DOI: 10.1093/jnci/djq289
Advance Access publication on August 17, 2010.

ARTICLE

Cigarette Smoking and Adenocarcinomas of the Esophagus and Esophagogastric Junction: A Pooled Analysis From the International BEACON Consortium

Michael B. Cook, Farin Kamangar, David C. Whiteman, Neal D. Freedman, Marilie D. Gammon, Leslie Bernstein, Linda M. Brown, Harvey A. Risch, Weimin Ye, Linda Sharp, Nirmala Pandeya, Penelope M. Webb, Anna H. Wu, Mary H. Ward, Carol Giffen, Alan G. Casson, Christian C. Abnet, Liam J. Murray, Douglas A. Corley, Olof Nyrén, Thomas L. Vaughan, Wong-Ho Chow

Manuscript received May 12, 2009; revised July 12, 2010; accepted July 13, 2010.

Correspondence to: Michael B. Cook, PhD, Hormonal and Reproductive Epidemiology Branch, Division of Cancer Epidemiology and Genetics, National Cancer Institute, National Institutes of Health, Department of Health and Human Services, 6120 Executive Blvd, EPS/Ste 550/Rm 5030, Bethesda, MD 20852-7234 (e-mail: michael.cook@nih.gov).

Background Previous studies that showed an association between smoking and adenocarcinomas of the esophagus and esophagogastric junction were limited in their ability to assess differences by tumor site, sex, dose–response, and duration of cigarette smoking cessation.

Methods We used primary data from 10 population-based case–control studies and two cohort studies from the Barrett's Esophagus and Esophageal Adenocarcinoma Consortium. Analyses were restricted to white non-Hispanic men and women. Patients were classified as having esophageal adenocarcinoma (n = 1540), esophagogastric junctional adenocarcinoma (n = 1450), or a combination of both (all adenocarcinoma; n = 2990). Control subjects (n = 9453) were population based. Associations between pack-years of cigarette smoking and risks of adenocarcinomas were assessed, as well as their potential modification by sex and duration of smoking cessation. Study-specific odds ratios (ORs) estimated using multivariable logistic regression models, adjusted for age, sex, body mass index, education, and gastroesophageal reflux, were pooled using a meta-analytic methodology to generate summary odds ratios. All statistical tests were two-sided.

Results The summary odds ratios demonstrated strong associations between cigarette smoking and esophageal adenocarcinoma (OR = 1.96, 95% confidence interval [CI] = 1.64 to 2.34), esophagogastric junctional adenocarcinoma (OR = 2.18, 95% CI = 1.84 to 2.58), and all adenocarcinoma (OR = 2.08, 95% CI = 1.83 to 2.37). In addition, there was a strong dose–response association between pack-years of cigarette smoking and each outcome ($P < .001$). Compared with current smokers, longer smoking cessation was associated with a decreased risk of all adenocarcinoma after adjusting for pack-years (<10 years of smoking cessation: OR = 0.82, 95% CI = 0.60 to 1.13; and ≥10 years of smoking cessation: OR = 0.71, 95% CI = 0.56 to 0.89). Sex-specific summary odds ratios were similar.

Conclusions Cigarette smoking is associated with increased risks of adenocarcinomas of the esophagus and esophagogastric junction in white men and women; compared with current smoking, smoking cessation was associated with reduced risks.

J Natl Cancer Inst 2010;102:1344–1353

The two main histological types of esophageal cancer are adenocarcinoma and squamous cell carcinoma, each being etiologically distinct (1). Incidence rates of esophageal adenocarcinoma have sharply increased during the past 30 years in many countries, especially among populations residing in the developed countries of the Western world, such as Denmark, Finland, Norway, Sweden, Switzerland, United Kingdom and the United States (2–5). Incidence rates of esophagogastric junctional adenocarcinoma, adenocarcinomas which traverse or are wholly within the esophageal–gastric junction, may also have increased during the same period (6), although the validity of such statistics and the precise relation between esophageal adenocarcinoma and esophagogastric junctional adenocarcinoma have been debated (7,8).

Several population-based case–control studies were initiated in the 1990s and the 2000s to investigate the etiology of esophageal adenocarcinoma and esophagogastric junctional adenocarcinoma (9–18). Some large-scale cohort studies have also studied the risk factors for these two cancers (19,20). These studies have thus far consistently identified male sex, white race, cigarette smoking, gastroesophageal acid reflux, and obesity as risk factors for

esophageal adenocarcinoma and esophagogastric junctional adenocarcinoma (9–22).

Although most of the published studies have shown smoking to be associated with increased risks of esophageal adenocarcinoma and esophagogastric junctional adenocarcinoma (9–14,16–19), the small size of these individual studies has limited the precision of resulting estimates of association. In addition, it is unknown whether a clear dose–response relationship between smoking and esophageal adenocarcinoma and esophagogastric junctional adenocarcinoma exists; an important consideration if causality is to be inferred. It is also not known whether the associations between smoking and esophageal adenocarcinoma and esophagogastric junctional adenocarcinoma are similar in men and women—a key etiologic question—given the large sex disparities in cancer incidence of these sites (23). It is also not clear whether the association with smoking is similar between esophageal adenocarcinoma and esophagogastric junctional adenocarcinoma. Last, it will be useful to know whether cigarette smoking cessation, and over what period of time, leads to reduced risks of esophageal adenocarcinoma and esophagogastric junctional adenocarcinoma because this is likely to have utility for public health.

In 2005, a consortium entitled Barrett's Esophagus and Esophageal Adenocarcinoma Consortium (BEACON) was formed by investigators of population-based case–control and cohort studies on esophageal adenocarcinoma and its precursor lesion, Barrett's esophagus (9–20). The BEACON was supported by the US National Cancer Institute with the objective of facilitating well-powered combined investigations of risk factors of esophageal adenocarcinoma and Barrett's esophagus and helping the development of new studies of etiology, prevention, and survival. In this study, we used a two-stage analytic approach to calculate study-specific estimates using the data available from 12 studies in BEACON and then combining these estimates using meta-analytic models. Ten of the 12 studies used a population-based case–control design to investigate potential risk factors of adenocarcinoma of the esophagus. The two prospective cohort studies have been used for assessments of different diseases and contributed esophageal adenocarcinoma and esophagogastric junctional adenocarcinoma case patients and unaffected randomly selected control subjects to the BEACON consortium. The primary objectives were to evaluate the association between cigarette smoking and esophageal adenocarcinoma and esophagogastric junctional adenocarcinoma, test for a dose–response association with pack-years, analyze whether the association differed between men and women, and assess whether smoking cessation resulted in a reduced risk of these cancers.

CONTEXT AND CAVEATS

Prior knowledge

Associations between cigarette smoking and esophageal adenocarcinoma and esophagogastric junctional adenocarcinoma are known, but it is not known whether there is a dose–response relationship with smoking, if cessation of smoking reduces the risk of adenocarcinomas, and if the associations are similar in men and women.

