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Familial risk of colon and rectal cancer in Iceland: Evidence for different etiologic factors?

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The aim of this study was to characterize the familial risk of colon and rectal cancer using 2 population-based registries in Iceland, the Icelandic Cancer Registry and a genealogy database. The standardized incidence ratio (SIR) was used to estimate the risk among relatives of colorectal cancer index cases diagnosed in Iceland over a 46-year period (1955–2000). The 2,770 colorectal cancer patients had 23,272 first-degree relatives. Among first-degree relatives, there was an increased risk of both colon (SIR 1.47, 95% confidence interval (CI) 1.34–1.62) and rectal cancer (SIR 1.24, 95% CI 1.04–1.47). An increased risk of colon cancer was observed among siblings of colon cancer patients (SIR 2.03, 95% CI 1.76–2.33), whereas no such increase was observed for parents or offspring. Furthermore, the risk of rectal cancer was only increased among brothers (SIR 2.46 95% CI 1.46–3.89) of rectal cancer patients and not among their sisters (SIR 1.0 95% CI 0.40–2.06). The added risk of colon cancer among first-degree relatives was independent of site of colon cancer in the proband. Our results confirm that family history of colorectal cancer is a risk factor for the disease. However, family history has a different association with colon cancer than with rectal cancer, suggesting that the 2 cancer types may have different etiologic factors. Our results have implications for colon and rectal cancer screening programs.

Key words: colonic neoplasia; rectal neoplasia; familial aggregation; screening

The etiology of colorectal cancer (CRC) has been shown to be due to both environmental and genetic factors.[1] Evidence for environmental influence comes from migration studies where a rise in incidence of colorectal cancer has been reported in populations moving from low-risk areas to high-risk areas.[2,3] Diet is thought to be the main environmental factor. Family history is also a known risk factor for colorectal cancer; first-degree relatives of patients with colorectal cancer have more than 2-fold relative risk of colorectal cancer.[4,5] Neither dietary studies nor studies on family history have succeeded in explaining the more than 10-fold variation in colorectal cancer incidence between low-risk and high-risk areas of the world.[6]

The Icelandic Cancer Project (ICP) was launched in 2001. The aim of the ICP is to create a population-based clinical genomics database and biobank, to study cancer from genetic predisposition to clinical outcome.[7] The present study was undertaken within the ICP to examine the familial aggregation of colorectal cancer in Iceland. This is important for determining familial aggregation at a population-wide level and, more specifically, for providing recommendations about screening of colorectal cancer in Iceland. In addition, the importance of family history of colorectal cancer as a risk factor for rectal cancer has recently been questioned.[5,8,9] It is therefore important to determine separately the colon and rectal cancer risk in first-degree relatives of colon and rectal cancer patients.

For the analysis of familial risk of colon and rectal cancer in Iceland, we used 2 registries of high quality, the Icelandic Cancer Registry (ICR), which has information on all cancers diagnosed in Iceland since 1955, and a comprehensive genealogy database, which permits the tracing of all relatives, thereby allowing unbiased analysis of familial aggregation of cancer in Iceland. The aim of the study was to use these tools to estimate the magnitude of colorectal cancer risk in relatives of colorectal cancer patients in Iceland and to explore whether there is a difference of colon or rectal cancer risk in relatives of patients.

Material and methods

The Icelandic Cancer Registry (ICR) provided information on all individuals in Iceland diagnosed with colorectal cancer during a 46-year interval (1955–2000); all these individuals were included in the study. The ICR has been in operation since 1954,[10,11] covers the entire population of Iceland and determines incidence of cancer by site. The ICR receives information from all 3 pathology and cytology laboratories in Iceland, in addition to hospitals, general practitioners, specialists and individual health workers.[12] Approximately 94.5% of diagnoses in the Cancer Registry have histological confirmation.[12] The colorectal cancer cases registered in the ICR have close to 100% registration and histological confirmation.[13,14]

