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Association Between Breast Cancer and Family Malignancies

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In a case-control study, the relationship between a family history of cancer of the breast, ovary, colon, uterus or prostate and the risk of breast cancer was investigated. The data consisted of family histories from 495 breast cancer cases and 785 controls aged 20–56 years. A positive association was found between the occurrence of breast cancer and a history of breast cancer in the families of the subjects affected. This relationship increased linearly with both the degree of kinship of the affected relatives and with their number. The risk of breast cancer associated with other types of cancer in the family was not significantly different from unity.
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INTRODUCTION

THE RELATIONSHIP between breast cancer and other epidemiologically linked types of cancers has mainly been studied at population level by examining the geographical variations in incidence rates, and at individual level by evaluating the individual risk of a second primary cancer [1]. To our knowledge, only two case-control studies have been performed to determine the association between a family history of cancer and the risk of breast cancer in a large population [2, 3].

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SUBJECTS AND METHODS

The data were obtained from a case-control study performed in five French public hospitals. The details of the methods used to select the cases and controls and to collect data were those described elsewhere [4] and are only summarised here. Cases had to be 20–56 years old, with a histologically defined breast cancer, confirmed within the past 7 months. All histological types were accepted. For every case, three types of controls could be selected: friends or colleagues of the case, and patients hospitalised for a malignant tumour or for a non-malignant condition. The diseases for which these controls were hospitalised had to be diagnosed within the past 12 months. The criteria for matching controls to cases were age at interview (within 5 years), years of birth (within 5 years), date of interview (within 14 months) and interviewer. Hospital controls had to be hospitalised in the same hospital as the case. 495 cases and 896 controls were interviewed. More than 99% of all the subjects agreed to be interviewed. Information was recorded on a structured questionnaire and concerned the following characteristics: basic demographic details, current and past medical history, menstrual and reproductive experience, life style factors, contracep-

Table 1a. Characteristics of breast cancer cases and controls

Number and type of relative	Cases (n = 495)	Controls (n = 785)	Homogeneity test
Sisters			
0	168 (34%)	281 (36%)	
1	143 (29%)	228 (29%)	
2	86 (17%)	140 (18%)	
3	40 (8%)	58 (7%)	NS
4	31 (6%)	36 (5%)	
5	13 (3%)	20 (2%)	
⩾ 6	11 (2%)	18 (2%)	
Unknown number	3 (1%)	6 (1%)	
Brothers			
0	158 (32%)	229 (29%)	
1	159 (32%)	271 (35%)	
2	94 (19%)	157 (20%)	
3	35 (7%)	70 (9%)	NS
4	22 (4%)	27 (4%)	
5	16 (3%)	17 (2%)	
⩾ 6	8 (2%)	10 (1%)	
Unknown number	3 (1%)	4 (1%)	
Maternal aunts			
0	146 (30%)	232 (30%)	
1	144 (29%)	217 (27%)	
2	91 (18%)	143 (18%)	
3	36 (7%)	70 (9%)	NS
4	26 (5%)	39 (5%)	
5	16 (3%)	17 (2%)	
⩾ 6	12 (3%)	20 (3%)	
Unknown number	24 (5%)	47 (6%)	
Paternal aunts			
0	153 (31%)	198 (25%)	
1	139 (28%)	210 (27%)	
2	68 (14%)	144 (18%)	
3	43 (9%)	68 (9%)	NS
4	20 (4%)	39 (5%)	
5	10 (2%)	25 (3%)	
⩾ 6	12 (2%)	22 (3%)	
Unknown number	50 (10%)	79 (10%)	

NS = Not significant.

Table 1b. Number (%) of subjects for whom the medical history of relatives was not known (including unknown family members)

Mother	10 (2%)	12 (2%)	NS
Father	27 (5%)	34 (4%)	NS
Sisters	3 (1%)	9 (1%)	NS
Brothers	6 (1%)	8 (1%)	NS
Maternal aunts	44 (9%)	67 (9%)	NS
Paternal aunts	83 (17%)	121 (15%)	NS
Maternal grandmother	114 (23%)	163 (21%)	NS
Paternal grandmother	157 (32%)	228 (29%)	NS

tive history and familial medical history. The latter concerned cancer of the breast, ovaries, uterus, colon and prostate among the mothers, fathers, sisters, brothers, aunts and grandmothers of the cases and controls. Other types of cancer were recorded as "others". Numbers of sisters, brothers and aunts was recorded. Information about male second degree relatives and age of the relatives at risk were not recorded. For the present investigation, the matching was broken, and the 111 controls hospitalised for a malignant tumour were excluded. Among the remaining 785 controls, 354 were friends or colleagues of cases and 431 were hospital controls.

