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

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**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. We investigated whether tobacco smoking and other factors increase risk for Barrett's esophagus. **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 Barrett's esophagus (n = 1059) with those from subjects with gastroesophageal reflux disease (gastroesophageal reflux disease controls, n = 1332), and population-based controls (n = 1143), using multivariable logistic regression models to test associations with cigarette smoking. We also tested whether cigarette smoking has synergistic effects with other exposures, which might further increase risk for Barrett's esophagus. **RESULTS:** Subjects with Barrett's esophagus 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 gastroesophageal reflux disease controls (OR = 1.61; 95% CI: 1.33–1.96). Increasing pack-years of smoking increased the risk for Barrett's esophagus. There was evidence of 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 (95% CI: 0.25–0.52). **CONCLUSIONS:** Cigarette smoking is a risk factor for Barrett's esophagus. The association was 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 development of Barrett's esophagus.

**Keywords:** BEACON; Esophageal Cancer; Population Study; Tobacco.

Barrett's esophagus is a columnar metaplasia of the distal esophagus associated with a 10- to 55-fold increased risk of esophageal adenocarcinoma.<sup>1–7</sup> Barrett's esophagus<sup>8–11</sup> and esophageal adenocarcinoma<sup>12–14</sup> have been increasing in incidence, particularly in developed countries with predominantly white populations. For ex-

ample, in the United States, esophageal adenocarcinoma in white populations has increased from 0.4 to >3 per 100,000 person-years during the last 35 years—a 650% increase.<sup>12,15</sup> This increasing incidence is not solely due to changes in diagnostic practice, and has been attributed to temporal changes in exposure to risk factors.<sup>16</sup>

The known risk factors for Barrett's esophagus and esophageal adenocarcinoma are few and include gastroesophageal reflux<sup>17,18</sup> and increasing body mass index (BMI).<sup>19–21</sup> Cigarette smoking has also been implicated in the etiology of esophageal adenocarcinoma,<sup>22</sup> but whether this is because smoking is a risk factor for early events in the carcinogenic pathway (ie, 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<sup>18,23–27</sup> and others not.<sup>28–32</sup>

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 gastroesophageal reflux disease (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 5 case-control studies in

**Abbreviations used in this paper:** BEACON, Barrett's and Esophageal Adenocarcinoma Consortium; BMI, body mass index; CI, confidence interval; FINBAR, Factors Influencing the Barrett's/Adenocarcinoma Relationship; GERD, gastroesophageal reflux disease; OR, odds ratio.

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the international Barrett's and Esophageal Adenocarcinoma Consortium (BEACON, <http://beacon.tlvnet.net/>).

## Materials and Methods

### Study Population

The BEACON consortium was formed in 2005 with support from the US 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 help development of new studies of etiology, prevention, and survival.

The following are 5 Barrett's esophagus case-control studies included in this BEACON analysis: the Factors Influencing the Barrett's/Adenocarcinoma Relationship (FINBAR) study based in Ireland<sup>33</sup>; Epidemiology and Incidence of Barrett's Esophagus study nested within Kaiser Permanente Northern California<sup>34</sup>; Study of Reflux Disease, based in western Washington state<sup>35</sup>; Study of Digestive Health based in Brisbane, Australia<sup>26</sup>; and Epidemiologic Case-Control Study of Barrett's Esophagus based at The University of North Carolina at Chapel Hill, NC. For comparison with Barrett's esophagus cases, 2 control groups were available: 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 2 groups are less affected by potential ascertainment bias than comparisons between Barrett's esophagus cases and population-based controls because it inherently controls for known and unknown potentially confounding factors associated with being referred for and undergoing an endoscopic procedure. In addition, because 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, and is also representative of the local population from which the Barrett's esophagus cases are referred and diagnosed. Studies that 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 2 control groups.<sup>36,37</sup> All 5 studies contributed individual patient data to the GERD control group and 4 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 5 studies provided 1320 cases of Barrett's esophagus, 1659 GERD controls, and 1434 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 pipe tobacco or cigars was defined as meeting a study-specific low threshold exposure (a period of  $\geq 6$  months or  $\geq 20$  times during the life-course). Because of the relatively small number of non-white Barrett's esophagus cases remaining (17 black, 31 His-

