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 ade-
nocarcinoma (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 ade-
ocarcinoma 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 inci-
dence 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 pe-
riod 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 esophag-
el adenocarcinoma and Barrett’s esophagus and helping the develop-
ment 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 ade-
ocarcinoma of the esophagus. The two prospective cohort studies
have been used for assessments of different diseases and contrib-
uted esophageal adenocarcinoma and esophagogastric junctional
adenocarcinoma case patients and unaffected randomly selected
control subjects to the BEACON consortium. The primary ob-
goal was 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.

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 esophagoga-

CONTEXT AND CAVEATS

Prior knowledge

Associations between cigarette smoking and esophageal adeno-
carcinoma and esophagogastric junctional adenocarcinoma are
known, but it is not known whether there is a dose–response rela-
tionship 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
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, \(<15, 15–29, 30–44, \geq45\) ), smoking intensity (<1, 1, and \(\geq1\) pack per day; based on the most common number of one pack per day), age of smoking initiation (<17, \(\geq17\) years), cigarette type (filtered only, nonfiltered only, or both), duration of smoking cessation (current smoker, <10, \(\geq10\) 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

<table>
<thead>
<tr>
<th>Study, first author, year (reference)</th>
<th>Design</th>
<th>Location</th>
<th>Period of recruitment</th>
<th>Control subjects† (n = 9453)</th>
<th>EA (n = 1540)</th>
<th>EGJA (n = 1450)</th>
<th>AA (n = 2990)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Australian Cancer Study (esophageal cancer component), Whiteman, 2008 (18)</td>
<td>Case–control</td>
<td>Australia</td>
<td>2001–2005</td>
<td>1512</td>
<td>359</td>
<td>419</td>
<td>778</td>
</tr>
</tbody>
</table>

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

* 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.
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 I2 statistic (26) was used to estimate the percentage of total variation across studies due to heterogeneity. An I2 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 STATATA 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*

<table>
<thead>
<tr>
<th>Exposure</th>
<th>Control subjects (n)</th>
<th>Case patients (n)</th>
<th>OR (95% CI)</th>
<th>$I^2$, ‡ %</th>
<th>Control subjects (n)</th>
<th>Case patients (n)</th>
<th>OR (95% CI)</th>
<th>$I^2$, ‡ %</th>
<th>Control subjects (n)</th>
<th>Case patients (n)</th>
<th>OR (95% CI)</th>
<th>$I^2$, ‡ %</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ever–cigarette smoking</strong></td>
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<tr>
<td>No</td>
<td>3563</td>
<td>358</td>
<td>1.00 (referent)</td>
<td></td>
<td>3493</td>
<td>322</td>
<td>1.00 (referent)</td>
<td></td>
<td>3563</td>
<td>680</td>
<td>1.00 (referent)</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>5214</td>
<td>1098</td>
<td>1.96 (1.64 to 2.34)</td>
<td>24</td>
<td>5122</td>
<td>1051</td>
<td>2.18 (1.84 to 2.58)</td>
<td>21</td>
<td>5214</td>
<td>2149</td>
<td>2.08 (1.83 to 2.37)</td>
<td>21</td>
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<td><strong>Pack-years of smoking</strong></td>
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<tr>
<td>0 (never-smokers)</td>
<td>3563</td>
<td>358</td>
<td>1.00 (referent)</td>
<td></td>
<td>3493</td>
<td>322</td>
<td>1.00 (referent)</td>
<td></td>
<td>3563</td>
<td>680</td>
<td>1.00 (referent)</td>
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<tr>
<td>&lt;15</td>
<td>1469</td>
<td>200</td>
<td>1.25 (1.02 to 1.53)</td>
<td>0</td>
<td>1423</td>
<td>183</td>
<td>1.32 (1.09 to 1.61)</td>
<td>28</td>
<td>1469</td>
<td>383</td>
<td>1.30 (1.07 to 1.58)</td>
<td>28</td>
</tr>
<tr>
<td>15 to &lt;30</td>
<td>900</td>
<td>197</td>
<td>1.96 (1.58 to 2.45)</td>
<td></td>
<td>906</td>
<td>217</td>
<td>2.44 (1.98 to 3.00)</td>
<td>0</td>
<td>900</td>
<td>414</td>
<td>2.19 (1.86 to 2.58)</td>
<td>0</td>
</tr>
<tr>
<td>30 to &lt;45</td>
<td>905</td>
<td>210</td>
<td>2.07 (1.64 to 2.58)</td>
<td>2</td>
<td>895</td>
<td>229</td>
<td>2.64 (2.07 to 3.38)</td>
<td>19</td>
<td>905</td>
<td>433</td>
<td>3.09 (2.49 to 3.83)</td>
<td>11</td>
</tr>
<tr>
<td>≥45</td>
<td>1688</td>
<td>458</td>
<td>2.71 (2.16 to 3.40)</td>
<td>24</td>
<td>1678</td>
<td>401</td>
<td>2.69 (2.23 to 3.23)</td>
<td>0</td>
<td>1688</td>
<td>859</td>
<td>2.73 (2.27 to 3.29)</td>
<td>32</td>
</tr>
<tr>
<td><strong>P trend</strong></td>
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</table>
| *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.

§ $P_{	ext{trend}}$ 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 adenocarcinomas. 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 weight assigned to each study, which reflects the availability of data and the quality of the study. **Factors Influencing the Barrett's Adenocarcinoma Relationship Study** (FAIRS): Larynx, Esophagus, and Oral Cavity Study; NIH–AARP = National Institutes of Health–AARP; NSBES = Nova Scotia Barrett Esophageal 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 263 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, P = 55%) (data not shown in Table 3).

### 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


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Notes
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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).