FAMILIAL ASSOCIATIONS OF COLON AND RECTAL CANCERS WITH OTHER CANCERS

Running title: Colon and rectal cancers.

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K.H. had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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ABSTRACT

BACKGROUND: Many studies have indicated that colon and rectal cancers differ in etiology and histology.

OBJECTIVE: The aim of this study was to investigate whether the associations of colon and rectal cancers with any other (discordant) cancer were site-specific.

DESIGN: A novel approach was implemented in which cancer risks were analyzed in families of increasing numbers of family members diagnosed with defined cancers. The novel assumption was that for a true familial association the risk should increase by the number of affected family members. In separate analyses familial risks were calculated after exclusion of putative families with hereditary non-polyposis colorectal cancer.

SETTINGS: The study was conducted using the Swedish Family-Cancer Database.

RESULTS: Relative risks of colorectal cancer and colon cancer were higher when family members were diagnosed with colon cancer than when family members were diagnosed with rectal cancer ($IRR_{colonrectal}$: 1.82 (95%CI 1.74-1.90) vs. 1.61 (95%CI 1.51-1.71) and IRR_{colon}: 1.92 (95%CI 1.83-2.02) vs. 1.56 (95%CI 1.45-1.69)). Relative risks for 10 discordant cancers were increased in colon or rectal cancer families whereas none of the relative risks differed significantly between colon and rectal cancers. After deleting hereditary non-polyposis colorectal cancer families, the relative risks of endometrial and ovarian cancers were no longer significant.

LIMITATIONS: Genetic data are unavailable in the database.

CONCLUSIONS: Our results suggested that familial risks for colon cancer were higher than risks for rectal cancer in families of colorectal cancer and colon cancer patients. The relationships of lung cancer and nervous system cancer to colorectal cancer were site-specific. The associations of colon and rectal cancers with lung cancer, myeloma and cancer of unknown primary appeared not to point out known syndromes and may suggest involvement of a novel predisposition.

INTRODUCTION

In a paper titled "Rectal and colon cancer: not just a different anatomic site" the authors point out that the two cancers differ in their embryological origin and metastatic patterns, in addition to many therapy-related factors (1). However, among environmental risk factors only physical activity appears to distinguish colon and rectal cancer, as a protective association has been noted for colon cancer only (2, 3). The reported familial risk has been higher for colon than rectal cancer but according to some studies the difference has been small and not significant (2, 4, 5). Among twins, familial risks and heritability estimates for colon and rectal cancers have been similar (6). Hereditary non-polyposis colorectal cancer (HNPCC), the most common colorectal cancer (CRC) syndrome, affects preferentially proximal colon but because HNPCC accounts for some 10% of familial CRC it does not alone dominate familial risk (7, 8). Combined high-penetrance genes are estimated to account for 14% of familial CRC and these include a number of genes with deleterious mutations (7, 9). Although CRC is known to be associated also with discordant familial cancers, such as endometrial and pancreatic cancers, only old data are available separately on colon cancer, associated with prostate, lung and breast cancers and rectal cancer, associated with prostate cancer and lymphocytic leukemia (10, 11). Data for associated discordant cancers may provide useful information about shared genetic and environmental risk factors.

We apply here a novel approach to search for potential differences in familial associations of colon and rectal cancers with themselves and with other cancers using the most recent update of the Swedish Family-Cancer Database. The novelty involves assessment of familial IRRs for cancer X in families with increasing numbers of colon or rectal cancers, or conversely, familial IRRs for colon or rectal cancer in families with increasing numbers of cancers X. Our aim is to find true familial associations for which the risk would be assumed to increase by the number of affected family members. In earlier studies from Iceland and Utah true familial associations were searched by comparing familial risks in multiple generations which is possible if extended family data are available (12, 13). We test also familial associations when a part of HNPCC related families are removed because they present double primaries of cancers found in HNPCC (14, 15).

METHODS

Swedish Family-Cancer Database (FCD) was created by combining the Multigeneration Register of Statistics Sweden, national Cancer Registry (started in 1958) and several other databases using unique national registration numbers. It includes all Swedish people born in 1932 or later (offspring generation) and their biological parents (parental generation). The FCD has so far been updated every two years and the latest version is FCD2012, including 15.7 million individuals.

