist.

Author Roles;
MBC: study concept and design, acquisition of data, analysis and interpretation of data, drafting of the manuscript, critical revision of the manuscript for important intellectual content, statistical analysis
NJS: study concept and design, acquisition of data, analysis and interpretation of data, drafting of the manuscript, critical revision of the manuscript for important intellectual content, obtained funding, study supervision
LAA: acquisition of data, analysis and interpretation of data, drafting of the manuscript, critical revision of the manuscript for important intellectual content
CG: acquisition of data, analysis and interpretation of data, critical revision of the manuscript for important intellectual content, technical, or material support
WHC: study concept and design, analysis and interpretation of data, drafting of the manuscript, critical revision of the manuscript for important intellectual content
TLV: study concept and design, acquisition of data, analysis and interpretation of data, drafting of the manuscript, critical revision of the manuscript for important intellectual content, obtained funding
DCW: study concept and design, acquisition of data, analysis and interpretation of data, drafting of the manuscript, critical revision of the manuscript for important intellectual content, obtained funding
DAC: study concept and design, acquisition of data, analysis and interpretation of data, drafting of the manuscript, critical revision of the manuscript for important intellectual content, obtained funding, study supervision

associations with cigarette smoking. We also tested whether cigarette smoking has synergistic effects with other exposures, which might further increase risk for BE.

Results—Subjects with BE were significantly more likely to have ever-smoked cigarettes than the population-based controls (odds ratio [OR]=1.67; 95% confidence interval [CI], 1.04–2.67) or GERD controls (OR=1.61; 95% CI, 1.33–1.96). Increasing pack-years of smoking increased the risk for BE. There was evidence for a synergy between ever-smoking and heartburn or regurgitation; the attributable proportion of disease among individuals who ever smoked and had heartburn or regurgitation was estimated to be 0.39 (0.25–0.52).

Conclusions—Cigarette smoking is a risk factor for BE. The association strengthened with increased exposure to smoking until ~ 20 pack-years, when it began to plateau. Smoking has synergistic effects with heartburn or regurgitation, indicating that there are various pathways by which tobacco smoking might contribute to the development of BE.

Keywords

BEACON; esophageal cancer; population study; tobacco

Introduction

Barrett's esophagus is a columnar metaplasia of the distal esophagus associated with a 10- to 55-fold increased risk of esophageal adenocarcinoma [1–7]. Barrett's esophagus [8–11] and esophageal adenocarcinoma [12–14] have been increasing in incidence, particularly in developed countries with predominantly Caucasian populations. For example, in the United States esophageal adenocarcinoma in whites has increased from 0.4 to more than 3 per 100,000 person-years during the last 35 years—a 650% increase [12, 15]. This increasing incidence is not solely due to changes in diagnostic practice, and has been attributed to temporal changes in exposure to risk factors [16].

The known risk factors for Barrett's esophagus and esophageal adenocarcinoma are few and include gastroesophageal reflux [17, 18] and increasing body mass index (BMI) [19–21]. Cigarette smoking has also been implicated in the etiology of esophageal adenocarcinoma [22], but whether this is because smoking is a risk factor for early events in the carcinogenic pathway (i.e. Barrett's esophagus) or for later events, such as the transformation of Barrett's esophagus to cancer, is unclear given the conflicting findings of previous studies of Barrett's esophagus risk factors, with some studies demonstrating a positive association between Barrett's esophagus and cigarette smoking [18, 23–27] and others not [28–32].

The inability to ascertain what, if any, relationship exists between Barrett's esophagus and smoking has been due, in part, to imprecision rendered by limited numbers of subjects available for analysis in individual studies. This limitation has also reduced the ability to discern interactions between exposures; if tobacco smoking does increase risk of Barrett's esophagus it could do so primarily through genotoxic mechanisms or by promoting GERD. Refining our understanding of the potential mechanism(s) of association is important with regard to the efficacy of preventative actions.

To better understand the relationship between Barrett's esophagus and one of its few potentially modifiable risk factors, we assessed whether cigarette smoking was associated with Barrett's esophagus, and the potential mechanism of association, by pooling, harmonizing, and analyzing individual patient data from five case-control studies in the international Barrett's and Esophageal Adenocarcinoma Consortium (BEACON, http://beacon.tlvnet.net/).

Methodology

Study Population

The BEACON consortium was formed in 2005 with support from the U.S. National Cancer Institute. It is composed of investigators from around the world and brings together population-based case-control and cohort studies of esophageal adenocarcinoma and Barrett's esophagus. The primary objectives of BEACON are to facilitate well-powered, combined investigations of risk factors in relation to these diseases, as well as helping the development of new studies of etiology, prevention and survival.

The five Barrett's esophagus case-control studies included in this BEACON analysis, with abbreviated names shown in italics, were: *FINBAR* (Factors INfluencing the Barrett's/Adenocarcinoma Relationship) study, based in Ireland [33]; Epidemiology and Incidence of Barrett's Esophagus study nested within Kaiser Permanente Northern California (*KPNC*), USA [34]; *Study of Reflux Disease*, based in western Washington State, USA [35]; *Study of Digestive Health*, based in Brisbane, Australia [26]; and Epidemiologic Case-Control Study of Barrett's Esophagus based at The University of North Carolina at Chapel Hill (*UNC-Chapel Hill*), USA. For comparison with Barrett's esophagus cases, two control groups were available: gastroesophageal reflux disease (GERD) and population-based. There are advantages for each of these comparison groups. GERD controls represent the population undergoing endoscopy from which Barrett's esophagus cases are diagnosed. Therefore, comparisons between these two groups are less affected by potential ascertainment bias than comparisons between Barrett's esophagus cases and population-based controls, insofar as it inherently controls for known and unknown potentially confounding factors associated with being referred for and undergoing an endoscopic procedure. In addition, since most cases are identified in the course of investigating gastroesophageal reflux, the use of GERD controls, to some degree, inherently adjusts for the presence, although not severity, of symptomatic gastroesophageal reflux. The major advantage of the population-based control group is that it enables the assessment of gastroesophageal reflux as both an effect-measure modifier and independent risk factor, while also being representative of the local population from which the Barrett's esophagus cases are referred and diagnosed. Studies which have conducted endoscopy on random samples of the general population provide more in-depth information on the relative advantages and disadvantages of each of these two control groups [36, 37]. All five studies contributed individual patient data to the GERD control group and four of the studies contributed individual patient data to the population-based control group. Study-specific definitions of the case and control groups are detailed in Table 1.

In total, the five studies provided 1,320 cases of Barrett's esophagus, 1,659 GERD controls, and 1,434 population-based controls. For this analysis, and if a study provided such data, we excluded individuals who had ever-smoked pipe tobacco or cigars (156 Barrett's esophagus cases, 132 GERD controls, 153 population-based controls), because comparing cigarette smokers with those who do not use other forms of tobacco provides a more accurate estimate of the effect of cigarette smoking. Ever-smoking of pipe tobacco or cigars was defined as meeting a study-specific low threshold exposure (a period of ≥6 months or ≥20 times over the life-course). Due to the relatively small number of non-white Barrett's esophagus cases remaining (17 black, 31 Hispanic, 39 other, 18 missing), we restricted our analysis to white study participants. After exclusions, there remained 1,059 Barrett's esophagus cases, 1,332 GERD controls, and 1,143 population-based controls for analysis. Data acquisition and data pooling for each study were approved by the Institutional Review Board or Research Ethics Committee of the institute(s) sponsoring the study.

