Family History of Breast, Ovarian and Endometrial Cancer and Risk of Breast Cancer

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Parazzini F (Istituto di Ricerche Farmacologiche 'Mario Negri', via Eritrea 62, 20157 Milan, Italy), La Vecchia C, Negri E, Franceschi S and Tozzi L. Family history of breast, ovarian and endometrial cancer and the risk of breast cancer. *International Journal of Epidemiology* 1993; 22: 614–618.
The relationship between family history of breast, ovarian and endometrial cancer and risk of breast cancer was analysed using data from a case-control study of breast cancer conducted in the greater Milan area, Northern Italy. The cases studied were 3415 women (median age 52 years, range 23–74) who had histologically confirmed breast cancer diagnosed within the year preceding the interview. The *controls* were 2916 women (median age 54 years; range 21–74) in hospital for a spectrum of acute illnesses excluding gynaecological, hormonal or neoplastic conditions. A total of 375 cases (11.0%) and 128 controls (4.4%) reported a history of breast cancer in first degree relatives. Compared with women with no family history of breast cancer, the RR was 2.7 (95% confidence interval [CI] : 2.2–3.3) in those with one first degree relative affected and 2.8 (95% CI : 1.3–5.7) in those with two or more affected relatives. In comparison with women without family history of ovarian cancer the RR of breast cancer was 1.4 (95% CI : 0.9–2.3) for those reporting one or more first degree relatives with ovarian cancer. However, the multivariate estimate for family history of ovarian cancer, including a term for familial breast cancer, decreased to 0.8 (95% CI : 0.5–1.4). The risk of breast cancer was similar in women reporting a family history of breast cancer (RR = 2.2) and in those reporting a family history of both breast and ovarian cancer (RR = 2.5), in comparison with women reporting no family history of breast and/or ovarian cancer. When the relation with family history of breast cancer was analysed in strata of women with and without family history of ovarian cancer, no difference was found in the RR estimates: the RR for family history of breast cancer was 2.8 in women with family history of ovarian cancer and 2.7 in those without history of ovarian cancer. No relation was found between history of endometrial cancer in first degree relatives and risk of breast cancer.

There is consistent evidence that a family history of breast cancer is associated with 2–3-fold increased risk of the disease.[1-4] Less well-defined is the relationship between breast cancer risk and family history of other female hormone-related cancers. An increased risk of breast cancer of about 50% was reported in women with a family history of ovarian cancer in the Cancer and Steroid Hormone (CASH) Study, a large population-based case-control study conducted in eight areas of the US,[5] but other data are scanty and not always consistent.[6-8] With regard to family history of endometrial cancer, a positive association was again observed in the CASH[5] study, which systematically examined the familial incidence and distribution of malignancies among relatives of breast cancer patients, and in another study conducted in the USA.[9]

To analyse the issue further, we considered the risk of breast cancer in women with a family history of breast, ovarian and endometrial cancer using data from a large case-control study of breast cancer conducted in Northern Italy.

SUBJECTS AND METHODS

The data were derived from an ongoing case-control study of breast cancer conducted in the greater Milan area, northern Italy, whose general design has already been described.[10,11] Trained interviewers identified and questioned women admitted to a network of hospitals for breast cancer and a wide spectrum of other conditions.

The *cases* studied were women < 75 years who had histologically confirmed breast cancer diagnosed within the year preceding the interview and had been admitted to the National Cancer Institute of Milan,

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several general and university hospitals and the Ospedale Maggiore (which includes the four largest teaching and general hospitals in Milan). A total of 3415 subjects (median age 52 years; range 23–74 years) were interviewed.

The *controls* were women residing in the same area who had been admitted for acute conditions to several specialized university clinics and to the Ospedale Maggiore of Milan for diseases other than malignant, hormonal, or gynaecological conditions. A total of 2916 controls (median age 54 years; range 21–74 years) were included. Of these, 29% were admitted for traumatic conditions (mostly fractures and sprains), 26% had non-traumatic orthopaedic disorders (mostly low back pain and disc disorders), 16% were admitted for acute surgical conditions (mostly abdominal, such as acute appendicitis or strangulated hernia), and 30% had other illnesses, e.g. ear, nose and throat or dental disorders.

A standard questionnaire was used to obtain data on personal characteristics and habits, reproductive and menstrual history and related medical and drug use history. Information was also collected on the number of sisters, and on breast, ovarian and endometrial cancer in first degree relatives (mother and sisters). The interviewers inspected clinical records whenever available for confirmation of data on family history. No information was collected on the ages of onset of tumours in relatives. Less than 3% of the eligible subjects (cases and controls) refused the interview. The present report is based on data collected before October 1991.

