Familial Occurrence of Carcinoid Tumors and Association with Other Malignant Neoplasms

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Abstract
Carcinoid tumors are generally thought to be sporadic, except for a small proportion that occur as a part of multiple endocrine neoplasia syndromes. Data regarding the familial occurrence of carcinoid as well as its potential association with other neoplasms are limited. A chart review was conducted on patients indexed for malignant carcinoid tumor of the gastrointestinal tract seen at the Mayo Clinic between 1988 and 1996. A survey of family history of malignancies and personal history of other tumors was mailed to all eligible patients. Data for 245 patients were analyzed. Observed rates of carcinoids and other malignancies were compared with Surveillance, Epidemiology, and End Results data. Estimates of the cumulative probability for first-degree relatives developing a carcinoid tumor were calculated. Nine (3.7%) patients with carcinoid tumor had at least one first-degree relative with the same malignancy. The rate of carcinoid tumor in first-degree relatives of probands was higher (P < 0.0001) than expected based on the Surveillance, Epidemiology, and End Results population data. Cumulative probability in a first-degree relative for developing a carcinoid tumor was calculated to be 1.5% at age 80. There was an increased risk for developing a carcinoid tumor among first-degree relatives of patients with carcinoid. Neither patients with carcinoid nor their first-degree relatives had an increased incidence of other malignancies.

Introduction
Carcinoids are neuroendocrine tumors, the cells of which are capable of secreting vasoactive substances such as serotonin, histamine, and bradykinin. These are relatively slow-growing tumors and, the majority of patients harboring gastrointestinal carcinoids are asymptomatic (1). Carcinoids of the small intestine are found in ~1 of 150 patients at autopsy (2), and carcinoids of the appendix are found in ~1 of 300 appendectomies (3). The most frequent sites for carcinoid tumors are the gastrointestinal tract (73–85%) and the bronchopulmonary system (10–28.7%). Carcinoids are occasionally found in the larynx, thymus, kidney, ovary, prostate, and skin (4, 5). Adenocarcinomas and carcinoids are the most common malignancies in the small intestine in adults (6, 7). In children, they rank second behind lymphoma among alimentary tract malignancies (8). Carcinoids appear to have increased in incidence during the past 20 years (5).

Carcinoid tumors were originally thought to possess a very low metastatic potential. In recent years, their natural history and malignant potential have become better understood (9). In ~40% of patients, metastases are already evident at the time of diagnosis. The overall 5-year survival rate of all carcinoid tumors, regardless of site, is ~50% (5). The epidemiology of carcinoid tumors is still poorly understood because of the rarity of large population-based studies (10).

Except for a small proportion of carcinoids, which occur as a part of MEN3 syndromes, carcinoid tumors are generally considered to be sporadic. However, a number of patients have been seen at the Mayo Clinic who had at least one first-degree relative with isolated carcinoids, without evidence of other MEN-associated findings. This suggests that some carcinoids may be familial, but no data are available on the percentage of carcinoids present in the familial histories of patients with carcinoid. In addition, the literature is contradictory as to whether patients with carcinoid tumor within the gastrointestinal tract have an increased incidence of other malignancies (2, 4, 11–15).

The purpose of this study was to determine the proportion of familial cases among patients with carcinoid tumor, calculate the risk of developing carcinoid for relatives of probands, and determine the prevalence of other malignant tumors among patients with carcinoids.

Materials and Methods
A chart review was conducted on all patients indexed for malignant carcinoid tumor in the gastrointestinal tract at Mayo Clinic between 1988 and 1996.

The presence of carcinoid tumor was documented by pathology from either a surgical biopsy performed at Mayo Clinic or outside excised material. Patients of both sexes, ages 20–70 years, were included in the study. The exclusion criteria included previous diagnosis of MEN 1 or MEN 2 or presence of MEN-associated endocrine tumors (medullary thyroid carcinoma and parathyroid, pancreatic, and suprarenal).

Two hundred forty-five eligible Mayo patients were identified based on the above criteria, as documented in their clinical records, of which 67 were deceased. A survey of the family history of carcinoid tumors and personal history of other
malignancies was mailed to all eligible patients. The questionnaire requested information on the patient’s current age, age of diagnosis of carcinoid tumor, prior or present diagnosis of other malignant tumors, and age at diagnosis. The questionnaire also inquired about the family history, including total number and ages of all living and deceased first-degree relatives, the presence of carcinoid tumor or other malignancy in first-degree relatives, and their ages at diagnosis. One repeat mailing followed nonresponse. For patients who agreed to participate in the study, additional information that was pertinent to the personal and family history of malignant tumors was obtained by telephone in all cases when there was a discrepancy between information provided in the questionnaire and information found in the medical record. For patients who were deceased at the time of data collection, the information was extracted from their Mayo medical charts only. These results were analyzed separately.