Study design

Pooled analysis of 10 population-based case–control studies and two cohort studies of white men and women from the Barrett's Esophagus and Esophageal Adenocarcinoma Consortium.

Contribution

Cigarette smoking showed a strong dose–response association with esophageal adenocarcinoma and esophagogastric junctional adenocarcinoma in white men and women; cessation of smoking decreased the risk of cancer, compared with current smokers; associations were not statistically significantly different between men and women.

Implications

Cigarette smoking is strongly associated with increased risk of these cancers in men and women in a dose–response manner, and smoking cessation reduces this increased risk.

Limitations

There may have been some misclassification in the analysis because it is difficult to differentiate esophageal adenocarcinoma from esophagogastric junctional adenocarcinoma, but this is unlikely to have affected the results.

From the Editors

Subjects and Methods

Study Population

The case patients and control subjects were identified in June 2008 from the 12 studies participating in BEACON. The 12 studies included 10 population-based case–control studies and two cohort studies (Table 1). The 10 case–control studies were as follows: the Population Health Study (9); the Larynx, Esophagus, and Oral Cavity Study (10); the United States Multi-Center Study (11); a nationwide Swedish study of esophageal cancer and esophagogastric junctional adenocarcinoma (12); the United Kingdom Study of Oesophageal Adenocarcinoma in Women (13); the Los Angeles County Multi-ethnic Case–control Study (14); the Nebraska Health Study II (15); the Nova Scotia Barrett Esophagus Study (16); the Factors Influencing the Barrett's Adenocarcinoma Relationship Study (17); and the nationwide Australian Cancer Study (esophageal cancer component) (18). The two cohort studies were the National Institutes of Health–AARP (NIH-AARP) Diet and Health Study with follow-up through 2003 (19); and the Kaiser-Permanente Multiphasic Health Checkup Study with follow-up to 2006 (20). For the NIH-AARP Study, all eligible case patients and a random sample of control subjects, four times as many as the case patients, were selected for the analysis. For the Kaiser-Permanente Multiphasic Health Checkup Study, all case patients and a random sample of control subjects, eight times as many as the case patients, were selected.

From these 12 studies, the BEACON database was able to provide 4214 case patients (2138 esophageal adenocarcinoma and 2076 esophagogastric junctional adenocarcinoma) and 13 750 control subjects eligible for the pooled analysis. We excluded participants who had smoked pipe tobacco (731 case patients and 1613 control subjects), cigars (406 case patients and 1139 control subjects), or used snuff (124 case patients and 224 control subjects), if the study provided such data, because comparing cigarette smokers with those who do not use other forms of tobacco provides a more

Table 1. Characteristics of the BEACON studies included in the pooled analysis*

Study, first author, year (reference)	Design	Location	Period of recruitment	Control subjects† (n = 9453)	EA (n = 1540)	EGJA (n = 1450)	AA (n = 2990)
Population Health Study, Brown, 1994 (9)	Case–control	United States	1986–1989	445	37	74	111
Larynx, Esophagus, and Oral Cavity Study, Vaughan, 1995 (10)	Case–control	United States	1983–1990	502	82	110	192
United States Multi-Center Study, Gammon, 1997 (11)	Case–control	United States	1993–1995	470	217	194	411
Swedish Esophageal Cancer Study, Lagergren, 2000 (12)	Case–control	Sweden	1995–1997	461	89	113	202
United Kingdom Study of Oesophageal Adenocarcinoma in Women, Cheng, 2000 (13)	Case–control	United Kingdom	1993–1996	61	60	—	60
Los Angeles County Multi-ethnic Case–control Study, Wu, 2001 (14)	Case–control	United States	1992–1997	636	128	155	283
Nebraska Health Study II, Chen, 2002 (15)	Case–control	United States	1988–1993	396	87	31	118
Nova Scotia Barrett Esophagus Study, Veugelers, 2006 (16)	Case–control	Canada	2001–2003	86	42	—	42
Factors Influencing the Barrett's Adenocarcinoma Relationship Study, Anderson, 2007 (17)	Case–control	Ireland	2002–2004	220	98	66	164
Australian Cancer Study (esophageal cancer component), Whiteman, 2008 (18)	Case–control	Australia	2001–2005	1512	359	419	778
National Institutes of Health–AARP Diet and Health Study, Freedman, 2007 (19)	Cohort	United States	1995–1996	2478	249	198	447
Kaiser-Permanente Multiphasic Health Checkup Study, Corley, 2008 (20)	Cohort	United States	1964–1973	2186	92	90	182

* The number (n) of control subjects and case patients (EA, EGJA, and AA) included in the analyses of cigarette smoking and adenocarcinomas of the esophagus and esophagogastric junction. Analyses were conducted using a two-stage strategy; first, study-specific odds ratios were estimated, followed by a second step of pooling the study-specific odds ratios in a meta-analysis to estimate summary odds ratios of association. Analyses excluded those who smoked pipe, cigar, or used snuff, and non-white subjects. — = the study did not have EGJA case patients; AA = all adenocarcinoma (EA and EGJA); BEACON = Barrett's Esophagus and Esophageal Adenocarcinoma Consortium; EA = esophageal adenocarcinoma; EGJA = esophagogastric junctional adenocarcinoma.

† The control subjects for the cohort studies constituted a random selection of those without cancer at the last date of follow-up.

accurate estimate of the effect of cigarette smoking. Because of the relatively small number of non-white non-Hispanic case patients in BEACON studies (50 black, 112 Hispanic, and 71 other race or ethnic groups), we restricted our analysis to white non-Hispanic study participants. After these exclusions, 2990 case patients (1540 esophageal adenocarcinoma and 1450 esophagogastric junctional adenocarcinoma) and 9453 control subjects remained in the analysis.

The characteristics of the participating studies are listed in Table 1. Data acquisition and data pooling for each study was approved by the institutional review board or research ethics committee of the institute(s) sponsoring the study.

Study Variables

The variables used in this analysis were case or control status (esophageal adenocarcinoma, esophagogastric junctional adenocarcinoma, or control), cigarette smoking status (ever vs never), total smoking exposure (pack-years; 0, <15, 15–29, 30–44, ≥45), smoking intensity (<1, 1, and >1 pack per day; based on the most common number of one pack per day), age of smoking initiation (<17, ≥17 years), cigarette type (filtered only, nonfiltered only, or both), duration of smoking cessation (current smoker, <10, ≥10 years), age, sex, education, body mass index (BMI; weight divided by square of height [kg/m^2]), gastroesophageal reflux status (yes vs no), and study center (for multicenter studies only). Nine of the 12 studies included in this analysis defined ever–cigarette smoking status as having smoked more than or equal to 100 cigarettes in their entire lifetime. The remaining three studies, two of which were of case–control design, used regular or daily smoking for a minimum continuous time period of 3, 6, or 12 months (13,14,19). Smoking duration was calculated as the age cigarette smoking was initiated to the age of quitting (for former smokers) or to the current age (for current smokers); current age was defined as age at diagnosis for case patients, age at interview for control subjects, and age at baseline for participants of cohort studies. For analysis, age at smoking initiation and duration of smoking cessation were dichotomized based on the median values among control subjects who smoked.