The Genetical Committee of the University of Iceland traced the families of the colorectal cancer patients to third-degree relatives (first-degree relatives include parents, siblings and offspring). The committee's data are based on the National Population Registry (NPR), which has been in operation since 1952, and provides each permanent resident of Iceland with a unique identification number. The NPR has complete coverage of all inhabitants of Iceland. In addition to data from the NPR, the Genetical Committee has traced pedigrees of Icelandic individuals back to 1840 through the use of birth-, death-, church- and marriage records. Relatives of cancer patients were followed from date of birth or the year 1955, whichever came later. They were followed until death in the NPR, to diagnosis of the cancer in question in the ICR or the end of the year 2000, whichever came earlier. The population-based cancer registration and the follow-up of individuals are made possible by the NPR. In the period 1961–2000, immigration ranged between 0.07 and 1.05% (per annual population), emigration ranged between 0.17 and 1.33% and the net change ranged between 0.02 and 0.67%.[13–15] Immigration/emigration was not controlled for. However, given the small percentage of immigration/emigration during the research period, the effects can be considered negligible. Calendar year from 1955 up to and including 2000 and patient age were used as stratification variables when calculating person–years. Patient age was defined by 5-year strata. All colorectal cancer cases were counted as both probands and relatives. However, each individual was counted only once when counting observed number of cases. Take 2 siblings A and B both with colon cancer. First, individual A would be counted as a proband and individual B as a relative. When individual B would be counted as a proband, individual A would not con-

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TABLE I – NUMBER OF COLON AND RECTAL CANCER PATIENTS AND THEIR FIRST DEGREE RELATIVES[1]

	Probands		First degree relatives		
	All ages	<60 years	All	Parents and offspring	Siblings
Colon and rectal cancer	2,770	553	23,272	15,588	7,684
Colon cancer	2,001	381	16,931	11,308	5,623
Rectal cancer	746	172	6,506	4,386	2,120

[1]The 23 probands with both colon cancer and rectal cancer are included in the total number of colorectal cancers, but not included in the number of colon and rectal cancers, respectively.

TABLE II – COLON OR RECTAL CANCER RISK IN FIRST DEGREE RELATIVES OF COLORECTAL CANCER PATIENTS

	Colon and rectal cancer			Colon cancer			Rectal cancer		
	Obs	SIR	CI, 95%	Obs	SIR	CI, 95%	Obs	SIR	CI, 95%
Total	552	1.41	1.30–1.53	421	1.47	1.34–1.62	131	1.24	1.04–1.47
Male	278	1.44	1.28–1.62	208	1.51	1.31–1.73	70	1.27	0.99–1.60
Female	292	1.39	1.23–1.55	231	1.44	1.25–1.65	61	1.21	0.93–1.55

tribute to the observed number of affected relatives. The risk of cancer was estimated as the ratio between the observed and expected number of cases (standardized incidence ratio, SIR). The SIR compares the observed number of cases in a cohort with an expected number obtained by applying calendar- and age-specific standard rates to the cohort age structure.[16] Confidence intervals (CI) and tests for trends were calculated assuming a Poisson distribution.[16] Since the confidence intervals were always 95%, 1 interval out of 20 is expected to exclude 1.00 by chance. The confidence intervals were calculated based on the assumption of independence. Since some individuals come from the same families, the assumption of independence leads to narrower confidence intervals. To test the existence of a trend, the χ^2 method was used.[16] This study was approved by the National Bioethics Committee and The Privacy and Data Protection Authority in Iceland. Statistical analysis was done using the statistical system R.[17]

