Original articles

Increased incidence of cancer in first degree relatives of women with double primary carcinomas of the breast and colon

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Abstract

Breast and colon cancer are among the most common cancers in the developed world. Several epidemiological studies suggest that the occurrence of one of these two cancers in a woman may predispose to the development of the other. The occurrence of both forms of cancer in the same woman may be because of chance or common susceptibility. In order to determine how frequently double primary cancers have a hereditary basis, we conducted a registry based study at a single Montreal hospital. Cancer rates in first degree relatives of patients with multiple primaries were compared with provincial age standardised incidence rates and relative risks (RRs) were estimated. In first degree relatives under 45 there was a total of 15 cancers observed, compared with 3.70 expected, giving an RR of 4.05 (95% CI: 2.27-6.68). The RR for colon cancer was significantly increased among male relatives. For relatives less than 45 years old at diagnosis, the RR for colon cancer was 66.7 (95% CI: 13.8-195) (three cases observed, 0.045 expected). For all ages the RR was 5.02 (95% CI: 2.04-10.5). The RR for breast cancer was 5.92 (95% CI: 1.91-13.8) for female relatives under 45 (five cases observed, 0.845 expected) and 2.14 (95% CI: 1.07-3.83) for breast cancer at any age. These results suggest that there may be genes that predispose to both breast and colon cancer in certain people.

(*J Med Genet* 1996;33:534-539)

Key words: breast cancer; colon cancer; family history.

Multiple primary cancers are characteristic of hereditary cancer syndromes. When these double primaries are observed more frequently than would be expected by chance, it is reasonable to look for a common genetic origin. Several studies have shown an increased incidence of breast cancer following colon cancer and vice versa.^{1,2} However, the overall risk increase is modest. In a combined analysis of seven cohort studies, there was a slightly in-

creased relative risk of a second primary of the breast after a primary colon cancer and vice versa (1.10, 95% CI: 1.03-1.17; 1.15, 95% CI: 0.99-1.31, respectively).³ Breast and colon cancer have several risk factors in common. For example, increased consumption of dietary fat has been reported to increase risk of both diseases.⁴ If multiple primary cancers are primarily the result of hereditary factors, we would expect to see an increased cancer risk in relatives, and this increase should be greater than that associated with each site alone. To test this hypothesis we identified cases of breast and colon cancer occurring in the same woman from the tumour registry of the Royal Victoria Hospital, Montreal, Quebec. A detailed family history of cancer was obtained from each case. We compared the observed rates of cancer in the relatives of cases of double primary cancer of the breast and colon with expected rates for the Quebec and Canadian populations.

Materials and methods

ASCERTAINMENT OF PROBANDS

The tumour registry of the Royal Victoria Hospital contains information on patients who are diagnosed with all types of cancer. The reporting of cancer cases to the Tumour Registry by the Department of Pathology is obligatory. All entries for the years 1950-92 were reviewed; in 63 cases cancer of the female breast was later followed by cancer of the colon (or vice versa). All 63 patients had been under the care of surgeons in the Royal Victoria Hospital. The patient records of affected women were studied and the relevant clinical information was extracted. The diagnosis in the proband was confirmed by examination of the patient's medical records and pathology report for 61 of the 63 cases. In no case was there disagreement between the registry details and the information provided by patient charts or by the proband herself. As far as is known, no women were referred to this hospital because of family history. No attempt was made to verify the diagnosis of cancer in first degree relatives. However, the diagnosis of cancer reported in first degree relatives is very likely to be accurate.^{5,6} No systematic attempt was made

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Received 5 September 1995
Revised version
accepted for publication
16 January 1996

Table 1 Relative risk of cancer in first degree relatives associated with a double primary of the breast and colon in the female proband

Site or type of cancer*	Age group (y)	Observed	Expected	Relative risk (95% confidence intervals)
All sites	<45	15	3.70	4.05 (2.27-6.68)
	<55	22	8.53	2.58 (1.61-3.90)
	All ages	43	32.3	1.33 (0.96-1.79)
Breast	<45	5	0.845	5.92 (1.91-13.8)
	<55	8	2.02	3.95 (1.70-7.79)
	All ages	11	5.14	2.14 (1.07-3.83)
Colon	<45	3	0.110	27.3 (5.48-79.6)
	<55	4	0.462	8.66 (2.33-22.2)
	All ages	9	2.99	3.01 (1.36-5.67)
Bladder	<45	0	0.070	—
	<55	0	0.235	—
	All ages	2	1.63	1.23 (0.14-4.44)
Malignant melanoma	<45	1	0.348	2.88 (0.04-16.0)
	<55	1	0.550	1.82 (0.02-10.1)
	All ages	3	0.956	3.14 (0.63-9.17)

* Sites refer to any cancer site seen more than once in the 26 pedigrees.