The NIH-AARP Diet and Health Study did not ascertain the age of smoking initiation from case patients and control subjects. The median age at smoking initiation was 17 years in a subset of the NIH-AARP Diet and Health Study cohort (40%) that

completed a follow-up questionnaire. Therefore, we estimated smoking duration by subtracting 17 years from current age (for current smokers) or age of last cigarette smoking (for former smokers). Smoking intensity in both cohort studies and smoking duration in the Kaiser-Permanente Multiphasic Health Checkup Study were ascertained in categories rather than asking for the precise number of years. Therefore, we recoded each category to the median of that category as determined using the distribution of years from all remaining studies.

Questionnaire data were ascertained at or near the time of cancer diagnosis for case patients and at age of recruitment for control subjects for the 10 population-based case–control studies in BEACON. For the two cohort studies, questionnaire data were ascertained at recruitment into the study (baseline). The median time between baseline and cancer diagnosis was 3.9 years for NIH-AARP Diet and Health Study (19) and 24.1 years for Kaiser Permanente Multiphasic Health Checkup Study (20). Data on gastroesophageal reflux were missing in seven studies (9,10,13,15, 16,19,20), age at smoking initiation in two studies (19, 20), cigarette type in seven studies (13,15–20), and duration of smoking cessation in one study (20). All other variables were available for all studies. A different methodology and/or categorization for the variable education were used in each study and, therefore, were study specific.

Statistical Analysis

We used a two-step analytic approach. First, we used multivariable logistic regression models to estimate study-specific odds ratios (ORs) and 95% confidence intervals (CIs) of the association between exposure and outcome in each study. The odds ratio approximates the relative risk when the outcome of interest is rare. Second, the study-specific odds ratios were pooled using random-effects meta-analysis to generate summary odds ratios (24). A study was excluded from an analysis if it was unable to generate a stable odds ratio. The main exposures of interest were cigarette smoking status (ever, never) and total smoking exposure (in units of pack-years). The main outcomes of interest were esophageal adenocarcinoma, esophagogastric junctional adenocarcinoma, and a combination of both (ie, all adenocarcinoma). Continuous variables were categorized in all analyses for ease of interpretation and to reduce the effect of any outliers. The only exception to this was the use of pack-years of smoking as a continuous variable when estimating a P value for trend (P_{trend}). For the analyses of the primary objectives, two multivariable logistic regression models were used—a minimally adjusted model that included the covariates age (categorical: <50, 50–59, 60–69, ≥70) and sex, and a fully adjusted model that included the covariates such as age (categorical: <50, 50–59, 60–69, ≥70), sex, BMI (categorical: <25, 25–29.9, ≥30), education (study specific), gastroesophageal reflux (where available), and study center (where appropriate). More extensive adjustment in the second model made the summary odds ratios slightly, but not materially, attenuated. We present only the results from the fully adjusted model. The same methodology was used for sex-specific analyses.

We also examined the association between smoking intensity, age of smoking initiation, cigarette type, and duration of smoking cessation with cancer risk, adjusting for pack-years of smoking, age, sex, BMI, education, gastroesophageal reflux, and study center. Last, we conducted analyses stratified by BMI and interaction models of BMI and pack-years of cigarette smoking to assess whether BMI modified the relationship between smoking and cancer risk.

To pool the study-specific odds ratios, we used both fixed-effects and random-effects meta-analytic models. The summary odds ratios from the two approaches were similar; thus, we only show the results from the random-effects models. Such models provide more conservative summary odds ratios when heterogeneity is present, although uncommon exceptions do exist (25). The I^2 statistic (26) was used to estimate the percentage of total variation across studies due to heterogeneity. An I^2 statistic of 0% indicates no observed heterogeneity that cannot be attributed to chance, whereas larger values indicate increasing heterogeneity. We also conducted a sensitivity analysis that omits each study in turn, reestimating the association each time to determine if any single study dominates the summary odds ratio. All analyses were performed using STATA software, version 10.1 (StataCorp LP, College Station, TX). All statistical tests were two-sided. P values less than .05 were considered to be statistically significant.

Results

The study design, study location, and numbers of case patients and control subjects for each of the 12 participating BEACON studies are described in Table 1. A total of 2990 all adenocarcinoma subjects, which included 1540 esophageal adenocarcinoma subjects from 12 studies and 1450 esophagogastric junctional adenocarcinoma subjects from 10 studies, were available for the analysis. A total of 9453 population-based control subjects were available for comparison. In the pooled analyses of ever–cigarette smoking, we observed statistically significant associations with esophageal adenocarcinoma (summary OR = 1.96, 95% CI = 1.64 to 2.34), esophagogastric junctional adenocarcinoma (summary OR = 2.18, 95% CI = 1.84 to 2.58), and all adenocarcinoma (summary OR = 2.08, 95% CI = 1.83 to 2.37) (Table 2). The I^2 values from the random-effects meta-analyses of ever–cigarette smoking indicated low levels of heterogeneity for esophageal adenocarcinoma (I^2 = 24%), esophagogastric junctional adenocarcinoma (I^2 = 21%), and all adenocarcinoma (I^2 = 21%). The low levels of heterogeneity are visually apparent from the forest plots shown in Figure 1, A–C, each of which displays the study-specific odds ratios as well as the summary odds ratio for a cancer group in relation to the exposure ever–cigarette smoking.

We next evaluated if there was a dose–response association between cigarette smoking and esophageal adenocarcinoma, esophagogastric junctional adenocarcinoma, and all adenocarcinoma (Table 2 and Supplementary Figure 1, A–C, available online). Analyses of total cigarette smoking exposure (pack-years) showed a highly statistically significant dose–response association (P_{trend} < .001) and consistency in estimates of risk for each category of pack-year exposure across outcome groups. For all adenocarcinoma, compared with never–cigarette smokers, statistically significant associations were noted in less than 15 pack-years (summary OR = 1.30, 95% CI = 1.07 to 1.58), 15–29 pack-years (summary OR = 2.19, 95% CI = 1.86 to 2.58), 30–44 pack-years (adjusted

Table 2. Summary odds ratios (ORs) and 95% confidence intervals (CIs) for the associations of ever–cigarette smoking and pack-years of cigarette smoking with risk of esophageal adenocarcinoma, esophagogastric junctional adenocarcinoma, and all adenocarcinoma*

