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Risk factors for metachronous contralateral breast cancer suggest two aetiological pathways

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ABSTRACT

Although many studies show an increased risk of metachronous contralateral breast cancer (CBC) in women with a positive family history and young age at diagnosis of the initial breast cancer, the aetiological pathways are still enigmatic.

In a cohort of 8478 primary breast cancer patients diagnosed between 1975 and 2006, 558 cases of metachronous CBC were identified. Using multivariate Cox proportional hazards models, we analysed risk factors assessed at the time of the first primary tumour, including patient demographics, tumour characteristics and treatment among 4681 breast cancer patients for whom data on key variables were available. The analysis was performed separately in patients who developed CBC without and with prior recurrence(s).

Risk of CBC without prior recurrent disease was increased by a positive family history [adjusted relative risk (RR) 2.8 (95% confidence interval (CI) 1.4–5.5)]; and decreased by endocrine treatment [RR 0.6 (95% CI 0.4–1.0)]. We found an increased risk of CBC with prior recurrent disease with younger age [RR 1.2 (95% CI 1.4–3.0)]; positive family history [RR 2.1 (95%CI 0.8–5.0)]; and extensive lymph node involvement [RR 2.0 (95% CI 1.2–3.6)].

Our results suggest that nodal status of the primary tumour may be as important a risk factor as family history or age, which indicates a high susceptibility to breast cancer or an impaired host defence mechanism. It may also imply that some CBCs are metastases from the first primary tumour, particularly in patients who present with recurrent disease before CBC.

1. Introduction

Because of the high incidence of breast cancer and 5-year survival rates of 80%, an estimated 550,000 women who have been diagnosed with breast cancer are alive in the UK today.[1] Based on data from the largest population-based study on contralateral breast cancer (CBC) to date, about 4% of these survivors can be expected to develop CBC.[2] For the purpose of monitoring programmes for women with breast cancer it is important to identify risk factors for developing CBC.

Young age at diagnosis of the first primary tumour has consistently been reported as a strong risk factor together with a positive family history of breast cancer. Primary lobular cancers have also been suggested as increasing risk of

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CBC,[2–5] whereas stage at diagnosis of the first primary tumour was generally not found to be associated with it.[3,5,6]

In the present study, we analysed the risk of CBC against demographic factors, tumour characteristics and treatment of the primary breast cancer in a large cohort of breast cancer patients with long-term follow-up treated at Guy's Hospital, London, UK.

2. Patients and methods

This study was carried out using prospectively collected data from 8478 women who were diagnosed with and treated for primary breast cancer at the Breast Clinic at Guy's Hospital between 1st January 1975 and 31st December 2006. We excluded 400 women who were diagnosed with stage IV primary breast cancer, five who had a prophylactic mastectomy of the contralateral breast and 20 who presented with CBC less than six months after the initial breast cancer diagnosis (Fig. 1).

Data on patient demographics, tumour characteristics and treatments were collected at the time of diagnosis of the initial breast cancer. Follow-up information was collected through record linkage of the patient identifiers with the hospital notes and information from the Breast Clinic, and included date of diagnosis of loco-regional, contralateral and distant recurrence and all treatments received (including surgical, radiotherapeutic and systemic therapy), as well as date and cause of death.

Data collection was carried out with approval of the Guy's NHS Research Ethics Committee.

2.1. Statistical analysis

CBC incidence rates and 95% confidence intervals (CI) were computed by category of age at diagnosis and 5-year period of diagnosis.

For the risk factor analysis, we excluded 3372 patients lacking information on family history of breast cancer, tumour size and/or nodal status of the primary tumour. Incidence rate ratios and their 95% CIs were derived from Cox proportional hazards models and used as the estimator of relative risk (RR). We considered a local or regional relapse or distant recurrence that occurred before CBC as a prior recurrence and analysed all risk factors separately in CBC patients without ($n = 197$) and with ($n = 118$) prior recurrence. We applied different strategies for calculating time at risk in these groups: follow-up time was recorded from the date of diagnosis of the primary tumour until the date of CBC diagnosis for women who developed CBC without a prior recurrence and, for women with unilateral breast cancer, the date of last contact, date of the first recurrence, date of death or the end of the study as defined for this analysis (31st December 2006), whichever occurred first. Follow-up time for women who developed CBC after a prior recurrence was calculated from the date of the recurrence until the date of CBC diagnosis and for women with unilateral breast cancer who developed a recurrence from the date of the first recurrence until the date of last contact, date of death or the end of the study, whichever occurred first.

