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Familial association of colorectal adenocarcinoma with cancers at other sites

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Abstract

Data on the familial associations of colorectal cancer (CRC) of adenocarcinoma histology are limited, but they are of interest because they may give us clues about as yet unknown family clusters. We calculated standardised incidence ratios (SIRs) for right- and left-sided colon cancer and rectal cancer in offspring using data from the Swedish Family-Cancer Database covering familial tumours from 1991 to 2000. The offspring were at an increased risk of developing colon adenocarcinoma when parents presented with CRC (SIR 1.81), endometrial (SIR 1.52) and kidney (SIR 1.42) cancers. The SIRs in siblings were increased when a co-sibling was diagnosed with CRC (SIR 3.26), myeloma (SIR 2.65) and leukaemia (SIR 2.53). Right-sided colon cancer was associated with familial pancreatic, squamous cell skin cancers, thyroid gland cancer and Hodgkin's disease. Left-sided colon cancer was associated with testicular cancers. Rectal cancer was associated with cervical and genital cancers in mothers. Most of the findings were consistent with data on known cancer syndromes. A new association was noted where rectal cancer in offspring was related to cervical and female genital cancers in mothers through an unknown mechanism. Hodgkin's disease and myeloma were also associated with right-sided colon cancer in offspring. The association with carcinoma of the testis, renal parenchyma, skin and leukaemia need to be confirmed in an independent series.

Keywords: Familial risk; Colorectal cancer; Adenocarcinoma; Site; Subsite; HNPCC

1. Introduction

Colorectal cancer (CRC) is one of the most common forms of neoplasia in Western industrial countries, accounting for over 10% of all cancers [1,2]. A family history of CRC is associated with an increased risk of the disease, as reviewed by Johns and Houlston [3–7]. Hereditary non-polyposis colorectal cancer (HNPCC), due to defective DNA mismatch repair, is the most common heritable cause of CRC [8,9]. The phenotype of HNPCC features an excess of early onset CRC (average age 45 years) with a propensity to involve the proximal (right-sided) colon, and a variety of extracolonic cancers, particularly carcinomas of the endometrium, ovary, stomach, small bowel, pancreas, hepatobiliary tract, brain and upper uroepithelium of ureter and renal pelvis, in addition to skin lesions [9–11]. Familial adenomatous polyposis (FAP) is another syndrome affecting CRC, but it is much rarer than HNPCC [12,13]; it is caused by mutations in the *APC* gene and is characterised by an early age of onset (39 years) and a risk of extracolonic tumours, such as papillary thyroid carcinomas, sarcomas and pancreatic carcinomas [9]. Hamartomatous syndromes are rare and they include Peutz–Jeghers syndrome, familial juvenile polyposis and Cowden's disease, but CRC is an uncommon

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manifestation in these syndromes [9,14,15]. Germline mutations in the *BML* and *MYH* genes have also been reported to increase the risk of CRC [16,17]. Even some identified low-penetrance genes may contribute to the familial aggregation of CRC but, overall, the available data suggest that most causes of familial CRC remain unknown [18,19]. Lack of correlation of CRC risk between spouses does not support any major role for the shared environment in the familial aggregation [20].

A familial association between CRC and another site may be a clue to shared risk factors, and, indeed, the published studies have been able to detect associations between sites that are manifestations in HNPCC [3,6]. Excluding known cancer syndromes, a consistent familial association of CRC with other sites provides evidence for an as yet unidentified cancer syndrome and the findings may help to optimise studies searching for new susceptibility genes, a strategy that has been used for example in families presenting with hereditary breast and colorectal cancers [21]. In the present study, we use the newest update of the nationwide Sweden Family-Cancer Database [22]. The Database has a nationwide coverage of families and their malignancies, all of which are medically-verified, thus guarding against bias. The size of the population allows us to analyse familial associations considering specifically right- and left-sided colon cancers, which may respond differently to familial risk, as in the case of HNPCC.

2. Patients and methods

The Swedish Family-Cancer Database includes all persons born in Sweden after 1931 with their biological parents, totalling over 10.3 million individuals [23]. Cancers were retrieved from the nationwide Swedish Cancer Registry from 1958 to 2000. Information on family history was collected on all first-degree relatives (parents, siblings, and children). Follow-up started on January 1, 1991 and terminated at death, emigration, or the closing date of the study, December 31, 2000, whichever came first. The Family-Cancer Database has some gaps in the parent-offspring links among those born between 1935 and 1940 who died between 1960 and 1991. However, because the current follow-up was started from 1991, this missing data should not bias the present estimates. A 4-digit diagnostic code according to the 7th version of the International Classification of Disease (ICD-7) was used. ICD codes 153.0–153.3 and 154.0, were used for CRC. Based on the codes, the anatomical location of colon was classified as right-sided sections (codes 153.0 and 153.1) and left-sided sections (codes 153.2 and 153.3). The splenic flexure was the dividing line between the left and right locations. The histological classification of CRC was used to define adenocarcinoma as a pathological anatomical diagnosis (PAD) code 096. The percentage of cytologically- or histologically-verified cases by site, gender and age at diagnosis was 98% for colon cancer, and 99% for rectal cancer.