Exposure	EA				EGJA†			AA		
	Control subjects (n)	Case patients (n)	OR (95% CI)	I^2,‡ %	Control subjects (n)	Case patients (n)	OR (95% CI)	I^2,‡ %	Control subjects (n)	Case patients (n)	OR (95% CI)	I^2,‡ %
Ever–cigarette smoking												
No	3563	358	1.00 (referent)		3493	322	1.00 (referent)		3563	680	1.00 (referent)	
Yes	5214	1098	1.96 (1.64 to 2.34)	24	5122	1051	2.18 (1.84 to 2.58)	21	5214	2149	2.08 (1.83 to 2.37)	21
Pack-years of smoking												
0 (never-smokers)	3563	358	1.00 (referent)		3493	322	1.00 (referent)		3563	680	1.00 (referent)	
<15	1469	200	1.25 (1.02 to 1.53)	0	1423	183	1.32 (0.99 to 1.75)	38	1469	383	1.30 (1.07 to 1.58)	28
15 to <30	930	197	1.96 (1.58 to 2.45)	0	906	217	2.44 (1.98 to 3.00)	0	930	414	2.19 (1.86 to 2.58)	0
30 to <45	905	210	2.07 (1.66 to 2.58)	2	895	229	2.64 (2.07 to 3.38)	19	905	439	2.38 (1.98 to 2.86)	11
≥45	1688	458	2.71 (2.16 to 3.40)	24	1678	401	2.68 (2.23 to 3.23)	0	1688	859	2.73 (2.27 to 3.29)	32
P_{trend}§			<.001				<.001				<.001	
P_{trend} (excluding never-smokers)§			<.001				<.001				<.001	

* Summary odds ratios were estimated using random-effects meta-analytic model. All 12 studies were included for analyses unless otherwise specified. Results were adjusted for age (categorical: <50, 50–59, 60–69, ≥70), sex, body mass index (categorical: <25, 25–29.9, ≥30), education (study specific), and gastroesophageal reflux (when available). AA = all adenocarcinoma (EA and EGJA combined); EA = esophageal adenocarcinoma; EGJA = esophagogastric junctional adenocarcinoma.

† Analyses only included the 10 studies that provided EGJA cases, shown in Table 1.

‡ I^2 is the percentage of total variation across studies because of heterogeneity.

§ P_{trend} values (two-sided) were calculated from meta-analytic pooling of study-specific odds ratios estimated from logistic regression models with continuous pack-years of cigarette smoking as the exposure variable adjusted for age (categorical: <50, 50–59, 60–69, ≥70), sex, body mass index (categorical: <25, 25–29.9, ≥30), education (study specific), and gastroesophageal reflux (when available).

Figure 1. The summary odds ratios and 95% confidence intervals (CI) for the association between cigarette smoking (ever vs never) and risk of cancer. **A**) Esophageal adenocarcinoma. **B**) Esophagogastric junctional adenocarcinoma. **C**) All adenocarcinoma. Summary odds ratios and 95% confidence intervals were estimated using a random-effects meta-analytic model. All statistical tests were two-sided. % Weight describes the weighting each study contributes to the summary odds ratio. The **dot** on each square represents the study-specific odds ratio, and the **size of the surrounding square** is an illustrative representation of study weighting. The **horizontal lines** represent the confidence intervals; if ending in an **arrow**, this indicates that the interval transcends the region plotted. The **diamond** represents the summary odds ratio and 95% confidence intervals. FINBAR = Factors Influencing the Barrett's Adenocarcinoma Relationship Study; LEO, Larynx, Esophagus, and Oral Cavity Study; NIH–AARP = National Institutes of Health–AARP; NSBES = Nova Scotia Barrett Esophagus Study.

OR = 2.38, 95% CI = 1.98 to 2.86), and greater than or equal to 45 pack-years (adjusted OR = 2.73, 95% CI = 2.27 to 3.29).

For sex-specific analyses, 2457 men and 533 women with all adenocarcinoma (1275 men and 265 women with esophageal adenocarcinoma; 1182 men and 268 women with esophagogastric junctional adenocarcinoma) were included. We observed a statistically significant association between ever–cigarette smoking and esophageal adenocarcinoma for men (summary OR = 2.10, 95% CI = 1.71 to 2.59) and women (summary OR = 1.74, 95% CI = 1.21 to 2.51), esophagogastric junctional adenocarcinoma for men (summary OR = 2.23, 95% CI = 1.88 to 2.63) and women (summary OR = 2.33, 95% CI = 1.60 to 3.39), and all adenocarcinoma for men (summary OR = 2.13, 95% CI = 1.86 to 2.44) and women (summary OR = 1.95, 95% CI = 1.40 to 2.71) (Supplementary Tables 1 and 2, available online). The slight differences in the summary odds ratios between men and women were not statistically significant (data not shown). Sex-specific analyses also showed statistically significant dose–response relationships in all adenocarcinoma, akin to summary odds ratios estimated from the sexes combined. This is explicitly emphasized by the summary odds ratios for the cigarette smoking pack-year categories of less than 15 pack-years (men: summary OR = 1.33, 95% CI = 1.06 to 1.68; women: summary OR = 1.33, 95% CI = 0.97 to 1.83), 15–29 pack-years (men: summary OR = 2.26, 95% CI = 1.88 to 2.73; women: summary OR = 2.03, 95% CI = 1.25 to 3.31), 30–44 pack-years (men: summary OR = 2.37, 95% CI = 1.97 to 2.85; women: summary OR = 2.24, 95% CI = 1.35 to 3.72), and greater than or equal to 45 pack-years (men: summary OR = 2.67, 95% CI = 2.15 to 3.32; women: summary OR = 3.59, 95% CI = 2.30 to 5.60), respectively (Supplementary Tables 1 and 2, available online).

Next, we examined if gastroesophageal reflux and BMI modified the relationship between cigarette smoking and adenocarcinoma risk. Adjusting for gastroesophageal reflux in the multivariable logistic regression models of the five studies that had gastroesophageal reflux data (11,12,14,17,18) had minimal effect on the study-specific and pooled summary odds ratios (data not shown). However, reflux was retained in these models as it is known to be a strong risk factor for esophageal adenocarcinoma and esophagogastric junctional adenocarcinoma (27,28). We also found no evidence to suggest that BMI modified the association between cigarette smoking and adenocarcinoma risk. Analyses stratified by a BMI value of 25 produced similar estimates of risk for adenocarcinoma, and a meta-analysis of the interaction term BMI multiplied by pack-years of cigarette smoking was also indicative of no statistical interaction ($P = .73$) (data not shown). In addition, imputation of age of smoking initiation in NIH-AARP by multivariable regression of age, sex, and BMI had minimal effect on risk estimates ascertained compared with those derived using the median age 17 (data not shown), so the latter method was retained for clarity. Sensitivity analyses were conducted for all pack-year analyses and it was visually apparent that no single study substantially dominated the values of the summary odds ratios (data not shown).