Table 2 Relative risk of cancer in female first degree relatives associated with a double primary of the breast and colon in the female proband

Site or type of cancer	Age group (y)	Observed	Expected	Relative risk (95% confidence intervals)
All sites	<45	11	2.43	4.52 (2.25-8.09)
	<55	16	5.29	3.02 (1.73-4.91)
	All ages	26	16.7	1.56 (1.01-2.28)
Breast	<45	5	0.84	5.92 (1.91-13.8)
	<55	8	2.02	3.95 (1.70-7.79)
	All ages	11	5.14	2.14 (1.07-3.84)
Colon	<45	0	0.065	—
	<55	1	0.254	3.93 (0.05-21.9)
	All ages	2	1.64	1.22 (0.14-4.41)
Malignant melanoma	<45	1	0.215	4.66 (0.06-25.92)
	<55	1	0.330	3.02 (0.04-16.83)
	All ages	2	0.527	3.79 (0.43-13.7)

to record information on second degree relatives, as this information is substantially less reliable than that gathered from first degree relatives.^{5,6}

FAMILY HISTORY

Forty of the 61 probands had died. It was possible to contact the proband or the proband's next of kin in 26 cases. The interview was conducted with the proband in 14 cases and with a family member in the remaining 12 cases. A detailed family history was taken from these 26 people, representing 41% of the original probands identified as described above. Six families were of French-Canadian origin, six were Jewish, 10 were originally from the UK, and four were of mixed European descent. The interviews were conducted in person or by telephone. The family history included age of death, age of diagnosis of cancer, and site (and if possible histological type) of cancer in all first degree relatives of the proband. No patient or next of kin refused to take part in the study.

STATISTICAL ANALYSIS

The observed number of cases in the first degree relatives was determined by review of family pedigrees. The expected number of cases for each cancer was derived from the product of the person years and the provincial cancer rate for each age range, divided by 100 000. People were considered to be at risk of other cancer until death or age in 1994. The expected number of cases was calculated for each of the

age ranges selected. The relative risk (RR) of cancer in a first degree relative associated with a family history of double primary cancer of the breast and colon was calculated by comparing observed to expected figures using Quebec provincial health statistics. Quebec figures for melanoma were not available and Canadian health statistics were used. The confidence intervals (CIs) were calculated assuming a Poisson distribution, $CI = O_L/E - O_U/E$, where O_L is the lower bound and O_U is upper bound. The formula used is very sensitive to the number of observations and its use is recommended when comparing observed incidence rates.⁷

Lower bound

$$O_L = O * \left(\left[1 - \left(\frac{1}{9 * O} \right) \right] - \left[\frac{Z_{\alpha/2}}{3 * \sqrt{O}} \right] \right)^3$$

Upper bound

$$O_U = (O + 1) * \left(\left(1 - \left[\frac{1}{9 * (O + 1)} \right] \right) + \left[\frac{Z_{\alpha/2}}{3 * \sqrt{(O + 1)}} \right] \right)^3$$

Results

There were 26 probands with two primary cancers. In 14 cases the breast cancer was diagnosed first (at a mean age of 63.0 years, range 29-88), and in 12 colon cancer was diagnosed first (at a mean age of 64.9 years, range 37-88). Four probands were diagnosed with both breast and colon cancer at less than 50 years of age. The mean interval between diagnosis of the two cancers was 8.27 years (range 1-38 years, median five years). The 26 probands had 193 first degree relatives (an average of 7.4 first degree relatives). There were 4685 man years and 6211 woman years of exposure until death or current age. A total of 43 cancers were reported in the 193 relatives (22.3%).