panic, 39 other, and 18 missing), we restricted our analysis to white study participants. After exclusions, there remained 1059 Barrett's esophagus cases, 1332 GERD controls, and 1143 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,  $\geq 45$ ). Additional exposure variables included duration of cigarette smoking (<30 years,  $\geq 30$  years), cigarette smoking intensity (<1, 1, and >1 packs/day), age of cigarette smoking initiation (<17,  $\geq 17$  years), and duration of cigarette smoking cessation (<20 years,  $\geq 20$  years). Cigarette smoking intensity and cigarette smoking duration in the University of North Carolina-Chapel Hill study were ascertained in categories and were recoded to the median of the categories using the distributions of the other 4 studies combined. Ever cigarette smoking was defined as either low threshold exposures ( $\geq 100$  cigarettes,  $\geq 20$  packs of cigarettes, 1 cigarette a day for  $\geq 6$  months) or by asking whether the patient had ever smoked. The following covariates were assessed for inclusion in regression models: age; sex; BMI (weight divided by square of height [ $\text{kg}/\text{m}^2$ ]); education; alcohol; fat, and trans-fat 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 (ie, non-steroidal anti-inflammatory drugs, antacids, proton pump inhibitors, and H<sub>2</sub>-receptor antagonists). A covariate was included in the fully adjusted models if it altered an estimate by >10% or it was considered a known confounder (eg, age, sex, BMI, and education).

### Statistical Analysis

We used a 2-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, so we present the random-effects models only, as such models are usually more conservative.<sup>38</sup> A study was excluded from the second-step of a specific variable's analysis if the logistic regression model failed because of instability. The  $I^2$  value and its 95% uncertainty interval were used to estimate the percentage of total variation across studies due to heterogeneity.<sup>39</sup> An  $I^2$  statistic of 0% indicates no observed heterogeneity that cannot be attributed to chance, and larger values indicate increasing heterogeneity.

Exposure variables were assessed in relation to the outcomes of Barrett's esophagus using the following 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 covariate's age (<50, 50–59, 60–69,  $\geq 70$  years) and sex. Fully adjusted models also included BMI (<18.5, 18.5–24, 25–29, 30–34, 35–39,  $\geq 40$ ) and education (categorical: school only, tech/diploma, university; unavailable and so unadjusted

**Table 1.** Recruitment, Criteria, and Numbers for Analysis in Each of the Barrett's Esophagus Case-Control Studies

| Study                     | Location                                 | BE cases, <i>n</i> | Barrett's esophagus case definition   | GERD controls, <i>n</i> | GERD control definitions  | Population-based controls, <i>n</i> | Population-based control definition   |
|---------------------------|--|--------------------|---|-------------------------|---|-------------------------------------|---|
| KPNC                      | Northern California, USA                 | 187                | Incident cases recruited from KPNC, October 2002 to September 2005. SIM and any length of macroscopic BE. Exclusions: gastric-type metaplasia only, indicative biopsy from squamocolumnar junction.   | 172                     | Prior to their index date: a GERD-related diagnosis code (ICD-9: 530.11 [reflux esophagitis] or 530.81 [gastroesophageal reflux]); a prescription $\geq$ 90-day supply of an 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 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, Australia          | 362                | Incident cases of BE, or of dysplasia in previously diagnosed BE, recruited from 2 major private pathology laboratories and the single public pathology laboratory serving metropolitan Brisbane, Australia, February 2003–June 2006. SIM and any length of macroscopic BE. | 287                     | Acute inflammatory changes on histology consistent with gastroesophageal reflux. Exclusions: Any other major pathology identified on endoscopy/histology.   | 562                                 | 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–September 2000. Endoscopy referral due to chronic GERD symptoms. SIM.  | 347                     | Referred for endoscopy due to reflux symptoms, but negative for SIM. Frequency-matched on the month of biopsy and clinic to the distribution of BE cases.   | 172                                 | Selected from geographic areas in close proximity to those of BE cases using a modified version of the Waksberg random-digit dialing method. Individually matched to BE cases on age ( $\pm$ 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 and $\geq$ 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                                 | 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 and 2006. SIM and any length of macroscopic BE.  | 309                     | GERD diagnosed by a physician: referred for endoscopy due to reflux symptoms, but negative for macroscopic BE and SIM. Sampled in 2:1 ratio to BE subjects.   | 0                                   | NA  |
| <b>Total</b>              |  | <b>1,059</b>       |   | <b>1332</b>             |   | <b>1143</b>                         |   |