**Statistical Methods.** Estimates of the cumulative probability for first-degree relatives being diagnosed with a carcinoid tumor were calculated using the method of Kaplan and Meier (16). Expected rates of cancers other than carcinoids are based on the SEER age- and sex-specific incidence rates for the time period from 1990 to 1994 (17). Expected rates for carcinoid tumors were based on the SEER age- and sex-specific incidence rates for the time period from 1990 to 1995.2 Observed incidence rates were calculated by dividing the total number of observed events by the total person years (sum of the individual follow-up times in years) at risk. Standard morbidity ratios were calculated by dividing the observed rates by the expected rate adjusted for age and sex (the sum of the products of each age- and sex-specific SEER rate multiplied by the study population total person years at risk within the corresponding age and sex category). Confidence intervals for the rate ratios were based on the assumption that the observed number of events has a Poisson distribution and the number of person years is fixed (18).

**Results**

**Probands with Carcinoid Tumor.** Two hundred forty-five patients (22 males and 123 females) were included in our analysis. Information was collected from medical charts and questionnaires for 178 probands. For an additional 67 patients who were deceased, data were obtained from medical records. The mean age of patients at the time of data collection was 52.7 ± 11.46 years. The mean age at diagnosis of carcinoid tumor was 52.7 ± 10.7 years (range, 17–70 years). The distribution of tumors within the gastrointestinal tract is presented in Table 1. The small bowel was the most common site (176 patients; 71.8%), followed by the colon (36 patients; 14.6%) and appendix (33 patients; 13.4%). In 31 (12.6%) patients, carcinoid was discovered as an incidental finding during surgery performed for another reason. In 179 (73%) patients, the tumor showed signs of local invasion or distant metastases at the time of diagnosis.

**Occurrence of Carcinoid Tumors in First-Degree Relatives of Probands.** Nine (3.7%) patients with carcinoid tumor had at least one first-degree relative (parent, sibling, or child) with the same malignancy. None of the index patients were related to each other. One patient had two affected relatives. There were a total of 1772 first-degree relatives of probands, and information about their age was available for 1498. The mean age of first-degree relatives at the time of data collection was 52.5 ± 21.5 years (range, 1–98 years). Carcinoid tumor was present in 10 (0.68%). The presence of carcinoid tumor in relatives was based on information in patient charts and questionnaires and confirmed by review of medical records of the relatives of four probands (which includes five relatives). The presence of carcinoid tumor in the relative was confirmed in two other cases by a telephone interview with the proband, who had definite knowledge of the diagnosis, location of tumor, and symptoms consistent with carcinoid syndrome (flushing and diarrhea) in the affected relative. Unfortunately, we were unable to obtain definite confirmation of carcinoid in three relatives, due to change of the proband’s address or death. Five (50%) of the affected relatives had a carcinoid in the small bowel, and two (20%) had a carcinoid in the colon. Information about the location of the carcinoid tumor was unavailable in three cases. The observed number of carcinoid tumors in first-degree relatives was significantly higher (P < 0.0001) than expected, based on the SEER data (Table 2).

Among first-degree relatives in our series, the incidence rate for carcinoid tumors, age-adjusted to the 1970 United States white population was 12.5 per 100,000 person-years (95% CI, 0.6–24.9) for males and 15.7 per 100,000 person-years (95% CI, 2.8–28.5) for females. The cumulative probability of developing carcinoid tumor for a first-degree relative at age 80 was calculated to be 1.5% (Table 3).

**Associated Tumors in Patients with Carcinoid Tumor.** In 66 of 245 (26.9%) of patients with carcinoid tumor, a second tumor other than carcinoid was identified. A total of 81 tumors were reported, 53 of which were malignant (Table 4). One tumor in addition to carcinoid was present in 51 patients, two additional tumors were present in 13 patients, and four additional tumors were present in one patient. Observed incidence rates are presented on the Table 5. The incidence of colorectal adenocarcinoma, adjusted for the sex and age of patients, was

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**Table 1** Location of primary carcinoid tumor within the gastrointestinal tract