Siblings were defined as the offspring of a common biological mother. The multiple counting method was used in counting the risks among siblings; the method has the theoretical advantage of providing an unbiased estimate of the risk to the siblings of a specified affected individual, regardless of the family size distribution, and this parameter will be equal to the offspring risk under any additive genetic models [24]. In the present study, we did not consider families ($N = 16$) who had presented more than 2 cases of CRC (i.e., a parent and 2 or more offspring affected). In order to study the cancer risks at different ages, the ages at diagnosis of both parents and offspring were divided into two categories: below or equal to 50 years and over 50 years. Thus, each parents-offspring pair definitely belongs to one and only one of the four diagnostic age groups: 1 younger age group (both parents and offspring diagnosed below or equal to 50 years), 1 older and 2 mixed age-groups.

Standardised incidence ratios (SIRs) were calculated as the ratio of observed (O) to expected (E) number of cases. The expected numbers were calculated from 5-year-age-, gender-, period- (10-year bands), area- (county), socio-economic status standardised rates [25]. Confidence Intervals (95% CI or 99% CI) were calculated assuming a Poisson distribution [25]; the higher significance level was used to address the problem of multiple comparisons. In the calculation of the CIs for sibling risks, the dependence between the affected pairs was taken into consideration [24]. The analysis of this study was implemented in the environment of the Statistical Analysis System release 8.2.

3. Results

The Family-Cancer Database included a total of 6 863 473 offspring with a parental linkage, and 6012 of these offspring were recoded with CRC during the period of 1991–2000. Among 6,484,564 parents in the Database, 31 100 were diagnosed with CRC, 9399 with right-sided colon cancer, 7055 with left-sided colon cancer and 11 545 with rectal cancer, considering only adenocarcinoma histology. Familial risks of colon and rectal cancer for offspring of parents with cancer and among siblings are shown in Table 1. The offspring were at a risk of developing colon adenocarcinoma when parents presented with colorectal (SIR 1.81), endometrial (1.52) and kidney (1.42) cancers. The SIRs of colon cancer in siblings when their sibling was diagnosed with cancer were increased for CRC (SIR 3.26), myeloma (2.65) and leukaemia (2.53). The risk of rectal cancer for offspring was increased only when parent was

Table 1
SIR for colorectal adenocarcinoma in offspring of affected parents and siblings by familial cancer

Familial cancer	Colon								Rectum							
	Parental proband				Sibling proband				Parent proband				Sibling proband			
	O	SIR	95% CI		O	SIR	95% CI		O	SIR	95% CI		O	SIR	95% CI	
Upper aerodigestive tract	23	0.84	0.53	1.27	5	1.08	0.34	2.54	19	0.88	0.53	1.37	3	0.81	0.15	2.40
Oesophagus	21	1.52	0.94	2.33	1	0.60	0.00	3.46	7	0.63	0.25	1.31	1	0.74	0.00	4.26
Stomach	105	1.09	0.89	1.32	7	1.62	0.64	3.36	73	0.95	0.74	1.19	2	0.57	0.05	2.10
Colorectum	338	**1.81**	1.62	2.02	55	**3.26**	2.46	4.25	259	**1.74**	1.53	1.96	28	**2.06**	1.37	2.98
Liver	57	1.01	0.76	1.30	2	0.49	0.05	1.82	44	0.97	0.71	1.30	1	0.31	0.00	1.77
Pancreas	68	1.22	0.95	1.55	9	2.13	0.97	4.07	44	0.99	0.72	1.33	2	0.59	0.06	2.16
Lung	105	0.93	0.76	1.12	20	1.29	0.78	1.99	94	1.04	0.84	1.27	13	1.03	0.55	1.77
Breast	178	1.09	0.93	1.26	43	0.94	0.68	1.27	126	0.97	0.80	1.15	42	1.14	0.82	1.54
Cervix	39	1.19	0.85	1.63	3	0.84	0.16	2.49	34	1.30	0.90	1.81	2	0.69	0.07	2.55
Endometrium	63	**1.52**	1.17	1.95	12	1.50	0.77	2.63	33	0.99	0.68	1.40	7	1.08	0.43	2.24
Ovary	40	1.04	0.74	1.42	7	1.00	0.40	2.08	37	1.20	0.84	1.65	5	0.89	0.28	2.09
Other female genitals	10	1.25	0.60	2.31	1	1.24	0.00	7.1	12	1.87	0.96	3.28	2	3.07	0.29	11.29
Prostate	232	0.99	0.87	1.13	21	1.32	0.82	2.02	202	1.08	0.93	1.24	5	0.39	0.12	0.92
Kidney	79	**1.42**	1.13	1.78	3	0.50	0.09	1.48	48	1.08	0.80	1.43	8	1.66	0.71	3.28
Urinary bladder	88	1.13	0.90	1.39	14	1.74	0.95	2.92	65	1.04	0.80	1.33	7	1.08	0.43	2.24
Melanoma	25	0.84	0.54	1.24	13	1.19	0.63	2.04	27	1.14	0.75	1.66	8	0.91	0.39	1.80
Skin, squamous cell	54	0.89	0.67	1.17	9	2.02	0.91	3.85	54	1.12	0.84	1.46	6	1.68	0.60	3.68
Nervous system	42	1.03	0.74	1.39	11	1.07	0.53	1.92	37	1.13	0.80	1.56	10	1.20	0.57	2.22
Thyroid gland	12	1.02	0.53	1.79	4	2.12	0.55	5.47	10	1.07	0.51	1.98	2	1.31	0.12	4.83
Endocrine glands	22	0.91	0.57	1.38	6	1.19	0.43	2.61	14	0.73	0.40	1.22	9	2.20	1.00	4.20
Connective tissue	8	0.79	0.34	1.56	1	0.72	0.00	4.11	8	0.99	0.42	1.96	2	1.76	0.17	6.47
Non-Hodgkin's lymphoma	40	0.92	0.66	1.26	5	0.60	0.19	1.40	45	1.30	0.95	1.74	5	0.74	0.23	1.74
Hodgkin's disease	9	1.18	0.53	2.25	1	1.20	0.00	6.88	7	1.16	0.46	2.40				
Myeloma	33	1.22	0.84	1.72	7	**2.65**	1.05	5.49	20	0.93	0.57	1.43	4	1.87	0.49	4.82
Leukaemia	43	0.91	0.66	1.23	13	**2.53**	1.34	4.34	30	0.80	0.54	1.14	4	0.96	0.25	2.49