BE, Barrett's esophagus; EA, esophageal adenocarcinoma; H2RA, H2-receptor antagonists; ICD-9, International Classification of Diseases, 9<sup>th</sup> revision; KPNC, Kaiser Permanente Northern California; NA, not available; PPI, proton pump inhibitors; SIM, specialized intestinal metaplasia.



for in University of North Carolina-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 (eg, ever-smoke × sex). Heartburn was generally described to the patient as having ever experienced burning pain or discomfort behind the breast bone, and regurgitation was generally described as food or stomach fluid coming back up into the mouth accompanied with a sour-taste; Kaiser Permanente Northern California excluded symptoms within 1 year before diagnosis of Barrett's esophagus, and FINBAR excluded symptoms within 5 years. In addition, FINBAR required symptoms to be frequent (>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.<sup>40,41</sup>

Spline models<sup>42</sup> 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 nonlinear relationships between an exposure and an outcome<sup>43,44</sup>—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 2 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), heartburn and regurgitation (population-based control comparisons only), alcohol, *H pylori*, and nonsteroidal anti-inflammatory drugs. For each combination of variables, we generated 4 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 3 interaction statistics: interaction contrast ratio, attributable proportion, and synergy index.<sup>45,46</sup> When the interaction contrast ratio and attributable proportion ≠ 0 and synergy index ≠ 1, there is evidence for departure from additivity (biological interaction). Interaction contrast ratio is the excess risk due to interaction relative to the risk without either exposure. Attributable proportion is the proportion of disease attributable to interaction among individuals with both exposures. Synergy index 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 (ie, under the assumption of no additive interaction). Confidence intervals for these metrics were estimated using the delta method.<sup>45</sup>

All analyses were performed using STATA software, version 11.1 (StataCorp LP, College Station, TX). All statistical tests were 2-sided and *P* values <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 because 3 of the 4 studies with population-based controls 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 1 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

**Table 2.** Descriptors of Participants Selected for Analysis of Cigarette Smoking in Relation to Barrett's Esophagus in the International BEACON Consortium

| Variable                                      | BE<br>(n = 1059) | GERD controls<br>(n = 1332) | <i>P</i> value | Population-based controls<br>(n = 1143) | <i>P</i> value |
|---|------------------|-----------------------------|----------------|---|----------------|
| Age, y, mean (SD)                             | 59 (12)          | 54 (14)                     | <.001          | 59 (12)                                 | .874           |
| Male sex, % (95% CI)                          | 68 (66–71)       | 52 (50–55)                  | <.001          | 64 (62–67)                              | .039           |
| Education (college or university), % (95% CI) | 66 (63–69)       | 64 (61–67)                  | .243           | 67 (64–69)                              | .763           |
| Body mass index, mean (SD)                    | 28.4 (5.1)       | 28.3 (5.3)                  | .759           | 27.6 (5.1)                              | <.001          |
| Heartburn, % (95% CI)                         | 83 (81–86)       | NA                          | NA             | 47 (44–50)                              | <.001          |
| Regurgitation, % (95% CI)                     | 76 (74–79)       | NA                          | NA             | 44 (42–47)                              | <.001          |
| Heartburn or regurgitation, % (95% CI)        | 91 (89–93)       | NA                          | NA             | 57 (54–60)                              | <.001          |
| Alcohol, % (95% CI)                           | 77 (75–80)       | 76 (73–78)                  | .328           | 82 (80–84)                              | .005           |
| Cigarette smoking, % (95% CI)                 | 63 (60–65)       | 50 (47–52)                  | <.001          | 49 (46–51)                              | <.001          |
| Pack-years, mean (SD)                         | 31 (26)          | 26 (25)                     | <.001          | 29 (29)                                 | .355           |
| Cigarettes/day, mean (SD)                     | 22 (14)          | 20 (14)                     | .007           | 21 (15)                                 | .169           |
| Years smoked, mean (SD)                       | 26 (14)          | 23 (14)                     | <.001          | 25 (14)                                 | .330           |

NOTE. *P* values were determined using the *t* test for continuous variables and the Pearson  $\chi^2$  test for categorical variables. *P* values in italics are statistically significant at  $\alpha = .05$ .