<table>
<thead>
<tr>
<th>Tumor site</th>
<th>No. of patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ileum</td>
<td>129 (52.6)</td>
</tr>
<tr>
<td>Jejunum</td>
<td>43 (17.5)</td>
</tr>
<tr>
<td>Duodenum</td>
<td>4 (1.6)</td>
</tr>
<tr>
<td>Appendix</td>
<td>33 (13.5)</td>
</tr>
<tr>
<td>Colon</td>
<td>12 (4.9)</td>
</tr>
<tr>
<td>Rectum</td>
<td>24 (9.8)</td>
</tr>
<tr>
<td>Total</td>
<td>245 (100.0)</td>
</tr>
</tbody>
</table>

**Table 2** Location of carcinoid tumor in first-degree relatives of index patients

<table>
<thead>
<tr>
<th>Location of carcinoid tumor</th>
<th>No. observed</th>
<th>No. expected</th>
<th>Risk ratio</th>
<th>95% confidence interval</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any location</td>
<td>10</td>
<td>1.437</td>
<td>6.957</td>
<td>3.336–12.901</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Small intestine</td>
<td>5</td>
<td>0.385</td>
<td>12.975</td>
<td>4.217–30.232</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Colon</td>
<td>2</td>
<td>0.130</td>
<td>15.365</td>
<td>1.859–55.313</td>
<td>0.008</td>
</tr>
</tbody>
</table>

*In three relatives, the location of carcinoid tumor within the gastrointestinal tract was unknown. Expected values are based on rates calculated from the SEER Public Use Data CD-ROM. Histology codes 8240–8241 were used to access carcinoid tumors in the SEER database. Rates were based on data from 1990–1995.*
significant higher than expected. After patients for whom data were collected only through chart review were excluded, the incidence of colorectal adenocarcinoma was only moderately elevated. Of 10 patients who had both carcinoid tumor and colorectal carcinoma, seven presented with symptoms related to colon cancer and the carcinoid tumor was detected as a coincidental finding. Excluding these patients, the incidence of colorectal carcinoma was not significantly higher than expected.

Other Malignant Tumors in Relatives of Proband with Carcinoid Tumor. One hundred twenty-nine of 245 patients with carcinoid (54.88%) reported a history of malignancy in a first-degree relative. The most commonly observed tumors in relatives are shown in Table 6. The incidence of gastric carcinoma was significantly increased, whereas the incidence of prostate and lung cancer was lower than expected among relatives of patients with carcinoid.

Discussion

In the gastrointestinal tract, carcinoid tumors are most commonly found in the small bowel (28.7%), appendix (18.9%), and rectum (12.6%; Ref. 3). One report suggested a high prevalence of rectal carcinoids (55%), compared to other gastrointestinal carcinoids (19). Small intestinal and colonic carcinoids have higher metastatic potential than do tumors in other locations (20), with a higher percentage of nonlocalized lesions (71.2% for small intestinal and 70.7% for colon), as opposed to the overall percentage of nonlocalized lesions for all carcinoids (45.3%; Ref. 5). In our series, there was a higher prevalence of small intestinal carcinoids (71.8%) and relatively small number of appendiceal (13.5%) and rectal (9.8%) carcinoids. Furthermore, 73% of our patients had a nonlocalized lesion at the time of diagnosis. The observed number of metastatic carcinoids and the increased incidence of ileal carcinoids as compared with population-based data are probably a reflection of the referral bias of our institution.

Several studies indicate that patients with carcinoid tumors are at increased risk for developing another primary malignancy (2, 11, 12). Chen et al. (13) postulated that small intestinal adenocarcinoma and carcinoid may have common endogenous or environmental risk factors. Kothari and Mangla (11) found that 36% of patients with ileal carcinoid had an associated malignancy. Brown and Smith (12) reported a patient with malignant carcinoid tumor of the ileum who subsequently developed four other tumors, two malignant (one being colon adenocarcinoma) and two benign. These authors suggested a 17–53% incidence of second primary malignancy in patients with carcinoids, based on a review of the literature from 1949 to 1970. Ballantyne et al. (21) found metachronous gastrointestinal malignant neoplasm in 6 of 54 patients with carcinoid of the colon. They recommended surveillance of the entire gastrointestinal tract in patients with colon carcinoid because of a high rate of other gastrointestinal malignant neoplasms. Some reports in the more recent literature describe concurrent carcinoid and intestinal adenocarcinoma (22, 23). However, a large population-based study of a 1029 patients with carcinoids failed to confirm a general excess cancer risk in patients with carcinoid tumors (14, 15). Because of contradictory literature data, it is important to clarify these concerns since they may have a significant impact on patient management and prognosis. In our series, 66 of 245 patients had a second tumor other than carcinoid. When compared with SEER data adjusted for age and sex, there was a significant increase in the number of colorectal cancers. A slightly smaller but still significant difference was present after exclusion of data based solely on the chart review (deceased patients). This probably represents higher mortality of patients with coexisting colorectal cancer. However, after exclusion of patients in whom carcinoids were detected as an incidental finding, the incidence of colorectal cancer among patients with carcinoid tumor was not higher than expected. Considering the relative indolence of carcinoid tumors, it is not clear whether or not all these patients would be diagnosed with carcinoid tumor during their lifetime, in the absence of a more aggressive tumor, such as colorectal cancer. Thus, our data do not support the association of carcinoids with other tumors or increased tumor susceptibility in patients with carcinoid.