In the FCD, 1.8 million people (11.46%) were cancer patients diagnosed by the end of 2012. The 3-digital codes of 7th revision of the International Classification of Diseases (ICD-7) were used to identify 36 most common cancers, including upper aerodigestive tract, salivary glands, esophagus, stomach, small intestine, colon, rectum, anus, liver, pancreas, nose, lung, breast, cervix, endometrium, uterus, ovary, other female genital, prostate, testis, other male genital, kidney, urinary bladder, melanoma, skin, eye, nervous system, thyroid gland, endocrine glands, bone, connective tissue, non-Hodgkin lymphoma, Hodgkin disease, myeloma, leukemia and cancer of unknown primary (CUP). According to the ICD-7 classification the demarcation of colon towards rectum is sigmoideum (code 153.3, part of colon) while for rectum no subsections are given.

According to child-mother-father triplets in the FCD, nuclear families could be formed. Multiple primary cancer information was used to identify HNPCC families. A likely HNPCC family was defined as follows: at least one family member in a nuclear family had a double primary of CRC and any of the following cancers: endometrium, ovary, small intestine, pancreas, brain, liver, kidney and bladder cancers. The order of multiple primaries was not crucial but CRC was always to be present. We admit that the definition was too narrow to cover all HNPCC but we could not exclude familial CRC because it would have partially defeated the purpose of this study. Anyway, our reasoning was to observe whether removal of the putative HNPCC families reduced familial risks (suggesting HNPCC relation) or they remained unaltered (unlikely HNPCC related).

The individuals of offspring generation were followed up from the beginning of 1958, the birth year, or the immigration year, whichever came latest. They were followed up until diagnosis of cancer, emigration or death, or at the end of 2012, whichever came first. Incidence rates could be calculated by dividing the number of new cancer cases over a given time period by the sum of each individual's person-years at risk. In this study we did not consider age of onset in spite of its known influence on familial risk (16). The reason was that we considered initially 36 different cancers for which the dependence of age is variable (17). Analysis of pairs of 36 different cancers by optimal ages would have been an utterly complex undertaking.

The incidence rate ratio (IRR) were used as a measure of assessing familial risks by comparing incidence rates for persons with affected relatives to incidence rates for those whose relatives had no cancer (negative family history). First, IRR for cancer X when family history (the number of first degree relatives (FDRs) affected with cancer) was colon or rectal cancer:

$$\text{IRR} = \frac{\text{Incidence rate of X with family history of colon or rectal cancer}}{\text{Incidence rate of X without family history of colon or rectal cancer}}$$

Then, the reverse analysis:

$$\text{IRR} = \frac{\text{Incidence rate of colon or rectal cancer with family history of X}}{\text{Incidence rate of colon or rectal cancer without family history of X}}$$

Poisson regression model, which assumes that the dependent variable (e.g., the number of cancer cases in a cohort study) has a Poisson distribution, was applied to estimate IRRs, confidence intervals (CI) and trend tests. GENMOD procedure in SAS was used to do the analysis. For estimating IRRs, family history was an independent categorized variable (negative family history, 1 proband with cancer, or at least two probands with cancer). Age group (5-year bands), sex, calendar period (5-year bands), residential area (large cities, South Sweden, North Sweden, or unspecified) and socioeconomic status (blue collar worker, white collar worker, farmer, private, professional, or other/unspecified) were added to the model as covariates and person-years were the offset. The group of negative family history was considered as the reference. As an example, to estimate IRR for colon cancer when one proband had rectal cancer, the incidence in such families was divided by the incidence of colon cancer in families with no family history of rectal cancer. Wald estimates were employed to calculate CI (95%, 99% and 99.9%). For

linear trend test, the model was refit. Since the number of probands with cancer was numeric, family history was regarded as continuous variable to test whether IRRs changed with the increasing number of probands with cancer and the other parameters in the model were unchanged.

The Ethical Committee of Lund University approved this study protocol.