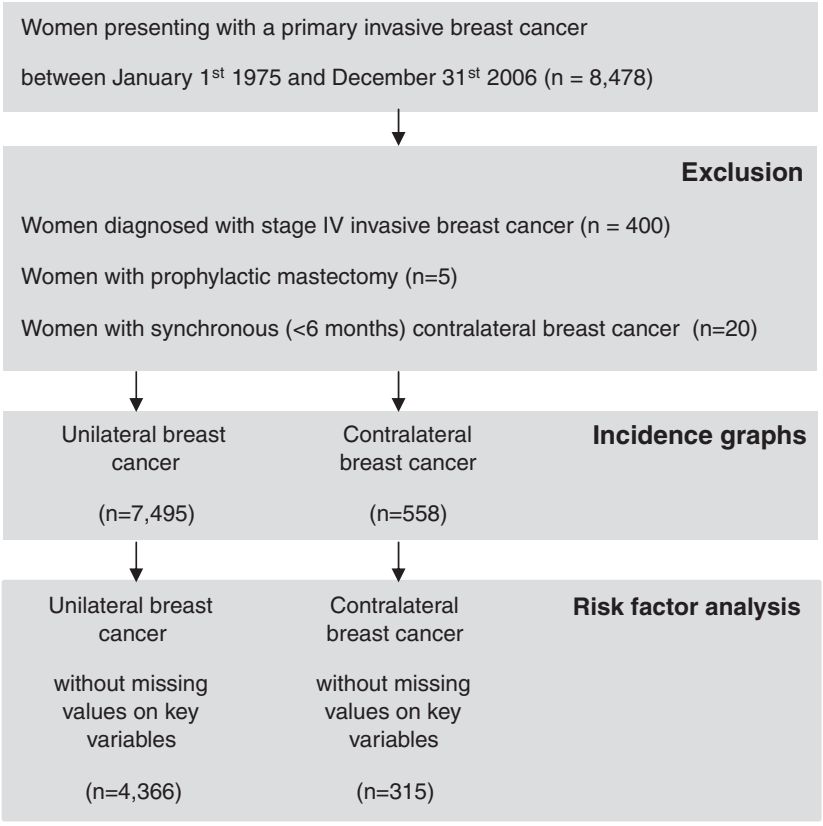

Fig. 1 – Flow chart of breast cancer patients included in the analyses.

Factors that were assessed for the risk of CBC included: patient demographics at baseline [age at diagnosis (⩽49, 50–69, ⩾70 years), period of diagnosis of the primary tumour (5-year intervals from 1975 onwards), family history of breast cancer (yes/no), number of pregnancies, hormonal status (pre- versus post-menopausal), current hormone use (yes/no)], tumour characteristics at baseline [clinical tumour size, lymph node status, tumour grade, ER, PR and Her2 receptor status] as well as treatment for the first primary tumour [surgery, radiotherapy, chemotherapy, and endocrine treatment]. All multivariate analyses were adjusted for age, tumour size, nodal status, endocrine treatment and period of the diagnosis of the primary tumour.

3. Results

Seven percent (558/8053) of women diagnosed with breast cancer developed CBC six months or more after their initial diagnosis. Median interval time between the date of diagnosis of the first primary breast cancer and CBC was 4.6 years (range 6 months to 26.8 years).

Overall incidence rate of CBC was 8.2/1000 person-years (95% CI 7.6–8.9). The incidence rate was 4.8/1000 person-years (95% CI 4.3–5.4) among women who did not develop a recurrence prior to CBC and 3.4/1000 person-years (95% CI 3.0–3.9) among women who did.