Analytic Variables

The primary exposure variables were cigarette smoking status (ever vs. never) and total cigarette smoking exposure (pack-years; 0, <15, 15–29, 30–44, ≥45). Additional exposure variables included duration of cigarette smoking (<30 years, ≥30 years), cigarette smoking intensity (<1, 1, and >1 packs/day), age of cigarette smoking initiation (<17, ≥17 years), and duration of cigarette smoking cessation (<20 years, ≥20 years). Cigarette smoking intensity and cigarette smoking duration in the UNC-Chapel Hill study were ascertained in categories and were thus recoded to the median of the categories using the distributions of the other four studies combined. Ever-cigarette smoking was defined as either low threshold exposures (≥100 cigarettes, >=20 packs of cigarettes, 1 cigarette a day for six months of longer) or by asking whether the patient had ever-smoked. Covariates assessed for inclusion in regression models included: age; sex; BMI (weight divided by square of height [kg/m^2]); education; alcohol; fat, and transfat consumption; calories per day; meat, vegetable, and fruit servings per day; fiber consumption; heartburn, and regurgitation (population-based control models only); esophagitis; *Helicobacter pylori* seropositivity; hiatal hernia; and medication use (non-steroidal anti-inflammatory drugs [NSAIDs], antacids, proton pump inhibitors [PPIs], H2-receptor antagonists [H2RAs]). A covariate was included in the fully adjusted models if it altered an estimate by >10% or it was considered a known confounder (age, sex, BMI, and education).

Statistical analysis

We used a two-step analytic approach. First, study-specific odds ratios (ORs) and 95% confidence intervals (CIs) for an exposure-outcome relationship were estimated from multivariable logistic regression models. Second, the study-specific ORs were combined using fixed-effects and random-effects meta-analytic models to generate summary ORs; both approaches gave similar estimates of association, thus we present only the random-effects models herein as such models are usually more conservative [38]. A study was excluded from the second-step of a specific variable's analysis if the logistic regression model failed due to instability. The I^2 value and its 95% uncertainty interval were used to estimate the percentage of total variation across studies due to heterogeneity [39]. An I^2 statistic of 0% indicates no observed heterogeneity that cannot be attributed to chance, whereas larger values indicate increasing heterogeneity.

Exposure variables were assessed in relation to the outcome of Barrett's esophagus using two comparison groups: GERD controls and population-based controls. Continuous variables were categorized to allow for nonlinear effects, for ease of interpretation, and to reduce the effect of any outliers; exceptions to this were the use of continuous variables for trends, product-terms, and spline models. Minimally adjusted models included the covariates age (years; <50, 50–59, 60–69, ≥70) and sex. Fully adjusted models also included BMI (<18.5, 18.5–24, 25–29, 30–34, 35–39, ≥40 kg/m^2) and education (categorical: school only, tech/diploma, university; unavailable and so unadjusted for in UNC-Chapel Hill study). These models were also stratified by sex, BMI, and heartburn or regurgitation (population-based control comparisons only) to assess relationships (ORs) for effect-measure modification, with p values estimated via random effects meta-analysis of study-specific estimated effects of product-terms (e.g., ever-smoke x sex). Heartburn was generally described to the patient as having ever experienced burning pain or discomfort behind the breast bone while regurgitation was generally described as food or stomach fluid coming back up into the mouth accompanied with a sour-taste; KPNC excluded symptoms within 1 year prior to diagnosis of Barrett's esophagus and FINBAR 5 years. In addition, FINBAR required symptoms to be frequent (*more than 50 times per year/about once a week*). Models of the additional exposures (cigarette smoking duration, intensity, initiation, and cessation) were also adjusted for total exposure (pack-years of cigarette smoking); because these

variables contribute to total exposure, association testing without adjustment for total exposure could be misleading [40, 41].

Spline models [42] were used to generate plots of the relationship between continuous pack-years of cigarette smoking and risk of Barrett's esophagus, compared with each control group and adjusted for age, sex, BMI, and study using the pooled dataset of individual patient data. Restricted cubic spline models allow for easy visualization of non-linear relationships between an exposure and an outcome [43, 44]—in this case, cigarette smoking and Barrett's esophagus. These models were plotted using a linear scale on the x-axis (pack-years of cigarette smoking) and a logarithmic (base 10) scale on the y-axis (OR).

To determine whether cigarette smoking biologically interacts with other exposures in relation to risk of Barrett's esophagus, we tested for departure from additivity. Positive departure from additivity implies that the number of cases attributable to two exposures in combination is larger than the sum of the numbers of cases that would be caused by each exposure separately. The covariates tested for biological interaction with ever-cigarette smoking were BMI (<27.5, ≥ 27.5 kg/m^2), heartburn and regurgitation (population-based control comparisons only), alcohol, *H. pylori*, and NSAIDs. For each combination of variables, we generated four exposure categories; using BMI as an example: A=never-smoker, low BMI; B=smoker, low BMI; C=never-smoker, high BMI; D=smoker, high BMI. These variables were modeled in the pooled dataset of individual patient data using logistic regression adjusted for age, sex, BMI, education, and study. Assuming that the OR approximates the relative risk, the output from these models was used to estimate three interaction statistics: interaction contrast ratio (ICR), attributable proportion (AP), and synergy index (S) [45, 46]. When the ICR and AP $\neq 0$, and S $\neq 1$ there is evidence for departure from additivity (biological interaction). ICR is the excess risk due to interaction relative to the risk without either exposure. AP is the proportion of disease attributable to interaction among individuals with both exposures. S is the ratio of the observed excess risk in individuals exposed to both factors relative to the expected excess risk assuming that both exposures are independent risk factors (i.e., under the assumption of no additive interaction). Confidence intervals for these metrics were estimated using the delta method [45].

All analyses were performed using STATA software, version 11.1 (StataCorp LP, College Station, TX). All statistical tests were two-sided and *p* values less than 0.05 were considered to be statistically significant.

Results

Descriptors of cases and controls included in the analysis are shown in Table 2. The population-based control distributions were more similar to the cases in terms of age and sex than the GERD controls, and this is likely due to three of the four studies with population-based controls having matched on these variables to the Barrett's esophagus case group; GERD controls were matched to the Barrett's esophagus group on age and sex in only one study (Table 1). However, in other respects, such as BMI and alcohol, GERD controls had distributions more similar to the Barrett's esophagus group, compared with the population-based control group.

Table 3 shows the estimates of association between cigarette smoking variables and Barrett's esophagus, compared with both GERD controls and population-based controls. Subjects with Barrett's esophagus were significantly more likely to have ever-smoked cigarettes than both the population controls (OR=1.67) and the GERD controls (OR=1.61), although the GERD study-specific estimates appeared to be less heterogeneous (I^2=11%, 95%UI:0–81%) than estimates from population-based control models (I^2=82%, 95%UI:54–

93%). Increasing pack-years of cigarette smoking was associated with an increasing OR for Barrett's esophagus compared with both control groups (Table 3, Figure 1), albeit the risk relationship was not strictly linear in the categories used for assessment; the ORs for Barrett's esophagus were approximately 1.5 for both <15 and 15–29 pack-years of smoking exposure groups, and approximately 2 for each of the higher exposure groups (30–44, and ≥45 pack-years of smoking), compared with each of the control groups and using never-smokers as the referent. The spline models, shown in Figure 2, are somewhat more indicative of a linear relationship—at least until approximately 20 pack-years of smoking—and this did not change when never-smokers were excluded. Conversely, the p value for trend for pack-years of smoking was statistically significant only when never-smokers were included for analysis (Table 3). Lastly, the additional cigarette smoking variables of duration, intensity, age of initiation, and duration of cessation were not associated with Barrett's esophagus, after adjustment for total exposure (Table 3).

