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Original Paper

Familial Risks in Second Primary Breast Cancer Based on a Family Cancer Database

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The nationwide Swedish Family Cancer Database was used to analyse the risk of breast cancer in daughters of mothers presenting second, bilateral breast cancer. The database contained information on family relationships and cancers of mothers and daughters when the daughter was born after 1940, totalling 55 411 maternal and 9966 daughters' primary breast cancers. Some 95% of the second breast cancers were diagnosed in the contralateral breast. Familial risk of breast cancer in daughters was 1.70 when the mothers had first breast cancer and 3.28 when the mothers had bilateral breast cancer. Thus, the increased familial effect of the second breast cancer was 1.93. The risk was highest in daughters diagnosed at a young age when the mother was diagnosed before 50 years of age. If the mothers had breast cancer following any other type of cancer, the familial effect was as for the first breast cancer (1.03). The age of onset for breast cancer in daughters was 0.7 years younger for those whose mother had bilateral as compared with unilateral breast cancer, although the difference was not statistically significant. The mothers with bilateral breast cancer whose daughters also had breast cancer were diagnosed with the first breast cancer 3.8 years younger than mothers whose daughters did not have breast cancer. The present results apply to a relatively young population of daughters (< 54 years of age). © **1999 Elsevier Science Ltd. All rights reserved.**

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INTRODUCTION

SECOND PRIMARY breast cancers are becoming more common because survival from the first primary cancer is improving. The causes of the second cancer may be the same as those of the first, including familial causes, but additionally treatment-related causes are involved. Quantification of the risk factors for second cancer are important for the follow-up of patients after the treatment for the primary cancer and for the counselling of first-degree relatives.

A family history of bilateral breast cancer has been found to be a risk factor for breast cancer in a series of hospital-based studies [1]. This relationship was subsequently examined in a number of population-based case-control studies, most, but not all, supporting the association of family history with the risk of bilateral breast cancer [2–5]. Two prospective studies have also found the association [6, 7]. In these studies familial cancer has usually been defined as cancer in any first-degree relative (mother, sister or daughter), obscuring the effect of age at onset, which is an important modifier of familial cancer risk [8]. Furthermore, all previous studies were based on interview data on the relatives and their cancers, which may introduce recall and ascertainment bias.

In the present study, we used the Swedish nationwide Family Cancer Database to investigate the degree of familial association in second female breast cancers. The advantages of this database are large numbers, unbiased retrieval of both the relatives and the cancer cases from registered sources and the possibility of defining familial cancer uniformly [9–12]. The aim was to obtain unbiased estimates for the familial component in the risk of second breast cancer. We use the terms 'second' and 'bilateral' breast cancer interchangably, even though we did not verify at an individual level that the second breast cancers were bilateral. Yet in the whole database some 95% of the second breast cancers were bilateral.

PATIENTS AND METHODS

Registers and source of subjects

The Family Cancer Database was formed from a 'Second Generation Register' maintained by Statistics Sweden, where

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children born in Sweden in or after 1941 were registered with their biological parents as families. By 1995 approximately 6 million individuals as offspring were registered together with their parents. The Swedish population was 8.8 million. Since previous studies [9–12] we have been able to include all children who died after 1960, thus making the database practically complete for studies on adult cancer.

The number of primary cancers in the first generation (parents) was 1/4 million each for males and females, distributing by site similar to cancers in the whole Swedish population. For this breast cancer study, the birth cohorts were defined as parents (first generation) born any time before 1956 and children (offspring, second generation) born from 1941 to 1975. All the 5 year birth cohorts included over 0.5 million children. The adult population of the second generation consisted of 1.98 million males and 1.87 million females, 50 400 of whom had primary cancer.

The Second Generation Register was linked to the Cancer Registry by the individual unique national registration number. The nationwide Swedish Cancer Registry includes cancer cases registered from 1958 up to 1994. Cancer registration is considered to be close to 100% currently [13]. Basal cell carcinoma of the skin is not included in the registration. A four digit diagnostic code according to the 7th revision of the International Classification of Diseases (ICD-7) was used. Cancers are also recorded according to the first or subsequent primary, and cancer *in situ*. The children entered in the present study were diagnosed for their first primary cancer from 1958 to 1994 at 15–53 years of age. Children diagnosed for their first primary before the age of 15 years were excluded from the study population. The oldest possible age at diagnosis, 53 years, in the offspring was reached by those born in 1941 if they were diagnosed after their birthday during 1994. Second breast cancers were only considered where the interval from the first cancer was 6 months or more. All the linked records were checked for identification and reasonable age at childbirth.

