The Association between Cancers of the Small and Large Bowel[1]

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Abstract

Malignant tumors of the small bowel are rare and little is known about their etiology, although adenocarcinomas share certain epidemiological features with colorectal cancer. This study investigated what cancers, if any, occurred as second neoplasms following adenocarcinomas, malignant carcinoid tumors, lymphomas, and sarcomas of the small bowel. For all 2581 cases of small bowel malignancy registered in one of the Surveillance, Epidemiology, and End-Results program areas, 1973–1988, the relative risk of a second malignancy was determined.

The risk of colorectal cancer was increased following adenocarcinoma of the small bowel, and the risk of adenocarcinoma of the small bowel was increased following colorectal cancer in both males and females. This study also found an association between small bowel sarcomas and malignant melanoma in males, consistent with earlier studies, and an association between prostate cancer and malignant carcinoid tumors of the small bowel, a new observation. We conclude that adenocarcinomas of the small bowel may share risk factors with colorectal cancer.

Introduction

While the small bowel comprises approximately 90% of the mucosal surface area of the gastrointestinal tract, malignant tumors of the colon and rectum are 50 times more common than malignant tumors of the small bowel (1). Adenocarcinomas and malignant carcinoid tumors constitute the major histological subtypes in the small bowel, with lymphomas and leiomyosarcomas occurring somewhat less frequently (2, 3).

Adenocarcinomas of the small bowel share some striking similarities with their large bowel counterparts. They share patterns of international variation in incidence (4). For both regions of the gastrointestinal tract, adenomatous polyps appear to be precursor lesions for adenocarcinomas (5). Indeed, patients with familial adenomatous polyposis have multiple adenomatous polyps both in the large bowel and in the small bowel and have a concomitant increased risk of adenocarcinomas in each of these regions (5).

Little is known about etiological factors for cancer of the small bowel. As with colorectal cancer, bile acids and their metabolites may play a significant role (1, 6). In addition, Crohn's disease patients have been shown to be at increased risk of adenocarcinoma of the small bowel (7).

Patterns of multiple primary neoplasms may sometimes provide clues as to shared etiological factors (8); *e.g.*, the association between breast cancer and colorectal cancer has suggested reproductive hormones or diet as a shared risk factor (9). Given the epidemiological similarities between cancers of the large and small bowel, we investigated whether they co-occurred in the same individuals. In addition, we examined the incidence of other multiple primary neoplasms in association with cancer of the small bowel in the hope that emerging relationships might shed light on possible risk factors for this disease.

Materials and Methods

The SEER[3] program collects data from various population-based tumor registries around the United States, comprising approximately 10% of the U.S. population. For this study, we utilized data on 1.4 million cases registered in any of the SEER registries between January 1, 1973, and December 31, 1988. Information collected on each case includes the site, histology, age, sex, and sequence number (whether this is a first or later malignancy for the given individual). In addition, each person is assigned a unique identifier, which is used for that person's subsequent malignancies. We excluded cases from Puerto Rico, those cases diagnosed by death certificate or autopsy, and noninvasive cancers.

A first primary cancer was defined as an invasive cancer with a sequence number of zero or one. Multiple primary cancers were defined as tumors with a sequence number of two or greater. Any multiple primary neoplasm for which the initial malignancy was not in the dataset (*i.e.*, the initial tumor occurred prior to 1973 or outside the geographic area of the registry) was excluded.

Our analytic and statistical approach has been previously described (9). Briefly, for each first primary cancer of a given site, the age and gender-specific person-months of follow-up were calculated and divided by 12 to give the age- and gender-specific person-years of follow-up. Thus, for each first primary cancer, the month and year of diagnosis is subtracted from the month and year of diagnosis of the second primary cancer, from the date of death, from the date of last known follow-up, or December 31, 1988, whichever occurred first. The expected number of second primary cancers was then calculated by multiplying the age- and gender-specific SEER incidence rate by the age- and gender-specific person-years of follow-up, and totaling the expected number

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[3] The abbreviations used are: SEER, Surveillance, Epidemiology, and End-Results (program); RR, relative risk; CI, confidence interval.