RESULTS

In the FCD, 8,635,688 individuals were enrolled and the total person-years at risk for the reference population were 286,060,994, with a mean follow-up of 33.1 years. 207,512 individuals were diagnosed with colorectal cancer. Among these patients, 64.2% had colon cancer and 35.7% had rectal cancer. 22,320 colon cancer patients and 13,047 rectal cancer patients were in the offspring generation used as index individuals to calculate IRRs. In non-HNPCC analysis (see Methods), 16,160 (0.37%) HNPCC families, including 41,201 individuals without cancer and 22,656 cancer patients, were excluded from 4,321,924 families found in the FCD.

Four pairs of analysis were done to compare the concordant and discordant risks for colon and rectal cancers in all families (Table 1, upper part). The reference group was families without colon or rectal cancers in the FDRs. All IRRs in the first two columns (1 cancer case in the family or 2 cancer cases in the family) were increased at <0.1% confidence levels and the trend tests were highly significant. When one and two FDRs were affected with colon and/or rectal cancer, the adjusted IRRs for concordant colon cancer were the highest (1.92 and 3.91, respectively). The IRR for colon cancer was 5.60 in families with three FDRs diagnosed with CRC. IRRs were higher for CRC and colon cancer when FDRs were diagnosed with colon cancer than when FDRs were diagnosed with rectal cancer (CRC: 1.82 (95%CI 1.74-1.90) vs 1.61 (95%CI 1.51-1.71) with non-overlapping 95%CI in families of one cancer, and 3.48 (95%CI 2.96-4.10) vs 3.09 (95%CI 2.22-4.32) in families of two cancers; colon cancer: 1.92 (95%CI 1.83-2.02) vs 1.56 (95%CI 1.45-1.69) with non-overlapping 95%CIs in families of one cancer, and 3.91(95%CI 3.24-4.71) vs 3.17 (95%CI 2.15-4.67) in families of two cancers). After excluding HNPCC families (Table 1, lower part), essentially all IRRs were slightly decreased

compared to all families. However, above significant differences between colon and rectal cancer with non-overlapping 95%CIs remained.

Of a total of 36 cancers, 10 had increased discordant risks for colon or rectal cancers, or had significant trend tests (Table 2). For any cancer (including all 36 cancers) the IRRs increased by the number of FDRs affected with either colon or rectal cancer, or vice versa; for example colon cancer IRR was 1.19 in families of one cancer, 1.35 in families of two cancers. When proband cancer was either colon or rectal cancer, the IRRs of small intestinal cancer, pancreatic cancer, myeloma or ovarian cancer were increased or their trend tests were significant (pancreatic and ovarian cancers at 5% level). The IRRs of stomach, endometrial and thyroid gland cancers increased (all at 1% level) only when FDRs had colon cancer. In the reverse analysis, the IRRs of both colon and rectal cancers were increased by the number of FDRs were diagnosed with small intestinal (at 5% level), pancreatic, endometrial cancers or CUP (at 5% level). The IRRs of rectal cancer were increased when two FDRs had stomach (IRR=1.89) or thyroid gland cancer (IRR=7.08). The IRR of lung cancer increased at 5% level only when FDRs had rectal cancer (IRR=1.11), and in its reverse analysis only the trend test was significant (P=0.0499). The IRRs of nervous system tumors were significantly increased at 1% level when one FDR affected with colon cancer (IRR=1.11) and in the reverse analysis (IRR=1.16). Of note, none of the IRRs differed significantly between colon and rectal cancers (i.e., 95%CIs overlapped). In the colon and rectal cancer families presenting with small intestinal cancer equal numbers of small intestinal adenocarcinomas and carcinoids were found. In the one proband families all significant association of Table 2 were with adenocarcinomas and IRRs increased to about 1.7. Associations with carcinoids were not significant, with the exception of the 5 cases in the two proband families which were all carcinoids (IRR=10.45; 95%CI: 4.59-23.83).