As shown in Figure 1, there were moderate-to-high levels of heterogeneity which were predominantly the product of the relatively lower estimates generated by the FINBAR study. When the FINBAR study was excluded, the summary ORs from the fully adjusted models slightly increased and the heterogeneity (I^2 values) decreased (Population-based controls: $OR_{ever\text{-}smoke}$=2.09 [*95%CI:1.54–2.83, I2=44%*]; $OR_{<15}$=1.93 [*95%CI:1.36–2.74, I2=30%*]; $OR_{15–29}$=1.75 [*0.93–3.30, 68%];* $OR_{30–44}$=2.49 [*1.70–3.65, 0%*]; $OR_{\geq 45}$=2.57 [*1.79–3.67, 0%*]; GERD controls: $OR_{ever\text{-}smoke}$=1.75 [*95%CI:1.43–2.15, I2=0%*]; $OR_{<15}$=1.32 [*0.95–1.84, 38%*]; $OR_{15–29}$=1.62 [*1.09–2.41,25%*]; $OR_{30–44}$=2.87 [*1.88–4.38, 19%*]; $OR_{\geq 45}$=2.12 [*1.50–3.00, 0%*]).

The stratified models tested whether the effect of a single exposure in relation to Barrett's esophagus was modified by another variable. When stratified by sex, the estimates for ever-smoking and categories of pack-years, in relation to Barrett's esophagus, were slightly higher in men ($OR_{ever\text{-}smoke}$=1.81 [*1.43–2.30, 0%*]) than women ($OR_{ever\text{-}smoke}$=1.32 [*0.91–1.92, 31%*]), compared with GERD controls (Supplementary Table 1). Although ever-smoking stratified by sex was statistically significant (p=0.041), pack-years of cigarette smoking was not (p=0.5). Estimates of risk were not statistically different by sex when using population-based controls as the comparison group. Analyses stratified by BMI indicated that associations between cigarette smoking and Barrett's esophagus may be stronger in those with a lower BMI (p=0.046), when using the population-based controls as the comparison group, while no pattern by BMI was discernable when compared with GERD controls (p=0.9; Supplementary Table 2). Analyses stratified by heartburn and regurgitation provided higher estimates for ever-smoking and pack-years of smoking in relation to Barrett's esophagus in individuals without such symptoms ($OR_{ever\text{-}smoke}$=3.35 [1.55–*7.26, 0%*]) compared with individuals who reported symptoms ($OR_{ever\text{-}smoke}$=1.99 [*1.50–2.65, 23%*]) when using population-based controls as the referent, although these differences were not statistically significant (Supplementary Table 3).

Table 4 shows the results from the interaction models to test departures from additivity, which are considered as evidence for the existence of biologic interaction. Unlike effect-measure modification of ORs across strata of a second variable each with an independent referent group, interaction models simultaneously tested the effects of two exposures in relation to Barrett's esophagus to assess whether there were synergistic effects. We found evidence for biologic interaction between ever-cigarette smoking and heartburn/regurgitation with an attributable proportion due to interaction amongst those exposed to both risk factors of 0.39 (*95%CI: 0.25–0.52*) (Table 4). Compared with the unexposed referent of population controls without heartburn/regurgitation who also never-smoked, the ORs for Barrett's esophagus for each exposure category were 9.35 (*95%CI: 6.08–14.39*) for

those exposed to heartburn/regurgitation only, 1.71 (*1.04–2.80*) for those exposed to smoking only, and 16.47 (*10.73–25.29*) for those exposed to both.

Discussion

The relationship between cigarette smoking and Barrett's esophagus is unclear. Given the high prevalence of smoking, and its status as one of the few potentially-modifiable risk factors for Barrett's esophagus, this relationship requires a more complete understanding. In this analysis of individual patient data from five studies within the international BEACON consortium, we found evidence for associations between ever-smoking and increasing pack-years with increased risk of Barrett's esophagus. We did not find independent associations with related exposure variables, such as duration of smoking or the average number of cigarettes smoked per day, suggesting that the cumulative exposure to cigarette smoke is the most important exposure in this relationship. We also found tentative evidence that the relationship between cigarette smoking and Barrett's esophagus may be stronger in men which could indicate sex differences in the role of smoking with respect to pathogenesis of Barrett's esophagus. Lastly, evidence for biological interaction between heartburn/regurgitation and cigarette smoking suggests varied mechanistic effects of cigarette smoking in the development of Barrett's esophagus.

Our understanding of the relationship between cigarette smoking and Barrett's esophagus has been hampered by inconsistent data from studies too small to fully assess the issue; some studies have found evidence for an association, using population-based controls [23, 24], endoscopy-negative controls [18, 25], or GERD controls [18, 28–30], while other studies have not found evidence for a relationship [47–50]. The analysis presented herein is much larger than any of these previous studies, and this larger sample size provided for greater statistical power and greater precision of risk estimates. In addition, the availability of GERD controls and population-based controls allowed for comparison to the source population undergoing endoscopy and the general population, respectively, with the latter also enabling assessment of heartburn/regurgitation as a potential effect-measure modifier and as a potential synergistic risk factor. A particular strength of the study is its use of pooled individual patient data through a large international consortium; this method provides more comparable statistical estimates than standard meta-analysis, which pool published odds ratios that differ in their variable definitions and the confounders included. Therefore, the results of this analysis are the strongest available data to date regarding cigarette smoking as a risk factor for Barrett's esophagus.

Barrett's esophagus is the recognized precursor lesion of esophageal adenocarcinoma, and, if cigarette smoking was a risk factor for Barrett's esophagus, one might expect to observe an association between smoking and esophageal adenocarcinoma as well. Indeed, studies of this malignancy compared with population-based or hospital controls also provide evidence for an association with cigarette smoking [50–55] including a recent pooled esophageal adenocarcinoma analysis from the international BEACON group [22]. Given the concordance of these data, associations between cigarette smoking and Barrett's esophagus, as well as cigarette smoking and esophageal adenocarcinoma, are likely to be real and, given the high prevalence of the exposure, may account for a large proportion (~40%) of esophageal adenocarcinomas [56]. It has not been known where smoking acts in the biological pathway. The current data suggest that smoking is associated with the risk of an early cancer precursor: Barrett's esophagus.

Most of our primary exposure analyses had moderate to high levels of heterogeneity, an effect predominantly caused by the lower estimates of association from the FINBAR study [33]. Omission of this study reduced the heterogeneity and had minimal effects on the

summary risk estimates attained, thus reinforcing the conclusions drawn. It is unknown why the associations between smoking and Barrett's esophagus were lower in the Irish study population; the proportion of population-based controls that reported ever-smoking was higher (55%) than the other studies (45–47%), but this slightly higher rate is insufficient to mask the association evidenced in the other studies. In addition, the distribution of pack-years of cigarette smoking was similar across control groups and studies while provision of individual patient data enabled similar confounding structures to be constructed for study-specific models. FINBAR's inclusion criteria did restrict recruitment of cases to those with long-segment Barrett's esophagus (≥3 cm, Table 1); a criterion not employed by the other four studies included in this analysis. However, this is unlikely to have led to lower estimates of association given that a previous analysis of KPNC data evidenced a stronger association of cigarette smoking with long-segment Barrett's esophagus (OR=1.72, 95%CI: 1.12, 2.63) compared with that for short-segment Barrett's esophagus (<3cm, OR=1.19, 95%CI:0.76, 1.85) [31]. Thus, it remains unexplained why the FINBAR estimates of association were lower relative to the other studies included in this pooled analysis.