The incidence of CBC was highest among women aged ⩽49 years when diagnosed with an initial breast cancer at 10.6/1000 person-years (95% CI 9.4–11.7), decreasing to 4.5/1000 person-years (95% CI 3.2–6.2) among women aged >70 (Fig. 2, panel A). Since 1975, the incidence rate of CBC has dropped from 10.8/1000 person-years (95% CI 9.2–12.6) for patients diagnosed between 1975 and 1979 to 1.6/1000 person-years (95% CI 0.74–3.25) for patients diagnosed between 2000 and 2006 (Fig. 2, panel B).

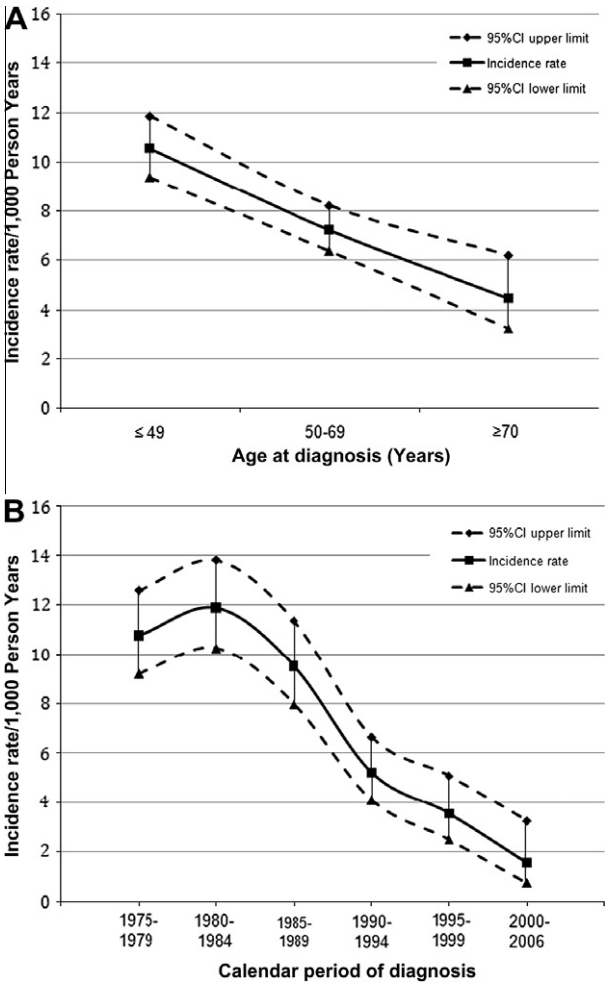

Fig. 2 – Incidence rates and 95% confidence intervals (CI) of contralateral breast cancer by age group at diagnosis (panel A), and by 5-year period of diagnosis date of the first primary breast cancer (panel B).

3.1. *Patient baseline characteristics*

Patients who developed CBC were younger when diagnosed with the initial breast cancer [median age of 50 years (range 24–84 years)] than patients who did not [median age 54 years (range 21–91 years)], and thus were more often premenopausal ($p < 0.0001$, χ^2 test). Also, they tended to present with ER-negative initial tumours ($p < 0.02$, χ^2 test) (Table 1).

3.2. *Risk factor analysis*

Relative risk of CBC without and with prior recurrence according to patient demographic factors, tumour characteristics and treatment are reported in Tables 2 and 3, respectively.

3.3. *Demographic factors*

Although the risk of developing CBC seemed to diminish with increasing age at diagnosis of the initial cancer in women who did not experience a prior recurrence, the association did not reach statistical significance [RR 1.19 (95% CI 0.88–1.59) and 0.65 (95% CI 0.35–1.21) for women aged ⩽49 years and ⩾70 years versus women aged 50–69 years, respectively], whereas young age seemed to be a particular risk factor in women who presented with recurrent disease prior to CBC [RR 2.10 (95% CI 1.44–3.06) when compared to women aged 50–69 years].

We found an increased risk of developing CBC both without and with prior recurrence among patients with a positive family history of breast cancer [RR 2.76 (95% CI 1.39–5.47) and 2.06 (95% CI 0.83–5.08) for patients with 1st and 2nd degree affected relatives versus none, without and with prior recurrence, respectively]. We found no evidence of an interaction between age at diagnosis of the primary tumour and family history of breast cancer ($p = 0.52$).