SD, standard deviation.

**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 <sup>2</sup> (95% UI) | n | n             | n    | OR   | 95% CI    | I <sup>2</sup> (95% UI) | n |  |
| Ever cigarette smoking                        |                     |      |      |           |                         |   |               |      |      |           |                         |   |  |
| No  | 325                 | 580  |      |           | Referent                | 4 | 382           | 643  |      |           | Referent                | 5 |  |
| 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                | 4 | 382           | 643  |      |           | Referent                | 5 |  |
| <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                 | 1122 |      | 0.057     |                         | 4 | 1006          | 1268 |      | 0.009     |                         | 5 |  |
| P for trend excluding never smokers           | 548                 | 542  |      | 0.193     |                         | 4 | 619           | 625  |      | 0.170     |                         | 5 |  |
| Smoking duration, <sup>a</sup> y              |                     |      |      |           |                         |   |               |      |      |           |                         |   |  |
| <30   | 328                 | 338  |      |           | Referent                | 4 | 352           | 395  |      |           | Referent                | 5 |  |
| ≥30   | 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, <sup>a</sup> packs per day |                     |      |      |           |                         |   |               |      |      |           |                         |   |  |
| <1  | 207                 | 230  |      |           | Referent                | 4 | 225           | 277  |      |           | Referent                | 5 |  |
| 1   | 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  | 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, <sup>a</sup> y     |                     |      |      |           |                         |   |               |      |      |           |                         |   |  |
| <17   | 259                 | 247  |      |           | Referent                | 4 | 258           | 239  |      |           | Referent                | 4 |  |
| ≥17   | 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, <sup>a</sup> y             |                     |      |      |           |                         |   |               |      |      |           |                         |   |  |
| <20   | 193                 | 164  |      |           | Referent                | 4 | 224           | 232  |      |           | Referent                | 5 |  |
| ≥20   | 205                 | 229  | 0.91 | 0.64–1.31 | 0 (0–76)                | 4 | 227           | 206  | 1.24 | 0.86–1.78 | 0 (0–58)                | 5 |  |

NOTE. 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 University of North Carolina).

UI, uncertainty interval.