Bold type, 95% CI does not include 1.00. Underlining bold type, 99% CI does not include 1.00.
CI, Confidence Interval; O, Observed; SIR, Standardised incidence ratios.

affected by CRC (SIR 1.74). The SIR was 2.06 when a sibling was diagnosed with CRC.

The familial risk of colon adenocarcinoma was further analysed by subsites of right- and left-sided colon cancers in Table 2. There were no large differences between the SIRs of right- and left-sided colon cancers when either a parent or a sibling was diagnosed with CRC, but the risks among siblings were clearly higher than those among offspring and parents. The association with other familial sites distinguished the right- and left-sided colon cancers. SIRs for right-sided colon cancer in offspring were 1.89 when a parent presented with endometrial cancer and 1.76 when a parent presented with kidney cancer; no increases were noted for the risk of left-sided colon cancer. Similarly, only SIRs for right-sided colon cancer were noted for siblings whose co-siblings were affected with pancreatic (SIR 3.66), skin (3.04) and thyroid gland (4.12) tumours. The left-side cancer associated only with sibling leukaemia (2.78). All these leukaemias were diagnosed in adults and were of different subtypes (2 acute lymphoid and 1 chronic lymphoid leukaemia, 1 of each: acute and chronic myeloid leukaemia, polycythemia vera and myelofibrosis).

Table 3 shows the familial SIRs for right-sided colon adenocarcinoma when parents and offspring were divided into two mutually exclusive diagnostic age groups of below or over 50 years. These two age group combinations illustrate the variation in SIRs, and no data are shown for the mixed age group combinations. As expected, more cancers were diagnosed after the diagnostic age of 50 years. The offspring were at a high risk of right-sided colon cancer before the age of 50 years when their parents were also diagnosed before the age of 50 years with CRC adenocarcinoma (SIR 7.51), cervical (2.67), endometrial (6.22) and kidney (7.46) cancers and myeloma (12.69). Myeloma was also associated with sibling colon cancer (13.87). In those diagnosed when they were aged over 50 years, the SIRs were increased when a parent presented with CRC (SIR 1.50), endometrial (1.75) and kidney (1.48) cancers. Among siblings, increased SIRs were noted when another sibling was diagnosed with CRC (SIR 2.87), pancreatic (4.31), skin (3.14) and thyroid cancers (5.68); all these thyroid cancer were non-medullary. When parental kidney cancer was further divided by subsites of renal parenchyma (ICD-7 180.0) and pelvis (ICD-7 180.1) without age stratification, higher risks of right-sided colon cancer

Table 2
SIR for colon adenocarcinoma in offspring of affected parents and siblings by familial cancer