Table 2. Reported history of cancer in at least one relative of cases and controls

Site	Cases (n = 495)	Controls (n = 785)	Unadjusted odds ratio*	95% CI
Breast	99	111	1.52	(1.11–2.07)
Colon	44	54	1.32	(0.85–2.04)
Uterus	37	69	0.84	(0.54–1.30)
Ovary	2	5	0.63	(0.08–3.67)
Prostate†	8	12	1.06	(0.39–2.80)
Others	145	266	0.81	(0.63–1.04)

* The reference category was composed of cases and controls who said none of their relatives was affected at the organ considered.
† First-degree relatives only.

As expected, a history of benign breast disease, a late age at first birth and an early age at menarche were found to be more common among cases than among controls [4]. These variables were included in an unconditional multivariate logistic analysis together with the matching variables and with other potential confounders, educational level, marital status and number of relatives potentially affectable. The GLIM system was used [5]. The Mantel–Haenzel method allowed evaluation of unadjusted odds ratios, and the Cornfield method to evaluate 95% confidence intervals (95% CI) [6]. The data were managed by a local system [7].

RESULTS

A familial history of cancer was classified as first degree if the cancer occurred in the mother, father or a sibship of the respondent, and as second degree if it occurred among aunts or grandmothers; otherwise, it was designated as "no familial history" (including when this history was not known). Cases and controls did not differ as regards the numbers of sisters, brothers and aunts (Table 1a). The proportions of unknown familial characteristics and of unknown family histories were similar for cases and controls (Table 1b). This remains true whatever the type of controls (friends/colleagues or hospitalised).

A positive association was found between the occurrence of breast cancer and a history of breast cancer in the families of the subjects affected (Table 2). This relationship increased linearly with both the degree of kinship of the affected relatives (Table 3) and with their number (Table 4). The effect of a family history of breast cancer on the risk of breast cancer was significantly greater (P = 0.006) for premenopausal than for postmenopausal women (Table 5).

The effect of a family history of colon cancer on the risk of breast cancer is nowhere significant (Tables 1–5) but the estimated odds ratios mimic those estimated with a family history of breast cancer.

For the other sites considered, no significant relation was found (Tables 2–5).

The risk of breast cancer in families with histories of cancer of the breast and of other sites was assessed (Table 6). An increased risk was found when breast and colon cancer were reported in a same family. Interaction calculation show however that this risk is not different from that found when only breast cancer occurred in the family.

Table 3. Reported history of cancer in relatives of cases and controls, according to degree of kinship

Site*	Pattern†	Cases (n = 495)	Controls (n = 785)	Unadjusted odds ratio‡	95% CI	P
Breast	2nd degree only	49	62	1.35	(0.89–2.03)	
	1st degree only	37	39	1.61	(1.00–2.64)	0.003
	1st and 2nd degrees	13	10	2.21	(0.90–5.50)	
Colon	2nd degree only	21	28	1.20	(0.65–2.21)	
	1st degree only	20	23	1.41	(0.74–2.70)	0.17
	1st and 2nd degrees	3	3	1.62	(0.26–10.1)	
Uterus	2nd degree only	24	39	0.97	(0.56–1.69)	
	1st degree only	13	27	0.75	(0.36–1.53)	0.24
	1st and 2nd degrees	0	3	0	(0.00–2.62)	

* Ovarian and prostatic sites of cancer were omitted because the numbers of affected relatives were too small.
† Second degree = females only.
‡ The reference category was composed of cases and controls who said none of their relatives was affected at the organ considered.

None of the present results was modified when the analysis was adjusted for matching factors and potential confounders.

DISCUSSION

The main aim of this study was to ascertain whether the occurrence in families of cancers at sites other than the breast was a risk factor for breast cancer. If this were the case, it would imply the existence of a familial factor common to breast cancer and other specific types of cancer.

In a study based on population statistics, Phipps *et al.* [8] found a higher incidence of colon cancer among the relatives of "familial" breast cancer patients (i.e. patients with at least two other breast cancer cases among their first degree relatives) than among sporadic breast cancer patients. In a recent case-control study [3], a significant increased risk of breast cancer associated with history of colorectal cancer among mothers and sisters was found. Our results though in the right direction, are not significant, possibly because of lack of power. Taken together, these findings are consistent with the existence of common aetiological factors for breast and colon cancers.

The results of several studies of the risk of breast cancer associated with a family history of prostatic cancer appear to be controversial [2, 9, 10]. The present findings do not clarify this controversial situation.

In the same study referred to above, Thiessen [2] observed that an increased risk of breast cancer was associated with a family history of uterine cancer.