In our series, a large number of patients with carcinoid were reported to have a first-degree relative with a malignant tumor (129 of 245). The distribution of these tumors was extensive, without a particular predilection. When compared with SEER data, the incidence of colorectal cancer was as expected and the number of lung cancers was somewhat lower than expected in age- and sex-matched population, but there was an increased number of “stomach” cancers. We did not observe a similar increase in gastric cancer among our primary patients with carcinoid. A probable explanation for this apparent increase in “gastric” cancers is that patients frequently identify as stomach cancer a variety of intraabdominal malign-
nancies. The reported incidence of prostate cancer among the relatives was lower than expected. This probably reflects different sensitivities in diagnostic modalities for prostate cancer as a function of time. Overall, our data do not support an increased general tumor susceptibility in relatives of patients with carcinoid, but there is a slightly increased risk for carcinoid in first-degree relatives.

Carcinoids are neuroendocrine neoplasms, which are encountered either sporadically or as part of a familial syndrome, most notably, MEN 1, and occasionally in MEN 2. When associated with these familial syndromes, carcinoids are more likely to develop in the foregut, especially in the thymus and lung. It is estimated that only ~4% of patients with carcinoids also have other endocrine tumors (24), and these are inherited in an autosomal dominant fashion. The majority of carcinoid tumors are thought to be sporadic, with only anecdotal reports in the older literature describing familial occurrences (25–27). Our results show that familial occurrence of carcinoid in some cases is more than incidental. Nine (3.7%) patients from our series had at least one affected first-degree relative. The calculated incidence rates for carcinoid tumors among first degree relatives were 12.5 per 100,000 person-years for males and 15.7 per 100,000 person-years for females, adjusted to the 1970 United States white population. This is much higher than the age-adjusted incidence rates for carcinoid tumors (all sites, including extraintestinal locations) reported by Modlin and Sandor (5), which were 1.20 and 1.28 per 100,000 population per year for white males and females, respectively. Carcinoid tumors in small bowel \( (P = 0.0001) \), colon \( (P = 0.008) \), and total number of gastrointestinal carcinoids \( (P < 0.0001) \) in first-degree relatives showed a similar increase over expected rates based on SEER data from 1990–1995.

The \( \text{MEN} \) \( 1 \) gene on chromosome 11q13 probably functions as a tumor suppressor gene. Recently, it has been shown that a majority (78%) of sporadic carcinoids display loss of heterozygosity for markers around the \( \text{MEN} \) \( 1 \) region, thus suggesting involvement of this gene in pathogenesis (28). Similar findings were noted in studies of sporadic parathyroid