3.4. *Primary tumour characteristics*

Large tumour size was found to increase the risk of CBC without a prior recurrence but it did not affect risk after a recurrence [RR 1.89 (95% CI 1.08–3.31), and 0.69 (95% CI 0.35–1.35) for primary tumours >5 cm compared to ⩽2 cm for CBC without and with prior recurrence, respectively]. Positive lymph nodes seemed to increase risk of CBC without prior recur-

Table 1 – Baseline characteristics of unilateral and contralateral breast cancer patients included in the risk factor analyses.

	Unilateral breast cancer patients (*n* = 4366)		Contralateral breast cancer patients (*n* = 315)	
	Number	(%)	Number	(%)
Patient characteristics at primary tumour				
Age at diagnosis (yr)				
⩽49	1551	(36)	152	(49)
50–69	2285	(52)	149	(47)
⩾70	530	(12)	14	(4)
Family history of breast cancer				
None	3361	(77)	231	(74)
2nd or 3rd degree	380	(9)	25	(8)
1st degree	524	(12)	45	(14)
1st and 2nd degree	101	(2)	14	(4)
Menopausal status				
Post-menopausal	2346	(54)	120	(38)
Pre-menopausal	1914	(44)	191	(61)
Missing	106	(2)	4	(1)
Full-term pregnancy				
⩾1	3072	(70)	236	(75)
Nulliparous	835	(19)	69	(22)
Missing	459	(11)	10	(3)
Primary tumour characteristics				
Tumour size (cm)				
⩽2	1762	(41)	115	(37)
>2–5	2245	(51)	174	(55)
>5	359	(8)	26	(8)
Number of positive lymph nodes				
None	2197	(50)	154	(49)
1–3	1355	(31)	93	(30)
4–9	484	(11)	36	(11)
⩾10	330	(8)	32	(10)
Histological grade				
1	422	(10)	14	(4)
2	1112	(25)	73	(23)
3	1060	(24)	68	(22)
Missing	1772	(41)	160	(50)
Histological Type				
Ductal	2569	(59)	158	(50)
Lobular	296	(7)	17	(5)
Other/unknown	1501	(34)	140	(45)
ER status				
Positive	2289	(52)	133	(42)
Negative	781	(18)	65	(21)
Missing	1296	(30)	117	(37)
PR status				
Positive	1762	(40)	101	(32)
Negative	1253	(29)	87	(28)
Missing	1351	(31)	127	(40)
Her2 status				
Positive	428	(10)	26	(8)
Negative	1531	(35)	105	(33)
Missing	2407	(55)	184	(59)
Treatment of primary tumour				
Surgery				
Mastectomy	2557	(58)	218	(69)
Breast conservation	1779	(41)	96	(31)
None	30	(1)	1	(<1)
Radiotherapy				
Yes	2129	(49)	130	(41)
No	2237	(51)	185	(59)
Chemotherapy				
Yes	1230	(28)	64	(20)
No	3136	(72)	251	(80)

Table 1 – continued

	Unilateral breast cancer patients (n = 4366)		Contralateral breast cancer patients (n = 315)	
	Number	(%)	Number	(%)
Endocrine therapy				
Yes	1807	(41)	59	(19)
No	2559	(59)	256	(81)

rence, but the association was not significant. After a recurrence, however, a large number of positive nodes doubled the risk [RR 2.03 (95% CI 1.15–3.57) for $\geqslant$10 positive nodes compared to none].

Clinical stage at diagnosis of the initial cancer seemed to increase risk of CBC [for CBC without prior recurrence: RR 1.01 (95% CI 0.75–1.37) and 2.35 (95% CI 0.94–5.90) for stage II and III compared to stage I, respectively, and for CBC with a prior recurrence RR 1.51 (95% CI 0.99–2.31) and 2.01 (95% CI 0.68–5.98) for stage II and III compared to stage I, respectively)].

High histological grade of the primary tumour increased risk in CBC patients without a recurrence [RR 1.30 (95% CI 1.05–1.61) for grade 3 compared to grade 1] and with non-significant similar magnitude in patients who developed a recurrence before CBC [RR 1.42 (95% CI 0.87–2.32) for grade 3 compared to grade 1].