Finally, we examined the association of smoking intensity (packs per day), age of smoking initiation (<17 or ≥17 years), cigarette type (filtered, nonfiltered, or both), and duration of cigarette smoking cessation (<10 or ≥10 years) in relation to all adenocarcinoma while adjusting for total dose (pack-years of cigarette smoking) (Table 3). The combined analytic group of all adenocarcinoma offered the highest statistical power as it contains all of the case patients. Cigarette smoking intensity, age of smoking initiation, and cigarette type were not associated with risk of all adenocarcinoma after adjustment for total dose. Compared with current cigarette smokers, smoking cessation of less than 10 years (summary OR = 0.82, 95% CI = 0.60 to 1.13) and greater than or equal to 10 years (summary OR = 0.71, 95% CI = 0.56 to 0.89) showed reduced risk of all adenocarcinoma. However, when compared with never–cigarette smokers, greater than or equal to 10 years of smoking cessation was still associated with an increased risk of all adenocarcinoma (summary OR = 1.72, 95% CI = 1.38 to 2.15, $I^2 = 55\%$) (data not shown in Table 3).

Table 3. Summary odds ratios (ORs) and 95% confidence intervals (CIs) for the associations of smoking intensity, age of smoking initiation, cigarette type, and duration of smoking cessation with all adenocarcinoma adjusted for total dose (pack-years of cigarette smoking)*

Exposure	Control subjects (n)	Case patients (n)	OR (95% CI)	I^2,† %
Smoking intensity,‡ pack per day				
<1	986	471	1.00 (referent)	
1	654	461	1.04 (0.79 to 1.38)	27
>1	842	675	0.92 (0.63 to 1.32)	38
Age of smoking initiation,§ y				
<17	1047	814	1.00 (referent)	
≥17	1475	830	1.02 (0.86 to 1.21)	11
Cigarette type‖				
Filtered only	457	295	1.00 (referent)	
Nonfiltered only	335	249	1.40 (0.86 to 2.28)	59
Both	565	260	0.96 (0.67 to 1.38)	18
Duration of smoking cessation, ¶ y				
0	1106	707	1.00 (referent)	
<10	769	357	0.82 (0.60 to 1.13)	56
≥10	2091	920	0.71 (0.56 to 0.89)	39

* Results were adjusted for pack-years of smoking (categorical: <15, 15–29.9, 30–44.9, ≥45), age (categorical: <50, 50–59, 60–69, ≥70), body mass index (categorical: <25, 25–29.9, ≥30), sex, education (study specific), and reflux (when available). Summary odds ratios and 95% confidence intervals were obtained from random-effects meta-analytic models. Age of smoking initiation and duration of cessation were dichotomized based on their median values among control subjects, 17 and 10 years, respectively. Studies were only included in an analysis if they were able to provide exposure variables and sufficient numbers of case patients and control subjects for generation of stable risk estimates.

† I^2 Percentage of total variation across studies because of heterogeneity.

‡ Nine BEACON studies were included in the analysis (9–12,14–18).

§ Ten BEACON studies were included in the analysis (9–18).

‖ Five BEACON studies were included in the analysis (9–12,14).

¶ Eleven BEACON studies were included in the analysis (9–19).

Discussion

The results of this pooled analysis demonstrate a consistent association between cigarette smoking and risk of esophageal

adenocarcinoma, esophagogastric junctional adenocarcinoma, and all adenocarcinoma. In addition, our results demonstrate that risk increases monotonically with increasing total dose (pack-years). Last, they show a risk reduction after smoking cessation, compared with current smokers.

In total, these results provide strong support for an association between cigarette smoking and adenocarcinomas of the esophagus and esophagogastric junction. Tobacco smoke is known to contain several carcinogens (29), which provides mechanistic support to our conclusions. In addition, the temporal relationships of these exposures and outcomes also provide supporting evidence; cigarette smoking is typically initiated many years before tumor diagnosis in smokers. Plausible biological mechanisms that may explain the association between cigarette smoking and adenocarcinoma, either singly or in combination, include the genotoxicity of tobacco smoke to esophageal cells (30), increased gastroesophageal reflux via induced transient lower esophageal sphincter relaxations from biologically active constituents of tobacco smoke (31,32), and changing constituents of cigarettes over time with increasing amounts of nitrosamines (33).

Summary odds ratios for analyses of cigarette smoking, shown herein, were similar for esophageal adenocarcinoma and esophagogastric junctional adenocarcinoma, although these cancers have other features in common, too. They are both more common among white men (21) and share several risk factors including obesity (34,35) and gastroesophageal reflux (36). Similarity of risk factors could, in part, be due to the fact that these two tumor types cannot always be accurately distinguished from one another. Occasionally, tumors may traverse the esophagogastric junction, which can make the site of origin diagnostically contentious. Although traversing cancers may lead to misclassification, the above similarities between esophageal adenocarcinoma and esophagogastric junctional adenocarcinoma, and the fact that all studies included in analyses of this pooling project present fairly homogeneous estimates of risk, should assuage concerns that these results are significantly altered via misclassification bias. Given the similarities between esophageal adenocarcinoma and esophagogastric junctional adenocarcinoma, we decided to combine these cancers into one analytic category—that of all adenocarcinoma.

Prospective studies (37) have shown that smoking also increases the risk of gastric noncardia adenocarcinoma by approximately twofold (hazard ratio = 2.04, 95% CI = 1.32 to 3.16) (19). Therefore, one may conclude that cigarette smoking increases the risk of all adenocarcinomas of the esophagus and stomach by an average of twofold, and that risk increases further with increasing total dose (pack-years of cigarette smoking). In comparison, smoking is a stronger risk factor for squamous cell carcinoma of the esophagus (10,11,19,38), the other major histological type of esophageal cancer.

Our pooled analysis, to our knowledge, provides the first precise sex-specific risk estimates of the associations between cigarette smoking and esophageal adenocarcinoma and esophagogastric junctional adenocarcinoma. Summary odds ratios of these associations were similar for men and women. These results are consistent with previous studies of lung cancer showing that the association with cigarette smoking is similar in both sexes (39,40). Estimating the proportions of esophageal adenocarcinoma or esophagogastric junctional adenocarcinoma that are associated with cigarette smoking is difficult because cigarette smoking prevalence varies by population and has changed over time, and the exact time period between exposures and outcome, which is etiologically relevant, is unclear. Because men have traditionally smoked more than women (41), cigarette smoking has likely caused many more adenocarcinomas of the esophagus and esophagogastric junction in men than in women, which may account for part of the sex differences in the incidence of these cancers. However, because the prevalence of smoking in the United States has been declining and converging between the sexes since 1965 (41), it is unlikely that smoking could explain the recent and continuing rise of esophageal adenocarcinoma (42) and the eightfold difference in sex disparity (23).

Cigarette smoking is one of the most extensively investigated exposures in epidemiological studies, and several models have been used for analysis of smoking in relation to health outcomes (43,44). In lung cancer studies, it has been argued that the contribution of smoking intensity and duration to risk of disease may not be equal, and therefore, using cumulative total exposure in terms of pack-years may not be an optimal strategy to deduce risk associations (43). Other authors have suggested using duration and intensity as separate variables in analytic models, but for a constant duration, increasing intensity means increased total exposure, so attributing the effect to intensity could be misleading (45,46). Therefore, as Samet et al. (41) noted, there is perhaps no single model that is entirely satisfactory. We chose categories of pack-years of cigarette smoking as the main exposure because of the following reasons: most studies have shown a dose–response association of this variable with lung and other cancers (47); interpretation of the results is relatively easy; results are meaningful for causal inferences and public health purposes; and no assumptions are made about linearity of the associations.