Familial cancer	Right-sided colon								Left-sided colon							
	Parental proband				Sibling proband				Parental proband				Sibling proband			
	O	SIR	95% CI		O	SIR	95% CI		O	SIR	95% CI		O	SIR	95% CI	
Upper aerodigestive tract	15	1.07	0.60	1.77	2	0.83	0.08	3.07	8	0.60	0.26	1.19	3	1.34	0.25	3.97
Oesophagus	9	1.27	0.58	2.42	1	1.18	0.00	6.74	12	1.79	0.92	3.13				
Stomach	60	1.21	0.92	1.56	5	2.25	0.71	5.29	45	0.96	0.70	1.29	2	0.96	0.09	3.51
Colorectum	170	**1.79**	1.53	2.08	31	**3.58**	2.43	5.09	168	**1.84**	1.57	2.14	24	**2.93**	1.87	4.36
Liver	28	0.96	0.64	1.40	2	0.96	0.09	3.53	29	1.05	0.70	1.51				
Pancreas	34	1.19	0.83	1.67	8	**3.66**	1.56	7.25	34	1.25	0.87	1.75	1	0.49	0.00	2.82
Lung	61	1.06	0.81	1.36	13	1.62	0.86	2.78	44	0.79	0.58	1.07	7	0.93	0.37	1.92
Breast	88	1.06	0.85	1.30	22	0.95	0.59	1.43	90	1.12	0.90	1.38	21	0.94	0.58	1.44
Cervix	21	1.25	0.77	1.92					18	1.13	0.67	1.79	3	1.72	0.32	5.10
Endometrium	40	**1.89**	1.35	2.58	7	1.71	0.68	3.54	23	1.13	0.72	1.70	5	1.28	0.40	3.01
Ovary	22	1.12	0.70	1.69	5	1.39	0.44	3.28	18	0.96	0.57	1.51	2	0.59	0.06	2.16
Other female genitals	5	1.22	0.39	2.88	1	2.43	0.00	13.93	5	1.28	0.40	3.01				
Prostate	124	1.04	0.86	1.24	11	1.34	0.67	2.41	108	0.94	0.77	1.14	10	1.30	0.62	2.39
Kidney	50	**1.76**	1.31	2.33	2	0.65	0.06	2.38	29	1.07	0.72	1.54	1	0.34	0.00	1.97
Urinary bladder	46	1.16	0.85	1.54	9	2.17	0.98	4.14	42	1.10	0.79	1.49	5	1.28	0.40	3.00
Melanoma	14	0.92	0.50	1.55	7	1.25	0.50	2.59	11	0.75	0.37	1.35	6	1.12	0.40	2.46
Skin, squamous cell	28	0.91	0.60	1.32	7	**3.04**	1.20	6.30	26	0.87	0.57	1.28	2	0.93	0.09	3.41
Nervous system	22	1.05	0.66	1.60	6	1.14	0.41	2.50	20	1.00	0.61	1.55	5	1.00	0.32	2.35
Thyroid gland	6	1.00	0.36	2.19	4	**4.12**	1.07	10.66	6	1.05	0.38	2.30				
Endocrine glands	11	0.89	0.44	1.61	4	1.55	0.40	4.01	11	0.93	0.46	1.67	2	0.81	0.08	2.99
Connective tissue	4	0.77	0.20	1.99	1	1.40	0.00	8.03	4	0.81	0.21	2.10				
Non-Hodgkin's lymphoma	28	1.27	0.84	1.83	5	1.16	0.37	2.73	12	0.57	0.29	0.99				
Hodgkin's disease	4	1.01	0.26	2.62					5	1.36	0.43	3.19	1	2.46	0.00	14.12
Myeloma	17	1.23	0.72	1.98	4	2.96	0.77	7.64	16	1.21	0.69	1.98	3	2.33	0.44	6.91
Leukaemia	16	0.66	0.38	1.08	6	2.29	0.82	5.01	27	1.17	0.77	1.71	7	**2.78**	1.10	5.76

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Underlining bold type, 99% CI does not include 1.00.

in offspring were observed when parents were diagnosed with carcinoma of the renal pelvis (SIR 2.78, $N = 7$, 95% CI 1.10–5.77) compared with carcinoma of the renal parenchyma (SIR 1.70, $N = 40$, 95% CI 1.21–2.31).

Risk for rectal cancer in offspring was analysed in the same age groups (Table 4). The offspring were at a high risk of rectal cancer before the age of 50 years when parents had CRC adenocarcinoma (SIR 6.42) and endometrial cancer (5.20) before the age of 50 years. In the older age group, besides an increased risk associated with parental CRC adenocarcinoma, maternal genital cancer was also associated with an increased risk of rectal cancer in the offspring (2.19). In the mixed age group combinations, the risk of rectal cancer in offspring before the age of 50 years associated with maternal cervical cancer diagnosed after 50 years of age (SIR 2.85, $N = 10$, 95% CI 1.36–5.27).

We considered the age of onset of the familial CRCs (only parental proband) compared with all offspring CRCs. The mean age of onset of right-sided colon cancer was 1.6 years younger when parents had CRC compared with offspring whose parents were unaffected (54.2 years). For left-sided colon and rectal cancers, the differences were 0.8 and 0.7 years, respectively. No differences in the age of onset were noticed for offspring CRCs between familial discordant sites.

We carried out an analysis in a reverse order: parental risk of CRC when offspring were diagnosed with diverse cancers (data not shown). When offspring were diagnosed with Hodgkin's disease, parents were at an increased risk of right-sided colon (SIR 2.54, 95% CI 1.15–4.84) and rectal cancers (SIR 2.19, 95% CI 1.04–4.04). Parents were at an increased risk of left-sided colon cancer when offspring were diagnosed with testicular cancer (SIR 2.06, 95% CI 1.09–3.53). None of these findings were significant at the 99% level.

4. Discussion

The multiple comparisons are a problem in this kind of exploratory study searching for new hypotheses on cancers clustering with CRC in families. Altogether some 400 comparisons were made and some were bound to give a significant result by chance. The internal comparison of analysing risks in the reverse order, risk in parents when offspring were probands (last paragraph of Section 3), would be helpful if the age distribution

Table 3
SIR for right-sided colon adenocarcinoma in offspring of affected parents and siblings by age at diagnosis