Analyses stratified by sex suggested that cigarette smoking may be a stronger risk factor for Barrett's esophagus among men than among women. However, this relationship was only observed when assessing ever-cigarette smoking in Barrett's esophagus cases compared with GERD controls; analyses of pack-years of cigarette smoking, and comparisons with population-based controls were null. Given the known genotoxic effects of tobacco smoke, evidence that effects of cigarette smoking are similar in men and women [57], and the number of tests conducted, we believe this result represents a chance finding.

Interaction analyses indicated that heartburn/regurgitation symptoms and ever-smoking biologically interact in the risk of Barrett's esophagus—the attributable proportion of disease amongst individuals exposed to these two factors was estimated to be 0.39 (95%CI: 0.25–0.52). Biological interaction of these variables in this setting is plausible, given evidence that tobacco smoke may not only have direct genotoxic effects [58] but may also induce transient lower esophageal sphincter relaxations (TLESRs) [5960, 61], increasing the likelihood, length and severity of gastroesophageal reflux—a major risk factor for Barrett's esophagus [18] and the sequela, esophageal adenocarcinoma [17]. Indeed, interaction between gastroesophageal reflux symptoms and smoking has been previously reported for Barrett's esophagus with dysplasia [26] and for esophageal adenocarcinoma [62].

There were several strengths of this analysis. First, the consortial approach enabled generation of the largest reported cohort of subjects with Barrett's esophagus in the world's literature upon which risk factor analysis has been performed. The large size of the pooled database enabled more precise estimates of association over previous studies, particularly in stratified analyses, spline models, and assessment of interaction. Second, although pooling and harmonization of data is a substantial undertaking and requires expertise, time, and resources, individual patient data allows for many benefits over meta-analysis of published estimates including building consistent models across studies, studying novel questions including interaction and using novel methods of analysis such as splines. Third, the availability of two control groups for comparison: population-based and GERD allows us to postulate where risk factors may be active in the pathogenesis of Barrett's esophagus. This is important given that it is feasible that a significant proportion of the population-based control group may unknowingly have Barrett's esophagus [63], although such misclassification would bias results toward the null.

Limitations of this analysis include the moderate-to-high levels of heterogeneity for some analyses. Although constituents of tobacco smoke have changed over time [64], the studies included in this analysis recruited incident cases and controls over a similar period (1997–

2006). Regardless, constituents of tobacco smoke are likely to have differed geographically as is population susceptibility to genotoxic exposures. The unexplained heterogeneity does warrant a cautious interpretation of summary estimates, although associations were largely consistent in a majority of studies included and similar summary estimates with low heterogeneity were estimated when the study which was the source of the most heterogeneity was omitted from analysis. Another limitation is the possibility of recall bias, given the case-control design of the included studies, although the intensity and duration of smoking are usually recalled relatively reliably [65]. Lastly, we did not adjust for dietary variables in this analysis; although previous studies suggest that diet has minimal effects on relationships between smoking and Barrett's esophagus, there remains the possibility of residual confounding through diet and other exposures.

In conclusion, cigarette smoking is a risk factor for Barrett's esophagus, with adjusted odds ratios for multiple measures of association in the 1.5–2 range. The association appears to strengthen with increased exposure to cigarette smoking until approximately 20 pack-years, where it begins to plateau. If smoking is a causative agent of Barrett's esophagus, it is an attractive modifiable risk factor, especially in high risk groups, such as elderly, obese males with GERD symptoms. Moreover, because the origins of BE are poorly understood, a better understanding of its risk factors and their biological interactions may allow inference as to the biological mechanisms involved in the nascent stages of Barrett's esophagus. Indeed, the evidence we present for a biological interaction between smoking and heartburn/regurgitation suggest that cigarette smoking has multifaceted effects in the development of this precancerous metaplasia.

References

1. Spechler SJ, Robbins AH, Rubins HB, Vincent ME, Heeren T, Doos WG, Colton T, Schimmel EM. Adenocarcinoma and Barrett's esophagus. An overrated risk? Gastroenterology. 1984; 87:927–33. [PubMed: 6468881]
2. Polepalle SC, McCallum RW. Barrett's esophagus. Current assessment and future perspectives. Gastroenterology Clinics of North America. 1990; 19:733–44. [PubMed: 2228171]
3. van der Burgh A, Dees J, Hop WC, van Blankenstein M. Oesophageal cancer is an uncommon cause of death in patients with Barrett's oesophagus. Gut. 1996; 39:5–8. [PubMed: 8881798]
4. Rana PS, Johnston DA. Incidence of adenocarcinoma and mortality in patients with Barrett's oesophagus diagnosed between 1976 and 1986: implications for endoscopic surveillance. Diseases of the Esophagus. 2000; 13:28–31. [PubMed: 11005328]
5. Conio M, Cameron AJ, Romero Y, Branch CD, Schleck CD, Burgart LJ, Zinsmeister AR, Melton LJ 3rd, Locke GR 3rd. Secular trends in the epidemiology and outcome of Barrett's oesophagus in Olmsted County, Minnesota. Gut. 2001; 48:304–9. [PubMed: 11171817]
6. Solaymani-Dodaran M, Logan RF, West J, Card T, Coupland C. Risk of oesophageal cancer in Barrett's oesophagus and gastro-oesophageal reflux. Gut. 2004; 53:1070–4. [PubMed: 15247170]
7. Cook MB, Wild CP, Everett SM, Hardie LJ, Bani-Hani KE, Martin IG, Forman D. Risk of mortality and cancer incidence in Barrett's esophagus. Cancer Epidemiology, Biomarkers and Prevention. 2007; 16:2090–6.
8. van Soest EM, Dieleman JP, Siersema PD, Sturkenboom MC, Kuipers EJ. Increasing incidence of Barrett's oesophagus in the general population. Gut. 2005; 54:1062–6. [PubMed: 15857935]
9. Kendall BJ, Whiteman DC. Temporal changes in the endoscopic frequency of new cases of Barrett's esophagus in an Australian health region. American Journal of Gastroenterology. 2006; 101:1178–1182. [PubMed: 16771933]
10. Irani S, Parkman HP, Thomas R, Krevsky B, Fisher RS, Axelrod P. Increased Barrett's esophagus for the decade between 1991 and 2000 at a single university medical center. Digestive Diseases and Sciences. 2005; 50:2141–6. [PubMed: 16240229]