Because of the fact that total exposure is affected by smoking intensity, smoking duration, age of smoking initiation, and years of smoking cessation, we adjusted for total exposure (pack-years) when analyzing these associations. After adjustment, we did not observe any association between smoking intensity, age of smoking initiation, and cigarette type, with risk of esophageal adenocarcinoma or esophagogastric junctional adenocarcinoma. Because total exposure is the product of intensity and duration, no effect of intensity after adjustment for total exposure suggests that for a constant total exposure, lower intensity and longer duration have approximately the same effect as higher intensity and shorter duration. More in-depth analyses, including wasted dose, which is defined as reduced carcinogenic potency of higher smoking intensities relative to lower intensities given equal total exposure (45,46,48,49), may reveal more details.

We noted that cigarette type was not statistically significantly associated with risk of esophageal adenocarcinoma or esophagogastric junctional adenocarcinoma after taking into consideration total exposure. Data on the effect of cigarette type on these cancers are sparse. However, for lung cancer, the body of evidence accumulated so far suggests that both filtered and nonfiltered cigarettes substantially increase the risk of cancer (50). Also, studies show that there is little difference, if any, between cigarette types in their carcinogenic potential or in the amount of tar or nicotine that smokers receive from them (50).

Because there was a dose–response relationship with pack-years in our analyses, we speculated that smoking cessation might truncate further increase in risk. Our analyses showed that even after adjusting for total pack-years, smoking cessation was associated with risk reduction. In other words, if one quits smoking today, one's risk would not only stop increasing but may also decrease over time. However, the summary odds ratios for greater than or equal to 10 years of smoking cessation suggested that risk does not decrease to the level of never–cigarette smokers. Indeed, the risk of all adenocarcinoma in those with greater than or equal to 10 years of smoking cessation was 1.7-fold of that of never–cigarette smokers (data not shown). Still, little is known about the long-term effects of smoking cessation on risk of all adenocarcinoma after adjusting for pack-years, and even this analysis had only adequate statistical power to stratify the sample into three groups of exposure. Using lung cancer as a model, most long-term studies with follow-up of up to 40 years have shown that although further increased risk of lung cancer is avoided by quitting, the risk will always remain higher in cigarette smokers than in never–cigarette smokers (50).

Although our results demonstrate clear relationships of cigarette smoking with esophageal adenocarcinoma and esophagogastric junctional adenocarcinoma, it is unlikely that smoking is solely responsible for the recent increase in cancer incidence. The prevalence of cigarette smoking started rising from 1881 (51) when James Bonsack invented the first cigarette-rolling machine; yet, incidence of esophageal adenocarcinoma was still very low 95 years later, in the mid-1970s (42). Prevalence of smoking among the United States male population started declining from 1965 (52) after publication of the first report of the United States Surgeon General on smoking and health (53); yet, esophageal adenocarcinoma rates, especially among white men, are still increasing (42). During the same period that esophageal adenocarcinoma and esophagogastric junctional adenocarcinoma rates have increased, incidence rates of esophageal squamous cell carcinoma, a cancer closely related to smoking, have decreased (42). Although a longer latency period for esophageal adenocarcinoma may account for part of the difference between esophageal adenocarcinoma and esophageal squamous cell carcinoma, it is unlikely to explain it all. Furthermore, because cigarette smoking on average increases esophageal adenocarcinoma risk by twofold and only a fraction of the population smoke, cigarette smoking can at most contribute only part of the recent four- or fivefold increased incidence observed in some populations (42).

This combined analysis has several notable strengths, including its large sample size, inclusion of population-based case–control and cohort studies, and availability of data on major confounders. The use of individual-level data permitted combined analyses with comparable variables, a feature not available in meta-analyses that use only published odds or risk ratios. There was no evidence of substantial heterogeneity between the study populations; results were robust to the choice of analytic methods (adjustment for confounders and random- vs fixed-effect models), analytic subgroups (men vs women and tumor location), and study design (case–control vs cohort).

This analysis may have several limitations. Because it is difficult to differentiate esophageal adenocarcinoma from esophagogastric junctional adenocarcinoma and adenocarcinomas of the lower stomach, there may have been misclassification. However, this misclassification may be less of a problem in this analysis, given the consistency of association across sites, and therefore, we decided to produce a combined analytic group pertaining to these sites—all adenocarcinoma. Also, case–control studies may be affected by recall bias and interviewer bias, although the intensity and duration of smoking are usually recalled relatively reliably (54), but the two cohort studies (which obtained exposure information before the outcome) included in our pooled analysis showed results similar to those of the case–control studies. Therefore, we believe these biases are unlikely to have had a major impact on the results.

In summary, we found a statistically significant dose–response association between cigarette smoking and adenocarcinomas of the esophagus and esophagogastric junction that was seen in both men and women. Smoking cessation reduced the risk with decreasing risk associated with longer duration since quitting. These results strongly suggest that cigarette smoking is causally related to these two cancers.

Supplementary Data

Supplementary data can be found at http://www.jnci.oxfordjournals.org/.

References

1. Kamangar F, Chow WH, Abnet CC, Dawsey SM. Environmental causes of esophageal cancer. *Gastroenterol Clin North Am.* 2009;38(1):27–57, vii.
2. Botterweck AA, Schouten LJ, Volovics A, Dorant E, van Den Brandt PA. Trends in incidence of adenocarcinoma of the oesophagus and gastric cardia in ten European countries. *Int J Epidemiol.* 2000;29(4):645–654.
3. Vizcaino AP, Moreno V, Lambert R, Parkin DM. Time trends incidence of both major histologic types of esophageal carcinomas in selected countries, 1973–1995. *Int J Cancer.* 2002;99(6):860–868.
4. Bosetti C, Levi F, Ferlay J, et al. Trends in oesophageal cancer incidence and mortality in Europe. *Int J Cancer.* 2008;122(5):1118–1129.
5. 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(5):855–859.
6. Devesa SS, Blot WJ, Fraumeni JF Jr. Changing patterns in the incidence of esophageal and gastric carcinoma in the United States. *Cancer.* 1998;83(10):2049–2053.
7. Corley DA, Kubo A. Influence of site classification on cancer incidence rates: an analysis of gastric cardia carcinomas. *J Natl Cancer Inst.* 2004;96(18):1383–1387.
8. Hamilton SR, Aaltonen LA. *Pathology and Genetics of Tumours of the Digestive System*. Lyon, France: IARC Press; 2000.
9. Brown LM, Silverman DT, Pottern LM, et al. Adenocarcinoma of the esophagus and esophagogastric junction in white men in the United States: alcohol, tobacco, and socioeconomic factors. *Cancer Causes Control.* 1994;5(4):333–340.
10. Vaughan TL, Davis S, Kristal A, Thomas DB. Obesity, alcohol, and tobacco as risk factors for cancers of the esophagus and gastric cardia: adenocarcinoma versus squamous cell carcinoma. *Cancer Epidemiol Biomarkers Prev.* 1995;4(2):85–92.
11. Gammon MD, Schoenberg JB, Ahsan H, et al. Tobacco, alcohol, and socioeconomic status and adenocarcinomas of the esophagus and gastric cardia. *J Natl Cancer Inst.* 1997;89(17):1277–1284.
12. 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(3):340–346.