Familial cancer	Both parents and offspring diagnosed before 50 years of age								Both parents and offspring diagnosed after 50 years of age							
	Parental proband				Sibling proband				Parental proband				Sibling proband			
	O	SIR	95% CI		O	SIR	95% CI		O	SIR	95% CI		O	SIR	95% CI	
Upper aerodigestive tract									6	0.59	0.21	1.30	2	1.01	0.10	3.73
Oesophagus									6	1.10	0.40	2.42	1	1.39	0.00	7.95
Stomach	2	2.69	0.25	9.91	1	2.64	0.00	15.12	44	1.10	0.80	1.48	4	2.15	0.56	5.55
Colorectum	10	**7.51**	3.57	13.86	13	**8.70**	4.61	14.92	108	**1.50**	1.23	1.82	21	**2.87**	1.78	4.40
Liver	1	3.68	0.00	21.11					18	0.79	0.47	1.25	2	1.14	0.11	4.19
Pancreas	1	3.12	0.00	17.86					24	1.08	0.69	1.61	8	**4.31**	1.84	8.54
Lung	1	1.18	0.00	6.78	3	2.29	0.43	6.77	48	1.15	0.85	1.53	10	1.47	0.70	2.72
Breast	3	0.65	0.12	1.91	7	1.40	0.55	2.89	59	1.06	0.80	1.36	15	0.80	0.45	1.33
Cervix	7	**2.67**	1.06	5.52					9	1.02	0.46	1.95				
Endometrium	4	**6.22**	1.62	16.10					25	**1.75**	1.13	2.58	7	1.99	0.79	4.13
Ovary	3	3.01	0.57	8.90	2	2.92	0.28	10.75	14	1.05	0.57	1.76	3	1.02	0.19	3.03
Other female genitals									3	0.94	0.18	2.78	1	3.01	0.00	17.27
Prostate					1	0.92	0.00	5.28	90	1.00	0.80	1.23	10	1.37	0.65	2.54
Kidney	5	**7.46**	2.35	17.54					31	**1.48**	1.01	2.11	2	0.77	0.07	2.84
Urinary bladder					2	2.94	0.28	10.80	29	0.99	0.66	1.42	7	2.01	0.80	4.16
Melanoma	1	0.98	0.00	5.62	1	0.74	0.00	4.22	10	1.08	0.52	2.00	6	1.40	0.51	3.08
Skin, squamous cell					1	2.46	0.00	14.13	22	0.92	0.57	1.39	6	**3.14**	1.13	6.88
Nervous system	1	0.81	0.00	4.67	1	0.82	0.00	4.72	12	0.87	0.45	1.52	6	1.47	0.53	3.23
Thyroid gland	1	2.21	0.00	12.66					4	0.98	0.25	2.52	4	**5.68**	1.48	14.69
Endocrine glands	1	1.96	0.00	11.24					7	0.85	0.34	1.76	4	1.96	0.51	5.07
Connective tissue	1	4.64	0.00	26.59					2	0.54	0.05	1.98	1	1.81	0.00	10.37
Non-Hodgkin's lymphoma									17	1.07	0.62	1.72	5	1.41	0.44	3.32
Hodgkin's disease									3	1.07	0.20	3.16				
Myeloma	2	**12.69**	1.20	46.69	3	**13.87**	2.61	41.05	13	1.23	0.65	2.11	1	0.87	0.00	5.01
Leukaemia					2	3.77	0.36	13.85	14	0.77	0.42	1.30	4	1.90	0.49	4.91

Bold type, 95% CI does not include 1.00.
Underlining bold type, 99% CI does not include 1.00.

of both parental and offspring populations were similar, which was not the case. One way to judge the likelihood of chance is to consider the level of statistical significance. For this reason, we gave both 95% and 99% CIs for the tabulated SIRs. Other formal methods that consider the number of comparisons include the Bonferroni correction, which we did not apply. In lacking independent studies, biological plausibility is another possibility to weight the value of the observed associations. We consider the level of statistical significance and biological plausibility in the subsequent discussion. Even this large study would not detect heritable cancers that, albeit with high risk, affect a small number of people; for example, there was no increase between colorectal cancers and breast cancer, although co-aggregation has been found in some families [21].

Rectal cancer showed no overall familial associations with other sites. When young offspring and parental probands (both diagnosed before the age 50 of years) were considered, a significant association with parental endometrial cancer was noted, probably as a manifestation of HNPCC. In older offspring and probands, associations were noted both with cervical and other female genital cancers. It is unlikely that these two cancers, related to chronic human papilloma virus (HPV) infection [26,27], would occur by chance in association with rectal cancer. Even offspring with right-sided colon cancer was associated with parental cervical cancer, when cancers were diagnosed after the age of 50 years. Anal cancer is a known target site for HPV, but there are no convincing data linking HPV to rectal or colon cancers [28]. The risk for rectal cancer is increased as a second tumour after a first cervical cancer [29]. An immunological mechanism could also explain the familial associations between rectal and cervical/genital cancers [30]. However, there was no significant association between rectal cancer and squamous cell skin cancer or non-Hodgkin's lymphoma, the two neoplasms which are usually considered markers of impaired immune response [31–33]. Thus, there may be an as yet unknown mechanisms.

Most of the familial association between colon cancer and other sites were known HPNCC sites, including the endometrium, renal pelvis and pancreas (Table 5). We have no possibility of determining whether HNPCC is the only reason for these associations or why pancreatic cancer was increased only among siblings. The known manifestation of papillary thyroid cancer in FAP may suggest that the co-occurrence of early-onset right-sided colon cancer and non-medullary thyroid cancer in siblings is due to this syndrome.