In case-control studies of ovarian cancer a significant 50% increase in the risk of epithelial ovarian cancer associated with a history of breast cancer among first-degree relatives was found [3, 11]. Because of the rarity of ovarian cancer and the subsequent reduced statistical power, the search for a familial association

Table 4. Risk of breast cancer in women according to the number of affected relatives

Site*	No.	Cases (n = 495)	Controls (n = 785)	Unadjusted odds ratio†	95% CI	P
Breast	1	79	96	1.40	(1.00–1.96)	
	2	17	12	2.27	(1.09–4.82)	0.003
	≥3	3	3			
Colon	1	40	49	1.32	(0.84–2.09)	
	2	2	4	1.30	(0.26–6.06)	NS
	≥3	2	1			
Uterus	1	33	63	0.82	(0.52–1.29)	
	2	3	6	1.04	(0.22–4.42)	NS
	≥3	1	0			

Because of the paucity of affected relatives, the odds ratios estimates have been calculated with the two last classes grouped.
* Ovarian and prostatic sites of cancer were omitted because the numbers of affected relatives never exceeded 1.
† The reference category was composed of cases and controls who said none of their relatives was affected at the organ considered.

Table 5. Unadjusted odds ratios for reported history of cancer in at least one relative of cases and controls, according to the menopausal status of the respondent

Site of cancer in at least one relative	Premenopausal			Postmenopausal		
	Cases (n = 381)	Controls (n = 562)	OR* (95% CI)	Cases (n = 114)	Controls (n = 223)	OR* (95% CI)
Breast	81	79	1.65 (1.16–2.36)	18	32	1.12 (0.57–2.19)
Colon	34	35	1.48 (0.88–2.48)	10	19	1.03 (0.43–2.44)
Uterus	31	54	0.83 (0.51–1.35)	6	15	0.77 (0.26–2.20)
Prostate	5	6	1.23 (0.32–4.59)	3	6	0.98 (0.19–4.50)

* The reference category was composed of cases and controls who said none of their relatives was affected at the organ considered.

Table 6. Risk of breast cancer in a woman according to the types of cancers in her relatives

Site	Cases (n = 495)	Controls (n = 785)	Unadjusted odds ratio*	95% CI
Breast without colon	88	105	1.45	(1.05–2.00)
Colon without breast	33	48	1.10	(0.68–1.77)
Breast and colon	11	6	3.17	(1.07–9.70)
Breast without uterus	87	98	1.49	(1.08–2.07)
Uterus without breast	25	56	0.69	(0.41–1.15)
Breast and uterus	12	13	1.48	(0.63–3.47)
Breast without prostate	96	109	1.50	(1.09–2.04)
Prostate without breast	5	10	0.85	(0.25–2.72)
Breast and prostate	3	2	2.55	(0.35–21.8)

The ovarian site was omitted because there were only 2 cases with ovarian cancer in their families.
* The reference category was composed of cases and controls who said none of their relatives was affected at the organs considered in each association.

between ovarian cancer and breast cancer is surely more relevant in a case-control study of ovarian cancer rather than breast cancer.

In breast cancer aetiology, the postulated genetic effect is reported to be greater among premenopausal than postmenopausal cases [12, 13]. Our findings support this hypothesis for breast cancer in the family, but not for prostate or colon, possibly because of lack of power.

To test the recall accuracy of the family histories of cancer among the controls, we compared the number of cases of various types of cancer reported among their relatives with the number expected. However, the number of years during which these relatives were at risk was not known, and we had to build a probability distribution on the number of years at risk. As no difference appeared between the expected and observed numbers of first-degree relatives of the controls with various types of cancer, the recall accuracy of the controls seems to have been adequate.

Cases might be more aware of cancers in their family than controls. However, as shown in Table 1, the proportions of relatives whose cancer status was not known were similar among cases and controls. Furthermore, in our study, there is no reason to assume that this presumed bias might differ according to family history of breast cancer or to menopausal status. King [14] recently provided evidence against such a bias in the reporting of breast cancer among first-degree relatives. Go *et al.* [15], in a study that involved contacting relatives or reviewing records to verify reports, found no differences between the accuracy of reports from women who themselves had had breast cancer and those who had not. In our study, such accuracy could not be checked, as the hospitals in which the relatives had been treated were not recorded. The lack of information on the number of years the relatives were at risk is another source of bias if the age distributions of the relatives of cases and controls are different. Such differences might lead to increased risk of breast cancer in a woman, either because of her birth rank, or because of the late age of her father or mother. In the literature, we did not find any association between birth rank and breast cancer. As regards the age of mothers at their daughters' birth, of five studies, four suggested that daughters born to young mothers had a lower risk of breast cancer [16–20]. Here, we had no information about the age of the respondents' mothers at delivery.