The discordant risks for colon and rectal cancer were also estimated in non-HNPCC families (Table 3). For endometrial, ovarian cancer and their reverse analysis, the IRRs and trend test were no longer significant. The IRRs of any cancer and their reverse analysis were slightly decreased compared to Table 2. For other cancers there were no essential differences between Tables 3 and 2. The IRRs of colon cancer were marginally higher in non-HNPCC families, when FDRs were diagnosed with CUP (1.15 vs 1.14 and 1.78 vs 1.62) or pancreatic cancer (1.18 vs

1.17 and 0.82 vs 0.76); the IRRs of rectal cancer were higher, when FDRs were diagnosed with CUP (1.16 vs 1.15 and 1.27 vs 1.19) or thyroid gland (1.08 vs 1.07 and 7.55 vs 7.08) cancer. When FDRs had rectal cancer, the IRRs of small intestinal cancer (1.16 vs 1.13 and 6.04 vs 5.24) and myeloma (1.24 vs 1.22 and 1.00 vs 0.89) were also slightly increased.

DISCUSSION

The recent study is the largest single family study on colon and rectal cancers. Although the colon and the rectum are often combined to the colorectum, they have very different functions. The colon absorbs nutrient and water, while rectum stores feces (18). Studies have also found that the etiology of colon cancer differ from that of rectal cancer. For instance, the alteration of mismatch repair (MMR) genes and adenomatous polyposis coli (APC) gene favor the development of colon cancer, whereas the cyclooxygenase COX-2 responsible for the synthesis of prostaglandinE_2 (PGE_2) is overexpressed mainly in rectal cancer (19). In addition, several environmental factors, such as physical activity and dietary fiber, are associated with colon cancer but less or null with rectal cancer (18). A family history of CRC is regarded as a risk factor for colon and rectal cancer (20). Wei et al found that the RRs of colon and rectal cancer were increased to 1.94 and 1.27 respectively (2). However, few studies have separated CRC as two cancer sites (colon and rectum) and reported separate family histories. In our study, four pairs of comparison were carried out to analyze the relationship between CRC, colon and rectal cancers. There were significant familial associations among CRC, colon and rectal cancers, and for most associations colon and rectal cancers did not differ. Although the IRRs of CRC and colon cancer were statistically higher in colon cancer families compared to rectal cancer families (IRR= 1.82 vs. 1.61 and 1.92 vs. 1.56) in families when 1 proband was diagnosed with cancer, the differences are modest.

In analyses of discordant cancers, ten cancers were related to colon and/ or rectal cancers. However, an important conclusion from the present large study was that we found no strong statistical support distinguishing discordant familial associations of colon and rectal cancers. Overall discordant associations were somewhat stronger for colon than rectal cancer, which was observed when all discordant associations were analyzed jointly.

For lung and nervous system cancers, the differences in IRRs between colon and rectal cancers were minor (overlapping 95%CI), yet only lung cancer was associated with rectal cancer with significant IRRs or trend tests and only nervous system cancer was associated with colon cancer with significant IRRs and trend tests. Therefore, the relationships of these two cancers to colorectal cancer were site-specific. The remaining eight cancer sites were related to both colon and rectal cancer. Since heavy smoking is thought to be a greater risk factor for rectal compared to colon cancer (21), the association between lung cancer and rectal cancer may be related to smoking. Lung cancer is reported to be associated with the rare Peutz-Jeghers syndrome, which is related to colon cancer but not rectal cancer (22). Thus no known syndromes may explain the association between lung cancer and rectal cancer. Brain cancer, accounted for a large part of nervous system cancer, is an extra-colonic cancer of at least two cancer syndromes (HNPCC and FAP) but the associations remained unchanged when patients with HNPCC related double primaries were removed (23). Among ten discordant cancer sites that were related to colon and/ or rectal cancers, myeloma and CUP did not belong to the known syndromes. Interestingly, familial associations of myeloma and CUP with each other, and a weaker association of myeloma and lung cancer have been found (24).

Strengths of the study are a complete coverage of families and correct assignment of the family relationships, thanks to the Multigeneration Register. Similarly, cancers were obtained from a high-level nation-wide cancer registry (25). The weaknesses were limited power to find familial associations with rarer cancers and, because of lacking genetic and polyposis-related data, incomplete identification of HNPCC families or rare CRC related syndromes.

