Risk Factors for Adenocarcinomas and Malignant Carcinoids of the Small Intestine: Preliminary Findings

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Abstract
Although the small intestine contains 75% of the mucosal surface of the gastrointestinal tract, it is the site of only 2% as many malignancies as the large bowel. The association of Crohn's disease with small intestine adenocarcinoma is well known, but the analytic epidemiology of small intestine malignancies has not received much attention. We reviewed the medical records of 19 patients with adenocarcinoma and 17 with malignant carcinoids identified from the Columbia-Presbyterian Medical Center Tumor Registry in the years 1980-1987. These were compared with 52 controls with nonmalignant conditions from the same time period. Three adenocarcinoma patients but no carcinoid patients or controls had previous Crohn's disease ($P < 0.004$). Three adenocarcinomas and three carcinoids, but no controls, had previous cholecystectomy ($P < 0.004$). Previous peptic ulcer disease was recorded for two patients with adenocarcinoma and three with carcinoid but no controls ($P < 0.02$, $P < 0.0002$). The age and sex-adjusted odds ratio for cigarette smoking was 4.6 (95% confidence interval, 1.0-20.7) for adenocarcinomas and 4.2 (0.8-22.4) for carcinoids. The adjusted odds ratio for alcohol consumption was 4.0 (1.0-15.9) for adenocarcinomas and 3.1 (0.7-13.9) for carcinoids. Further studies are warranted to confirm these associations and to identify potential protective factors in the small intestine.

Introduction
Malignant tumors of the small intestine are extremely rare, occurring less than 1/50th as frequently as malignancies of the large intestine, despite the fact that their surface area constitutes 75% of the total surface area of the gastrointestinal tract (1). The major histological subtypes of small bowel malignancies are adenocarcinomas and malignant carcinoids (2). The adenocarcinomas occur predominantly in the duodenum, but despite this, it is clear that they share certain features with large bowel malignancies. For example, their international incidence covaries with that of colorectal cancer and not with gastric cancer (3). They appear to arise out of adenomatous polyps, as do colorectal malignancies, and are increased in association with familial adenomatous polyposis (4). In addition, we have shown recently that there is an increased risk for adenocarcinoma of the small intestine in individuals with colorectal cancer, and vice versa (5).

Adenocarcinoma and malignant carcinoids each constitute about 35-40% of small bowel malignancies (2). Little is known about the etiology of either of these tumor types. The only known risk factor is Crohn's disease, which predisposes strongly to the development of adenocarcinoma (6-11). Lowenfels and others have suggested that bile secretion and metabolism are somehow tied to the incidence of adenocarcinoma, particularly given its anatomic predominance in the duodenum (12, 13). In contrast, carcinoid tumors occur primarily in the ileum (14). Carcinoids are often relatively asymptomatic, and as a result their diagnosis frequently appears to be an incidental finding (14). Only one previous study has investigated risk factors for small bowel cancer (15). It found a possible link of diet to small bowel cancers, but no association with alcohol or tobacco. However, it did not analyze by histological subtype. In this study, we report a small-scale case-control study conducted for the purpose of collecting preliminary evidence regarding possible risk factors for a future large-scale study.

Materials and Methods
In this hypothesis-generating study, we used cases of adenocarcinoma or malignant carcinoid of the small intestine which were diagnosed between 1980 and 1987 and were identified by the Columbia-Presbyterian Tumor Registry. We identified 23 patients with small bowel adenocarcinoma and 17 with malignant carcinoid tumors. The records of two of the adenocarcinoma patients could not be obtained, and an additional two adenocarcinoma patients were excluded because review of the pathology showed that they were really adenocarcinomas arising in other sites.