Results

A total of 2,770 individuals (1,376 males; 1,394 females) were diagnosed with colorectal cancer in Iceland during the period 1955–2000. At diagnosis of colon or rectal cancer in the probands, 553 patients were under the age of 60 years, 1,655 patients were 60–80 years and 562 patients were above 80 years. The mean age at diagnosis of colon or rectal cancer in the probands was approximately 70 years (SEM 0.24). A total of 2,001 probands had only colon cancer, 746 had only rectal cancer and 23 had both colon and rectal cancer (Table I). The 23,272 first-degree relatives of colorectal cancer patients generated 526,345 person–years at risk; of those, 552 individuals were diagnosed with colon or rectal cancer compared with the expected number of 391.5 giving a 40% increased risk for colorectal cancer, which was statistically significant (SIR; 1.41 95% CI 1.30–1.53) (Table II). This increased risk was due to increased risk of both colon (1.47 95% CI 1.34–1.62) and rectal cancer (1.24 95% CI 1.04–1.47) among first-degree relatives of CRC patients (Table II). Second- or third-degree relatives had no increased risk of either colon or rectal cancer. No statistically significant increased risk of cancer of the esophagus, stomach, liver, pancreas, prostate, brain, thyroid, breast (females), cervix, uterus or ovary was observed for first-, second- or third-degree relatives of colorectal cancer patients.

Among 16,931 first-degree relatives of colon cancer patients, there was a statistically significant increased risk of colon cancer and a slight, nonsignificant increase of rectal cancer (Table III). This increased risk of colon and rectal cancer was due to statistically significant increased risk of colon and rectal cancer in siblings of colon cancer patients. Parents and offspring of colon cancer patients did not have an increased risk of colon or rectal cancer (Table III). Among 6,506 first-degree relatives of rectal cancer patients, 143 patients were diagnosed with colon or rectal cancer. Brothers of rectal cancer patients had statistically significant increased risk of both colon and rectal cancer (Table IV). Risk of rectal cancer was not increased in sisters (Table IV); this is the only difference in risk between the genders observed for first-degree relatives of colorectal cancer patients. Sisters of rectal cancer patients had increased risk of colon cancer that was close to statistical significance (Table IV). Parents and offspring of rectal cancer patients did not show an increased risk of colon or rectal cancer (Table IV).

The point estimates for the relative risk of colon cancer were higher for relatives of probands diagnosed with colon cancer before the age of 60 (Table V). This increased risk was statistically significant in siblings of colon cancer probands, but not in parents or offspring (Table V). No relative of probands diagnosed with rectal cancer before the age of 60 had colon cancer. First-degree relatives of rectal cancer probands diagnosed before the age of 60 did not have a significant increase in rectal cancer risk (Table V). The risk estimates in first-degree relatives increases as the age of the probands decreases, and a trend test with the chi-square method showed that this trend was statistically significant ($p = 0.006$). The added risk of colon cancer among first-degree relatives was independent of site of colon cancer in the proband. The results did not change when the relatives of probands who had both colon and rectal cancer were included (data not shown). No statistical difference (Poisson trend test, $p = 0.29$) was observed in risk of colon cancer in first-degree relatives of patients with right compared to left-sided colon cancer (data not shown).

Discussion

Our study shows familial aggregation of colorectal cancer in the Icelandic population, with a 40% increased risk of colorectal cancer among first-degree relatives of colorectal cancer patients (SIR: 1.41 95% CI 1.24–1.60)(Table II). This is consistent with previous studies. The increased risk was due to increased risk among siblings of colon cancer patients and brothers of rectal cancer patients. The risk was more than 3-fold in siblings of colon cancer patients who were diagnosed before the age of 60. The risk of parents and offspring of colorectal cancer patients did not contribute to this increased risk, and surprisingly, the risk of rectal cancer in sisters of rectal cancer patients was not increased. Family history is a well-known risk factor for colorectal cancer. The clustering of cancer cases in families alone does not, however, permit inference of the potential etiological role of genetic factors. Excess clustering in families could be due to several factors, including common genes, shared environment, interaction between genetic and environmental factors, or chance. An inference of a genetic component might be justifiable if the clustering showed a pattern