Fifteen first degree relatives had cancer diagnosed at the age of 45 years or earlier. The expected number is 3.70, giving a relative risk (RR) (observed/expected ratio) of cancer at any site associated with a double primary in the proband of 4.05 (95% confidence interval (CI): 2.27-6.68). For cancer at all ages, the observed figure was not significantly greater than that expected (table 1).

Eleven of 110 female first degree relatives had breast cancer (age range 31-70 years). There were five woman who had breast cancer diagnosed at less than 45 years of age. As only 0.84 cases are expected, this results in an RR for breast cancer of 5.92 (95% CI: 1.91-13.81) (table 2). If both the relative and the proband were diagnosed with breast cancer at less than 45 years of age then the RR was 26.9 (95% CI: 5.41-77.3). However, all three cases in this category came from one family (see below).

Table 3 Relative risk of cancer in male first degree relatives associated with a double primary of the breast and colon in the female proband

Site or type of cancer	Age group (y)	Observed	Expected	Relative risk (95% confidence intervals)
All sites	<45	4	1.27	3.15 (0.85–8.07)
	<55	6	3.25	1.85 (0.68–4.02)
	All ages	17	15.6	1.09 (0.64–1.75)
Breast	<45	3	0.045	66.7 (13.4–195)
	<55	3	0.208	14.4 (2.90–42.2)
	All ages	7	1.37	5.09 (2.04–10.5)
Colon	<45	0	0.052	—
	<55	0	0.168	—
	All ages	2	1.17	1.71 (0.19–6.18)
Malignant melanoma	<45	0	0.133	—
	<55	0	0.220	—
	All ages	1	0.428	2.33 (0.93–13.0)

Colon cancer diagnosed at less than 45 years old was seen in three first degree relatives, whereas 0.11 were expected, giving an RR of 27.26 (95% CI: 5.45–79.64). The risk remained increased for colon cancer at any age: nine cases were observed and 3.01 were expected. The RR was significantly increased for men only (tables 1–3). Seven of 93 male first degree relatives had colon cancer (age range 30–73 years), including three men who had colon cancer diagnosed in their thirties (ages 30, 33, and 34). This results in an RR of 66.67 (95% CI: 13.4–19.5). Two of the three cases of colon cancer seen in men under 45 were accounted for by relatives of three probands who themselves had been diagnosed with colon cancer at less than 45 years of age. This latter group resulted in an RR of 432 (95% CI: 48.5–1560). As for breast cancer, these two cases of very early onset colon cancer came from one family (figure).

The only other cancers that were seen more than once were melanoma and bladder cancer. There was no significantly increased frequency of these cancers (tables 1–3).

Much of the excess colon and breast cancer risk could be attributed to one pedigree (figure). This pedigree contains three female first degree relatives with breast cancer, diagnosed at ages 31 to 38, and two male first degree relatives with colon cancer, diagnosed at the ages of 33 and 34. Because of the possibility that this one large family might account for all the increased risk seen, the person years were recalculated and the data were analysed after excluding this family. For both sexes, and cancer at all sites in those under 45, there was a fall in the RR from 4.02 to 2.82, but this remained significant (95% CI: 1.35–5.20). The values for other age groups did not change appreciably. In women, the RR for cancer at any site is still significantly raised: 3.42 (95% CI: 1.47–6.73) for those less than 45 years old at time of diagnosis, and 2.54 (95% CI: 1.35–4.34) for those under 55 years old. The RR for colon cancer in males at all ages falls to 3.67 but remains significant (95% CI: 1.18–8.57). The RR associated with breast cancer in the younger age groups also falls (2.46, 95% CI: 0.28–8.87).

This one large family has a clear excess of both young onset breast and colorectal cancer. Therefore this pedigree has been studied in more detail. Pathological confirmation of all diagnoses of cancer was obtained. The possibility of a germline mutation in several of

the known cancer susceptibility genes, predisposing to breast or colon cancer, was studied by linkage and mutation analysis. In one affected subject, mutations were sought in exons 2–11 of TP53 with single strand conformation analysis, using a standard protocol.⁸ No mutation was found. In addition, markers adjacent to or within the BRCA1, BRCA2, hMLH1, and hMSH2 loci were assessed by linkage analysis in this family using MLINK in the LINKAGE program. The results show that when it is assumed that a single locus is responsible for both breast and colon cancer, the highest positive lod score is +0.096 with D2S119 near hMSH2, but in no case could a common haplotype be found in all affected subjects.