Table 1 Number of cases and person-years of follow-up in SEER for cancer of small bowel and for other malignancies investigated

First primary cancer	Persons at risk	Person years of follow-up after minimum interval of 6 months
Men		
Small bowel	1,369	
Adenocarcinoma	491 (35.9)[a]	750
Carcinoid	478 (34.9)	1,597
Lymphoma	203 (14.8)	710
Sarcoma	197 (14.4)	396
Colon and rectum	75,866	227,235
Melanoma	19,642	71,128
Prostate	106,163	359,425
Retroperitoneum	762	1,616
Stomach	18,120	22,177
Women		
Small bowel	1,212	
Adenocarcinoma	433 (35.7)	830
Carcinoid	488 (40.3)	1,655
Lymphoma	137 (11.3)	489
Sarcoma	154 (12.7)	434
Colon and rectum	75,772	242,723
Breast	154,981	695,152
Ovary	22,966	61,491
Stomach	11,206	15,961

[a] Numbers in parens, percentages.

of cases. The number of second primary cancers at a given site within a pair was then determined and the observed/expected ratio calculated (referred to as the RR). We utilized a Poisson distribution to calculate the 95% CI around the RR. We calculated the RR both excluding the initial 6 months of follow-up and including it to eliminate a potential bias from medical surveillance (9).

Results

There were 1369 malignant tumors of the small bowel registered in SEER among men and 1212 among women. Adenocarcinomas and malignant carcinoid tumors each constituted approximately 35–40% in both sexes (see Table 1).

While a variety of second malignant neoplasms were associated with each of the histological subtypes of small bowel cancer (listed in Table 1), most did not show a statistically significant increase and were probably the result of chance. Table 2 shows the second malignancies which were found to be statistically significant in association with malignant tumors of the small bowel. In addition, Table 2 shows the relative risk of these small bowel malignancies following the same tumor sites. The results in Table 2 are given for a minimum time interval of 6 months to exclude synchronous malignancies. Similar results were obtained when no minimum time interval was used (data not shown).

Only three second malignancies were found to be consistently associated with malignant tumors of the small bowel. Colorectal cancer was found to be increased following adenocarcinoma of the small bowel in both men and women with an RR of 5.0 (95% CI, 2.3–9.4) in men and 3.7 (95% CI, 1.3–8.0) in women. Following colorectal cancer, the RR of adenocarcinoma of the small bowel was 7.1 (95% CI, 4.7–10.3) in men and 9.0 (95% CI, 6.0–12.9) in women. Interestingly, there was no association between adenocarcinoma of the small bowel and either gastric cancer or female breast cancer.

The second association observed was between sarcomas of the small bowel and malignant melanoma (Table 2). This association was observed only in men; the RR of melanoma following small bowel sarcoma was 33.3 (95% CI, 3.7–120.4), and the RR of small bowel sarcoma following melanoma was 19.1 (95% CI, 5.1–48.8). No association was observed among women. The third association was between malignant carcinoid tumors and prostate cancer. The RR was approximately 2.5 in both directions (Table 2).

Discussion

The association of a pair of malignancies co-occurring in the same individuals can be a sign of shared risk factors between them (8, 9). This is especially true when the direction of the association goes both ways; *i.e.*, cancer A is increased following cancer B and cancer B is increased following cancer A. No prior study has explored this phenomenon in detail among malignant tumors of the small bowel.

The epidemiology of adenocarcinoma of the small bowel is similar to that of adenocarcinoma of the large bowel, despite their widely differing incidence rates. Their incidence rates co-vary in different countries (4), and they both appear to have adenomatous polyps as precursor lesions (5). The occurrence of both cancers in the same patients is somewhat surprising because the majority of adenocarcinomas of the small bowel occurs in the duodenum (1–3, 6), suggesting an association with gastric cancers, which was not found. These observations add support to the parallels between adenocarcinomas of the small bowel and large bowel and suggest that shared etiological factors may be in play.

While the data available in this study were not able to explore familial relationships, future studies could and should explore whether these two malignancies occur in the same families. It would also be interesting to investigate the subsite distributions of the small and large bowel malignancies in these patients where both malignancies occurred. At the present time, we are beginning an investigation of risk factors for adenocarcinoma of the small bowel. The risk factors we will focus on will be those generally associated with large bowel carcinoma, *e.g.*, family history, diet, cholecystectomy.