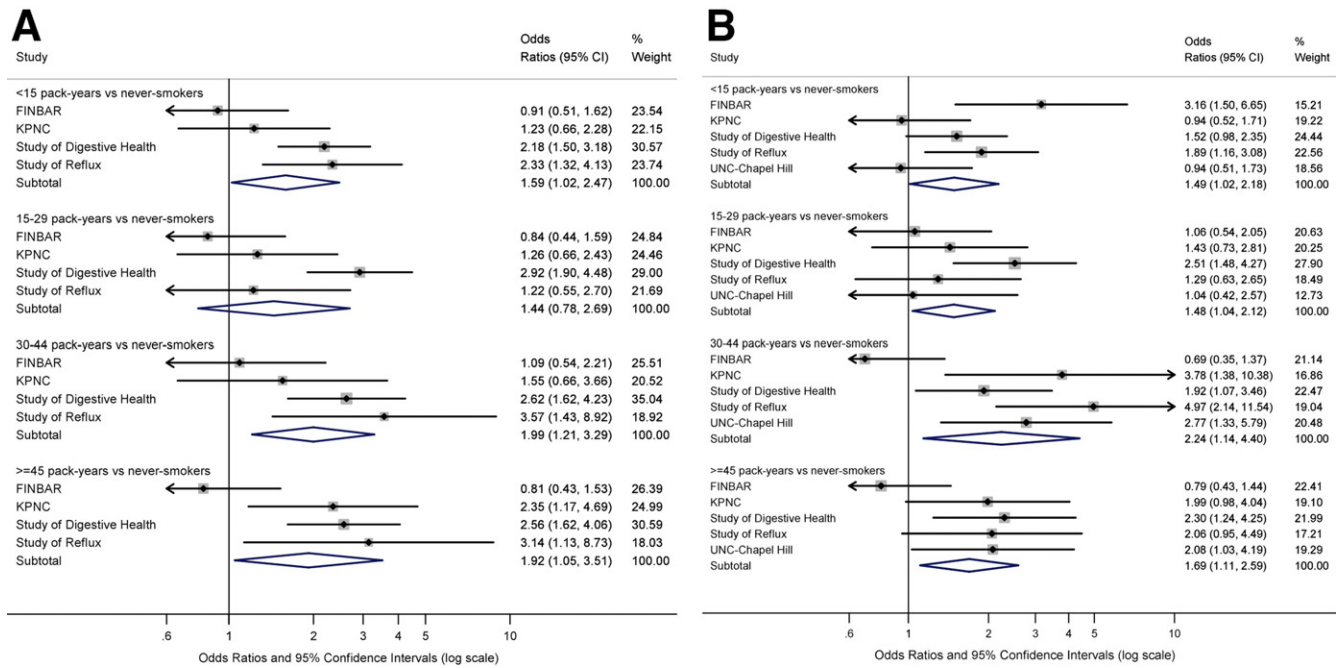
<sup>a</sup>Also adjusted for pack-years of smoking (categorical: <15, 15–29, 30–44, ≥45).

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% uncertainty interval: 0–81%) than estimates from population-based control models ( $I^2 = 82\%$ , 95% uncertainty interval: 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), although 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 to 29 pack-years of smoking exposure groups, and approximately 2 for each of the higher exposure groups (ie, 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 that 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 heterogeneity ( $I^2$  values) decreased (population-based controls: OR<sub>ever-smoke</sub> = 2.09; 95% CI: 1.54–2.83;  $I^2 = 44\%$ ; OR<sub><15</sub> = 1.93; 95% CI: 1.36–2.74;  $I^2 = 30\%$ ; OR<sub>15–29</sub> = 1.75; 95% CI: 0.93–3.30;  $I^2 = 68\%$ ; OR<sub>30–44</sub> = 2.49; 95% CI: 1.70–3.65;  $I^2 = 0\%$ ; OR<sub>≥45</sub> = 2.57; 95% CI: 1.79–3.67;  $I^2 = 0\%$ ; GERD controls: OR<sub>ever-smoke</sub> = 1.75; 95% CI: 1.43–2.15;  $I^2 = 0\%$ ; OR<sub><15</sub> = 1.32; 95% CI: 0.95–1.84;  $I^2 = 38\%$ ; OR<sub>15–29</sub> = 1.62; 95% CI: 1.09–2.41;  $I^2 = 25\%$ ; OR<sub>30–44</sub> = 2.87; 95% CI: 1.88–4.38;  $I^2 = 19\%$ ; OR<sub>≥45</sub> = 2.12; 95% CI: 1.50–3.00;  $I^2 = 0\%$ ).