TABLE III – RISK OF COLON OR RECTAL CANCER IN 16,931 FIRST DEGREE RELATIVES OF COLON CANCER PATIENTS

Relatives	Gender	Colon			Rectum		
		Obs	SIR	CI, 95%	Obs	SIR	CI, 95%
All	M+F	327	1.55	1.38–1.73	93	1.19	0.96–1.46
	Male	166	1.63	1.39–1.90	44	1.08	0.78–1.45
	Female	161	1.47	1.25–1.72	49	1.31	0.97–1.73
Parents and offspring	M+F	124	1.12	0.93–1.33	31	0.76	0.51–1.08
	Male	62	1.17	0.90–1.50	11	0.52	0.26–0.93
	Female	62	1.07	0.82–1.37	20	1.01	0.62–1.56
Siblings	M+F	203	2.03	1.76–2.33	58	1.56	1.19–2.02
	Male	104	2.14	1.75–2.59	31	1.58	1.07–2.24
	Female	99	1.93	1.57–2.35	27	1.54	1.01–2.24

TABLE IV – RELATIVE RISK OF COLON OR RECTAL CANCER IN 6,506 FIRST DEGREE RELATIVES OF RECTAL CANCER PATIENTS

Relatives	Gender	Colon			Rectum		
		Obs	SIR	CI, 95%	Obs	SIR	CI, 95%
All	M+F	103	1.22	0.996–1.48	40	1.28	0.92–1.75
	Male	52	1.31	0.98–1.72	26	1.63	1.06–2.39
	Female	51	1.14	0.85–1.50	14	0.92	0.50–1.54
Parents and offspring	M+F	37	0.81	0.57–1.12	15	0.89	0.50–1.47
	Male	18	0.83	0.49–1.31	8	0.92	0.40–1.81
	Female	19	0.80	0.48–1.25	7	0.86	0.34–1.77
Siblings	M+F	62	1.61	1.23–2.06	25	1.75	1.13–2.58
	Male	32	1.79	1.22–2.53	18	2.46	1.46–3.89
	Female	30	1.45	0.98–2.07	7	1.00	0.40–2.06

TABLE V – RELATIVE RISK OF COLON AND RECTAL CANCER AMONG FIRST DEGREE RELATIVES OF COLON CANCER PATIENTS DIAGNOSED BEFORE THE AGE OF 60[1]

Relatives	Gender	Colon			Rectum		
		Obs	SIR	CI, 95%	Obs	SIR	CI, 95%
All	M+F	69	2.16	1.68–2.73	9	1.93	0.88–3.66
	Male	38	2.34	1.66–3.21	6	2.17	0.79–4.72
	Female	31	1.97	1.34–2.80	3	1.20	0.24–3.51
Parents and offspring	M+F	26	1.44	0.94–2.12	3	1.08	0.22–3.16
	Male	12	1.33	0.69–2.32	2	1.39	0.16–5.02
	Female	14	1.56	0.85–2.62	1	0.75	0.02–9.74
Siblings	M+F	43	3.14	2.27–4.23	6	2.43	0.89–5.29
	Male	26	3.77	2.46–5.52	4	3.01	0.81–7.71
	Female	17	2.49	1.45–3.99	2	1.75	0.20–6.32

[1]The relative risk of each cancer site is considered separately.

consistent with Mendelian inheritance and higher risk among relatives of patients diagnosed at an early age.[18] The confidence intervals were not corrected for dependency in families. Since our sampling was not family-based (*i.e.*, not sampling sibships *etc.*), correcting for dependency in families would only lead to insignificant changes in confidence intervals.

The data used in the present study come from 2 population-based registries, the Icelandic Cancer Registry, and the genealogy registry of the Genetical Committee of the University of Iceland. The linkage between the 2 databases allows unbiased and accurate estimation of familial risks of cancer. This is particularly important, since the accuracy of self-reporting of family history has been shown to be between 65 and 89% compared to more objective sources.[19–21] In our material, we have been able to differentiate between colon and rectal cancer in the probands as exposures. A limiting factor of the present study is the few observed cases of colorectal cancer due to the small population of Iceland (census size approximately 160,000 in the year 1955 and 290,000 in the year 2000).[15,22,23] An increased risk of colorectal cancer was observed among first-degree relatives of colorectal cancer patients, although the risk estimates are lower than in most other studies (Table II), mainly because the risk of colon or rectal cancer in our study was not increased in parents and offspring of colorectal cancer patients. (Table II). The present study is based on histologically verified diagnoses obtained from centralized registries. The risk estimates are therefore more likely to be lower than those obtained in studies based on less objective resources. Also, should no high-risk mutations be segregating in the Icelandic population, one would certainly expect lower estimates of risk in Iceland compared to countries with high-risk mutations.

