Colorectal Cancer in Patients with Esophageal Adenocarcinoma

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Abstract

The incidence of adenocarcinoma of the esophagus and gastric cardia has been rising rapidly in Western Europe and the United States, especially among white males. Previous reports, based on case series, have suggested an association between colonic neoplasia and Barrett's esophagus, a metaplastic condition of the lower esophagus that can lead to adenocarcinoma. We analyzed cancer incidence data from 1973 to 1989 from the nine population-based registries of the Surveillance, Epidemiology, and End Results program of the United States National Cancer Institute to investigate this association, using malignancies as an outcome. Using a case-control design, we measured the odds of being diagnosed with colorectal adenocarcinoma some time in life among persons diagnosed with adenocarcinomas of the esophagus or gastric cardia relative to persons diagnosed with squamous cell carcinomas of the esophagus. Among white males the odds ratio was 1.44 (95% confidence interval, 1.03–2.02). This association appeared to be independent of which cancer occurred first. In contrast, white females with adenocarcinomas were less likely to be diagnosed with colorectal cancer than those with squamous cell carcinomas (odds ratio, 0.39; 95% confidence interval, 0.19–0.78). These associations appeared to be specific for colorectal tissue because there was no relationship between histological type of esophageal cancer and prostate cancer in men or breast cancer in women. We conclude that men with esophageal adenocarcinoma may be more likely to be diagnosed with colorectal cancer in their lifetime than expected; the opposite association may exist for women. These data provide additional evidence that some colorectal and esophageal adenocarcinomas share a common etiology. Prospective studies of both men and women with malignant and premalignant lesions of the colon and esophagus are needed to establish the clinical significance of these findings while taking into account gender, and to identify underlying mechanisms.

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Introduction

The incidence of AEC in the United States and Europe has been rising steadily since the 1970s, with the increase among white men exceeding that of any other type of cancer (1–6). The reasons for this increase remain unknown. It is well recognized that Barrett's esophagus, a condition in which the stratified squamous epithelium of the esophagus is replaced by a metaplastic columnar epithelium, is a common precursor of the disease (7). It is hypothesized that almost all esophageal adenocarcinomas develop as a complication of Barrett's metaplasia (8).

Several authors have reported an increase in the prevalence of colorectal neoplasia (carcinoma and adenomatous polyps) in a clinical series of patients with Barrett's metaplasia (9–11). There is also one report suggesting an increased risk of esophageal adenocarcinoma among patients with colon cancer (12). If an association between neoplasia of the esophagus and colon truly exists, it may have significance in two areas. The first is clinical: since colon and rectal cancers are relatively common and treatable, colonoscopy may be an effective screening procedure among persons with Barrett's esophagus. Increased attention to symptoms of gastroesophageal reflux in patients with colon neoplasia may also help identify those with Barrett's metaplasia, for whom cancer surveillance and aggressive treatment may prevent progression to invasive cancer. Second, an understanding of the underlying reasons for the association would likely yield important new information about the etiology of these conditions.

We measured the association between AEC and colorectal cancer by means of a case-control study using data from nine population-based cancer registries supported by the SEER program of the United States National Cancer Institute.

Materials and Methods

Histologically-verified cases of esophageal or gastric cardia cancer diagnosed between 1973 and 1989 among whites and blacks were identified from the SEER registry data. These registries cover approximately 12% of the United States population and include the states of Connecticut, Hawaii, Iowa, New Mexico, and Utah, and the greater San Francisco/Oakland, Detroit, Seattle (since 1974), and Atlanta (since 1975) metropolitan areas (13). Eligible cases were defined by ICD-O site codes 150.0–151.0 (14). Patients with adenocarcinoma (ICD-O histological codes 8140–8573) were cases and those with SEC (ICD-O codes 8050–8082) were controls.

The abbreviations used are: AEC, adenocarcinomas of the esophagus and gastric cardia; SEER, Surveillance, Epidemiology, and End Results; ICD-O, International Classification of Diseases for Oncology; SEC, squamous cell carcinoma; OR, odds ratio; CI, confidence interval; EC, esophageal cancer.
This control group was chosen for three reasons: (a) Barrett’s metaplasia is not a precursor for squamous cell carcinoma of the esophagus, and an increased risk of colorectal cancer in patients with squamous cell carcinoma of the esophagus has not been reported (15-16); (b) patients with adenocarcinoma and squamous cell carcinoma present with similar symptoms. The diagnostic work-up is therefore comparable, which renders detection bias unlikely; and (c) the treatment, follow-up, and survival are similar for the two histological types.

