Familial risk of colon and rectal cancer in Iceland

Evidence for different etiologic factors?

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Abstract

Aims

The aim of the present study was to characterise the familial risk of colon and rectal cancer in Iceland.

Methods

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). All data was retrieved from population based registries (The Icelandic Cancer Registry and a Genealogy database from The Genetical Committee of the University of Iceland).

Results

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 to colon cancer patients (SIR 2.03, 95% CI 1.76-2.33) whereas no such increase was observed for parents and 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. Risk of other cancers outside the colon and rectum was not increased.

Conclusions

Family history of colorectal cancer is supported as a risk factor for the disease. Family history has different association with colon and rectal cancer giving evidence to different etiologic factors for colon and rectal cancer. Siblings of colon cancer patients should be offered colonoscopy as screening for colorectal cancer and brothers to rectal cancer patients should be subjected to endoscopy screening for rectal cancer.

Introduction

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 to patients with colorectal cancer have more than a twofold 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] and 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 two 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 if there is a difference of colon or rectal cancer risk in relatives of patients.

Materials and Methods

The Icelandic Cancer Registry (ICR) provided information on all individuals in Iceland diagnosed with colorectal cancer during a forty-six 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 three 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 (1st degree relatives include parents, siblings and offspring). The committee's data is 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 Committe 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 and 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 is made possible by the NPR. In the period 1961-2000, immigration ranged between 0.07-1.05% (per annual population), emigration ranged between 0.17-1.33%, and the net change ranged between 0.02--0.67% [13][14][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. 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%, one interval out of 20 is expected to exclude 1.00 by chance. The confidence intervals were calculated based on the assumption of independence. Since the individuals come from the same families, the assumption of independence leads to narrower confidence intervals. In order 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 over 80 years old. 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 1). 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 2). This increased risk was due to increased risk both for 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 2). Second or third degree relatives had no increased risk of either colon or rectal cancer. No statistically significant increased risk for cancer of the oesophagus, stomach, ~~rectum~~, 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, non-significant increase of rectal cancer (Table 3). 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 3). Among 6,506 first degree relatives to 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 4). Risk of rectal cancer was not increased in sisters (table 4); 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 4). Parents and offspring of rectal cancer patients did not show an increased risk of colon or rectal cancer (Table 4).

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 5). This increased risk was statistically significant in siblings of colon cancer probands but not in parents and offspring (Table 5). 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 6). The risk estimates in first degree relatives increases as the age of the probands decreases (Table 7) 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 (Table 8). The results did not change when the relatives of probands who had both colon and rectal cancer were included (data not shown).

Discussion

Our study suggests 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 2). This is in line with previous studies. The increased risk was due to increased risk among siblings of colon cancer patients and in brothers of rectal cancer patients. The risk was more than threefold in siblings to 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 consistent with Mendelian inheritance and higher risk among relatives of patients diagnosed at an early age [18].

The data used in the present study come from two population-based registries, The Icelandic Cancer Registry, and the genealogy registry of The Genetical Committee of the University of Iceland. The linkage between the two 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][20][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 1995 and 290,000 in the year 2000) [15][22][23].
Our study confirms an increased risk of colorectal cancer among first degree relatives of colorectal cancer patients but our risk estimates are lower than in most other studies (Table 2), mainly because the risk of colon or rectal cancer in our study was not increased in parents and offspring of colorectal cancer patients.

Relative risk of familial aggregation of colorectal cancer is about twofold in previous epidemiologic registry studies [5][24][25][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][28][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][31][32][33] or shared environment in the same family during the same period [1].

Low risk for colorectal cancer in parents and offspring in our 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 fullfilled the Amsterdam and Bethesda criteria suggested that HNPCC might be very rare in Iceland [34][35]. A further support of this hypothesis is lend by the fact that there was no observed difference in risk of colon cancer in first degree relatives of patients with right compared to left sided colon cancer in the present study. (Table 3). There was no added risk of extracolonic cancers observed in first degree relatives of colorectal cancer patients. Since HNPCC families have an increased risk of cancer in the stomach, endometrium, ovary, pancreas, and brain, [36][37], these findings further

suggest that the occurrence of HNPCC may be very rare in Iceland. The low incidence of dominantly inherited traits of colorectal cancer in Iceland is probably the explanation of the weak association with family history found in Iceland.