CONCLUSION

The present study showed that family history of colon cancer was a stronger risk factor than that of rectal cancer for CRC and colon cancers. For discordant cancers, lung cancer associated with rectal cancer and nervous system cancer with colon cancer. The discordant associations of with lung cancer, myeloma and CUP cannot be ascribed to the known syndromes. For the oncology clinic the message is that for the daily practice familial risks of colon and rectal cancers are similar and a family history alone does not easily distinguish HNPCC from other possible causes.

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Table 1 Discordant and concordant adjusted incidence rate ratios for colon and rectal cancers in all (upper part) and non-HNPCC families (lower part)

Risk in offspring	Proband cancer	One proband with cancer			Two probands with cancer			At least three probands with cancer			Trend test P-value
		Cases	IRR[a]	95%CI[b]	Cases	IRR	95%CI	Cases	IRR	95%CI	
Colon	CRC	3063	***1.81***[d]	(1.73--1.89)	249	***3.10***	(2.69--3.57)	24	***5.60***	(3.55--8.83)	**<.0001**[e]
Rectum		1723	***1.68***	(1.57--1.80)	132	***2.71***	(2.15--3.42)	12	***4.66***	(2.17--10.01)	**<.0001**
CRC	Colon	3335	***1.82***	(1.74--1.90)	202	***3.48***	(2.96--4.10)	8	**3.24**[c]	(1.43--7.38)	**<.0001**
	Rectum	1778	***1.61***	(1.51--1.71)	60	***3.09***	(2.22--4.32)	0	.	.	**<.0001**
Colon	Colon	2184	***1.92***	(1.83--2.02)	140	***3.91***	(3.24--4.71)	6	**3.90**	(1.59--9.57)	**<.0001**
	Rectum	1078	***1.56***	(1.45--1.69)	38	***3.17***	(2.15--4.67)	0	.	.	**<.0001**
Rectum	Colon	1151	***1.67***	(1.53--1.82)	62	***2.86***	(2.00--4.11)	2	2.21	(0.30--16.37)	**<.0001**
	Rectum	700	***1.70***	(1.51--1.92)	22	***3.06***	(1.59--5.88)	0	.	.	**<.0001**
Colon	CRC	2579	***1.72***	(1.64--1.81)	175	***2.66***	(2.23--3.16)	11	***3.75***	(1.88--7.47)	**<.0001**
Rectum		1501	***1.62***	(1.52--1.73)	107	***2.63***	(2.11--3.27)	7	**3.86**	(1.64--9.06)	**<.0001**
CRC	Colon	2817	***1.74***	(1.67--1.82)	133	***2.89***	(2.39--3.51)	2	1.30	(0.27--6.22)	**<.0001**
	Rectum	1520	***1.55***	(1.45--1.65)	47	***2.90***	(2.00--4.19)	0	.	.	**<.0001**
Colon	Colon	1820	***1.83***	(1.73--1.93)	88	***3.12***	(2.45--3.98)	0	.	.	**<.0001**
	Rectum	905	***1.49***	(1.37--1.62)	32	***3.20***	(2.06--4.96)	0	.	.	**<.0001**
Rectum	Colon	997	***1.61***	(1.48--1.76)	45	***2.58***	(1.75--3.79)	2	3.43	(0.55--21.31)	**<.0001**
	Rectum	615	***1.66***	(1.50--1.83)	15	***2.46***	(1.31--4.64)	0	.	.	**<.0001**

a: IRR=incidence rate ratio;

b: CI=confidence interval;

c: Bold and underlined value denotes significantly increased RR at the two-sided 1% level;

d: Bold, underlined and Italics value denotes significantly increased RR at the two-sided 0.1% level;

e: Bold type denotes that trend test was statistically significant.