11. Alcedo J, Ferrandez A, Arenas J, Sopena F, Ortego J, Sainz R, Lanas A. Trends in Barrett's esophagus diagnosis in Southern Europe: implications for surveillance. Diseases of the Esophagus. 2009; 22:239–48. [PubMed: 19425201]
12. Cook MB, Chow WH, Devesa SS. Oesophageal cancer incidence in the United States by race, sex, and histologic type, 1977–2005. Br J Cancer. 2009; 101:855–9. [PubMed: 19672254]
13. Voutilainen M. Epidemiological trends in oesophageal cancer in the Nordic countries. Scandinavian Journal of Gastroenterology. 2008; 43:323–7. [PubMed: 18938769]
14. Lepage C, Rachet B, Jooste V, Faivre J, Coleman MP. Continuing Rapid Increase in Esophageal Adenocarcinoma in England and Wales. American Journal of Gastroenterology. 2008
15. Surveillance Epidemiology and End Results (SEER) Program. (www.seer.cancer.gov) SEER*Stat Database: Incidence - SEER 9 Regs Research Data, Nov 2009 Sub (1973–2007) <Katrina/Rita Population Adjustment> - Linked To County Attributes - Total U.S., 1969–2007 Counties, National Cancer Institute, DCCPS, Surveillance Research Program, Cancer Statistics Branch, released April 2010, based on the November 2009 submission.
16. Olsen CM, Pandeya N, Green AC, Webb PM. Whiteman DC, Study ftAC. Population Attributable Fractions of Adenocarcinoma of the Esophagus and Gastroesophageal Junction. American Journal of Epidemiology. 2011
17. Lagergren J, Bergstrom R, Lindgren A, Nyren O. Symptomatic gastroesophageal reflux as a risk factor for esophageal adenocarcinoma. N Engl J Med. 1999; 340:825–31. [PubMed: 10080844]
18. 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]
19. Steevens J, Schouten LJ, Driessen AL, Huysentruyt CJ, Keulemans YC, Goldbohm RA, van den Brandt PA. A prospective cohort study on overweight, smoking, alcohol consumption, and risk of Barrett's esophagus. Cancer Epidemiology Biomarkers & Prevention.
20. Whiteman DC, Sadeghi S, Pandeya N, Smithers BM, Gotley DC, Bain CJ, Webb PM, Green AC. Combined effects of obesity, acid reflux and smoking on the risk of adenocarcinomas of the oesophagus. Gut. 2008; 57:173–80. [PubMed: 17932103]
21. Corley DA, Kubo A, Zhao W. Abdominal obesity and the risk of esophageal and gastric cardia carcinomas. Cancer Epidemiology, Biomarkers and Prevention. 2008; 17:352–8.
22. Cook MB, Kamangar F, Whiteman DC, Freedman ND, Gammon MD, Bernstein L, Brown LM, Risch HA, Ye W, Sharp L, Pandeya N, Webb PM, Wu AH, Ward MH, Giffen C, Casson AG, Abnet CC, Murray LJ, Corley DA, Nyrén O, Vaughan TL, Chow W-H. Cigarette Smoking and Adenocarcinomas of the Esophagus and Esophagogastric Junction: A Pooled Analysis From the International BEACON Consortium. Journal of the National Cancer Institute. 2010; 102:1344–1353. [PubMed: 20716718]
23. Ronkainen J, Aro P, Storskrubb T, Johansson SE, Lind T, Bolling-Sternevald E, Vieth M, Stolte M, Talley NJ, Agreus L. Prevalence of Barrett's esophagus in the general population: an endoscopic study. Gastroenterology. 2005; 129:1825–31. [PubMed: 16344051]
24. Johansson J, Hakansson HO, Mellblom L, Kempas A, Johansson KE, Granath F, Nyren O. Risk factors for Barrett's oesophagus: a population-based approach. Scandinavian Journal of Gastroenterology. 2007; 42:148–56. [PubMed: 17327933]
25. Hirota WK, Loughney TM, Lazas DJ, Maydonovitch CL, Rholl V, Wong RK. Specialized intestinal metaplasia, dysplasia, and cancer of the esophagus and esophagogastric junction: prevalence and clinical data. Gastroenterology. 1999; 116:277–85. [PubMed: 9922307]
26. Smith KJ, O'Brien SM, Green AC, Webb PM, Whiteman DC. Current and past smoking significantly increase risk for Barrett's esophagus. Clin Gastroenterol Hepatol. 2009; 7:840–8. [PubMed: 19410015]
27. Edelstein ZR, Bronner MP, Rosen SN, Vaughan TL. Risk factors for Barrett's esophagus among patients with gastroesophageal reflux disease: a community clinic-based case-control study. American Journal of Gastroenterology. 2009; 104:834–42. [PubMed: 19319131]
28. Avidan B, Sonnenberg A, Schnell TG, Sontag SJ. Hiatal hernia and acid reflux frequency predict presence and length of Barrett's esophagus. Digestive Diseases and Sciences. 2002; 47:256–64. [PubMed: 11855539]

29. Fouad YM, Makhlouf MM, Tawfik HM, el-Amin H, Ghany WA, el-Khayat HR. Barrett's esophagus: prevalence and risk factors in patients with chronic GERD in Upper Egypt. World J Gastroenterol. 2009; 15:3511–5. [PubMed: 19630106]
30. Gerson LB, Ullah N, Fass R, Green C, Shetler K, Singh G. Does body mass index differ between patients with Barrett's oesophagus and patients with chronic gastro-oesophageal reflux disease? Alimentary Pharmacology and Therapeutics. 2007; 25:1079–86. [PubMed: 17439509]
31. Kubo A, Levin TR, Block G, Rumore G, Quesenberry CP Jr, Buffler P, Corley DA. Cigarette smoking and the risk of Barrett's esophagus. Cancer Causes and Control. 2008
32. Anderson LA, Watson RG, Murphy SJ, Johnston BT, Comber H, Mc Guigan J, Reynolds JV, Murray LJ. Risk factors for Barrett's oesophagus and oesophageal adenocarcinoma: results from the FINBAR study. World J Gastroenterol. 2007; 13:1585–94. [PubMed: 17461453]
33. Anderson LA, Cantwell MM, Watson RG, Johnston BT, Murphy SJ, Ferguson HR, McGuigan J, Comber H, Reynolds JV, Murray LJ. The association between alcohol and reflux esophagitis, Barrett's esophagus, and esophageal adenocarcinoma. Gastroenterology. 2009; 136:799–805. [PubMed: 19162028]
34. Kubo A, Levin TR, Block G, Rumore GJ, Quesenberry CP Jr, Buffler P, Corley DA. Alcohol types and sociodemographic characteristics as risk factors for Barrett's esophagus. Gastroenterology. 2009; 136:806–15. [PubMed: 19111726]
35. Thompson OM, Beresford SA, Kirk EA, Vaughan TL. Vegetable and fruit intakes and risk of Barrett's esophagus in men and women. American Journal of Clinical Nutrition. 2009; 89:890–6. [PubMed: 19144726]
36. Aro P, Ronkainen J, Storskrubb T, Bolling-Sternevald E, Carlsson R, Johansson SE, Vieth M, Stolte M, Engstrand L, Talley NJ, Agreus L. Valid symptom reporting at upper endoscopy in a random sample of the Swedish adult general population: the Kalixanda study. Scandinavian Journal of Gastroenterology. 2004; 39:1280–8. [PubMed: 15743007]
37. Zagari RM, Fuccio L, Wallander MA, Johansson S, Fiocca R, Casanova S, Farahmand BY, Winchester CC, Roda E, Bazzoli F. Gastro-oesophageal reflux symptoms, oesophagitis and Barrett's oesophagus in the general population: the Loiano-Monghidoro study. Gut. 2008; 57:1354–9. [PubMed: 18424568]
38. Poole C, Greenland S. Random-effects meta-analyses are not always conservative. American Journal of Epidemiology. 1999; 150:469–475. [PubMed: 10472946]
39. Higgins JPT, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ. 2003; 327:557–560. [PubMed: 12958120]
40. Lubin JH, Caporaso N, Wichmann HE, Schaffrath-Rosario A, Alavanja MC. Cigarette smoking and lung cancer: modeling effect modification of total exposure and intensity. Epidemiology. 2007; 18:639–48. [PubMed: 17700253]
41. Lubin JH, Caporaso NE. Cigarette smoking and lung cancer: modeling total exposure and intensity. Cancer Epidemiology, Biomarkers and Prevention. 2006; 15:517–23.
42. Buis ML. POSTRCSPLINE: Stata module containing post-estimation commands for models using a restricted cubic spline. 2009
43. Marrie RA, Dawson NV, Garland A. Quantile regression and restricted cubic splines are useful for exploring relationships between continuous variables. Journal of Clinical Epidemiology. 2009; 62:511–7 e1. [PubMed: 19135859]
44. Desquilbet L, Mariotti F. Dose-response analyses using restricted cubic spline functions in public health research. Statistics in Medicine. 2010
45. Hosmer DW, Lemeshow S. Confidence interval estimation of interaction. Epidemiology. 1992; 3:452–6. [PubMed: 1391139]
46. Rothman, KJ.; Greenland, S.; Lash, TL. Modern epidemiology. Wolters Kluwer Health/Lippincott Williams & Wilkins; 2008.
47. Eloubeidi MA, Provenzale D. Clinical and demographic predictors of Barrett's esophagus among patients with gastroesophageal reflux disease: a multivariable analysis in veterans. [see comment]. Journal of Clinical Gastroenterology. 2001; 33:306–9. [PubMed: 11588545]
48. Gray MR, Donnelly RJ, Kingsnorth AN. The role of smoking and alcohol in metaplasia and cancer risk in Barrett's columnar lined oesophagus. Gut. 1993; 34:727–31. [PubMed: 8314502]