The occurrence of colorectal adenocarcinomas both before and after the diagnosis of EC was compared in cases and controls. Colorectal cancer was defined as ICD-O site codes 153.0-154.1 with histology codes 8140-8573. The analyses were carried out using the following time intervals for diagnosis of the colorectal cancer relative to the diagnosis of the esophageal cancer: (a) 4 months or more after EC; (b) synchronous with EC (defined as less than 4 months before or after the diagnosis of EC); (c) between 4 months and 5 years before EC; (d) 5 years or more before EC; and (e) ever.

In order to evaluate whether the observed association of esophageal adenocarcinoma with colorectal adenocarcinoma was specific to the colon and rectum or part of a broader association with adenocarcinomas of other organs, perhaps reflecting a methodological problem, we also measured the association between EC and prostate (ICD-O code 185) adenocarcinomas in males and breast (ICD-O code 174) adenocarcinomas in females.

ORs and 95% CIs were calculated using logistical regression models as performed by the computer program EGRET (17). Patient age and year of diagnosis of EC were controlled in all models as continuous variables. Regression models in which these characteristics were controlled as categorical (indicator) variables yielded essentially identical results. Survival (in months) after diagnosis of EC was controlled in the analyses of ever, synchronous, and subsequent colorectal cancer.

### Results

Between 1973 and 1989, 16,568 microscopically confirmed cases of AEC and SEC were diagnosed in the 9 SEER areas among whites and blacks. In 594 cases (3.6%) information about previous tumors was missing; these were excluded from further analyses.

There were 5684 AECs (cases) and 4122 SECs (controls) diagnosed in white males (Table 1). Among the cases, 111 patients had been diagnosed with previous, synchronous, or subsequent colorectal cancer. Among the controls, 55 had been diagnosed with colorectal cancer. The mean age at diagnosis of male cases was slightly lower than that of controls: 64.4 (SD = 11.4) and 66.6 (SD = 9.9), respectively. The 5-year actuarial survival was 7.3% (95% CI = 6.5-8.1%) for cases and 5.5% (95% CI = 4.7-6.3%) for controls. After adjusting for the potential confounding effects of age at diagnosis, year of diagnosis, and survival, we found that among white males the OR for the association of esophageal or gastric cardia adenocarcinoma with ever diagnosis of colorectal cancer was 1.44 (95% CI = 1.03-2.02). Adjusted ORs for the different time periods of possible colorectal cancer diagnosis are also presented in Table 1. The positive association between AEC and colorectal cancer was present in all time periods, although the higher risk was not statistically significant in any one alone.

In black males, 4 colorectal tumors were diagnosed among 1112 cases (1.9%), and 10 tumors were diagnosed among 1924 controls (0.5%); the adjusted OR was 2.76 (95% CI = 0.84-9.00). Small numbers prohibited meaningful analyses of different time periods in black males.

In white females, we found the opposite association. Among 1212 cases, 12 colorectal cancers were diagnosed, whereas 39 colorectal cancers were diagnosed among 2101 controls (Table 1). On average, female cases were somewhat older than female controls: 70.0 (SD = 12.3) years and 68.4 (SD = 10.4) years, respectively. The 5-year actuarial survival was 8.7% (95% CI = 6.9-10.5%) in cases and 7.5% (95% CI = 6.3-9.7%) in controls. The adjusted OR for ever having had colorectal cancer was 0.39

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**Table 1** Presence and timing of colorectal cancer diagnosis in white patients with cancer of the esophagus or gastric cardia (EC): adenocarcinoma (cases) versus squamous cell carcinoma (controls)

<table>
<thead>
<tr>
<th></th>
<th>No. of cases</th>
<th>No. of controls</th>
<th>Odds ratio*</th>
<th>(95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>White males</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never colorectal cancer</td>
<td>5573</td>
<td>4067</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>Ever colorectal cancer</td>
<td>111</td>
<td>55</td>
<td>1.44</td>
<td>(1.03-2.02)</td>
</tr>
<tr>
<td>Timing of colorectal cancer diagnosis</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4+ months after EC</td>
<td>12</td>
<td>4</td>
<td>2.00</td>
<td>(0.63-6.32)</td>
</tr>
<tr>
<td>&lt;4 months before or after EC</td>
<td>34</td>
<td>17</td>
<td>1.63</td>
<td>(0.89-3.01)</td>
</tr>
<tr>
<td>4 months to 5 years before EC</td>
<td>38</td>
<td>22</td>
<td>1.24</td>
<td>(0.73-2.12)</td>
</tr>
<tr>
<td>5+ years before EC</td>
<td>27</td>
<td>12</td>
<td>1.45</td>
<td>(0.73-2.89)</td>
</tr>
<tr>
<td><strong>White females</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never colorectal cancer</td>
<td>1200</td>
<td>2062</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>Ever colorectal cancer</td>
<td>12</td>
<td>39</td>
<td>0.39</td>
<td>(0.19-0.78)</td>
</tr>
<tr>
<td>Timing of colorectal cancer diagnosis</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>4+ months after EC</td>
<td>2</td>
<td>5</td>
<td>0.76</td>
<td>(0.15-4.00)</td>
</tr>
<tr>
<td>&lt;4 months before or after EC</td>
<td>5</td>
<td>2</td>
<td>2.86</td>
<td>(0.52-15.82)</td>
</tr>
<tr>
<td>4 months to 5 years before EC</td>
<td>4</td>
<td>20</td>
<td>0.30</td>
<td>(0.10-0.90)</td>
</tr>
<tr>
<td>5+ years before EC</td>
<td>1</td>
<td>12</td>
<td>0.11</td>
<td>(0.01-0.88)</td>
</tr>
</tbody>
</table>

