Familial Risk of Small Intestinal Carcinoid and Adenocarcinoma

ELHAM KHARAZMI,[*] EERO PUKKALA,[‡,§] KRISTINA SUNDQUIST,[‖,¶] and KARI HEMMINKI[*,‖]

[*]Division of Molecular Genetic Epidemiology, German Cancer Research Center, Heidelberg, Germany; [‡]Finnish Cancer Registry, Institute for Statistical and Epidemiological Cancer Research, Helsinki, Finland; [§]School of Health Sciences, University of Tampere, Tampere, Finland; [‖]Center for Primary Health Care Research, Lund University, Malmö, Sweden; and [¶]Stanford Prevention Research Center, Stanford University School of Medicine, Stanford, California

BACKGROUND & AIMS: **Small intestinal cancer (SIC) is rare, and its etiology is poorly understood. We compared clusters of families with SICs of different histologic subtypes.**

METHODS: **By using the nationwide family cancer data sets of Sweden and Finland, we identified a cohort of 9964 first-degree relatives of 1799 patients with SIC, diagnosed from 1961 through 2009. Data were collected from time periods as long as 47 years (mean, 35.4 y), and cancer incidence was determined. Standardized incidence ratios (SIRs) were calculated and stratified by sex, age, time period, and cancer type, using the incidence rates for the entire national population as the reference.**

RESULTS: **Among the 1799 SIC cases, 1.1% had a sibling with SIC, so the SIR was 11.8 (95% confidence interval [CI], 7.2–18.2); 1.1% had a parent or child with SIC (SIR, 3.5; 95% CI, 2.0–5.6). The SIR of concordant carcinoid histology of SIC among siblings was 28.4 (95% CI, 14.7–49.6; n = 12) and in parent–child pairs was 9.9 (95% CI, 5.4–16.6; n = 14). The familial risk of concordant histologic subtypes increased for siblings diagnosed with adenocarcinoma, but only 2 familial cases were identified. In family members of patients with SIC of the adenocarcinoma subtype, risks of colorectal and bladder cancer were modestly but significantly increased compared with the general population. Family members of patients with SIC of the carcinoid subtype had an increased risk for kidney cancer and polycythemia vera.**

CONCLUSIONS: **Based on data from our population-based study, first-degree relatives of patients with small intestinal carcinoid tumors have developed these tumors with high incidence. Because of the rareness of this tumor, the absolute risk remains moderate even within families. Gastroenterologists could inform patients with small intestinal carcinoids about the familial risk and encourage counseling for their first-degree relatives. Studies are needed to identify genetic factors that affect susceptibility to SIC.**

Keywords: Inherited; Risk Factor; Pathogenesis; Genetics.

The small intestine is the part of the digestive tract between the stomach and the colon, but in contrast to cancers of the stomach and the colon, small intestinal cancer (SIC) is rare, accounting for only 2% of all gastrointestinal cancers. The understanding of SIC etiology is very limited because of the small number of cases and the heterogeneity of tumor types.[1] Each subtype has its own distinct clinical behavior and, therefore, dictates a different treatment approach. Unfortunately, malignant SIC lesions often are discovered when they have metastasized to distant sites or at surgery indicated for other diagnoses. The different tissues of origin suggest that each type may have a unique etiology, adding to the difficulty of obtaining an adequate sample size for analysis.

Neuroendocrine carcinoid tumors and adenocarcinomas are the most common histologic subtypes of SIC. Carcinoid tumors are slow-growing neuroendocrine neoplasms that produce vasoactive substances. They manifest in multiple endocrine neoplasia 1 (MEN1) and neurofibromatosis 1, which are rare familial tumor syndromes.[2,3] Familial risk of carcinoid tumors has been found for SIC and colon cancer.[4] A significantly increased risk of subsequent SIC was found in patients diagnosed with parathyroid adenoma, which may indicate the presence of MEN1; a similarly increased risk of carcinoid histology of SIC was found after endocrine gland tumors.[5,6] Familial adenomatous polyposis (FAP), hereditary nonpolyposis colorectal cancer (HNPCC), MUTYH-associated polyposis, Peutz–Jeghers syndrome, and cystic fibrosis may predispose to adenocarcinoma of SIC. However, SIC is a rare tumor in any of the listed syndromes.