Invasive lobular histological type of the primary tumour did not confer a risk of CBC without or with prior recurrence, nor did PR and Her2 status in the sub-group of patients for whom this information was available. Having an ER-negative primary tumour increased the risk of CBC after a recurrence [RR 1.74 (95% CI 1.12–2.71)].

3.5. *Treatment*

Surgery and chemotherapy were not associated with the risk of CBC without or with a prior recurrence, while radiotherapy increased risk after a recurrence [RR 1.92 (95% CI 1.28–2.86)]. In contrast, endocrine treatment reduced the risk of developing CBC without prior recurrence by 38% [RR 0.62 (95% CI 0.39–0.98)]. In a subset of 80 patients for whom information on the ER status of the contralateral tumour was available, the incidence rate of ER-negative CBC was not different between patients who did and did not receive Tamoxifen (data not shown).

4. Discussion

We observed a clear decline in the incidence of CBC in patients diagnosed after 1980 and this is likely attributable to the introduction of Tamoxifen and other adjuvant endocrine therapy in the treatment of breast cancer. We found that patients who presented with a primary tumour at a young age, had affected relatives, presented with a large primary tumour, or a high number of positive lymph nodes were at an increased risk of developing CBC. With the exception of tumour size, the patterns of risk factors were similar in women who developed CBC without and with a prior recurrence. A protective effect of endocrine treatment was observed only in women who did not present with a recurrence prior to CBC.

Our study is based on prospectively collected data, including a long-term follow-up. Since we have complete follow-up for recurrences, we were able to stratify the analysis by CBC with and without a recurrence, as they can be expected to make up two distinct groups of CBC patients. The number of women developing CBC was limited and some data on the main risk factors were unavailable, which reduced the statistical power of this study. However, this would impact our ability to detect modest differences and is unlikely to inflate the risk estimates.

The incidence rate of CBC observed in this cohort of 8.2 per 1000 person-years is at the higher end of incidence rates reported in the 16 cohort studies,[3] where the range ran from 3.8 to 8.0. Most studies report only CBCs that are a first occurrence after the primary tumour. When we considered only those CBCs that were not preceded by a recurrence, our observed incidence rate of 4.8 is within the range of previously published figures. The reduction in incidence rate in patients diagnosed since 1980 may reflect the sharply increased use of Tamoxifen and other endocrine therapies in the treatment of breast cancer during this time. The protective effect of endocrine treatment would include cells with carcinogenic potential in the contralateral breast as well as circulating tumour cells that could give rise to metastatic disease in the contralateral breast. This is supported by our risk factor analyses, where we found no clear associations between treatment of the primary tumour and risk of CBC, except for a near 40% reduction in risk in women given endocrine treatment for their initial cancer and not experiencing a recurrence before CBC. This is in accordance with previous reports of clinical trials[7–9] and a population-based study,[10] where endocrine treatment was found to have an equally strong protective effect. In contrast to previous reports,[8,11–14] we did not observe any difference in incidence rates of ER positive or negative tumours with Tamoxifen use. This may be due to the small sample size available to us.

The point estimates for the risk conferred by age were not as strong as previously reported,[3] nor was there a clear relationship with the risk of CBC without a prior recurrence. This may be due to our choice of categories. The strongest risk of age is found in the very young,[2] so this effect may be diluted by including all patients up to 49 years of age in the youngest age category. Women who present with breast cancer at a younger age may have more aggressive tumours, which may explain why the risk is only observed in the CBC group that also experienced a recurrence. Having 1st, and especially having 1st and 2nd degree affected relatives also increased risk of

Table 2 – Relative risks (RR) and 95% confidence intervals (CI) of contralateral breast cancer (CBC) without prior recurrent disease according to age groups, degree of family history of breast cancer, parity, menstrual status, tumour size, histology, nodal status, hormone receptor status and surgical procedure, radiotherapy, chemotherapy and endocrine therapy.

