

## Short Communication

# Familial Risk for Colorectal Cancers Are Mainly Due to Heritable Causes

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### Abstract

A family history is an identified risk factor for colorectal cancer (CRC). However, it is not known to what extent the risk is due to environmental or heritable genetic factors. We wanted to examine this question for familial CRC adenocarcinoma based on the nationwide Swedish Family-Cancer Database on 10.3 million individuals whose invasive cancers were followed up to year 2000. Standardized incidence ratios (SIRs) for offspring, siblings, and spouses were calculated based on 5-year age, sex, period (10-year bands), area (county), and socioeconomic status standardized rates. A significant risk was observed in the parent-offspring comparison among different subsites (left-sided and right-sided colon, rectum, and all CRC), the SIRs ranging from 1.74 to 1.84. When husbands were probands, the SIR in

wives was 0.92 for colon cancer (left-sided 0.67 and right-sided 1.07), 0.98 for rectal cancer, and 0.96 for CRC. The risks for husbands when wives were probands were quite similar. None of the SIRs between spouses were significant, indicating lack of concordance between spouses that resided together for a minimum of 30 years. The risks between siblings were also increased particularly for cancer in the right-sided colon (SIR 6.89). The effect of shared childhood environmental effects were probed by analyzing the risks by age difference between the siblings. However, the risks were independent of the age difference. Data among spouses and siblings consistently point to the importance of heritable factors in familial CRC. (Cancer Epidemiol Biomarkers Prev 2004;13(7):1253-6)

### Introduction

The large international variation in the incidence of colorectal cancer (CRC) and migrant studies suggest that the causes of CRC are mainly environmental (1-6). Diet, overweight, and physical activity are important environmental factors linked to the risk of CRC (4, 7-9). Familial aggregation among first-degree and second-degree relatives is thought to make up some 20% of the CRC burden, but Mendelian conditions account for only a proportion of the familial clustering (10). The most common Mendelian condition, hereditary nonpolyposis CRC (HNPCC), has been estimated to account for 3% of all CRC in Finland (11, 12). Epidemiologic data from Sweden suggest that 20% to 50% of familial CRC up to age 61 may be due to HNPCC, but the proportion may vary depending on the population and its age structure (13). In an older population, the contribution of HNPCC

would be expected to be less. In Sweden, 12.5% of 0- to 66-year-old patients with CRC have an affected parent, giving a population attributable proportion of 6.9%, equal to that of breast cancer (14). In addition to the previously known Mendelian conditions, recent data suggest that germline mutations in the *bml* and *myh* genes may also increase the risk of CRC (15, 16) and that some low penetrance genes may also contribute to familial risk (17, 18). Although no direct assessment is available as to the proportion of familial aggregation that can be accounted for by the known susceptibility genes, the proportion is less than half.

A search for the causes of familial clustering of cancer is important for cancer prevention and for etiologic understanding of the carcinogenic mechanisms. Familial clustering may be due to shared genes or a shared environment; for CRC, shared environmental effects may be particularly relevant because families share dietary customs and recreational habits. We have assessed the contribution of environmental sharing in all cancers by studying correlation of cancer risk between spouses from earlier versions of the Swedish Family-Cancer Database (19, 20). No appreciable spouse concordance was noted for colon or rectal cancer. Spouse correlation may not be sensitive to environmental effects that exert their action early in life. In the present work, based on the most recent update of the Family-Cancer Database (21), we assess also shared childhood effects by comparing the risk between siblings according to their age difference.

Received 10/21/03; revised 2/16/04; accepted 2/19/04.

**Grant support:** Deutsche Krebshilfe and Swedish Cancer Society. The Family-Cancer Database was created by linking registers maintained at Statistics Sweden and the Swedish Cancer Registry.

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The assumption is that, if environmental effects were important, siblings with a small age difference would have a higher risk than those with a large age difference; if heritable causes overwhelmed, the risk would be independent of the age difference. Additional novel features of the present study are that we only consider the main histologic type, adenocarcinoma, and that we analyze separately the right-sided and left-sided colon and the rectum to gain information about HNPCC, which most commonly affects right-sided colon (10). The Database offers unique possibilities for reliable estimation of familial risks because the data on family relationships and cancers were obtained from registered sources of practically complete coverage.