The histological slides of the 19 remaining adenocarcinoma patients and of the 17 malignant carcinoid patients were reviewed by a pathologist (H. R.) and the diagnoses were confirmed. For controls, we wanted patients with benign conditions which were not gastrointestinal in origin, which required hospitalization, and which could be identified through the records of the Department of Pathology. Our controls consisted of patients diagnosed at Columbia-Presbyterian Medical Center between 1980 and 1987 with benign cystic disease, proliferative endometrium, benign prostatic hypertrophy, or herniorrhaphy. The controls were selected randomly over the time period of the study from the files. Controls with a history of cancer were excluded (two cases). In this way, 52 controls were obtained. The medical record was reviewed for each case and control.
aged at diagnosis, race, marital status, religion, and type of hospital room (private, semiprivate, ward). We also obtained information on history of Crohn's disease, previous cholecystectomy, and peptic ulcer disease. For patients with multiple hospitalizations, information was obtained initially from the hospitalization at the time of the small bowel malignancy diagnosis. When possible, information was verified for subsequent or earlier admissions.

Information regarding blood type was missing in 70\% of the controls because most of the controls did not undergo a major surgical procedure. Therefore, a systematic sampling of blood bank files between 1980 and 1987 was performed, collecting the blood type on every fifth file. A total of 300 blood bank files was thus reviewed.

Logistic regression analyses were performed using BMDP (BMDP Statistical Software, Inc., Los Angeles, CA) with age and sex as covariates. Adjusted odds ratios and confidence intervals were derived from the regression coefficients as described by Kelsey (16).

Results
Table 1 shows a comparison of the demographic characteristics of the adenocarcinoma and carcinoid cases as well as the controls. The two case groups appear to be somewhat older than the control group. The sex and race distributions were similar among the three groups. As has been reported in the past, the adenocarcinomas were predominantly in the duodenum, while the malignant carcinoid tumors were primarily in the distal ileum.

Analyzing cigarette smoking and alcohol consumption as dichotomous exposures, we found both smoking and alcohol to be associated with adenocarcinoma of the small intestine, adjusted for age and sex as described by Kelsey (16).

**Table 1** Characteristics of adenocarcinoma and carcinoid cases and controls

<table>
<thead>
<tr>
<th>Variable</th>
<th>Adenocarcinoma</th>
<th>Carcinoid</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td>n (%)</td>
<td>n (%)</td>
<td>n (%)</td>
</tr>
<tr>
<td>Male</td>
<td>9/47</td>
<td>7/41</td>
<td>29/56</td>
</tr>
<tr>
<td>Female</td>
<td>10/53</td>
<td>10/59</td>
<td>23/44</td>
</tr>
<tr>
<td>Age (mean ± SD)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>70.7 ± 7.2</td>
<td>67.7 ± 10.7</td>
<td>55.8 ± 18.0</td>
</tr>
<tr>
<td>Female</td>
<td>59.8 ± 11.3</td>
<td>62.9 ± 10.8</td>
<td>52.2 ± 11.5</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asian</td>
<td>1/5</td>
<td>0/0</td>
<td>0/0</td>
</tr>
<tr>
<td>Black</td>
<td>4/21</td>
<td>5/29</td>
<td>7/13</td>
</tr>
<tr>
<td>Hispanic</td>
<td>1/5</td>
<td>2/12</td>
<td>3/6</td>
</tr>
<tr>
<td>White</td>
<td>13/68</td>
<td>10/59</td>
<td>42/81</td>
</tr>
<tr>
<td>Subsite</td>
<td>Duodenum</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>12/63</td>
<td>2/12</td>
<td></td>
</tr>
<tr>
<td>Jejunum</td>
<td>3/16</td>
<td>1/6</td>
<td></td>
</tr>
<tr>
<td>Ileum</td>
<td>4/21</td>
<td>14/82</td>
<td></td>
</tr>
</tbody>
</table>

\* n, number.

**Table 2** Association of cigarette smoking and alcohol consumption with adenocarcinomas and malignant carcinoids of the small intestine, adjusted for age and sex

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Adenocarcinoma</th>
<th>Carcinoid</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cigarette smoking</td>
<td>6.2 (1.5-26.7)</td>
<td>5.8 (1.1-30.3)</td>
</tr>
<tr>
<td>Alcohol</td>
<td>5.5 (1.4-21.4)</td>
<td>4.4 (1.1-18.5)</td>
</tr>
</tbody>
</table>

\* OR, odds ratio. \* CI, confidence interval.