49. Conio M, Filiberti R, Blanchi S, Ferraris R, Marchi S, Ravelli P, Lapertosa G, Iaquinto G, Sablich R, Gusmaroli R, Aste H, Giacosa A. Risk factors for Barrett's esophagus: a case-control study. Int J Cancer. 2002; 97:225–9. [PubMed: 11774268]
50. Veugelers PJ, Porter GA, Guernsey DL, Casson AG. Obesity and lifestyle risk factors for gastroesophageal reflux disease, Barrett esophagus and esophageal adenocarcinoma. Diseases of the Esophagus. 2006; 19:321–8. [PubMed: 16984526]
51. Steevens J, Schouten LJ, Goldbohm RA, van den Brandt PA. Alcohol consumption, cigarette smoking and risk of subtypes of oesophageal and gastric cancer: a prospective cohort study. Gut. 2010; 59:39–48. [PubMed: 19828467]
52. Lagergren J, Bergstrom R, Lindgren A, Nyren O. The role of tobacco, snuff and alcohol use in the aetiology of cancer of the oesophagus and gastric cardia. Int J Cancer. 2000; 85:340–6. [PubMed: 10652424]
53. Freedman ND, Abnet CC, Leitzmann MF, Mouw T, Subar AF, Hollenbeck AR, Schatzkin A. A prospective study of tobacco, alcohol, and the risk of esophageal and gastric cancer subtypes. Am J Epidemiol. 2007; 165:1424–33. [PubMed: 17420181]
54. Zhang ZF, Kurtz RC, Sun M, Karpeh M Jr, Yu GP, Gargon N, Fein JS, Georgopoulos SK, Harlap S. Adenocarcinomas of the esophagus and gastric cardia: medical conditions, tobacco, alcohol, and socioeconomic factors. Cancer Epidemiology, Biomarkers and Prevention. 1996; 5:761–8.
55. Kabat GC, Ng SK, Wynder EL. Tobacco, alcohol intake, and diet in relation to adenocarcinoma of the esophagus and gastric cardia. Cancer Causes and Control. 1993; 4:123–32. [PubMed: 8481491]
56. Gammon MD, Schoenberg JB, Ahsan H, Risch HA, Vaughan TL, Chow WH, Rotterdam H, West AB, Dubrow R, Stanford JL, Mayne ST, Farrow DC, Niwa S, Blot WJ, Fraumeni JF Jr. Tobacco, alcohol, and socioeconomic status and adenocarcinomas of the esophagus and gastric cardia. J Natl Cancer Inst. 1997; 89:1277–84. [PubMed: 9293918]
57. Freedman ND, Leitzmann MF, Hollenbeck AR, Schatzkin A, Abnet CC. Cigarette smoking and subsequent risk of lung cancer in men and women: analysis of a prospective cohort study. The Lancet Oncology. 2008; 9:649–56. [PubMed: 18556244]
58. Olliver JR, Hardie LJ, Gong Y, Dexter S, Chalmers D, Harris KM, Wild CP. Risk factors, DNA damage, and disease progression in Barrett's esophagus. Cancer Epidemiology, Biomarkers and Prevention. 2005; 14:620–5.
59. Smit CF, Copper MP, van Leeuwen JA, Schoots IG, Stanojcic LD. Effect of cigarette smoking on gastropharyngeal and gastroesophageal reflux. Annals of Otology, Rhinology and Laryngology. 2001; 110:190–3.
60. Kahrilas PJ, Gupta RR. Mechanisms of acid reflux associated with cigarette smoking. Gut. 1990; 31:4–10. [PubMed: 2318431]
61. Dennish GW, Castell DO. Inhibitory effect of smoking on the lower esophageal sphincter. N Engl J Med. 1971; 284:1136–7. [PubMed: 5553487]
62. Pandeya N, Webb PM, Sadeghi S, Green AC, Whiteman DC. Gastro-oesophageal reflux symptoms and the risks of oesophageal cancer: are the effects modified by smoking, NSAIDs or acid suppressants? Gut. 2010; 59:31–8. [PubMed: 19875392]
63. Shaheen N. Is there a "Barrett's iceberg?". Gastroenterology. 2002; 123:636–9. [PubMed: 12145816]
64. Hoffmann D, Djordjevic MV, Hoffmann I. The changing cigarette. Prev Med. 1997; 26:427–34. [PubMed: 9245661]
65. Brigham J, Lessov-Schlaggar CN, Javitz HS, McElroy M, Krasnow R, Swan GE. Reliability of adult retrospective recall of lifetime tobacco use. Nicotine & Tobacco Research. 2008; 10:287–299. [PubMed: 18236293]