Another consistent finding was a bidirectional association between sarcomas of the small bowel and melanoma. This association was observed only among men. Given the large number of relative risks calculated in this study, this may represent a chance association. Interestingly, an analysis of the Connecticut Tumor Registry (10) found an excess risk of soft tissue sarcomas following malignant melanoma in men (RR, 8.7) and a nonstatistically elevated risk (RR, 4.5) among women. This was not felt to be due to radiation effect or the result of misdiagnosed metastatic melanoma. In addition, in the Connecticut Tumor Registry there was an observed increased risk of melanoma following soft tissue sarcomas among women (RR, 3.2) although this elevated risk was not statistically significant and there was no similar increase among men. Thus, the association in our study between sarcoma of the small bowel and malignant melanoma may reflect a more generalized association between soft tissue sarcomas and melanoma.

A third association was observed between prostate cancer and malignant carcinoid tumors of the small bowel. This was bidirectional. It has not been previously described and may represent a chance association.

Table 2 Relative risk of second primary cancer by sex and first primary site with minimum 6-month time interval between diagnoses[a]

First primary cancer	Second primary cancer	O	E	RR (CI)
Men				
SB adenocarcinoma	Colorectal	9	1.8	4.97 (2.27–9.44)
Colorectal	SB adenocarcinoma	28	4.0	7.09 (4.71–10.25)
SB sarcoma	Melanoma	2	0.06	33.33 (3.74–120.4)
Melanoma	SB sarcoma	4	0.2	19.05 (5.12–48.77)
SB carcinoid	Prostate	12	5.1	2.34 (1.21–4.09)
Prostate	SB carcinoid	14	5.4	2.62 (1.43–4.39)
Women				
SB adenocarcinoma	Colorectal	6	1.6	3.66 (1.34–7.96)
Colorectal	SB adenocarcinoma	29	3.2	8.98 (6.01–12.89)
SB sarcoma	Melanoma	0	0.05	
Melanoma	SB sarcoma	0	0.1	

[a] O, observed number of second malignancies; E, expected number of second malignancies; RR, O/E; CI, 95% confidence interval; SB, small bowel.

This study found an association between colorectal cancer and adenocarcinoma of the small bowel, confirming other parallels between the two malignancies and suggesting that future etiological research into adenocarcinoma of the small bowel should focus on risk factors associated with colorectal cancer. The study also found an association between sarcoma of the small bowel and malignant melanoma, possibly reflecting a more general association between soft tissue sarcomas and melanoma, and a hitherto unobserved association between prostate cancer and malignant carcinoid tumors. These associations require further research and confirmation.

References

1. Ross, R. K., Hartnett, N. M., Bernstein, L., and Henderson, B. E. Epidemiology of adenocarcinomas of the small intestine: is bile a small bowel carcinogen? Br. J. Cancer, *63:* 143–145, 1991.

2. Ashley, S. W., Wells, S. A., Jr. Tumors of the small intestine. Semin. Oncol., *15:* 115–128, 1988.

3. Weiss, N. S., and Yang C. T. Incidence of histologic types of cancer of the small intestine. J. Natl. Cancer Inst., *78:* 653–656, 1987.

4. Lowenfels, A. B. Why are small-bowel tumours so rare? Lancet, *1:* 24–26, 1973.

5. Sellner, F. Investigations on the significance of the adenoma-carcinoma sequence in the small bowel. Cancer (Phila.), *66:* 702–715, 1990.

6. Lowenfels, A. B. Does bile promote extra-colonic cancer? Lancet, *2:* 239–241, 1978.

7. Lightdale, C. J., Sternberg, S. S., Posner, G., and Sherlock, P. Carcinoma complicating Crohn's disease. Report of seven cases and review of the literature. Am. J. Med., *59:* 262–268, 1975.

8. Neugut, A. I., and Robinson, E. Multiple primary neoplasms. Cancer J., *5:* 245–248, 1992.

9. Neugut, A. I., Murray, T. I., Lee, W. C., and Robinson, E. The association between breast cancer and colorectal cancer in men: an analysis of SEER program data. Cancer (Phila.), *68:* 2069–2073, 1991.

10. Tucker, M. A., Boice, J. D., Jr, and Hoffman, D. A. Second cancer following cutaneous melanoma and cancers of the brain, thyroid, connective tissue, bone, and eye in Connecticut, 1935–82. Natl. Cancer Inst. Monogr., *68:* 161–189, 1985.

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