Discussion
Because of its rarity, there has been only one case-control study of small intestine cancer (15). In part, this is because it does not constitute a major public health problem. However, it would be of interest to know precisely why it is so rare, as this information may be useful in understanding and preventing cancer at other sites within the gastrointestinal tract.

Our study is the second attempt to generate some hypotheses for potential risk factors for further study in future large-scale investigations. Despite the small sample sizes, we did not believe it reasonable to combine the adenocarcinomas and malignant carcinoids into a single case group, given the large differences in their anatomic distribution, cells of origin, natural history, and behavior, and response to therapy.

The present study has several limitations. Because of the rarity of these malignancies, the sample sizes for both case groups were small, although this would be primarily a problem with regard to the absence of associations. In addition, because of the small numbers, small misclassification errors could have major impacts on the observed associations. We were limited to patients from one major university medical...
center, which could potentially limit the generalizability of our findings. Thus, the observation that the subset distribution of the adenocarcinomas and malignant carcinoid tumors was consistent with previous studies was reassuring in this regard (Table 1).

Another limitation was our reliance on the medical record regarding exposure information. This limited the exposure variables we could investigate. In addition, because the recording of quantitative information for smoking and alcohol use was variable, our information regarding these variables was limited to yes/no. The reporting of information on past medical history may have been a reflection of the intensity of medical surveillance, leading to the diagnosis rather than a true causal association.

Crohn’s disease has been found to have a relative risk as high as 100 for the subsequent development of adenocarcinoma, and in general, these malignancies have involved the terminal ileum, reflecting the distribution of Crohn’s disease itself. It is reassuring to find an association with Crohn’s disease in our study as well, in essence serving as a positive control, especially because three Crohn’s disease-associated adenocarcinomas were in the ileum rather than the duodenum.

An association between previous cholecystectomy and adenocarcinomas (see Table 2) is of interest in light of a possible association with large bowel malignancies as well (17). The association with malignant carcinoid tumors is an unexpected finding, but may reflect a causal association as well. The cholecystectomy rates among the cases also are elevated compared with a previous study of cholecystectomy at our medical center (17); it was found that 9.2% of women and 6.7% of men had a history of previous cholecystectomy.

The association of previous peptic ulcer disease with both malignancies is also a new finding. Peptic ulcer disease is a hyperacidity syndrome, which would alter the alkaline environment of the small intestine. Lightdale et al. (18), have suggested that it is precisely this alkaline environment which protects the small intestine against neoplasia. Thus, it is intriguing that peptic ulcer disease was found to be associated with both types of malignancies.

One previous study examined the association between alcohol and smoking exposure and cancer of the small intestine (15), although that study was not histological subtype-specific. No association was found with these exposures. This is the first study to find an association between cigarette smoking, alcohol consumption, and cancer of the small intestine. In addition, we recently have accumulated evidence from a population-based tumor registry also suggesting that cigarette smoking may play a role in the etiology of small bowel adenocarcinomas.2

In summary, this study is the first to systematically investigate potential risk factors for the two major subtypes of small intestine cancer. It confirmed the association between Crohn’s disease and adenocarcinoma in the ileum, and suggested that previous cholecystectomy and/or peptic ulcer disease also may be associated with both adenocarcinomas and malignant carcinoid tumors of the small intestine. The study also found that both cigarette smoking and alcohol consumption were associated with both types of tumor, and were independent risk factors. Larger studies are warranted to confirm and further explore these associations and to define the factors protecting the small bowel against carcinogenesis.

References


Table 3 Association of medical history risk factors with adenocarcinoma and malignant carcinoids of the small intestine

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Adenocarcinoma</th>
<th>Carcinoid</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>%</td>
<td>n</td>
</tr>
<tr>
<td>Crohn’s disease</td>
<td>3</td>
<td>16b</td>
<td>0</td>
</tr>
<tr>
<td>Cholecystectomy</td>
<td>3</td>
<td>16b</td>
<td>3</td>
</tr>
<tr>
<td>Peptic ulcer disease</td>
<td>2</td>
<td>11c</td>
<td>3</td>
</tr>
</tbody>
</table>

a n number.
b P = 0.004.
c P = 0.02.
d P = 0.002.
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