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

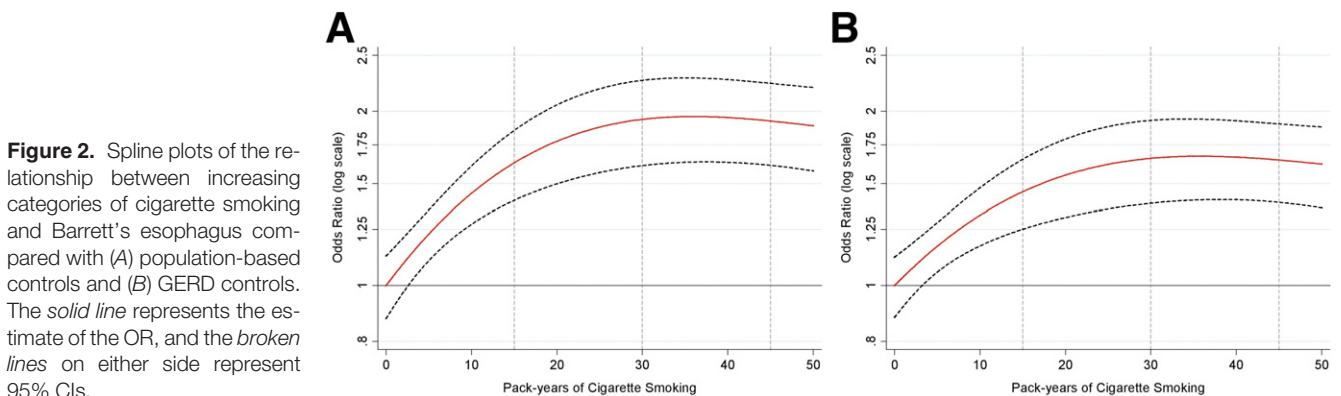


**Figure 1.** Forest plots of the relationship between increasing categories of cigarette smoking and Barrett’s esophagus compared with (A) population-based controls and (B) GERD controls. Each study’s estimate is represented by the corresponding *black square* with the arms representing 95% CIs. The *gray box* overlaying each estimate represents the weight that it contributes to the pooled estimate. The pooled estimates are designated by the *diamonds* that follow each subgroup; the widths of the *diamonds* represent the 95% CIs. KPNC, Kaiser Permanente Northern California; UNC, University of North Carolina.

men ( $OR_{\text{ever-smoke}} = 1.81$ ; 95% CI: 1.43–2.30;  $I^2 = 0\%$ ) than women ( $OR_{\text{ever-smoke}} = 1.32$ ; 95% CI: 0.91–1.92;  $I^2 = 31\%$ ) compared with GERD controls (Supplementary Table 1). Although ever-smoking stratified by sex was statistically significant ( $P = .041$ ), pack-years of cigarette smoking was not ( $P = .5$ ). 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 might be stronger in those with a lower BMI ( $P = .046$ ), when using the population-based controls as the comparison group, although no pattern by BMI was discernable when compared with GERD controls ( $P = .9$ ; 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

( $OR_{\text{ever-smoke}} = 3.35$ ; 95% CI: 1.55–7.26;  $I^2 = 0\%$ ) compared with individuals who reported symptoms ( $OR_{\text{ever-smoke}} = 1.99$ ; 95% CI: 1.50–2.65;  $I^2 = 23\%$ ) 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 2 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 among those exposed to both risk



**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) GERD controls. The *solid line* represents the estimate of the OR, and the *broken lines* on either side represent 95% CIs.

**Table 4.** Interaction Statistics for Departure From Additivity

| Variables tested for interaction with ever-smoking | Departure from additivity             |                                      |                                     |
|--|---------------------------------------|--------------------------------------|-------------------------------------|
|  | ICR (95% CI)<br>(null hypothesis = 0) | AP (95% CI)<br>(null hypothesis = 0) | S (95% CI)<br>(null hypothesis = 0) |
| Barrett's esophagus vs population-based controls   |                                       |                                      |                                     |
| BMI  | 0.06 (−0.58 to 0.69)                  | 0.03 (−0.24 to 0.29)                 | 1.05 (0.64 to 1.71)                 |
| Heartburn  | <i>2.75 (0.67 to 4.82)</i>            | <i>0.27 (0.10 to 0.44)</i>           | <i>1.43 (1.10 to 1.86)</i>          |
| Regurgitation                                      | <i>4.58 (2.16 to 7.00)</i>            | <i>0.41 (0.27 to 0.55)</i>           | <i>1.82 (1.38 to 2.40)</i>          |
| Heartburn or regurgitation                         | <i>6.41 (2.71 to 10.10)</i>           | <i>0.39 (0.25 to 0.52)</i>           | <i>1.71 (1.34 to 2.18)</i>          |
| Alcohol  | −0.24 (−0.98 to 0.49)                 | −0.18 (−0.72 to 0.35)                | 0.59 (0.17 to 1.99)                 |
| <i>H pylori</i>                                    | 0.16 (−0.79 to 1.11)                  | 0.06 (−0.32 to 0.45)                 | 1.12 (0.54 to 2.35)                 |
| NSAID  | 0.31 (−0.16 to 0.77)                  | 0.20 (−0.09 to 0.50)                 | 2.55 (0.23 to 28.62)                |
| Barrett's esophagus vs GERD control                |                                       |                                      |                                     |
| BMI  | −0.26 (−0.72 to 0.20)                 | −0.20 (−0.55 to 0.16)                | 0.54 (0.20 to 1.51)                 |
| Alcohol  | 0.36 (−0.06 to 0.78)                  | 0.27 (−0.06 to 0.60)                 | —                                   |
| <i>H pylori</i>                                    | −0.07 (−0.78 to 0.63)                 | −0.05 (−0.56 to 0.46)                | 0.83 (0.18 to 3.85)                 |
| NSAID  | 0.42 (−0.03 to 0.86)                  | 0.27 (0.00 to 0.55)                  | 5.22 (0.05 to 561.36)               |