For mothers, the 12 5 year birth cohorts covering years from 1896 to 1955 were considered for cancers diagnosed from 1958 to 1994. Person-years were calculated by taking the mean number of living persons in each period and multiplying by the length of the period. The age-specific incidence rates were calculated by using the year and month of birth and adjusting to the world standard population by the direct method of standardisation [14]. Parity in daughters was constructed for all women in the second generation from the information on children in the database and standardised by the direct method of standardisation. Confidence intervals (CI 95%) were calculated by assuming Poisson distribution. Relative risks (RRs) were calculated based on the age- and parity-standardised rates using all breast cancer as a reference rate. The Kolmogorov–Smirnov test was used to test differences in age of onset.

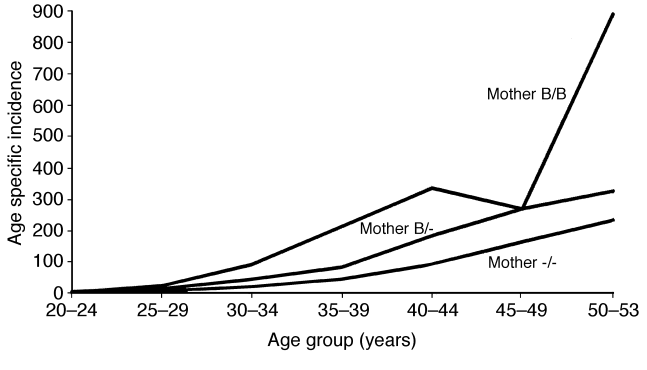

Figure 1. Age-specific incidence per 100 000 of breast cancer in daughters of mothers without breast cancer (−/−), of mothers with a first breast cancer only (B/−) and of mothers with bilateral breast cancer (B/B).

RESULTS

All the subjects were identified from the database, in which the first generation of mothers was considered as probands and the second generation as daughters (offspring). There was a total of 9966 female breast cancers in the adult second generation of the Family Cancer Database. Of these, 889 were daughters of women with primary breast cancer ($n = 55\,411$). Because the Family Cancer Database included a second generation starting from the year 1941, the occurrence of breast cancers was heavily weighted towards the oldest 5 year birth cohorts and the latest years of diagnosis. The oldest possible age at diagnosis was 53 years. The Swedish Cancer Registry had data on the laterality of breast cancer from the late 1960s. According to these data, the second breast cancer was listed in approximately 95% of the cases in the contralateral breast from the first breast cancer. However, in cases where the diagnosis of the second cancer was recorded less than 1 month after the first breast cancer, the majority was in the ipsilateral breast. We thus restricted the analysis to those diagnosed 6 months or later after the first breast cancer.

The age-specific incidence of breast cancer in daughters by breast cancer in mothers, is shown in Figure 1. The incidence in daughters whose mothers had breast cancer was clearly and consistently above the incidence in daughters whose mothers had no cancer. The highest age-specific incidence was for daughters whose mothers had bilateral breast cancer. There appeared to be an early-onset and a late-onset component in daughters of mothers with bilateral breast cancer, but this may be due to chance because the total number of subjects was only 82.

The incidence rates and RRs of breast cancer in daughters are shown in Table 1 after age and parity adjustment. Even though parity adjustment was used, it had no effect because the unadjusted data agreed within 1% for all the RRs. Using those daughters whose mothers have one primary breast cancer as referents (RR = 1.00), RRs of the daughters whose mothers had no cancer was 0.59, a significant decrease. Thus, the familial risk of breast cancer was 1.70 (0.59/1.00).

Table 1. *Age and parity adjusted incidence of breast cancer in daughters based on the mother's breast cancer*

Mother's cancer (first/second)	Daughter's cancer		
	n	Incidence (95% CI) (cases/10^5 person-years)	Relative risk
Breast/ –	715	112.9 (101.1–124.7)	1.00
Breast/breast	82	218.2 (144.3–292.1)	1.93*
Breast/other	92	149.1 (109.4–188.8)	1.32
Other/breast	36	116.7 (65.0–168.3)	1.03
Other/other	94	68.5 (50.4–86.5)	0.61*
None/ –	7530	66.2 (64.0–68.3)	0.59*
Other/ –	1411	68.8 (63.9–73.6)	0.61*

*Significant difference ($P < 0.05$). CI, confidence interval.