Abbreviations used in this paper: CI, confidence interval; FAP, familial adenomatous polyposis; HNPCC, hereditary nonpolyposis colorectal cancer; MEN1, multiple endocrine neoplasia 1; SIC, small intestinal cancer; SIRs, standardized incidence ratios.

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Table 1. Basic Characteristics

	All data (including unaffected family members)					Concordant familial cases		
Index cases	Index cases	Parent	Sibling	Children	FDR[a]	Parent/child	Sibling	FDR
SIC								
Total number	1799	3596	3156	3212	9964	18	20	38
Age at end of follow-up evaluation, mean (range)	58.3 (2–76)	76.5 (25–104)	57.9 (0–76)	32.9 (0–58)	56.3 (0–104)	72.6	48.6	60.6
Follow-up time, mean (range)	42.1 (2–47)	30.6 (0–47)	43.5 (0–47)	32.7 (0–47)	35.4 (0–47)			
Sex								
Male	1060	1798	1584	1659	5041	5	6	11
Female	738	1798	1572	1553	4923	2	6	8
Unlike sex[b]						11	8	19
Mean difference in familial concordant cases								
Calendar year						15.9	8.3	12.1
Age at diagnosis, *y*						13.9	10.3	12.1
Small intestinal carcinoid								
Total number	1107	2198	1918	2047	6163	14	12	26
Age at end of follow-up evaluation, mean (range)	58.4 (8–76)	75.7 (20–102)	57.1 (0–76)	31.9 (0–53)	55.1 (0–102)	69.2	55.3	62.2
Follow-up time, mean (range)	43.4 (7–47)	31.6 (0–47)	43.4 (0–47)	31.6 (0–47)	35.4 (0–47)			
Sex								
Male	597	1103	972	1058	3133	4	6	10
Female	510	1095	946	989	3030	2	2	4
Unlike sex[b]						8	4	12
Mean difference in familial concordant cases								
Calendar year						16.4	9.3	12.9
Age at diagnosis, *y*						13.6	7.8	10.7
Small intestinal adenocarcinoma								
Total number	583	1145	1028	990	3163	1	2	3
Age at end of follow-up period, mean (range)	58.9 (20–76)	76.7 (26–102)	58.5 (7–76)	34.2 (0–58)	57.2 (0–102)	76.0	42.0	59.0
Follow-up time, mean (range)	41.6 (8–47)	29.5 (0–47)	43.5 (0–47)	33.9 (0–47)	35.5 (0–47)			
Sex								
Male	339	577	504	500	1581	0	0	0
Female	244	568	524	490	1582	0	2	2
Unlike sex[b]						1	0	1
Mean difference in familial concordant cases								
Calendar year						12	1	6.5
Age at diagnosis, *y*						16	10	13

[a]Any first-degree relative (FDR) of the index case.
[b]Indicates that the index case and his/her affected relative belong to different sexes.

Family history is an important piece of the puzzle and may lead to a better understanding of the risk factors associated with this rare disease. Familial risk estimates are useful for genetic counseling, etiologic understanding, and design of gene identification studies. To gain statistical power, we combine the nationwide family cancer data sets of Sweden and Finland to study familial clustering of SIC between concordant and discordant sites. In both countries family relationships and cancer data are retrieved from registered sources of high quality, thus avoiding biases of the interview studies in which participants report cancers in their family members.[7]

Materials and Methods

Combined nationwide family cancer data sets of Sweden and Finland were used for this population-based study. A cohort of 9964 first-degree relatives of 1799 SIC patients diagnosed in 1961–2009 was followed up for cancer incidence (Table 1). Sweden and Finland both have population registers and nationwide cancer registries, through which all diagnosed SIC cases and any cancer in their family members can be identified.

Statistics Sweden maintains a multigeneration register that covers offspring born after 1931 along with their biological parents. We have linked this register to the Swedish Cancer Registry (1961–2008) to create the Swedish Family Cancer Data Set with a total population of more than 12 million individuals. The completeness of cancer registration in Sweden is now considered to be close to 90%.[8] A 4-digit diagnostic code according to the International Classification of Diseases, 7th revision, was combined with a 3-digit pathologic anatomic diagnosis code provided by the Swedish Cancer Registry. The follow-up period for Swedish data were from 1961 to 2008.