## Subjects and Methods

The Swedish Family-Cancer Database includes all persons born in Sweden after 1931 with their biological parents, totaling over 10.3 million individuals (20, 21), which is unique by both its size and its population-based structure. Cancers were retrieved from the nationwide Swedish Cancer Registry from years 1958 to 2000. Family history information was collected on all first-degree relatives (parents, siblings, and children). Follow-up was started on January 1, 1991 and terminated on death, emigration, or the closing data of the study, December 31, 2000, whichever came first. The Family-Cancer Database has a gap among those born between 1935 and 1940 who died between 1960 and 1991. Many of these individuals lack links to parents in the Database, but because the current follow-up was started from 1991, the lacking parental links should not bias the present estimates.

*International Classification of Diseases* codes 153.0 to 153.3 and 154.0 were used for CRC. Based on the codes, the anatomic 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 of the left and right locations. The histologic classification of CRC was used to define adenocarcinoma as a pathologic anatomic diagnosis code 096. The percentage of cytologically or histologically verified cases by site, sex, and age at diagnosis was 98% for colon cancer and 99% for rectal cancer.

Spouses were defined as the parents with at least one common child and had to live in a shared address in at least four subsequent decennial censuses; thus, the minimal cohabitation was 30 years. 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 providing an unbiased estimate of the risk to the siblings of a specified affected individual, regardless of family size distribution, and that this parameter will be equal to the offspring risk under any additive genetic models (22).

Standardized incidence ratios (SIRs) were calculated as the ratio of observed to expected number of cases. The expected numbers were calculated from 5-year age, sex, period (10-year bands), area (county), and socioeconomic status standardized rates defined in the same as was used for the observed numbers (23). 95% Confidence intervals (95% CI) were calculated assuming a Poisson

distribution (23). In the calculation of 95% CI for sibling risks, the dependence between affected pairs was taken into consideration (24). The analysis of this study was implemented in the environment of the SAS release 8.2.

## Results

The Family-Cancer Database includes totally 6,863,473 offspring with a parental linkage. A total of 6,773 and 31,100 CRCs were recorded in offspring and parents, respectively, during the period of 1991 to 2000. Of these, 597 were observed to have a parent affected with CRC. Familial risk for offspring when a parent had CRC is shown in Table 1. For colon and rectal adenocarcinoma, the SIRs in offspring were 1.81 and 1.74 by parental CRC adenocarcinoma. The SIRs among different subsites (left-sided and right-sided colon, rectum, and all CRC) in offspring ranged from 1.74 to 1.84, indicating that SIRs were independent at the subsites.

A total of 253,467 pairs of spouses met the entrance criteria for study of living together in the shared address in at least four consecutive censuses (i.e., a minimum of 30 years). Table 2 shows the comparison of risk between wives and husbands when one of the spouses was diagnosed with CRC. When husband was a proband, the SIR in wives was 0.92 for colon cancer (left-sided 0.67 and right-sided 0.96), 0.98 for rectal cancer, and 0.96 for CRC. None of these were significant. The situation for husbands was quite similar: the SIRs ranged from 0.89 for the left-sided colon to 0.98 for left-sided colon cancer.

The overall SIRs for risk between siblings were 6.89 (95% CI 3.93-11.21) for the right-sided colon, 1.81 (95% CI 0.47-4.68) for the left-sided colon, and 1.96 (95% CI 0.97-3.51) for the rectum. The age difference between siblings was first divided into three categories: <3, 3 to 5, and >5 years. The SIRs among siblings for left-sided and right-sided colon and rectum are shown in Fig. 1. Filled points show that the 95% CI of the SIR did not include 1.00. There were no cases among siblings when the age difference was <3 years for left-sided colon; the SIRs for the 3 to 5 and >5 years showed a small decline from 2.49 to 2.25. The SIRs in the right-sided colon varied more dramatically than those in the left-sided colon. The SIR in the right-sided colon was significant in the age difference category of <3 years (7.00). It reached the highest value of 10.98 in the third category but a lower value (2.49) in between. For the rectum, the SIR was maximal (2.88) in the first category and decreased in the second category (1.55) and increased to 1.75 in the third category (Fig. 1, *left*).