It is possible that an allele of BRCA1 is cosegregating with the breast cancer cases in this family, as excluding the colon cancer cases resulted in an increase in the lod score from –0.17 to +0.16 using D17S855. Similarly, the linkage results with D3S1076, adjacent to hMLH1 on chromosome 3p, suggest a mutation in this gene may be responsible for the colon cancer in this family, as excluding the breast cancer cases resulted in the lod score increasing from –0.39 to +0.18. These linkage results are based on marker studies of only three affected persons (figure), and cannot be conclusive. It also possible that a novel gene could be linked to the cancers in this family.

Discussion

Reports of possible associations of breast and colorectal cancer within families go back at least as far as 1904.⁹ A number of cohort and case control studies have examined the familial relationship between breast and colon cancer, but the results are conflicting, with some studies showing no relationship^{10–13} and others suggesting a moderate positive association.^{14–17} No studies have attempted specifically to study the family history of double primary cancers of the breast and colon, but others have shown that one indicator of increased likelihood of genetic factors playing an important role in a malignant disease is the incidence of two distinct primary tumours in one person.¹⁸ However, as both cancers are common in the developed world, it is possible that two cancers in the same woman could be seen by chance, and would therefore not be expected to be associated with a family history of cancer. This study has shown that in families ascertained through a woman with a double primary cancer of the breast and colon, there were significantly increased risks in that family for developing early onset breast cancer and colon cancer. Risks were also significantly increased for any cancer in younger women. This suggests that chance is not a likely explanation for these data.

When the data are reanalysed using different age group categories, it can be seen that the main excess of cancer occurs in those under 45 at diagnosis (RR 4.05, table 1), particularly if the proband had both breast and colon cancer diagnosed at less than 50 years of age (RR for all cancers, 10.7, 95% CI: 3.9–23.3). Breast

cancer in female relatives and colon cancer in male relatives account for most of the increased risk. In the age group 45 to 54, there are too few observed cases to generate significant data (point estimate of RR: 1.45), but in the 55 to 74 age group, results similar to those seen for all ages were obtained (RR of any cancer, 1.22, 95% CI: 0.75–1.89; compare with table 1). Therefore, not surprisingly, there is a significant deficit of cancer in the 75+ age group (all cancers, RR 0.14, 95% CI: 0.0018–0.75).

By comparing our results with those obtained in prospective cohort studies, it can be seen that risks for colon cancer in men and breast cancer in younger women associated with a family history of a double primary of these cancers is greater than the risk associated with a family history of each of these cancers alone. From two continuing cohort studies, 119 116 US health workers provided details of family history of cancer.¹⁹ Using a person years approach, based on 73 cases, it was estimated that the RR of colorectal cancer associated with a family history of this cancer was 1.72 (95% CI: 1.33–2.20). For the five cases diagnosed at under 45, the RR was 5.37 (95% CI: 1.98–17.4). In our series, the corresponding risks were 3.01 (95% CI: 1.36–5.67) and 27.3 (95%

CI: 5.48–79.6), based on nine and three cases, respectively. For breast cancer, a comparison can be made with a component of the study group discussed above. In the Nurses' Health Study, of 117 988 women followed up from 1976 to 1988 there were 2389 incident cases of breast cancer, among whom 220 had a mother with breast cancer.²⁰ The age adjusted RR associated with a maternal history of breast cancer was 1.8 (95% CI: 1.5–2.0) and if the mother was diagnosed before the age of 40, the RR was 2.1 (95% CI: 1.6–2.8). Risks associated with sisters with breast cancer were similar. We showed RRs of 5.92 (95% CI: 1.91–13.8) for those under 45 and 2.14 (95% CI: 1.07–3.84) for breast cancer at any age. Thus our data are consistent with the hypothesis that the risk of either cancer in relatives of probands with double primaries is greater than that associated with either one cancer alone.