Table 4
SIR for rectal adenocarcinoma in offspring of affected parents and siblings by age at diagnosis

Familial cancer	Both parents and offspring diagnosed before 50 years of age								Both parents and offspring diagnosed after 50 years of age							
	Parental proband				Sibling proband				Parental proband				Sibling proband			
	O	SIR	95% CI		O	SIR	95% CI		O	SIR	95% CI		O	SIR	95% CI	
Upper aerodigestive tract					1	1.46	0.00	8.37	15	0.95	0.53	1.58	2	0.66	0.06	2.42
Oesophagus									7	0.82	0.33	1.70	1	0.88	0.00	5.04
Stomach					1	1.65	0.00	9.45	58	0.93	0.71	1.21	2	0.68	0.06	2.51
Colorectum	12	**6.42**	3.30	11.24	6	2.48	0.89	5.44	182	**1.61**	1.38	1.86	24	**2.10**	1.34	3.13
Liver	1	2.71	0.00	15.54					38	1.06	0.75	1.46	1	0.37	0.00	2.11
Pancreas					1	1.81	0.00	10.39	30	0.87	0.58	1.24	1	0.35	0.00	2.00
Lung	2	1.73	0.16	6.34	3	1.41	0.26	4.16	67	1.02	0.79	1.30	10	0.94	0.45	1.74
Breast	6	0.94	0.34	2.05	6	0.76	0.27	1.66	93	1.05	0.85	1.29	36	1.22	0.85	1.68
Cervix	5	1.28	0.40	3.01					14	1.03	0.56	1.72	2	1.00	0.09	3.66
Endometrium	5	**5.20**	1.64	12.23	2	2.01	0.19	7.39	21	0.92	0.57	1.42	5	0.91	0.29	2.13
Ovary	2	1.40	0.13	5.16	2	1.88	0.18	6.90	30	1.42	0.96	2.03	3	0.65	0.12	1.93
Other female genitals					1	7.94	0.00	45.51	11	**2.19**	1.09	3.93	1	1.90	0.00	10.90
Prostate									160	1.12	0.96	1.31	5	0.44	0.14	1.04
Kidney	1	1.09	0.00	6.25	1	1.20	0.00	6.89	34	1.03	0.71	1.44	7	1.74	0.69	3.61
Urinary bladder					3	2.73	0.51	8.08	49	1.06	0.78	1.40	4	0.74	0.19	1.91
Melanoma	3	2.23	0.42	6.60	3	1.41	0.27	4.19	15	1.01	0.56	1.67	5	0.74	0.24	1.75
Skin, squamous all									45	1.19	0.87	1.60	6	2.03	0.73	4.44
Nervous system	2	1.17	0.11	4.32	2	1.07	0.10	3.93	29	1.32	0.89	1.90	8	1.23	0.53	2.44
Thyroid gland	1	1.64	0.00	9.38	2	4.98	0.47	18.30	4	0.62	0.16	1.62				
Endocrine glands					2	2.36	0.22	8.70	12	0.92	0.47	1.60	7	2.15	0.85	4.46
Connective tissue	1	3.34	0.00	19.17					5	0.86	0.27	2.03	2	2.24	0.21	8.23
Non-Hodgkin's lymphoma					1	0.82	0.00	4.68	34	1.35	0.94	1.89	4	0.72	0.19	1.86
Hodgkin's disease	1	2.41	0.00	13.84					5	1.16	0.37	2.72				
Myeloma	1	4.43	0.00	25.42	1	2.93	0.00	16.81	12	0.72	0.37	1.27	3	1.65	0.31	4.89
Leukaemia	1	1.21	0.00	6.94					21	0.74	0.46	1.13	4	1.20	0.31	3.09

Bold type, 95% CI does not include 1.00.
Underlining bold type, 99% CI does not include 1.00.

The sites in Table 5, not discussed above, include the renal parenchyma, squamous cell skin cancer, myeloma and leukaemia. The associations were limited to right-sided colon for the other sites, except leukaemia which were associated with left-sided colon cancer; none of the associations were significant at the 99% level. The

Table 5
Summary SIRs for familial associations in colon adenocarcinoma in offspring and siblings

Familial cancer	Offspring colon adenocarcinoma										HNPCC site
					Right-sided						
	Overall		Left-sided		Overall		Both parents and offspring diagnosed after 50 years of age		Both parents and offspring diagnosed after 50 years of age		
	Parental proband	Sibling proband	Parental proband	Sibling proband	Parental proband	Sibling proband	Parental proband	Sibling proband	Parental proband	Sibling proband	
Colorectum	**1.81**	**3.26**	**1.84**	**2.93**	**1.79**	**3.58**	**7.51**	**8.70**	**1.50**	**2.87**	√
Pancreas	1.22	2.13	1.25	0.49	1.19	**3.66**	3.12		1.08	**4.31**	√
Cervix	1.19	0.84	1.13	1.72	1.25		**2.67**		1.02		
Endometrium	**1.52**	1.50	1.13	1.28	**1.89**	1.71	**6.22**		**1.75**	1.99	√
Kidney	**1.42**	0.50	1.07	0.34	**1.76**	0.65	**7.46**		**1.48**	0.77	
Renal pelvis	**1.45**	0.63	1.20	0.43	**1.70**	0.82	**6.64**		1.45	0.98	
Renal parenchyma	1.63		0.42		**2.78**		22.14		2.13		√
Skin, squamous cell	0.89	2.02	0.87	0.93	0.91	**3.04**		2.46	0.92	**3.14**	√
Thyroid gland	1.02	2.12	1.05		1.00	**4.12**	2.21		0.98	**5.68**	
Myeloma	1.22	**2.65**	1.21	2.33	1.23	2.96	**12.69**	**13.87**	1.23	0.87	
Leukaemia	0.91	**2.53**	1.17	**2.78**	0.66	2.29		3.77	0.77	1.90	

Bold type, 95% CI does not include 1.00.
Underlining bold type, 99% CI does not include 1.00.

association with myeloma has been observed in a previous study from the Database [6]. The risk was observed both in offspring of affected parents and among siblings, which adds to the credibility of the finding. The associations with cancers of the renal parenchyma and skin and with leukaemia were found in only one comparison and must be considered tentative. However, renal parenchymal cancers have been noted in CRC kindreds in the United States of America (USA) [34]. All leukaemias were diagnosed in adults and included diverse subtypes.