The age difference was divided into two categories at 4 years (Fig. 1, *right*). The SIR for the right-sided colon was about 3-fold higher than those for the left-sided colon

**Table 1. Familial risk in offspring when a parent had CRC**

Offspring Site	Observed	Expected	SIR	95% CI	
Colon	338	186.6	<b>1.81</b>	1.62	2.02
Right	170	95.2	<b>1.79</b>	1.53	2.08
Left	168	91.4	<b>1.84</b>	1.57	2.14
Rectum	259	149.3	<b>1.74</b>	1.53	1.96
CRC	597	335.8	<b>1.78</b>	1.64	1.93

**Table 2. Risk in wife and husband when the spouse was diagnosed with CRC**

Site	Wife				Husband			
	Observed	Expected	SIR	95% CI	Observed	Expected	SIR	95% CI
Colon	55	59.8	0.92	0.69-1.20	49	52.0	0.94	0.70-1.25
Right	40	37.5	1.07	0.76-1.46	28	28.5	0.98	0.65-1.42
Left	15	22.4	0.67	0.37-1.11	21	23.5	0.89	0.55-1.37
Rectum	34	34.6	0.98	0.68-1.38	40	41.2	0.97	0.69-1.32
CRC	89	93.2	0.96	0.77-1.18	89	93.2	0.96	0.77-1.18

and the rectum. However, the SIRs did not depend on the age difference.

We carried out analysis of familial risks by the size of sibship in families of affected and unaffected parents, with no significant differences in SIRs (data not shown).

## Discussion

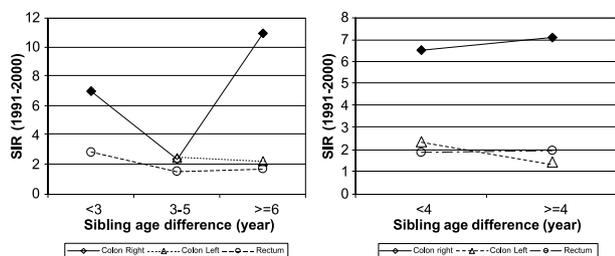
According to a Nordic twin study, 60% of the variation in unmeasured normally distributed liability in CRC were assigned to random environmental effects and 35% to heritable factors; shared environmental effects accounted for 5%, but this effect was not significant (25). In a family study on heritable and environmental components in CRC, lung cancer, and melanoma, the heritable effects were estimated at 10% to 18%. The nonshared environment accounted for the main effect, but shared and childhood environments could also be apportioned (26). However, there is no detailed understanding of the environment factors.

In the present study, familial risk of 1.78 for CRC agreed with the magnitude of 2.00 in a previous study in which the population was younger than that in the present study (27). In contrast to the familial risk between parents and offspring, the SIRs between spouses were not increased. No significant concordance was found between spouses, arguing against the influence of shared residential environment, dietary habits, or lifestyle among spouses that lived together for a minimum of 30 years. The results on spouses are in line with previous data from Sweden (28) and remain puzzling because of the assumed major role of diet and physical activity on CRC (4, 7, 8). The novel data on risks between siblings with varying age differences were consistent with the

data on spouses. Age difference did not influence the risk among siblings, thus suggesting that heritable factors are important for sibling risk. A further indication for the lack of environmental effects was that sibship size did not change the observed familial risk, in accordance to a previous study, which also excluded the effect of birth order (29).

As an unexpected result, we noted that the sibling risk for right-sided colon cancer exceeded that of left-sided colon and rectal cancers and was much higher than the SIR for offspring of affected parents. To our knowledge, no previous study has analyzed specifically the sibling risk for right-sided colon cancer, and our earlier study on all CRC noted no large difference between SIRs from parental or sibling probands probably because familial right-sided colon cancer is a minor proportion of all familial CRC (30). However, some earlier studies have observed higher risks for CRC among siblings than among offspring of affected parents, as reviewed by Johns and Houlston (31). The suggested implication of such a finding would be a recessive mode of inheritance. However, because the right-sided colon is the primary target of HNPCC, we need to be able to exclude any differential clinical management of HNPCC cases depending on the presenting proband; this option requires further investigation. Nevertheless, regarding the theme of the present study, the sibling risk for right-sided colon cancer did not depend on the age difference of the siblings.

In summary, assuming that the known susceptibility genes account for less than half of familial CRC (13, 17, 18), the present data suggest that important heritable factors are yet to be found for CRC. One challenging finding in the present study was the high sibling risk for cancer in the right-sided colon. This site is preferentially involved in HNPCC, but considering the relatively low risk in the corresponding offspring-parent comparison, other conditions may contribute to the high risk between siblings.



**Figure 1.** Sibling risk by age difference (*filled points* are used to mark that the 95% CIs of the SIRs do not include 1.00). *Left*, age difference was divided into three categories; *right*, age difference was divided into two categories at 4 years.

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*Cancer Epidemiol Biomarkers Prev* 2004;13:1253-1256.

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