NOTE. Italicized estimate and confidence interval represents statistical significance ( $P < .05$ ).

AP, attributable proportion due to interaction; ICR, interaction contrast ratio; NSAID, nonsteroidal anti-inflammatory drugs; synergy index.

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 (95% CI: 1.04–2.80) for those exposed to smoking only, and 16.47 (95% CI: 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 5 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 mean 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 might 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,<sup>23,24</sup> endoscopy-negative controls,<sup>18,25</sup> or GERD controls,<sup>18,28–30</sup> and other

studies have not found evidence for a relationship.<sup>47–50</sup> The analysis presented here 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 with 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 ORs 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 can expect to observe an association between smoking and esophageal adenocarcinoma as well. Studies of this malignancy compared with population-based or hospital controls also provide evidence for an association with cigarette smoking,<sup>50–55</sup> including a recent pooled esophageal adenocarcinoma analysis from the international BEACON group.<sup>22</sup> 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, might account for a large proportion (~40%) of esophageal adenocarcinomas.<sup>56</sup> 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, that is, 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.<sup>33</sup> Omission of this study reduced the heterogeneity and had minimal effects on the summary risk estimates attained, reinforcing the conclusions drawn. It is not known 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, and provision of individual patient data enabled similar confounding structures to be constructed for study-specific models. FINBAR's inclusion criteria did restrict recruitment of patients to those with long-segment Barrett's esophagus ( $\geq 3$  cm; Table 1); a criterion not used by the other 4 studies included in this analysis. However, this is unlikely to have led to lower estimates of association, given that a previous analysis of Kaiser Permanente Northern California 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 ( $< 3$  cm; OR = 1.19; 95% CI: 0.76–1.85).<sup>31</sup> 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 might 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,<sup>57</sup> 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 among individuals exposed to these 2 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 might not only have direct genotoxic effects,<sup>58</sup> but might also induce transient lower esophageal sphincter relaxations,<sup>59–61</sup> increasing the likelihood, length, and severity of gastroesophageal reflux, a major risk factor for Barrett's<sup>18</sup> and the sequela, esophageal adenocarcinoma.<sup>17</sup> Interaction between gastroesophageal reflux symptoms and smoking has been reported previously for Barrett's esophagus with dysplasia<sup>26</sup> and for esophageal adenocarcinoma.<sup>62</sup>

There were several strengths of this analysis. First, the consortial approach enabled generation of the largest re-

ported 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 than 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 2 control groups for comparison, that is, population-based and GERD, allows us to postulate where risk factors might be active in the pathogenesis of Barrett's esophagus. This is important because it is feasible that a significant proportion of the population-based control group might unknowingly have Barrett's esophagus,<sup>63</sup> 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,<sup>64</sup> the studies included in this analysis recruited incident cases and controls during 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 that 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.<sup>65</sup> 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 ORs for multiple measures of association in the 1.5 to 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. In addition, because the origins of Barrett's esophagus are poorly understood, a better understanding of its risk factors and their biological interactions might allow inference of the biological mechanisms involved in the nascent stages of Barrett's esophagus. 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.

## Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Gastroenterology* at [www.gastrojournal.org](http://www.gastrojournal.org), and at doi: 10.1053/j.gastro.2011.12.049.

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#### Conflicts of interest

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