Data Analysis

We computed the relative risks (RR) of breast cancer according to family history of breast, ovarian and endometrial cancer, together with their 95% confidence intervals (CI). To allow simultaneously for the effect of the number of sisters and other potentially confounding factors, we used unconditional logistic regression, with maximum likelihood fitting.[12] Included in the regression equations were terms for age, years of education, age at first birth, age at menarche and at menopause, number of sisters and family history of breast, ovarian and endometrial cancer.

RESULTS

The distribution of cases and controls according to age, education, reproductive and menstrual history and number of sisters is shown in Table 1. As expected, cases tended to be more educated, to report later age at first birth and at menopause and earlier menarche than controls.

TABLE 1 *Distribution of 3415[a] breast cancer cases and 2916 controls according to selected variables. Milan, Italy 1983–1991*

	Breast cancer		Controls	
	No.	(%)	No.	(%)
Age (years)				
<35	139	(4)	245	(8)
35–44	656	(19)	492	(17)
45–54	1036	(30)	790	(27)
55–64	951	(28)	812	(28)
65–74	633	(19)	577	(20)
Education (years)				
<7	1727	(51)	1688	(58)
7–11	957	(28)	727	(25)
≥12	731	(21)	501	(17)
Parity				
Nulliparae	640	(19)	624	(21)
Parae	2775	(81)	2292	(79)
Age at first birth				
<25	1090	(39)	1123	(50)
25–29	1100	(40)	795	(35)
≥30	585	(21)	374	(16)
Age at menarche (years)				
<15	2940	(86)	2422	(83)
≥15	475	(14)	494	(17)
Age at menopause (years)				
Premenopause	1425	(42)	1087	(37)
≤45	351	(10)	413	(14)
45–49	575	(17)	569	(20)
≥50	1058	(31)	843	(29)
Number of sisters				
0	945	(28)	733	(25)
1	1091	(32)	866	(30)
≥2	1379	(40)	1317	(45)

[a] In some cases the sum of strata does not add up to the total because of missing values.

The relation between history of breast, ovarian and endometrial cancer in first degree relatives and risk of breast cancer is considered in Table 2.

Compared with women with no family history of breast cancer, the RR for the disease was 2.7 in those with one first degree relative and 2.8 in those with two relatives affected. An increased risk of breast cancer emerged in women with a family history of ovarian cancer, too: in comparison with women with no such history, the RR for breast cancer was 1.4 (95% CI : 0.9–2.3) for those reporting one or more first degree relatives with ovarian cancer. No relation was found between history of endometrial cancer in first degree relatives and risk of breast cancer. Multivariate estimates were consistent with the age-adjusted ones for breast and endometrial cancer history in first

degree relatives, but the multivariate estimate for family history of ovarian cancer, including the term for familial breast cancer, decreased to 0.8 (95% CI : 0.5–1.4). In fact, when the data were stratified for family breast cancer, a family history of ovarian cancer did not increase the risk of breast cancer either in women with a family history of breast cancer or in those without.

The risk of breast cancer was similar in women who reported a family history of breast cancer and in those who reported a family history of both breast and ovarian cancer, the RR estimates being respectively 2.7 and 2.5 in comparison with women reporting no family history of breast and/or ovarian cancer (Table 3). No association was observed for women with history of ovarian cancer only (RR = 0.9).

We analysed further the relation between family history of breast cancer and the risk of breast cancer according to age at diagnosis of breast cancer, affected relative (mother or sister) and the presence of ovarian

TABLE 2   *Distribution of 3415[a] breast cancer cases and 2916 controls, and corresponding relative risks according to history of breast, ovarian and endometrial cancer in first degree relatives. Milan Italy 1983-1991*

Family history of	Breast cancer	Controls	RR (95% CI)[b]	
			Age-adjusted	MRL[c]
Breast cancer				
No	3033	2786	1[d]	1[d]
1 relative affected	348	119	2.7 (2.2–3.3)	2.7 (2.2–3.4)
$\geq$ 2 relatives affected	27	9	2.8 (1.3–5.7)	2.8 (1.3–5.9)
Ovarian cancer				
No	3361	2885	1[d]	1[d]
Yes	50	30	1.4 (0.9–2.3)	0.8 (0.5–1.4)
Endometrial cancer				
No	3261	2808	1[d]	1[d]
Yes	147	106	1.2 1(0.9–1.5)	1.1 (0.8–1.4)

[a] In some cases, the sum of strata does not add up to the total because of missing values.
[b] RR = relative risk. CI = confidence interval.
[c] Estimates from multiple logistic regression equations including terms for age, education, age at first birth, age at menarche and menopause, number of sisters and the above listed variables.
[d] Reference category.