*Adjusted for age at diagnosis and year of diagnosis of esophageal cancer (EC) (all timeframes) and survival after diagnosis of EC (only for analyses of ever, synchronous, and subsequent colorectal cancer).
These analyses took into account the potential confounding effects of age and year of diagnosis of esophageal cancer and survival time after diagnosis of esophageal cancer. The results were not substantially changed after exclusion of cancers arising from the gastric cardia or gastroesophageal junction from the case group. The associations were also of similar magnitude when tumors arising in rectum were excluded from analyses.

Several aspects of our analytic approach are worth noting. By using the extensive data from the SEER cancer registries, we were able to examine the link between Barrett's-associating neoplasia and colorectal neoplasia using a different methodology than has been attempted previously. Since there is no suspected temporal order to the association between esophageal and colorectal neoplasia, we used a case-control design to measure the association, and included both previous and subsequent diagnoses of colorectal cancer as "exposures," rather than restricting to diagnoses that took place prior to the onset of the disease that determined case-control status. This facilitated the calculation of a single summary measure of association while still allowing the examination of associations by the order in which the cancers occurred; it also allowed adjustment for survival time. Because patients with esophageal adenocarcinoma will generally get a thorough physical examination as part of their work-up, nonsymptomatic colorectal cancer may have been diagnosed in some cases. To avoid this potential detection bias, we chose patients with esophageal squamous cell carcinoma as controls rather than persons from the general population. As a check on the validity of our methods, we compared the frequency of prostate and breast cancer among cases and controls, reasoning that a valid design would show no association between either of these common cancers and histological type of esophageal cancer. Thus it was reassuring that the risks of prostate cancer and breast cancer appeared to be quite similar in cases and controls.

In interpreting our findings, we first considered a methodological issue. All SEER registries record a set of identifiers for each new person diagnosed with cancer so that multiple primary tumors occurring in a person can be identified. The order of occurrence of the tumors is recorded in FTOB's associated record, and the order of occurrence of the tumors is recorded in SEER registries, we were able to examine the link between Barrett's-associating neoplasia and colorectal neoplasia using a different methodology than has been attempted previously. Since there is no suspected temporal order to the association between esophageal and colorectal neoplasia, we used a case-control design to measure the association, and included both previous and subsequent diagnoses of colorectal cancer as "exposures," rather than restricting to diagnoses that took place prior to the onset of the disease that determined case-control status. This facilitated the calculation of a single summary measure of association while still allowing the examination of associations by the order in which the cancers occurred; it also allowed adjustment for survival time. Because patients with esophageal adenocarcinoma will generally get a thorough physical examination as part of their work-up, nonsymptomatic colorectal cancer may have been diagnosed in some cases. To avoid this potential detection bias, we chose patients with esophageal squamous cell carcinoma as controls rather than persons from the general population.

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a sequence number. However, specific information about the tumor, such as site and date of diagnosis, is not available from the pooled data of the SEER program if the tumor was diagnosed before the start of the registry. Of all patients with EC diagnosed between 1973 and 1989 and registered in one of the SEER registries, 3.6% were known to have been diagnosed with a previous tumor, but with unknown site and histology. Since in the early 1970s relatively more SECs were diagnosed than in the 1980s, missing information on previous tumors was somewhat more common among controls (4.5%) than among cases (2.6%). We attempted to minimize this potential source of bias by adjusting for year of diagnosis in the analyses. To determine whether our findings were sensitive to this limitation, we reanalyzed the risk of ever having had colorectal cancer diagnosed starting 5 years before the esophageal cancer among patients diagnosed at least 5 years after the start of each SEER registry. A second reanalysis was performed that was restricted to patients diagnosed at least 10 years after the starting dates of the registries and including colon cancer diagnoses as early as 10 years before the diagnosis of esophageal cancer. We reasoned that (apart from nondifferential incompleteness of the registry) a colorectal carcinoma diagnosed in these two groups of subjects within the previous 5 or 10 years, respectively, would have been registered by SEER. These reanalyses did not change our conclusions.