13. Cheng KK, Sharp L, McKinney PA, et al. A case-control study of oesophageal adenocarcinoma in women: a preventable disease. *Br J Cancer.* 2000; 83(1):127–132.
14. Wu AH, Wan P, Bernstein L. A multiethnic population-based study of smoking, alcohol and body size and risk of adenocarcinomas of the stomach and esophagus (United States). *Cancer Causes Control.* 2001;12(8): 721–732.
15. Chen H, Ward MH, Graubard BI, et al. Dietary patterns and adenocarcinoma of the esophagus and distal stomach. *Am J Clin Nutr.* 2002;75(1): 137–144.
16. Veugelers PJ, Porter GA, Guernsey DL, Casson AG. Obesity and lifestyle risk factors for gastroesophageal reflux disease, Barrett esophagus and esophageal adenocarcinoma. *Dis Esophagus.* 2006;19(5):321–328.
17. Anderson LA, Watson RG, Murphy SJ, et al. Risk factors for Barrett's oesophagus and oesophageal adenocarcinoma: results from the FINBAR study. *World J Gastroenterol.* 2007;13(10):1585–1594.
18. Whiteman DC, Sadeghi S, Pandeya N, et al. Combined effects of obesity, acid reflux and smoking on the risk of adenocarcinomas of the oesophagus. *Gut.* 2008;57(2):173–180.
19. Freedman ND, Abnet CC, Leitzmann MF, et al. A prospective study of tobacco, alcohol, and the risk of esophageal and gastric cancer subtypes. *Am J Epidemiol.* 2007;165(12):1424–1433.
20. Corley DA, Kubo A, Zhao W. Abdominal obesity and the risk of esophageal and gastric cardia carcinomas. *Cancer Epidemiol Biomarkers Prev.* 2008; 17(2):352–358.
21. Brown LM, Devesa SS. Epidemiologic trends in esophageal and gastric cancer in the United States. *Surg Oncol Clin N Am.* 2002;11(2):235–256.
22. Abnet CC, Freedman ND, Hollenbeck AR, Fraumeni JF Jr, Leitzmann M, Schatzkin A. A prospective study of BMI and risk of oesophageal and gastric adenocarcinoma. *Eur J Cancer.* 2008;44(3):465–471.
23. Cook MB, Dawsey SM, Freedman ND, et al. Sex disparities in cancer incidence by period and age. *Cancer Epidemiol Biomarkers Prev.* 2009;18(4): 1174–1182.
24. Smith-Warner SA, Spiegelman D, Ritz J, et al. Methods for pooling results of epidemiologic studies: the Pooling Project of Prospective Studies of Diet and Cancer. *Am J Epidemiol.* 2006;163(11):1053–1064.
25. Poole C, Greenland S. Random-effects meta-analyses are not always conservative. *Am J Epidemiol.* 1999;150(5):469–475.
26. Higgins JPT, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ.* 2003;327(7414):557–560.
27. Derakhshan MH, Malekzadeh R, Watabe H, et al. Combination of gastric atrophy, reflux symptoms and histological subtype indicates two distinct aetiologies of gastric cardia cancer. *Gut.* 2008;57(3):298–305.
28. Ye W, Chow WH, Lagergren J, Yin L, Nyren O. Risk of adenocarcinomas of the esophagus and gastric cardia in patients with gastroesophageal reflux diseases and after antireflux surgery. *Gastroenterology.* 2001;121(6): 1286–1293.
29. Hecht SS. Tobacco carcinogens, their biomarkers and tobacco-induced cancer. *Nat Rev Cancer.* 2003;3(10):733–744.
30. Olliver JR, Hardie LJ, Gong Y, et al. Risk factors, DNA damage, and disease progression in Barrett's esophagus. *Cancer Epidemiol Biomarkers Prev.* 2005;14(3):620–625.
31. Smit CF, Copper MP, van Leeuwen JA, Schoots IG, Stanojcic LD. Effect of cigarette smoking on gastropharyngeal and gastroesophageal reflux. *Ann Otol Rhinol Laryngol.* 2001;110(2):190–193.
32. Kadakia SC, Kikendall JW, Maydonovitch C, Johnson LF. Effect of cigarette smoking on gastroesophageal reflux measured by 24-h ambulatory esophageal pH monitoring. *Am J Gastroenterol.* 1995;90(10): 1785–1790.
33. Cockburn MG, Wu AH, Bernstein L. Etiologic clues from the similarity of histology-specific trends in esophageal and lung cancers. *Cancer Causes Control.* 2005;16(9):1065–1074.
34. Chow WH, Blot WJ, Vaughan TL, et al. Body mass index and risk of adenocarcinomas of the esophagus and gastric cardia. *J Natl Cancer Inst.* 1998;90(2):150–155.
35. Lagergren J, Bergstrom R, Nyren O. Association between body mass and adenocarcinoma of the esophagus and gastric cardia. *Ann Intern Med.* 1999;130(11):883–890.
36. Lagergren J, Bergstrom R, Lindgren A, Nyren O. Symptomatic gastroesophageal reflux as a risk factor for esophageal adenocarcinoma. *N Engl J Med.* 1999;340(11):825–831.
37. Tredaniel J, Boffetta P, Buiatti E, Saracci R, Hirsch A. Tobacco smoking and gastric cancer: review and meta-analysis. *Int J Cancer.* 1997;72(4):565–573.
38. Brown LM, Hoover RN, Greenberg RS, et al. Are racial differences in squamous cell esophageal cancer explained by alcohol and tobacco use? *J Natl Cancer Inst.* 1994;86(17):1340–1345.
39. 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. *Lancet Oncol.* 2008;9(7):649–656.
40. Bain C, Feskanich D, Speizer FE, et al. Lung cancer rates in men and women with comparable histories of smoking. *J Natl Cancer Inst.* 2004; 96(11):826–834.
41. Rock VJ, Malarcher A, Kahende JW, Asman K, Husten C, Caraballo R. Cigarette smoking among adults—United States, 2006. *MMWR Morb Mortal Wkly Rep.* 2007;56(44):1157–1161.
42. Brown LM, Devesa SS, Chow WH. Incidence of adenocarcinoma of the esophagus among white Americans by sex, stage, and age. *J Natl Cancer Inst.* 2008;100(16):1184–1187.
43. Leffondre K, Abrahamowicz M, Siemiatycki J, Rachet B. Modeling smoking history: a comparison of different approaches. *Am J Epidemiol.* 2002;156(9):813–823.
44. Samet JM, Thun MJ, de Gonzalez AB. Models of smoking and lung cancer risk: a means to an end. *Epidemiology.* 2007;18(5):649–651.
45. Lubin JH, Caporaso NE. Cigarette smoking and lung cancer: modeling total exposure and intensity. *Cancer Epidemiol Biomarkers Prev.* 2006;15(3): 517–523.
46. 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(5):639–648.
47. IARC Working Group on the Evaluation of Carcinogenic Risks to Humans, International Agency for Research on Cancer, National Cancer Institute (U.S.). Tobacco smoke and involuntary smoking. *IARC Monogr Eval Carcinog Risks Hum.* 2004;83:1–1438. http://monographs.iarc.fr/ENG/Monographs/vol83/index.php.
48. Lubin JH, Alavanja MC, Caporaso N, et al. Cigarette smoking and cancer risk: modeling total exposure and intensity. *Am J Epidemiol.* 2007;166(4): 479–489.
49. Lubin JH, Virtamo J, Weinstein SJ, Albanes D. Cigarette smoking and cancer: intensity patterns in the alpha-tocopherol, beta-carotene cancer prevention study in Finnish men. *Am J Epidemiol.* 2008;167(8):970–975.
50. U.S. Department of Health and Human Services. *The Health Consequences of Smoking: A Report of the Surgeon General.* Atlanta, GA: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health; 2004.
51. Mackay J, Eriksen MP, Shafey O. American Cancer Society. *The Tobacco Atlas.* 2nd ed. Atlanta, GA: American Cancer Society; 2006.
52. U.S. Department of Health and Human Services. *Reducing the Health Consequences of Smoking—25 Years of Progress: A Report of the Surgeon General.* U.S. Department of Health and Human Services, Public Health Service, Centers for Disease Control, Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health, 1989.
53. U.S. Department of Health and Human Services. *Smoking and Health: Report of the Advisory Committee of the Surgeon General of the Public Health Service.* U.S. Department of Health and Human Services, Public Health Service, Centers for Disease Control, Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health; 1964.
54. Brigham J, Lessov-Schlaggar CN, Javitz HS, McElroy M, Krasnow R, Swan GE. Reliability of adult retrospective recall of lifetime tobacco use. *Nicotine Tob Res.* 2008;10(2):287–299.