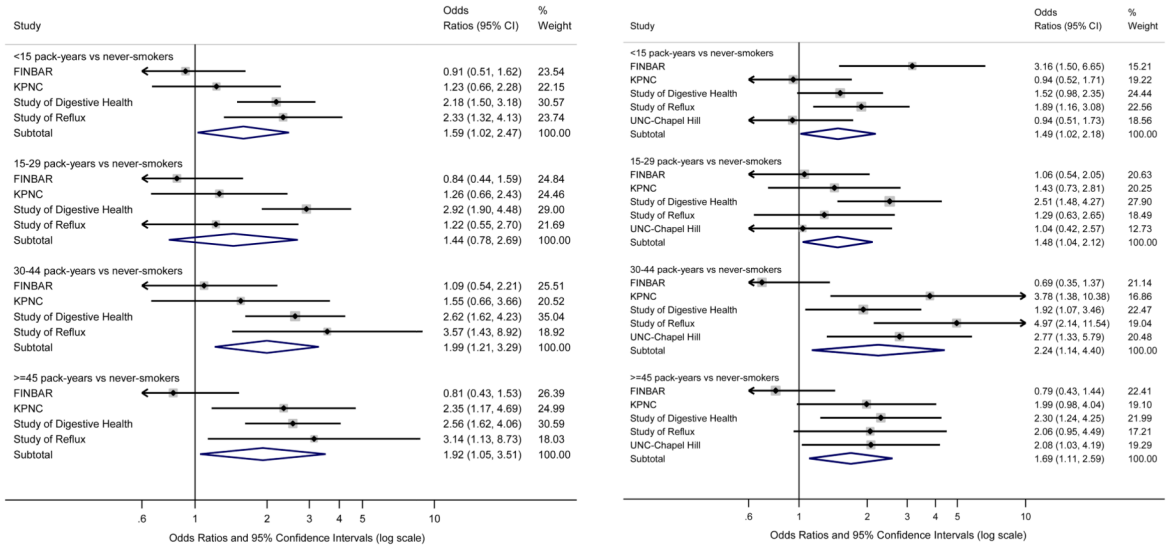

Figure 1.

Forest plots of the relationship between increasing categories of cigarette smoking and Barrett's esophagus compared with (A) population- based controls; and (B) gastroesophageal reflux (GERD) controls. Each study's estimate is represented by the corresponding black square with the arms representing 95 percent confidence intervals. The grey-box overlaying each estimate represents the weight which it contributes to the pooled estimate. The pooled estimates are designated by the diamonds which follow each subgroup; the widths of the diamonds represent the 95 percent confidence intervals.

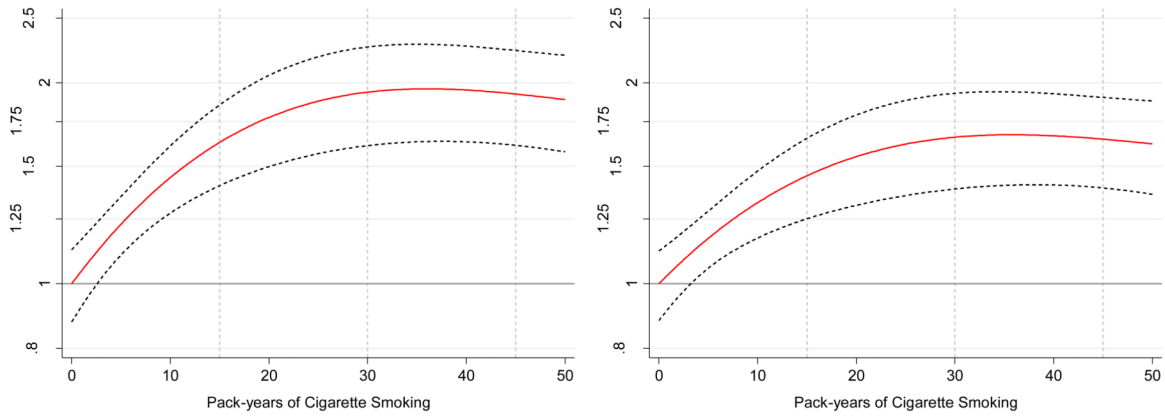

Figure 2.

Spline plots of the relationship between increasing categories of cigarette smoking and Barrett's esophagus compared with (A) population-based controls; and (B) gastroesophageal reflux (GERD) controls. The solid line represents the estimate of the odds ratio while the broken lines either side represent 95 percent confidence intervals.

Table 1

Recruitment, criteria and numbers for analysis in each of the Barrett's esophagus case-control studies.

Study	Location	Barrett's Esophagus Cases (*n*)	Barrett's Esophagus Case Definition	GERD Controls (*n*)	GERD Control Definition	Population based Controls (*n*)	Population-based Control Definition
KPNC	Northern California, USA	187	Incident cases recruited from KPNC, October 2002 – September 2005. SIM & any length of macroscopic BE. Exclusions: gastric-type metaplasia only, indicative biopsy from squamocolumnar junction only.	172	GERD: prior to their index date: a GERD-related diagnosis code (ICD-9: 530.11 [reflux esophagitis] or 530.81 [gastroesophageal reflux]); a prescription ≥90 day supply of a H2RA or PPI in the previous year; recent esophagogastroduodenoscopy that was negative for esophageal columnar metaplasia (macroscopic or histologic) of any type. Frequency matched on age at the index date, sex, and geographic region to the distribution of BE cases. Exclusions: previous BE diagnosis.	185	KPNC members without an electronic diagnosis of BE at the time the BE cases were identified, frequency matched on age at index date, sex, and geographic region to the distribution of BE cases.
Study of Digestive Health	Brisbane, Queensland, Austraia	362	Incident cases of BE, or of dysplasia in previously diagnosed BE, recruited from two major private pathology laboratories and the single public pathology laboratory serving metropolitan Brisbane, Australia, February 2003 – June 2006. SIM & any length of macroscopic BE.	287	GERD: acute inflammatory changes on histology consistent with gastroesophageal reflux. Exclusions: Any other major pathology identified on endoscopy/histology.	562	Population-based controls, randomly selected from the Australian Electoral roll. Frequency matched on age and sex to a case series. Control participants had to reside within the same geographical region as the BE cases and GERD controls.
Study of Reflux Disease	Washington, USA	149	Incident cases recruited from 5 community gastroenterology clinics, October 1997 –	347	GERD: referred for endoscopy due to reflux symptoms, but negative for SIM. Frequency-matched on the month of biopsy and	172	Population-based controls, selected from geographic areas in close proximity to those of BE cases using a modified version of the Waksberg random-digit dialing method.

Study	Location	Barrett's Esophagus Cases (*n*)	Barrett's Esophagus Case Definition	GERD Controls (*n*)	GERD Control Definition	Population based Controls (*n*)	Population-based Control Definition
			September 2000. Endoscopy referral due to chronic GERD symptoms. SIM.		clinic to the distribution of BE cases.		Individually matched to BE cases on age (+/−3 years) and sex.
FINBAR	Northern Ireland and Republic of Ireland	187	Incident and prevalent cases recruited from the island of Ireland, March 2002 – December 2004. SIM & ≥3 cm of macroscopic BE. Exclusions: dysplasia.	217	Erosive esophagitis (incident and prevalent diagnoses):macroscopically diagnosed (grades 2–4 in the Savary Miller/Hetzel-Dent classification/grades B, C, or D in the LA classification), recruited from Northern Ireland, September 2004 – July 2005. Exclusions: BE, macroscopic or histologic evidence of infection, dysmotility, gastric outlet obstruction. Frequency matched on age and sex to the distribution of EA patients.	224	Population-based controls. Northern Ireland: selected at random from General Practice Master Index of each province. Republic of Ireland: selected at random from 4 general practices to reflect the urban/rural distribution of EA patients in the Republic of Ireland. Frequency matched on age and sex to the distribution of EA patients. Recruited from the island of Ireland between March 2002 – December 2000.
UNC-Chapel Hill	North Carolina, USA	174	Incident and prevalent cases recruited from an endoscopy clinic-based study between 2001–2006. SIM & any length of macroscopic BE.	309	GERD diagnosed by a physician: referred for endoscopy due to reflux symptoms, but negative for macroscopic BE & SIM. Sampled in 2:1 ratio to BE subjects.	0	N/A
		1,059		1,332		1,143	

Abbreviations: BE, Barrett's esopagus; EA, esophageal adenocarcinoma; GERD, gastroesophageal reflux disease; SIM, specialized intestinal metaplasia.