Table 2 Discordant adjusted incidence rate ratios for colon and rectal cancers

Risk in offspring	Proband cancer	One proband with cancer			Two probands with cancer			Trend test P-value
		Cases	IRR[a]	95%CI[b]	Cases	IRR	95%CI	
Stomach	Colon	332	**1.15**[c]	(1.02--1.30)	19	**2.06**[d]	(1.28--3.32)	**0.0021**[f]
	Rectum	168	0.97	(0.84--1.13)	1	0.32	(0.05--2.23)	0.5142
Colon	Stomach	732	1.05	(0.70--1.57)	11	1.04	(0.04--26.27)	0.8109
Rectum		446	1.07	(0.97--1.17)	12	**1.89**	(1.07--3.32)	0.0737
Small intestine	Colon	133	***1.39***[e]	(1.16--1.66)	3	1.03	(0.33--3.20)	**0.0006**
	Rectum	64	1.13	(0.87--1.46)	5	***5.24***	(2.10--13.08)	0.1623
Colon	Small intestine	98	**1.31**	(1.04--1.64)	0	.	.	**0.0275**
Rectum		62	**1.38**	(1.05--1.82)	0	.	.	**0.0305**
Pancreas	Colon	398	1.12	(0.99--1.26)	16	1.37	(0.77--2.44)	**0.0378**
	Rectum	243	1.15	(0.97--1.35)	6	1.51	(0.54--4.25)	0.0909
Colon	Pancreas	546	***1.17***	(1.07--1.27)	4	0.76	(0.29--2.01)	**0.0008**
Rectum		315	1.12	(1.00--1.26)	9	**2.76**	(1.40--5.46)	**0.0224**
Lung	Colon	1389	1.04	(0.97--1.13)	38	0.88	(0.56--1.38)	0.3892
	Rectum	875	**1.11**	(1.02--1.21)	14	0.96	(0.49--1.88)	**0.0282**
Colon	Lung	1221	1.06	(1.00--1.13)	44	1.10	(0.80--1.53)	0.0620
Rectum		751	1.09	(1.00--1.18)	26	1.07	(0.69--1.66)	**0.0499**
Endometrium	Colon	707	**1.14**	(1.02--1.27)	37	**1.87**	(1.17--2.98)	**0.0074**
	Rectum	369	1.00	(0.89--1.13)	12	1.87	(1.00--3.51)	0.6174
Colon	Endometrium	594	***1.27***	(1.14--1.41)	14	**2.41**	(1.24--4.71)	**<.0001**
Rectum		318	1.13	(1.00--1.26)	7	1.93	(0.89--4.22)	**0.0311**
Ovary	Colon	555	1.07	(0.98--1.18)	23	1.49	(0.97--2.30)	**0.0476**
	Rectum	340	**1.12**	(1.01--1.24)	6	1.22	(0.57--2.59)	**0.0258**
Colon	Ovary	419	1.07	(0.98--1.18)	2	0.54	(0.14--2.10)	0.1980
Rectum		266	1.13	(0.99--1.30)	4	1.72	(0.57--5.18)	0.0632
Nervous system	Colon	1053	**1.11**	(1.04--1.19)	37	1.41	(0.98--2.03)	**0.0011**
	Rectum	580	1.04	(0.95--1.14)	11	1.31	(0.70--2.47)	0.2900
Colon	Nervous system	560	**1.16**	(1.05--1.27)	7	1.03	(0.45--2.34)	**0.0107**
Rectum		325	1.12	(0.98--1.29)	1	0.24	(0.02--2.66)	0.1740
Thyroid gland	Colon	298	**1.19**	(1.05--1.35)	9	1.33	(0.65--2.72)	**0.0072**
	Rectum	168	1.14	(0.97--1.34)	3	1.39	(0.43--4.49)	0.0972
Colon	Thyroid gland	140	1.04	(0.88--1.21)	2	2.78	(0.74--10.44)	0.5095
Rectum		86	1.07	(0.87--1.31)	3	***7.08***	(2.40--20.88)	0.2951
Myeloma	Colon	256	**1.14**	(1.02--1.28)	11	1.58	(0.93--2.67)	**0.0076**
	Rectum	160	**1.22**	(1.06--1.41)	2	0.89	(0.25--3.14)	**0.0104**
Colon	Myeloma	276	1.10	(0.97--1.24)	3	1.50	(0.46--4.84)	0.1283
Rectum		151	1.00	(0.85--1.18)	0	.	.	0.9978
CUP[g]	Colon	475	0.97	(0.83--1.15)	23	1.46	(0.70--3.01)	0.9487
	Rectum	319	1.10	(0.89--1.37)	7	1.31	(0.32--5.37)	0.3389
Colon	CUP	629	**1.14**	(1.01--1.27)	9	1.62	(0.66--3.98)	**0.0186**
Rectum		383	1.15	(1.00--1.33)	4	1.19	(0.30--4.67)	0.0502
Any	Colon	24541	***1.11***	(1.08--1.13)	941	***1.37***	(1.20--1.55)	**<.0001**
	Rectum	14153	***1.09***	(1.05--1.13)	260	1.19	(0.90--1.58)	**<.0001**
Colon	Any	9058	***1.19***	(1.15--1.23)	3724	***1.35***	(1.29--1.41)	**<.0001**
Rectum		5381	***1.17***	(1.12--1.23)	2190	***1.29***	(1.22--1.38)	**<.0001**
Any discordant	Colon	21206	***1.05***	(1.02--1.08)	739	**1.20**	(1.04--1.38)	**<.0001**
	Rectum	12375	1.05	(1.00--1.09)	200	1.02	(0.74--1.42)	**0.0365**
Colon	Any discordant	8635	***1.09***	(1.05--1.12)	2833	***1.12***	(1.07--1.18)	**<.0001**
Rectum		5066	**1.06**	(1.01--1.11)	1704	***1.11***	(1.04--1.18)	**<.0001**