Similarly, any other but breast cancer in mothers as the first (other/−) or second (other/other) cancer conveyed a risk in daughters of 0.61. The second breast cancer in mothers increased the risk in the daughter to 1.93, a significant increase. The overall familial risk of bilateral breast cancer was thus 3.28 (1.93×1.70). Breast as the first and any other cancer as a second cancer conveyed a risk of 1.32 whilst the reverse order, any other as a first and breast as a second cancer caused no increased risk, RR being 1.03.

The age of onset is often younger in familial cancers and we calculated RRs for the second breast cancer depending on the age of onset of the first breast cancer. RR was 3.79 in daughters ($n = 11$) who were diagnosed before the age of 44 years as compared with 2.05 at ages of 44–53 years ($n = 10$), when their mothers were diagnosed before the age of 50 years. When the mothers were diagnosed after the age of 49 years the respective RRs were 2.22 ($n = 18$) and 1.49 ($n = 42$). We also determined the mean and median age of onset for the daughter's breast cancer. The means were 41.6 (95% CI 41.1–42.1; median 42.5) and 40.9 years (95% CI 39.5–42.3; median 41) in daughters whose mothers had either one breast cancer or additionally a second breast cancer, respectively.

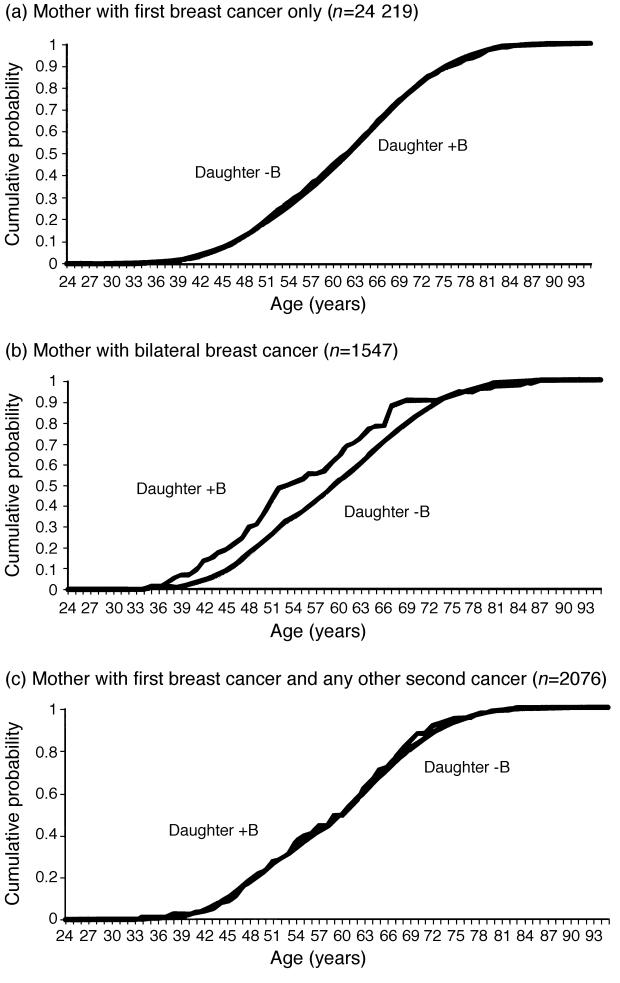

Figure 2. Cumulative probability of the first breast cancer in mothers by age of onset for daughters who had (+B) or did not have (−B) breast cancer. The mean age of onset is given. (a) Mother with first breast cancer only, (b) mother with bilateral breast cancer, (c) mother with first breast cancer and any other second cancer.

The differences were not statistically significant but the trend was consistent with familial cases being diagnosed at earlier ages.