In the reverse comparison, parental risk of right-sided colon and rectal cancers were increased if offspring were diagnosed with Hodgkin's disease. Left-sided colon cancer was increased in parents of testicular cancer patients. None of these results were significant at the 99% level, and, to our knowledge, they have not been reported before. However, because the association with Hodgkin's disease was observed at two sites, the likelihood of a chance finding appears to be small.

The strongest evidence for an association of CRC with other sites was obtained for cervical and other genital cancers and for haemato-lymphoproliferative diseases such as leukaemia, myeloma and Hodgkin's disease. The common dominator for these neoplasms is that they are known to be under immune surveillance. They, including colon cancer, increase in patients that have been immunosuppressed because of organ transplantation or because of acquired immune deficiency (AIDS) [32,35–39]. Although some other cancers also increase, and although no increases were observed for non-Hodgkin's lymphoma, as noted above, the number of immune responsive sites associating with the familial risk of colon cancer agrees with the hypothesis of immune function deficiencies as a possible mechanism of the observed familial clustering. Among haemato-lymphoproliferative diseases and colon cancer, the associations were seen mainly between siblings, which could suggest a recessive mechanism. An entirely different, but more speculative, mechanism could be that these cancers are mediated by the Bloom syndrome gene, *BML*, which may or may not predispose to the risk of CRC, even in a heterozygous state [17,40]. In a homozygous state, mutations in this gene cause many neoplasms, including leukaemias [41].

In conclusion, our results were obtained from the largest collection of medically-verified cases of familial cancer in the world. Most of the findings on site-specific colon and rectal cancer associations with other sites in family members were consistent with data on known cancer syndromes. New associations, where rectal cancer was related to cervical and female genital cancers in mothers through an unknown mechanism were observed. Hodgkin's disease and myeloma were also associated with right-sided colon cancer. The association of carcinoma of the renal parenchyma and skin with right-sided colon cancer, that of leukaemia with left-sided colon cancer and that of testicular cancer with rectal cancer await confirmation in an independent series.

Conflicts of Interest

None declared.

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References

1. IARC, editor. GLOBOCAN 2000. Cancer incidence, mortality and prevalence worldwide. lyon: IARC Press; 2001.
2. Centre for Epidemiology. Cancer incidence in Sweden 2000. Stockholm: The National Board of Health and Welfare; 2002.
3. Goldgar DE, Easton DF, Cannon-Albright LA, Skolnick MH. Systematic population-based assessment of cancer risk in first-degree relatives of cancer probands. *J Natl Cancer Inst* 1994, **86**, 1600–1607.
4. Fuchs C, Giovannucci E, Colditz G, Hunter D, Speizer F, Willett W. A prospective study of family history and the risk of colorectal cancer. *N Engl J Med* 1994, **331**, 1669–1674.
5. Carstensen B, Soll-Johanning H, Villadsen E, Söndergaard J, Lynge E. Familial aggregation of colorectal cancer in the general population. *Int J Cancer* 1996, **68**, 428–435.
6. Hemminki K, Li X. Familial colorectal adenocarcinoma from the Swedish Family-Cancer Database. *Int J Cancer* 2001, **94**, 743–748.
7. Johns LE, Houlston RS. A systematic review and meta-analysis of familial colorectal cancer risk. *Am J Gastroenterol* 2001, **96**, 2992–3003.
8. Wheeler J, Bodmer W, Mortensen N. DNA mismatch repair genes and colorectal cancer. *Gut* 2000, **47**, 148–153.
9. Lynch HT, de la Chapelle A. Hereditary colorectal cancer. *N Engl J Med* 2003, **348**, 919–932.
10. Lynch H, de la Chapelle A. Genetic susceptibility to non-polyposis colorectal cancer. *J Med Genet* 1999, **36**, 801–818.
11. Aarnio M, Sankila R, Pukkala E, Salovaara R, Aaltonen L, De La Chapelle A, *et al*. Cancer risk in mutation carriers of DNA-mismatch-repair genes. *Int J Cancer* 1999, **81**, 214–218.
12. Bjork J, Akerbrant H, Iselius L, Alm T, Hultcrantz R. Epidemiology of familial adenomatous polyposis in Sweden: changes over time and differences in phenotype between males and females. *Scand J Gastroenterol* 1999, **34**, 1230–1235.
13. Olsson L, Lindblom A. Family history of colorectal cancer in a Sweden county. *Fam Cancer* 2003, **2**, 87–93.
14. Eng C. Genetics of Cowden syndrome: through the looking glass of oncology. *Int J Oncol* 1998, **12**, 701–710.
15. Hemminki A, Markie D, Tomlinson I, Avizienyte E, Roth S, Loukola A, *et al*. A serine/threonine kinase gene defective in Peutz-Jeghers syndrome. *Nature* 1998, **391**, 184–187.
16. Al-Tassan N, Chmiel NH, Maynard J, Fleming N, Livingston AL, Williams GT, *et al*. Inherited variants of MYH associated with somatic G:C–>T:A mutations in colorectal tumors. *Nat Genet* 2002, **30**, 227–232.