Funding

This work was supported in part by the Intramural Program of the National Institutes of Health (NIH). The Population Health Study was funded by the Intramural Program of the NIH. The Larynx, Esophagus, and Oral Cavity Study was funded by R01-CA30022 and R37-CA41530 (both awarded to

T.L.V., David Thomas, Scott Davis, Bonnie Worthington Roberts, Ruth Little, and Mary Rogers). The US Multi-Center Study was funded by U01-CA57949 (awarded to T.L.V.), U01-CA57983 (awarded to M.D.G.), and U01-CA57923 (awarded to H.A.R). The Swedish Esophageal Cancer Study was funded by R01 CA57947–03 (awarded to O.N. and Hans-Olov Adami). The United Kingdom Study of Oesophageal Cancer in Women was funded by Chief Scientist Office (Scotland) (awarded to Patricia McKinney), the Locally Organised Research Scheme (East Anglia) (awarded to Nick E. Day), Special Trustees of the Nottingham University Hospitals (awarded to Clair Chilvers), and the Medical Research Council (awarded to Paula Cook Mozaffari). The Los Angeles County Multi-ethnic Case–control Study was funded by 3RT-0122 ("Smoking and Risk of Proximal Vs. Distal Gastric Cancer," awarded to A.H.W.) and 10RT-0251 ("Smoking, microsatellite instability & gastric cancers," awarded to A.H.W.) from the California Tobacco-Related Research Program and CA59636 (awarded to L.B.) from the National Cancer Institute. The Nebraska Health Study was funded by the Intramural Program of the NIH. The Nova Scotia Barrett Esophagus Study was supported by the Nova Scotia Health Research Foundation ("Molecular mechanisms and lifestyle risk factor interactions in the pathogenesis of human esophageal adenocarcinoma," N419, to A.G.C.). The Factors Influencing the Barrett's Adenocarcinoma Relationship Study was funded by an Ireland-Northern Ireland Co-operation Research Project Grant sponsored by the Northern Ireland Research and Development Office, and the Health Research Board, Ireland (All-Ireland case–control study of Oesophageal Adenocarcinoma and Barrett's Oesophagus, awarded to L.J.M. and Harry Comber); The Australian Cancer Study was supported by the Queensland Cancer Fund and the National Health and Medical Research Council of Australia (Program no. 199600, awarded to D.C.W., Adele C. Green, Nicholas K. Hayward, Peter G. Parsons, David M. Purdie, and Penelope M. Webb). NIH–AARP was funded by the Intramural Program of the NIH. Reported analyses with the Kaiser-Permanente Multiphasic Health Checkup Study were funded by NIH R01 DK063616 (Epidemiology and Incidence of Barrett's Esophagus, Kaiser Permanente, awarded to D.A.C.) and NIH R21DKO77742 (Barrett's Esophagus: Risk Factors in Women, awarded to D.A.C. and Nicholas J. Shaheen).

Notes

Dr. M. B. Cook had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. The funders of the individual studies had no role in the design, analysis, or interpretation of the data, or in writing or publication decisions related to this article.

Affiliations of authors: Division of Cancer Epidemiology and Genetics, National Cancer Institute, National Institutes of Health, Department of Health and Human Services, Bethesda, MD (MBC, FK, NDF, MHW, CCA, W-HC); Department of Public Health Analysis, School of Community Health and Policy, Morgan State University, Baltimore, MD (FK); Division of Genetics and Population Health, Queensland Institute of Medical Research, Brisbane, Queensland, Australia (DCW, NP, PMW); Department of Epidemiology, University of North Carolina School of Public Health, Chapel Hill, NC (MDG); Department of Population Sciences, Beckman Research Institute and City of Hope Comprehensive Cancer Center, Duarte, CA (LB); Statistics and Epidemiology Division, RTI International, Rockville, MD (LMB); Department of Epidemiology and Public Health, Yale University School of Medicine, New Haven, CT (HAR); Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, Sweden (WY, ON); National Cancer Registry Ireland, Cork, Ireland (LS); Department of Preventive Medicine, Keck School of Medicine, USC Norris Comprehensive Cancer Center, Los Angeles, CA (AHW); Information Management Services, Silver Spring, Bethesda, MD (CG); Department of Surgery, University of Saskatchewan, Saskatoon, SK, Canada (AGC); Cancer Epidemiology and Health Services Research, Centre for Public Health, Queen's University, Belfast, Northern Ireland (LJM); Division of Research and Oakland Medical Center, Kaiser Permanente, Northern California, Oakland, CA (DAC); Program in Epidemiology, Fred Hutchinson Cancer Research Center, Seattle, WA (TLV).