It is now well established and confirmed in our study that a woman's family history of breast cancer has a major influence on her risk of developing breast cancer, due to the presence of a genetic component or to a common environmental factor. Several studies using segregation analysis have now provided evidence for an inherited component of susceptibility to breast cancer [21]. Numerous epidemiological observations imply the existence of heterogeneity in breast cancer aetiology. One source of the genetic heterogeneity of breast cancer in families was revealed by a description of families in which the disease appeared together with other specific neoplasms [2, 15, 22–25]. However the rarity of families of this type implies that noticeable effects are not seen in population-based studies. Genetic studies on large samples of pedigrees have shown that certain families were more genetically homogeneous than others [26, 27]; this applied, in particular, to a subgroup composed of families exhibiting breast cancer pathology only [28]. A relationship between the risk of breast cancer and family history of other sites of cancer would support the existence of a common familial factor (genetic or not) for these cancers. Further genetic epidemiological studies using segregation analysis might allow the definition of the mode of inheritance of this possible joint susceptibility. Linkage analysis would confirm the genetic relationship statistically detected, and help to locate the involved gene on the chromosome map.

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Carboplatin and Cyclophosphamide Salvage Therapy for Ovarian Cancer Patients Relapsing after Cisplatin Combination Chemotherapy

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30 ovarian cancer patients with a relapse after prior cisplatin combination chemotherapy were treated in a phase II study with cyclophosphamide 100 mg/m² orally on days 1–7 and carboplatin 300 mg/m² intravenously on day 8. Treatment was well tolerated. The major side-effect was thrombocytopenia. 28 patients were evaluable for response. The response was 5 CRs (18%), 4 PRs (14%) 15 SDs (53%) and 4 PDs (14%), for an overall response rate of 32%. The overall progression-free survival lasted from 2 to 23 months, median 8 months. Overall survival ranged from 2 to 35+ months, median 12 months. Patients with a therapy-free interval of more than 1 year showed a higher response rate (46%) than patients with a shorter therapy-free interval (20%). It is concluded that platinum containing second-line chemotherapy, after treatment that already contained cisplatin, is only warranted to palliate symptoms.
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INTRODUCTION

OVARIAN CANCER causes about 6% of all cancer deaths in Europe and the United States [1, 2]. The introduction of cisplatin combination chemotherapy in the treatment of advanced ovarian cancer has significantly improved the response rate, progression-free and overall survival [3–8]. However, even patients with a histologically proven complete response have a relapse rate of approximately 50% [3, 7, 9–15].

In patients with primary chemotherapy resistance salvage chemotherapy is ineffective [16]. Patients who respond to cisplatin and relapse after a therapy-free interval have a more favorable prognosis. Response rates up to 70% can be achieved with cisplatin retreatment in complete responders to first-line cisplatin combination chemotherapy once they relapse [17].

Carboplatin has almost the same activity as cisplatin in the treatment of ovarian cancer, but is significantly less neuro- and nephrotoxic [18 19]. Since the majority of the patients who relapse after cisplatin chemotherapy have a decreased renal function and some degree of neurotoxicity, salvage chemotherapy with carboplatin appears to be more attractive than that with cisplatin. We have investigated the value of salvage combination chemotherapy with carboplatin and cyclophosphamide.

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PATIENTS AND METHODS

Patient eligibility criteria included: histologically proven epithelial ovarian carcinoma, progressive and measurable disease, prior treatment with cisplatin combination chemotherapy, a therapy-free interval of at least 3 months, white blood cells (WBC) $> 3.0 \times 10^9$/l, platelets $> 75 \times 10^9$/l.

30 patients were entered in the study. Histological tumour type was endometrioid adenocarcinoma in 2 patients, serous

Table 1. Patients' characteristics at the start of carboplatin and cyclophosphamide (n = 30)

Age; median (range)	56	(42–71)
Creatinine (μmol/l); median (range)	96	(59–156)
Tumour size:		
< 2 cm		2
2–5 cm		16
> 5 cm		12
Ascites		16
Response to prior therapy		
Pathological complete response		10
Microscopic disease		1
Clinical complete response		10
Partial response		1
Progressive disease		1
Adjuvant chemotherapy		7
Prior chemotherapy; median (range)		
Total dose cisplatin (mg)	675	(350–1200)
No. of cycles	9	(3–15)
Therapy duration (mos)	12	(4–29)
Therapy-free interval (mos)	12	(3–60)