### Table 5: The incidence of malignant tumors among probands with carcinoid

<table>
<thead>
<tr>
<th>Location and type of tumor</th>
<th>No. observed</th>
<th>No. expected</th>
<th>Risk ratio</th>
<th>95% confidence interval</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colorectal adenocarcinoma</td>
<td>10 [6]</td>
<td>3.0 [2.3]</td>
<td>3.299 [2.660]</td>
<td>1.582–4.071 [0.975–5.786]</td>
<td>0.000</td>
</tr>
<tr>
<td></td>
<td>2 [1]*</td>
<td>2.9 [2.2]*</td>
<td>0.682 [0.452]*</td>
<td>0.808–2.454 [0.011–2.509]*</td>
<td>0.445</td>
</tr>
<tr>
<td>Breast carcinoma</td>
<td>10 [8]</td>
<td>5.9 [4.4]</td>
<td>1.701 [1.836]</td>
<td>0.815–3.129 [0.793–3.615]</td>
<td>0.08</td>
</tr>
<tr>
<td>Lung carcinoma</td>
<td>2 [1]</td>
<td>4.6 [3.4]</td>
<td>0.440 [0.297]</td>
<td>0.053–1.582 [0.008–1.648]</td>
<td>0.16</td>
</tr>
<tr>
<td>Uterine (corpus) cancer</td>
<td>1 [0]</td>
<td>2.1 [1.5]</td>
<td>0.49 [0.0]</td>
<td>0.012–2.70 [0.0–2.45]</td>
<td>0.38</td>
</tr>
<tr>
<td>Kidney cancer</td>
<td>1 [1]</td>
<td>0.8 [0.6]</td>
<td>1.2 [1.7]</td>
<td>0.03–6.69 [0.04–9.18]</td>
<td>0.45</td>
</tr>
<tr>
<td>Ovarian carcinoma</td>
<td>3 [3]</td>
<td>1.6 [1.2]</td>
<td>1.9 [2.6]</td>
<td>0.38–5.40 [0.53–7.44]</td>
<td>0.12</td>
</tr>
<tr>
<td>Thyroid carcinoma</td>
<td>2 [2]</td>
<td>0.7 [0.5]</td>
<td>2.8 [3.9]</td>
<td>0.34–10.22 [0.47–13.96]</td>
<td>0.09</td>
</tr>
<tr>
<td>Bladder carcinoma</td>
<td>3 [2]</td>
<td>1.2 [0.8]</td>
<td>2.6 [2.4]</td>
<td>0.54–7.6 [0.29–8.5]</td>
<td>0.12</td>
</tr>
<tr>
<td>Testicular carcinoma</td>
<td>1 [0]</td>
<td>0.8 [0.6]</td>
<td>1.2 [0]</td>
<td>0.03–6.83 [0–6.26]</td>
<td>0.55</td>
</tr>
<tr>
<td>Prostate carcinoma</td>
<td>3 [3]</td>
<td>3.8 [2.8]</td>
<td>0.787 [1.055]</td>
<td>0.163–2.296 [0.218–3.077]</td>
<td>0.47</td>
</tr>
<tr>
<td>Gastric carcinoma</td>
<td>0 [0]</td>
<td>0.5 [0.4]</td>
<td>3.461 [3.643]</td>
<td>1.977–5.620 [1.933–6.235]</td>
<td>0.61 [0.67]</td>
</tr>
</tbody>
</table>

*Numbers in brackets are numbers after exclusion of data based on the chart review only. Rates are not shown for cervical cancer, skin cancer, and peritoneal/pleural tumors, for which data on histology were not available.

Numbers represent data after exclusion of patients in whom carcinoid was discovered as a coincidental finding during surgery for colorectal cancer.

### Table 6: The incidence of malignant tumors among first-degree relatives

<table>
<thead>
<tr>
<th>Type of cancer</th>
<th>No. observed</th>
<th>No. expected</th>
<th>Risk ratio</th>
<th>95% confidence interval</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colon/rectum</td>
<td>28 [24]</td>
<td>28.5 [22.0]</td>
<td>0.982 [1.092]</td>
<td>0.652–1.419 [0.699–1.624]</td>
<td>0.51</td>
</tr>
<tr>
<td>Breast</td>
<td>31 [29]</td>
<td>38.4 [30.2]</td>
<td>0.805 [0.960]</td>
<td>0.547–1.143 [0.643–1.379]</td>
<td>0.13</td>
</tr>
<tr>
<td>Lung</td>
<td>25 [19]</td>
<td>37.0 [28.5]</td>
<td>0.675 [0.666]</td>
<td>0.437–0.997 [0.401–1.039]</td>
<td>0.02</td>
</tr>
<tr>
<td>Prostate</td>
<td>18 [16]</td>
<td>42.5 [32.0]</td>
<td>0.424 [0.499]</td>
<td>0.251–0.670 [0.285–0.822]</td>
<td>(&lt;0.0001)</td>
</tr>
</tbody>
</table>

*Numbers in brackets are after exclusion of data based on the chart review only. Data are based on exclusion of 15% of relatives for whom no information on age was known.*
tumors, when a somatic MEN1 mutation contributed to tumorigenesis in a substantial number of tumors (30%; Ref. 29). Similar to familial hyperparathyroidism (30), it is possible that specific mutations within the MEN1 or some other gene produces familial carcinoid without expression of other endocrine tumors. Additional molecular studies are necessary to explore this possibility.

In summary, our data indicate that first-degree relatives of patients with carcinoid have an increased risk of developing a carcinoid tumor. However, the low incidence of carcinoid tumors in the population of interest in conjunction with the limitations of our diagnostic modalities in identifying small, potentially curable carcinoid tumors would amount to a low-efficiency screening program. In addition, we did not find a statistically significant increased risk of developing of colorectal adenocarcinoma among patients with carcinoid or their relatives. Furthermore, screening procedures recommended for the general population should also apply to this group of individuals.

References


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