In clinical series, several authors have noted an association between premalignant or malignant lesions in the esophagus and colon. In 1985, Sontag et al. (9) reported on 63 new patients with Barrett’s esophagus. Five patients had a history of colon cancer within the previous 3 years, and three patients had a history of polypectomies of benign tumors. Colonoscopy revealed three or more patients to have malignant tumors in the sigmoid colon and hepatic flexure, and 16 patients to have benign polyps. In a prospective study, Robertson et al. (10) compared the results of colonoscopy in 32 patients with Barrett’s esophagus with those obtained in a sex- and age-matched control group of 64 patients thought to have the irritable bowel syndrome. Three patients with Barrett’s metaplasia were diagnosed with malignant colorectal tumors and another five patients had benign polyps (25% with neoplasia). In the control group, only 3 (5%) patients were diagnosed with benign polyps, and none with cancer. Lyons et al. (11) performed colonoscopy in 99 patients with Barrett’s esophagus and 54 patients with gastroesophageal reflux disease complicated by strictures. In 46 patients (46%) with Barrett’s esophagus, adenomatous polyps \((n = 34)\) or carcinoma \((n = 12)\) was found, while only 13 patients (24%) with reflux disease had benign polyps and none had cancer. In a study by Tripp et al. (18), colonoscopy was performed in 36 patients with Barrett’s esophagus. All patients were free of colonic symptoms although 3 patients had a personal history of colorectal adenomas. No malignancies were found, but benign adenomas were found in 12 (33%) patients. This percentage was similar to that reported by the investigators in persons who underwent colonoscopy at their institution for clinical indications, primarily rectal bleeding and abnormal barium enemas (38%). Similarly, Riner et al. (19) noted 39% of patients with Barrett’s esophagus to have colonic neoplasms (9 polyps and 2 adenocarcinomas). In contrast Ramage et al. (20) found no elevation in prevalence of colorectal neoplasms in a small population of Barrett’s esophagus patients. In the only study examining esophageal neoplasia following colon cancer, Kingston et al. (12) reported 4 cases of esophageal cancer (cell type not specified) occurring within 26 months among 157 persons with large bowel cancer.

Among the reports described above, only that of Robertson et al. (10) presented the results by sex. In males, 7 of 21 cases (33%) had colorectal neoplasia (including 3 carcinomas) compared to 2 of 42 controls (5%), none of whom had carcinomas. In females, 1 of 11 Barrett’s esophagus patients (9%) and 1 of 22 control patients (5%) with the irritable bowel syndrome had a benign adenomatous poly. No colorectal cancer was found in any of the female subjects. This finding of a stronger association among males than females, while based on small numbers, is consistent with the results of the present study.

Thus the present population-based study and previous clinical studies provide considerable evidence for a link between colorectal neoplasia and adenocarcinoma-associated neoplasia of the esophagus and gastric cardia. However, both the underlying reasons for this association and its clinical relevance need to be determined. The fact that this association appears to be independent of the temporal order of the neoplasia, and to hold for both malignant and premalignant disease argues against a treatment effect. Therefore, a common genetic susceptibility to develop AEC and colorectal cancer may exist. In addition, the two types of cancer may share one or more environmental risk factors.

One possible area of overlap is diet, particularly fat intake. A high fat intake appears to increase colon cancer risk, and also predisposes to gastroesophageal reflux, a cofactor in the development of Barrett’s metaplasia (21). There is some epidemiological evidence that a high fat diet increases risk of esophageal adenocarcinomas (22). A second area of overlap might be related to bile acids. It is hypothesized that one mechanism by which high fat diets may increase colon cancer risk is by increasing tissue exposure to bile acids (21). Similarly, there is a suggestion from animal experiments that biliary reflux may predispose to esophageal adenocarcinomas (23–24). However, these postulated mechanisms do not account for the apparent lack of association or even negative association among women. Although statistically significant in the present study, the association in women needs to be more carefully considered in future studies.

In addition to helping to focus research on environmental and genetic factors in the etiology of esophageal and colorectal cancer, an association between these diseases may also have important implications for clinical practice. This could be in terms of both screening persons with colorectal neoplasia for the presence of Barrett’s metaplasia, dysplasia, and early cancer, and screening persons with Barrett’s metaplasia for colorectal neoplasia.

In conclusion, we believe that our findings provide additional evidence for a potentially important association between neoplasia in the esophagus and colon which may be modified by gender. These findings warrant further attention in larger, well controlled studies of both men and women with premalignant conditions of the esophagus and colon.

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References


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