Shared environmental or hormonal factors could account for the increased RRs seen in the relatives. A number of studies have suggested that dietary risk factors, such as saturated fat intake, may be common to both diseases.² Similarly, reproductive and hormonal factors may contribute to the incidence of colorectal cancer.²¹ Prospective studies have shown

Family 111

Family 111. The common haplotype seen for the four chromosome 3 markers used is boxed. Boxes in square brackets are inferred haplotypes. The X denotes an inferred recombination. The numbers immediately under the symbols are individual numbers. The filled in symbols denote affected persons. Br = breast cancer; Co = colon cancer; Sk = skin cancer; Thy = thyroid cancer; Thro = throat cancer. The number next to the cancer site refers to the age at diagnosis of cancer.

that oestrogen replacement therapy is protective against colorectal cancer.²² There may be an increased risk of colorectal cancer associated with adjuvant tamoxifen therapy for early stage breast cancer.²³ There is a notable lack of excess of colon cancer in the female relatives of the double primary cases in this study. It is not clear why this is the case, but chance and shared (protecting) hormonal factors may be important.

The adenoma-carcinoma sequence is a plausible explanation for the origin of colorectal carcinomas.²⁴ We do not have data on the prevalence of colonic polyps in our pedigrees, but previous case control studies have addressed this issue. From the most thorough study, it appears that colonic adenomas are not more frequent in breast cancer patients than in unaffected controls.²⁵

Several inherited cancer syndromes include colon carcinoma. The two major types are familial adenomatous polyposis and hereditary non-polyposis colorectal cancer (HNPCC). Neither of these syndromes is clearly associated with a significantly increased risk of breast carcinoma.^{26,27} Hereditary breast cancer is principally attributable to mutations in two genes, BRCA1 and BRCA2. There appears to be an increased risk of colorectal cancer in pedigrees containing BRCA1 mutations,²⁸ but this requires further investigation. None of the 26 probands in our series appeared to be members of breast-ovarian cancer pedigrees. A case of multiple primary cancer of the breast and colon in a male who has inherited the disease related haplotype at BRCA2 has also been reported,²⁹ but there was no excess of breast cancer in men with colorectal cancer in a SEER based study.³⁰

The gene TP53 is mutated in many families with the Li-Fraumeni syndrome, but is only rarely found to be mutated in multiple cancer families that do not fulfil the restricted or extended criteria of Li-Fraumeni syndrome.³¹ While the presence of early onset breast cancer would support the possibility of mutations in this gene, the absence of paediatric cancers and the presence of multiple cases of colon cancer suggest that mutations in TP53 would not be expected in family 111. The absence of mutation in exons 2–11 of TP53 fulfils this expectation. On the basis of the haplotype and linkage results with markers adjacent to the BRCA2 and hMSH2 loci, these genes do not appear to be causally implicated in the cancers in this family. The possibility that a mutant allele of one gene (BRCA1) is segregating with the breast cancer in this family, and another gene (hMLH1) is associated with the colon cancer is supported by haplotype results (figure, and data not shown), but must remain conjectural because of the small number of typed subjects.

The possibility that breast and colorectal carcinoma in a family share underlying aetiological factors is reliably shown by the large population based study of Goldgar *et al.*¹⁷ Using the Utah population database, they showed that first degree relatives of probands with colon cancer were at an increased risk of breast cancer (early onset colon cancer: RR 1.40, 95% CI,

1.1–1.8; colon cancer at any age: RR 1.23, 95% CI, 1.1–1.4). The reverse association was also positive, first degree relatives of breast cancer probands having increased risks of colon cancer (early onset breast cancer, RR 1.72, 95% CI: 1.3–2.2; breast cancer at any age, RR 1.35; 95% CI: 1.2–1.5). Although the risks appear to be smaller than those found in our study, Goldgar *et al.*¹⁷ studied relatives of cases with single primaries, whereas we studied relatives of cases of double primaries, where genetic effects are thought to be more pronounced.

This study has shown that first degree relatives of women with double primary cancers of the breast and colon are at increased risk of breast and colon cancer. Environmental, hormonal, and genetic factors are all likely to be important. The relative contribution of genetic factors to the cancers in these families may be greater than is currently appreciated.

We thank the probands and their families for cooperation, Jean-Sebastien Brunet for statistical advice, and the two referees for their comments. The study was supported in part by the Canadian Genetic Diseases Network.

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