a: IRR=incidence rate ratio;

b: CI=confidence interval;

c: Bold type denotes significantly increased RR at the two-sided 5% level;

d: Bold and underlined value denotes significantly increased RR at the two-sided 1% level;

e: Bold, underlined and Italics value denotes significantly increased RR at the two-sided 0.1% level;

f: Bold type denotes that trend test was statistically significant;

g: CUP=cancer of unknown primary.

Table 3 Discordant adjusted incidence rate ratios for colon and rectal cancers in non-HNPCC families

Risk in offspring	Proband cancer	One proband with cancer			Two proband with cancer			Trend test P-value
		Cases	IRR[a]	95%CI[b]	Cases	IRR	95%CI	
Stomach	Colon	306	1.13	(1.00--1.28)	16	**2.06**[d]	(1.22--3.49)	**0.0091**[f]
	Rectum	158	0.97	(0.83--1.13)	1	0.36	(0.05--2.58)	0.4976
Colon	Stomach	672	1.05	(0.69--1.59)	11	1.12	(0.04--28.37)	0.8317
Rectum		420	1.07	(0.97--1.17)	12	**1.99**[c]	(1.14--3.47)	0.0730
Small intestine	Colon	114	**1.30**	(1.09--1.55)	2	0.83	(0.23--3.02)	**0.0096**
	Rectum	61	1.16	(0.89--1.51)	5	***6.04***[e]	(2.42--15.05)	0.1131
Colon	Small intestine	86	1.28	(1.00--1.63)	0	.	.	0.0600
Rectum		57	**1.38**	(1.03--1.84)	0	.	.	**0.0380**
Pancreas	Colon	362	1.09	(0.95--1.25)	13	1.32	(0.65--2.68)	0.1798
	Rectum	240	1.20	(1.00--1.43)	4	1.14	(0.29--4.40)	**0.0447**
Colon	Pancreas	510	***1.18***	(1.08--1.29)	4	0.82	(0.31--2.19)	**0.0004**
Rectum		301	**1.14**	(1.01--1.28)	8	**2.60**	(1.27--5.33)	**0.0177**
Lung	Colon	1295	1.04	(0.95--1.13)	34	0.94	(0.55--1.58)	0.4552
	Rectum	824	**1.10**	(1.01--1.20)	12	0.93	(0.45--1.91)	0.0504
Colon	Lung	1121	1.06	(0.99--1.13)	42	1.14	(0.82--1.59)	0.0791
Rectum		706	1.08	(0.99--1.18)	24	1.05	(0.67--1.66)	0.0777
Endometrium	Colon	607	1.07	(0.94--1.21)	25	1.52	(0.82--2.82)	0.2222
	Rectum	335	0.98	(0.88--1.10)	6	1.08	(0.48--2.39)	0.8048
Colon	Endometrium	467	1.11	(0.98--1.26)	9	1.78	(0.73--4.32)	0.0875
Rectum		284	1.10	(0.97--1.24)	6	1.86	(0.81--4.28)	0.1022
Ovary	Colon	490	1.03	(0.94--1.13)	15	1.17	(0.70--1.94)	0.4346
	Rectum	311	1.10	(0.99--1.23)	5	1.15	(0.50--2.65)	0.0790
Colon	Ovary	373	1.05	(0.96--1.16)	2	0.60	(0.16--2.30)	0.3714