Table 2

Descriptors of Participants Selected for Analysis of Cigarette Smoking in Relation to Barrett's Esophagus in the International BEACON Consortium

Variable	BE (n=1,059)	GERD Controls (n=1,332)		Population-based Controls (n=1,143)	
	Mean (SD)/Percentage (95%CI)	Mean (SD)/Percentage (95%CI)	P value	Mean (SD)/Percentage (95%CI)	P value
Age (years)	59 (12)	54 (14)	*<0.001*	59 (12)	*0.874*
Sex (% male)	68 (66–71)	52 (50–55)	*<0.001*	64 (62–67)	*0.039*
Education (% college or university)	66 (63–69)	64 (61–67)	*0.243*	67 (64–69)	*0.763*
Body mass index (kg/m^2)	28.4 (5.1)	28.3 (5.3)	*0.759*	27.6 (5.1)	*<0.001*
Heartburn (%)	83 (81–86)	n/a	n/a	47 (44–50)	*<0.001*
Regurgitation (%)	76 (74–79)	n/a	n/a	44 (42–47)	*<0.001*
Heartburn or Regurgitation (%)	91 (89–93)	n/a	n/a	57 (54–60)	*<0.001*
Alcohol (%)	77 (75–80)	76 (73–78)	*0.328*	82 (80–84)	*0.005*
Cigarette smoking (%)	63 (60–65)	50 (47–52)	*<0.001*	49 (46–51)	*<0.001*
Pack-years	31 (26)	26 (25)	*<0.001*	29 (29)	*0.355*
Cigarettes/day	22 (14)	20 (14)	*0.007*	21 (15)	*0.169*
Years Smoked	26 (14)	23 (14)	*<0.001*	25 (14)	*0.330*

The mean and standard deviation of each variable are provided, unless the variable is stated to be a percenatge (%) in which case the numbers in parentheses are the 95 percent confidence interval (95%CI) of the percentage. P values were determined using the t-test for continuous variables and the Pearson chi-squared test for categorical variables. P values in italics are statistically significant at alpha=0.05.

Table 3

Fully adjusted odds ratios and 95% confidence intervals for the association between cigarette smoking and risk of Barrett's esophagus.

	Barrett's Esophagus											
		Population Controls						GERD Controls				
	n	*n*	OR	95% CI	I^2 (95%UI)	*N*	*n*	*n*	OR	95% CI	I^2 (95%UI)	*N*
Ever cigarette smoking												
No	325	580		referent			382	643		referent		
Yes	548	541	1.67	1.04 – 2.67	82 (54–93)	4	638	635	1.61	1.33 – 1.96	11 (0–81)	5
Pack-years of smoking												
0 (never smokers)	325	580		referent			382	643		referent		
<15	185	205	1.59	1.02 – 2.47	64 (0–88)	4	208	269	1.49	1.02 – 2.18	57 (0–84)	5
15 to <30	129	134	1.44	0.78 – 2.69	76 (33–91)	4	137	136	1.48	1.04 – 2.12	27 (0–71)	5
30 to <45	102	85	1.99	1.21 – 3.29	49 (0–83)	4	124	91	2.24	1.14 – 4.40	75 (38–90)	5
≥45	132	118	1.92	1.05 – 3.51	70 (12–89)	4	155	129	1.69	1.11 – 2.59	49 (0–81)	5
p for trend	*873*	*1,122*		*0.057*		4	*1,006*	*1,268*		*0.009*		5
p for trend excluding never smokers	*548*	*542*		*0.193*		4	*619*	*625*		*0.170*		5
Smoking duration*												
<30 years	328	338		referent			352	395		referent		
≥30 years	220	204	0.95	0.68 – 1.35	0 (0–81)	4	267	230	0.98	0.69 – 1.40	0 (0–76)	5
Smoking intensity*												
<1 pack per day	207	230		referent			225	277		referent		
1 pack per day	163	151	1.16	0.79 – 1.68	3 (0–85)	4	188	170	1.02	0.71 – 1.46	0 (0–78)	5
>1 pack per day	178	161	1.02	0.63 – 1.65	0 (0–53)	4	206	178	0.97	0.44 – 2.13	59 (0–85)	5
Age of smoking initiation*												
<17 years	259	247		referent			258	239		referent		
≥17 years	289	294	0.96	0.70 – 1.32	21 (0–88)	4	287	269	0.96	0.65 – 1.41	44 (0–81)	4
Smoking cessation*												
<20 years	193	164		referent			224	232		referent		
≥20 years	205	229	0.91	0.64 – 1.31	0 (0–76)	4	227	206	1.24	0.86 – 1.78	0 (0–58)	5

Results were adjusted for age (categorical: <50, 50–59, 60–69, ≥ 70), sex, body mass index (categorical: <25, 25–29, 30–34, 35–39 ≥ 40), and education (except UNC).

* Also adjusted for pack-years of smoking (categorical: <15, 15–29, 30–44, ≥45). Abbreviations: GERD, gastroesophageal reflux disease; OR, odds ratio; UI, uncertainty interval.

Table 4

Interaction statistics for departure from additivity

Variables Tested for Interaction with Ever-smoking	Departure from Additivity		
	ICR (95%CI) [*null hypothesis=0*]	**AP (95%CI) [*null hypothesis=0*]**	**S (95%CI) [*null hypothesis=1*]**
Barrett's Esophagus vs. Population-based Controls			
BMI	0.06 (−0.58, 0.69)	0.03 (−0.24, 0.29)	1.05 (0.64, 1.71)
Heartburn	*2.75 (0.67, 4.82)*	*0.27 (0.10, 0.44)*	*1.43 (1.10, 1.86)*
Regurgitation	*4.58 (2.16, 7.00)*	*0.41 (0.27, 0.55)*	*1.82 (1.38, 2.40)*
Heartburn or Regurgitation	*6.41 (2.71, 10.10)*	*0.39 (0.25, 0.52)*	*1.71 (1.34, 2.18)*
Alcohol	−0.24 (−0.98, 0.49)	−0.18 (−0.72, 0.35)	0.59 (0.17, 1.99)
Helicobacter pylori	0.16 (−0.79, 1.11)	0.06 (−0.32, 0.45)	1.12 (0.54, 2.35)
NSAID	0.31 (−0.16, 0.77)	0.20 (−0.09, 0.50)	2.55 (0.23, 28.62)
Barrett's Esophagus vs. GERD Controls			
BMI	−0.26 (−0.72, 0.20)	−0.20 (−0.55, 0.16)	0.54 (0.20, 1.51)
Alcohol	0.36 (−0.06, 0.78)	0.27 (−0.06, 0.60)	–
Helicobacter pylori	−0.07 (−0.78, 0.63)	−0.05 (−0.56, 0.46)	0.83 (0.18, 3.85)
NSAID	0.42 (−0.03, 0.86)	0.27 (0.00, 0.55)	5.22 (0.05, 561.36)

Abbreviations: AP, attributable proportion due to interaction; ICR, interaction contrast ratio; OR, odds ratio; S, synergy index. Italicized estimate and confidence interval represents statistical significance ($p<0.05$).