TABLE 3   *Distribution of 3415[a] breast cancer cases and 2916 controls according to history of breast and ovarian cancer or both in first degree relatives and corresponding relative risks. Milan, Italy 1983-1991*

	Breast cancer	Controls	RR (95% CI)[b]	
			Age-adjusted	MRL[c]
No family history of breast and/or ovarian cancer	3016	2768	1[d]	1[d]
Family history of				
breast cancer only	342	116	2.7 (2.2–3.3)	2.7 (2.2–3.4)
ovarian cancer only	17	18	0.9 (0.4–1.7)	0.8 (0.4–1.6)
breast and ovarian cancer	33	12	2.5 (1.3–4.8)	2.6 (1.3–5.0)

[a] In some cases, the sum of strata does not add up to the total because of missing values.
[b] RR = relative risk. CI = confidence interval.
[c] Estimates from multiple logistic regression equations including terms for age, education, age at first birth, age at menarche and menopause, and number of sisters.
[d] Reference category.

TABLE 4 *Relative risk (and 95% CI) of breast cancer in women with history of breast cancer in first degree relatives in strata of age at diagnosis, affected relative and family history of ovarian cancer. Milan, Italy 1983–1991*

	Stratum		Relative risk[a] (95% CI)
Age at breast cancer			
diagnosis (years)	<45	(68)[b]	2.5 (1.6–4.0)
	≥45	(307)	2.7 (2.1–3.3)
Affected relative	Mother	(219)	2.8 (2.1–3.7)
	Sister	(172)	2.1 (1.6–2.8)
Family history of			
ovarian cancer	No	(342)	2.7 (2.2–3.3)
	Yes	(33)	2.8 (1.9–4.1)

[a] Reference category 'No family history of breast cancer'. Estimates from multiple logistic regression equations including terms for education, age at first birth, age at menarche and at menopause, number of sisters and the above variables.

[b] Number of breast cancer cases are given in parenthesis.

cancer in the family (Table 4). No consistent difference was found in the RR estimates among different strata of these covariates.

DISCUSSION

The results of this study offer further evidence that a family history of breast cancer is an indicator of risk of the disease.[1–4] A family history of ovarian cancer was apparently associated with the risk of breast cancer in the unadjusted analysis, but this finding disappeared when analysis took into account a family history of breast cancer. No association emerged with a family history of endometrial cancer.

Recall bias is probably the major potential bias in case-control studies on family history of diseases. Cases with breast cancer might be more aware of their family cancer history (particularly female cancers) than controls. However, in our study only first degree relatives were considered and the relationship between breast cancer and family history of the disease was consistent among different strata of age and socioeconomic status; in particular it was confirmed in younger women and upper social classes. Furthermore, no relation emerged with another female tumour such as endometrial cancer. With regard to selection bias, cases and controls were drawn from comparable catchment areas and participation was almost complete.

Several studies have shown an increased risk of breast cancer in women with a history of the disease in their relatives,[1–4] the estimated RRs tending to be systematically higher at younger ages.[13,14]

Less clear is the relation between breast cancer risk and history of ovarian and endometrial cancer. Indirect support to the suggestion of an association between breast and ovarian cancer derives from the observation in some families of cases of ovarian and breast cancer (breast-ovarian cancer syndrome),[15,16] which, however, could not provide quantitative information on the impact of this syndrome at a population level. Further, there are epidemiological data showing an increased risk of ovarian cancer in women with a family history of breast cancer.[17,18] An increased risk of breast cancer in women with family history of ovarian cancer was reported in a recent analysis of the CASH study.[5] In that study, in women aged 45–54 years a first degree relative with ovarian cancer was associated with a twofold risk, an increase equivalent to that for a first degree relative with breast cancer. However, in the CASH analyis the potential confounding effect of a family history of breast cancer was not taken into account in evaluating the role of ovarian cancer history in relatives on the risk of breast cancer.

In this study, women with a family history of breast cancer more often reported a family history of ovarian cancer than those with no history of breast cancer, thus giving some apparent support to the suggested breast-ovarian cancer syndrome. However, the simultaneous presence of both diseases in relatives did not increase the risk of breast cancer, and hence the determinant of risk appeared to be a family history of breast cancer.

No association emerged between breast cancer risk and history of endometrial cancer in first degree relatives. This is in agreement with the findings from the CASH study.[5] Furthermore, no relation emerged in a population-based study of endometrial cancer on young women conducted in California,[19] and in other studies which have analysed the risk of endometrial cancer in women with a family history of breast tumours.[20,21]

In conclusion, in this study it appears that genetic— or familial—factors as measured by the collection of family histories, are probably not a common determinant of breast cancer risk on a population level. There was a significant association between family history of breast cancer and breast cancer risk, but this association was limited on a population level (accounting for <5% of breast cancer cases.[22]) Family history of endometrial cancer was not an important determinant of subsequent breast cancer risk, and also an apparent association with ovarian cancer was largely or totally explained by the simultaneous history of breast and ovarian cancer in the same family.

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