Rectum		246	1.13	(0.98--1.30)	4	1.85	(0.61--5.56)	0.0795
Nervous system	Colon	967	**1.10**	(1.02--1.18)	30	1.36	(0.89--2.06)	**0.0079**
	Rectum	537	1.03	(0.93--1.12)	10	1.36	(0.70--2.64)	0.4889
Colon	Nervous system	518	**1.17**	(1.06--1.29)	6	0.97	(0.39--2.38)	**0.0105**
Rectum		297	1.10	(0.93--1.29)	0	.	.	0.2867
Thyroid gland	Colon	275	**1.18**	(1.03--1.36)	6	1.05	(0.42--2.59)	**0.0214**
	Rectum	153	1.10	(0.93--1.30)	3	1.57	(0.49--5.00)	0.2193
Colon	Thyroid gland	132	1.06	(0.90--1.25)	1	1.54	(0.23--10.31)	0.4616
Rectum		82	1.08	(0.88--1.33)	3	***7.55***	(2.62--21.77)	0.2569
Myeloma	Colon	237	**1.13**	(1.01--1.27)	9	1.53	(0.87--2.68)	**0.0147**
	Rectum	154	**1.24**	(1.07--1.44)	2	1.00	(0.28--3.57)	**0.0062**
Colon	Myeloma	253	1.09	(0.96--1.24)	3	1.62	(0.49--5.29)	0.1721
Rectum		144	1.01	(0.86--1.19)	0	.	.	0.9083
CUP[g]	Colon	438	0.96	(0.81--1.13)	20	1.50	(0.71--3.17)	0.9468
	Rectum	302	1.10	(0.91--1.33)	6	1.26	(0.34--4.73)	0.2916
Colon	CUP	586	**1.15**	(1.02--1.29)	9	1.78	(0.72--4.41)	**0.0157**
Rectum		364	1.16	(1.00--1.34)	4	1.27	(0.32--5.02)	**0.0491**
Any	Colon	22405	***1.09***	(1.06--1.12)	738	***1.28***	(1.11--1.48)	**<.0001**
	Rectum	13159	***1.08***	(1.04--1.12)	220	1.15	(0.84--1.56)	**0.0002**
Colon	Any	8357	***1.17***	(1.13--1.22)	3303	***1.29***	(1.23--1.36)	**<.0001**
Rectum		5076	***1.16***	(1.11--1.21)	2003	***1.26***	(1.18--1.33)	**<.0001**
Any discordant	Colon	19588	**1.04**	(1.01--1.07)	605	1.16	(0.99--1.36)	**0.0019**
	Rectum	11639	1.04	(1.00--1.09)	173	1.00	(0.70--1.42)	0.0680
Colon	Any discordant	7953	***1.08***	(1.04--1.12)	2570	***1.10***	(1.05--1.17)	**<.0001**
Rectum		4779	**1.05**	(1.01--1.11)	1596	***1.10***	(1.03--1.17)	**<.0001**

a: IRR=incidence rate ratio;

b: CI=confidence interval;

c: Bold type denotes significantly increased RR at the two-sided 5% level;

d: Bold and underlined value denotes significantly increased RR at the two-sided 1% level;

e: Bold, underlined and Italics value denotes significantly increased RR at the two-sided 0.1% level;

f: Bold type denotes that trend test was statistically significant;

g: CUP=cancer of unknown primary.