In our study the risk of colorectal cancer in first degree relatives of colorectal cancer patients increases as the age of the probands decreases (Table 7). This is in accordance with previous observations [5][25][28] and supports the idea of genetic disposition of colorectal cancer [18].

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 there is 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 4). 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]. Gender difference in the risk of rectal cancer, as opposed to colon cancer, suggests a different etiology for these two cancers. In addition to environmental factors which may affect men more than women, [39] X-linked inheritance may also play a role.

Colonoscopy screening has been recommended in groups with a life time risk of developing colorectal cancer which is about 10% or more [40][41].

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 localisation 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 two 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. At last we conclude that siblings of colon cancer patients should be subjected to a colonoscopy screening program to rule out colorectal cancer and brothers to rectal cancer patients should be subjected to an endoscopy screening program to rule out rectal cancer.

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Table 1. Number of colon and rectal cancer patients and their first degree relatives. 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.

	Probands		First degree relatives		
	All ages	<60 years	All	Parents and offspring	Siblings
Colon and rectal cancer	2770	553	23272	15588	7684
Colon cancer	2001	381	16931	11308	5623
Rectal cancer	746	172	6506	4386	2120

Table 2. 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

Table 3. Risk of colon or rectal cancer in 16931 first degree relatives of colon cancer patients

		Colon			Rectum		
Relatives	Gender	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 4. Relative risk of colon or rectal cancer in 6506 first degree relatives of rectal cancer patients.

		Colon			Rectum		
Relatives	Gender	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 5. Relative risk of colon cancer among first degree relatives of colon cancer patients diagnosed before the age of 60.

		Colon		
Relatives	Gender	Obs	SIR	CI, 95%
All	M+F	69	2.16	1.68-2.73
	Male	38	2.34	1.66-3.21
	Female	31	1.97	1.34-2.80
Parents and offspring	M+F	26	1.44	0.94-2.12
	Male	12	1.33	0.69-2.32
	Female	14	1.56	0.85-2.62
Siblings	M+F	43	3.14	2.27-4.23
	Male	26	3.77	2.46-5.52
	Female	17	2.49	1.45-3.99

Table 6. Relative risk of rectal cancer among first degree relatives of rectal cancer patients diagnosed before the age of 60.

		Rectum		
Relatives	Gender	Obs	SIR	CI, 95%
All	M+F	9	1.93	0.88-3.66
	Male	6	2.17	0.79-4.72
	Female	3	1.20	0.24-3.51
Parents and offspring	M+F	3	1.08	0.22-3.16
	Male	2	1.39	0.16-5.02
	Female	1	0.75	0.02-9.74
Siblings	M+F	6	2.43	0.89-5.29
	Male	4	3.01	0.81-7.71
	Female	2	1.75	0.20-6.32

Table 7. Risk of colorectal cancer in first degree relatives of colorectal cancer patients by age groups of the colorectal cancer patients (< = 62 years, 63-79 years and > = 80 years old).

Age at diagnosis of colorectal cancer in index cases	Number of first degree relatives	Colon and rectal cancer		
		Obs	SIR*	CI, 95%
< = 62	5742	126	1.64	1.36-1.95
63-79	12179	299	1.44	1.28-1.61
> = 80	5353	127	1.21	1.01-1.44
Total	23274	552	1.41	1.30-1.53

* Trend test with the χ^2 method (16). χ^2=7.49 and p=0.006

Table 8. Relative risk of colon cancer in first degree relatives of colon cancer patients by site of colon cancer in the colon cancer patients.

Relatives	Site	Number of first degree relatives	Obs	SIR	CI, 95%
All	Proximal	7522	159	1.69	1.31-2.18
	Distal	6009	108	1.48	1.11-1.99
Siblings	Proximal	2589	98	2.08	1.48-2.93
	Distal	1973	68	2.11	1.39-3.20
Parents and	Proximal	4933	61	1.30	0.89-1.90
	Distal	4036	40	0.99	0.64-1.58

Proximal: Cecum, appendix, ascending colon, transverse colon and splenic flexure.
Distal: Descending and sigmoid colon.

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