The age of onset of the primary breast cancer was studied in mothers depending on whether the daughter had a breast cancer. When the mother had one breast cancer the mean age at diagnosis was 62 years irrespective of the daughter's breast cancer (Figure 2a). When the mother had a primary breast cancer and a non-breast second cancer the mean age was 59.2 and 59.7 years, respectively, for those whose daughter had or did not have breast cancer. The mean age was 56.0 years (95% CI 53.2–58.8) in women with bilateral breast cancer and a daughter with breast cancer, as compared with 59.8 years (95% 59.3–60.3) in those whose daughter did not have breast cancer. The difference was significant ($P < 0.05$) by the Kolmogorov-Smirnov test. We also tested for the interval between the first and second breast cancer in women whose daughter had or did not have breast cancer, but there was no difference (data not shown).

DISCUSSION

Quantification of the familial susceptibility to second cancer is important for the follow-up of patients after the treatment for the primary cancer and for counselling of first-degree relatives. Risk assessment should be based on an unambiguous definition of the familial relationship, such as mother–daughter in this study (rather than proband–first-degree relative) and an unbiased retrieval of relatives and their cancers (for a discussion see [2, 4, 15]). This may be particularly problematic with technical diagnosis such as 'bilateral' or 'second' cancer, where the terminology even in the medical profession has remained somewhat ambiguous (see [16]). Thus access to a family cancer database, where all familial relationships and cancers are fully registered and where coverage is close to 100% is a great advantage. Although we have no way of confirming that the diagnosis 'second cancers' is in fact a second primary and not a recurrence, the restriction of the analysis to those diagnosed after 6 months of the first primary should assure correct definition. These cancers were almost all in the contralateral breast.

Assuming that the risk factors of the second breast cancer are identical to those of the first breast cancer, the familial risks transmitted from the mother to the daughter should be independent of the mother's unilateral or bilateral disease, clearly contrary to the findings of familial RRs of 1.70 and 3.28 in the respective unilateral and bilateral cases. The data were age and parity adjusted, excluding the possible effect of these variables. The observed excess risks were 1.70 for the first and 1.93 for the second breast cancer. If there was any effect of treatment on the risk of the second breast cancer, independent of familial effects, the relative familial effect on the second cancer would be decreased and the familial estimate inflated. Interestingly, the mother's second breast cancer following any non-breast first cancer conveyed a familial breast cancer risk of 1.03. Thus, the non-breast cancer did not modify the familial effect of breast cancer.

The above estimates of familial risk, 1.70 for first breast cancer agree with previous results from recent register-based studies, but are lower than those reported in interview studies [15]. In two register studies, the familial risk of the first breast cancer in the first-degree female relatives was estimated at 1.6–1.8 times greater than in the controls [17, 18]. Our

present results are almost identical to a separate study on first breast cancer, where the familial RR was 1.8 [19].

It is difficult to compare any two studies on this subject because of different designs, definitions and study bases, but the present familial risks in bilateral breast cancer appeared lower than those observed in the American studies [1, 4] and higher than those observed in the European case–control studies [2, 5]. In two prospective studies on bilateral breast cancer, the familial risks in bilateral disease were 1.91 and 1.96 [6, 7], a remarkable agreement with the present risk of 1.93.

Age of onset is an important modifier of familial breast cancer risk, both in the first and bilateral cancer [4, 6, 8, 20]. This was evident in the present study in three separate analyses. Firstly, the RR of breast cancer in daughters of mothers with bilateral disease was maximal at young ages (< 40 years, Figure 1). The RR of second breast cancer was 3.79 in those diagnosed before the age 44 years, if their mothers were diagnosed before the age 50 years. In older daughters of older mothers, the respective RR was 1.49. Secondly, the mean age of onset in this group was 0.7 years younger than that in daughters whose mothers only had the first breast cancer (the difference was not statistically significant). Thirdly, the mothers with bilateral disease were diagnosed earlier for their first breast cancer when they had a daughter with breast cancer (56.0 years compared with 59.8 years in those whose daughters had no breast cancer).

The Swedish nationwide Family Cancer Database is the largest population-based dataset ever used for studies on familial cancer. The coverage of families and cancers is practically complete and the estimates on familial risks are free from ascertainment and recall biases, which may be particular problems in studies of bilateral cancer [16]. However, the agreement of the present results with those observed in prospective studies of bilateral breast cancer suggests that the errors are small in the prospective design, even though information on the relatives and their cancers has to be obtained by interview. The breast cancer risk of 3.28 in the daughters of mothers with bilateral breast cancer and of 1.70 in the daughters of mothers with unilateral breast cancer should be well established for the present population.

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