17. Gruber SB, Ellis NA, Scott KK, Almog R, Kolachana P, Bonner JD, *et al*. BLM heterozygosity and the risk of colorectal cancer. *Science* 2002, **297**, 2013.
18. Houlston RS, Tomlinson IP. Polymorphisms and colorectal tumor risk. *Gastroenterology* 2001, **121**, 282–301.
19. De Jong MM, Nolte IM, Te Meerman GJ, Van Der Graaf WT, De Vries EG, Sijmons RH, *et al*. Low-penetrance genes and their involvement in Colorectal Cancer susceptibility. *Cancer Epidemiol Biomarkers Prev* 2002, **11**, 1332–1352.
20. Hemminki K, Li X. Familial risks of cancer as a guide to gene identification and mode of inheritance. *Int J Cancer* 2004, **110**, 291–294.
21. Meijers-Heijboer H, Wijnen J, Vasen H, Wasielewski M, Wagner A, Hollestelle A, *et al*. The CHEK2 1100delC mutation identifies families with a hereditary breast and colorectal cancer phenotype. *Am J Hum Genet* 2003, **72**, 1308–1314.
22. Hemminki K, Li X, Czene K. Familial risk of cancer: data for clinical counseling and cancer genetics. *Int J Cancer* 2004, **108**, 109–114.
23. Hemminki K, Li X, Plna K, Granström C, Vaittinen P. The nation-wide Swedish Family-Cancer Database: updated structure and familial rates. *Acta Oncol* 2001, **40**, 772–777.
24. Hemminki K, Vaittinen P, Dong C, Easton D. Sibling risks in cancer: clues to recessive or X-linked genes. *Br J Cancer* 2001, **84**, 388–391.
25. Esteve J, Benhamou E, Raymond L. *Statistical methods in cancer research*. Lyon, IARC, 1994.
26. IARC. Human papillomaviruses. Lyon: IARC; 1995.
27. Zur Hausen H. Viruses in human cancers. *Eur J Cancer* 1999, **35**, 1174–1181.
28. Frisch M, Glimelius B, van den Brule A, Wohlfahrt J, Meijer C, Walboomers J, *et al*. Sexually transmitted infection as a cause of anal cancer. *New Engl J Med* 1997, **337**, 1350–1358.
29. Hemminki K, Jiang Y, Dong C. Second primary cancers after anogenital, skin, oral, esophageal and rectal cancers: etiological links. *Int J Cancer* 2001, **93**, 294–298.
30. Hemminki K, Dong C, Vaittinen P. Familial risks in cervix cancer: is there a hereditary component. *Int J Cancer* 1999, **82**, 775–781.
31. Birkeland S, Storm H, Lamm L, Barlow L, Blohme L, Forsberg B, *et al*. Cancer risk after renal transplantation in the Nordic countries, 1964–1986. *Int J Cancer* 1995, **60**, 183–189.
32. IARC. IARC Monographs on the evaluation of carcinogenic risks to humans. Lyon: IARC; 1996.
33. Hemminki K, Jiang Y, Steineck G. Skin cancer and non-Hodgkin's lymphoma as second malignancies: markers of impaired immune function. *Eur J Cancer* 2003, **39**, 223–229.
34. Teruya-Feldstein J, Greene J, Cohen L, Popplewell L, Ellis NA, Offit K. Analysis of mismatch repair defects in the familial occurrence of lymphoma and colorectal cancer. *Leuk Lymphoma* 2002, **43**, 1619–1626.
35. Kinlen L. Immunosuppression and cancer. In Vainio H, Magee P, McGregor D, McMichael A, eds. *Mechanisms of carcinogenesis in risk identification*. Lyon, IARC, 1992. pp. 237–253.
36. Cooksley CD, Hwang LY, Waller DK, Ford CE. HIV-related malignancies: community-based study using linkage of cancer registry and HIV registry data. *Int J STD AIDS* 1999, **10**, 795–802.
37. Haagsma EB, Hagens VE, Schaapveld M, van den Berg AP, de Vries EG, Klompmaker IJ, *et al*. Increased cancer risk after liver transplantation: a population-based study. *J Hepatol* 2001, **34**, 84–91.
38. Yeguez JF, Martinez SA, Sands DR, Sands LR, Hellinger MD. Colorectal malignancies in HIV-positive patients. *Am Surg* 2003, **69**, 981–987.
39. Adami J, Gabel H, Lindelof B, Ekstrom K, Rydh B, Glimelius B, *et al*. Cancer risk following organ transplantation: a nationwide cohort study in Sweden. *Br J Cancer* 2003, **89**, 1221–1227.
40. Cleary SP, Zhang W, Di Nicola N, Aronson M, Aube J, Steinman A, *et al*. Heterozygosity for the BLM (Ash) mutation and cancer risk. *Cancer Res* 2003, **63**, 1769–1771.
41. German J, Ellis N. Bloom syndrome. In Vogelstein B, Kinzzler K, eds. *The genetic basis of human cancer*. New York, McGraw-Hill, 1998. pp. 301–315.