Relative risk of familial aggregation of colorectal cancer is about 2-fold in previous epidemiologic registry studies.[5,24–26] This increased risk has been found in parents, offspring and siblings of colorectal cancer patients, with a stronger association in siblings compared to parents and offspring in most studies.[5,25,26] The etiology is thought to be a mixture of genetic and environmental factors.[1,27–29] Strong association in parents and offspring could result from high frequency of a dominant inherited trait like HNPCC and FAP.[27] Higher association in siblings has been explained by a recessive gene action[30–33] or shared environment in the same family during the same period.[1]

The low risk of colorectal cancer in parents and offspring observed in the present study could be due to fewer mutations in the Icelandic population, which are inherited dominantly and

cause colorectal cancer. A search for families in Iceland that fulfill the Amsterdam and Bethesda criteria have suggested that HNPCC might be very rare in Iceland.[34,35] No added risk of extra-colonic cancers was observed in first-degree relatives of colorectal cancer patients. Since HNPCC families have an increased risk of cancer in the endometrium, ovary, stomach, biliary tract, uro-epithelium, kidney and central nervous system,[36,37] in addition to an increased risk of colorectal cancer, these findings further suggest that the occurrence of HNPCC may be very rare in Iceland.

The risk of colorectal cancer in first-degree relatives of colorectal cancer patients increases as the age of the probands decreases. This is in accordance with previous observations[5,25,28] and may indicate genetic disposition of colorectal cancer.[18] Familial environmental exposure might also lead to an association between increased risk and younger age at diagnosis. However, a study on the risk of spouses of CRC patients and on shared childhood environments does not support higher risk due to environmental risk factors.[26] An analysis of cancer risk in spouses of probands who have shared household with probands over some time is needed to assess contributions of genetic and environmental factors in colorectal cancer risk. In a recent publication, Wei *et al*. conclude that some risk factors differ in their association with colon and rectal cancer (family history, physical activity, height), arguing for different etiologies for colon and rectal cancer. They point out that there is a weaker association between family history and rectal cancer than that between family history and colon cancer.[8]

In most studies, the frequency of colorectal cancer is equally distributed among men and women, whereas the risk of colorectal cancer increases more with age in men than in women.[38] Higher risk in men has been explained by a less healthy lifestyle of men.[39] The only gender difference in colorectal cancer risk observed in our study is that brothers of rectal cancer patients have increased risk of rectal cancer while sisters of rectal cancer patients do not (Table IV). This gender difference causes a weaker association of rectal cancer to family history compared to colon cancer, potentially explaining the weaker association between family history and rectal cancer observed in other studies.[8,9] The difference was statistically significant (Poisson trend test, $p = 0.037$). Gender differences in the risk of rectal cancer, as opposed to colon cancer, suggest a different etiology for these 2 cancers. In addition to environmental factors, which may affect men more than women,[39] X-linked inheritance may also play a role.

The definition of rectal cancer *versus* colon cancer is from an anatomic and surgical point of view. Our results suggest that a difference may exist in the inheritance of cancer arising in different parts of the anatomic-surgical rectum. As the localization of the transition from rectal mucosa to colonic mucosa is presently unknown, this calls for the determination of that transition.

We conclude that family history of colorectal cancer is supported as a risk factor for the disease in Iceland, and that gender difference in the risk of rectal cancer, as opposed to colon cancer, suggests a different etiology for these 2 cancers. Furthermore, we conclude that incidence of dominantly inherited traits of colorectal cancer is low in Iceland, and that high risk among siblings compared with parents and offspring for both colon and rectal cancer suggests a recessive gene action.

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