	Follow-up time (person-years)	CBC patients (number)	Univariate		Multivariate*	
			RR	95% CI	RR	95% CI
Patient characteristics at primary tumour						
Age at diagnosis (yr)						
⩽49	15,795	87	1.26	0.94–1.68	1.19	0.89–1.60
50–69	21,995	99	1.00	Reference	1.00	Reference
⩾70	3649	11	0.66	0.36–1.24	0.65	0.35–1.21
Family history of breast cancer						
None	32,142	142	1.00	Reference	1.00	Reference
2nd or 3rd degree	3462	17	1.11	0.67–1.84	1.13	0.68–1.87
1st degree	4962	29	1.32	0.89–1.97	1.38	0.93–2.07
1st and 2nd degree	873	9	2.33	1.19–4.58	2.76	1.39–5.47
Menopausal status						
Post-menopausal	20,501	83	1.00	Reference	1.00	Reference
Pre-menopausal	20,134	111	1.41	1.06–1.88	1.02	0.63–1.63
Full-term pregnancy						
⩾1	30,990	148	1.00	Reference	1.00	Reference
Nulliparous	7957	42	1.10	0.78–1.55	1.11	0.79–1.57
Primary tumour characteristics						
Clinical tumour size (cm)						
⩽2	18,782	72	1.00	Reference	1.00	Reference
>2–5	20,366	110	1.42	1.05–1.91	1.51	1.12–2.04
>5	2291	15	1.78	1.02–3.10	1.89	1.08–3.31
Number of positive lymph nodes						
None	24,636	123	1.00	Reference	1.00	Reference
1–3	12,133	48	0.79	0.57–1.11	0.85	0.60–1.19
4–9	3210	16	1.03	0.61–1.74	1.12	0.66–1.91
⩾10	1460	10	1.48	0.77–2.83	1.62	0.84–3.12
Histological grade						
1	16,245	52	1.00	Reference	1.00	Reference
2	11,171	40	1.25	0.90–1.72	1.17	0.85–1.63
3	8630	46	1.32	1.07–1.64	1.30	1.05–1.61
Histological type						
Ductal	25,219	102	1.00	Reference	1.00	Reference
Lobular	2763	12	1.06	0.58–1.94	1.15	0.63–2.10
ER status						
Positive	20,661	86	1.00	Reference	1.00	Reference
Negative	6760	45	1.63	1.14–2.34	1.32	0.91–1.91
PR status						
Positive	16,377	69	1.00	Reference	1.00	Reference
Negative	11,043	62	1.35	0.95–1.90	1.23	0.87–1.73
Her2 status						
Positive	3051	16	1.00	Reference	1.00	Reference
Negative	12,546	63	0.94	0.54–1.62	1.02	0.59–1.77
Treatment of primary tumour						
Surgery						
Mastectomy	25,860	141	1.00	Reference	1.00	Reference
Breast conservation	15,474	56	0.64	0.47–0.87	0.97	0.67–1.40
Radiotherapy						
No	24,080	125	1.00	Reference	1.00	Reference
Yes	17,254	72	0.78	0.58–1.05	1.19	0.85–1.66
Chemotherapy						
No	32,991	158	1.00	Reference	1.00	Reference
Yes	8343	39	0.99	0.69–1.40	1.04	0.67–1.61
Endocrine therapy						
No	27,822	163	1.00	Reference	1.00	Reference
Yes	13,617	34	0.39	0.27–0.57	0.62	0.39–0.98

* Multivariate models are adjusted for age at diagnosis of first primary breast cancer (continuous), period of diagnosis of the first primary breast cancer (5-year categories), family history of breast cancer (yes/no), tumour size (continuous), lymph node status (yes/no) and endocrine treatment (yes/no).

Table 3 – Relative risks (RR) and 95% confidence intervals (CI) of contralateral breast cancer (CBC) with prior recurrent disease according to age groups, degree of family history of breast cancer, parity, menstrual status, tumour size, histology, nodal status, hormone receptor status and surgical procedure, radiotherapy, chemotherapy and endocrine therapy.

	Follow-up time (person-years)	CBC patients (number)	Univariate		Multivariate*	
			RR	95% CI	RR	95% CI
Patient characteristics at primary tumour						
Age at diagnosis (yr)						
⩽49	1901	65	1.70	1.18–2.46	2.04	1.40–2.97
50–69	2439	50	1.00	Reference	1.00	Reference
⩾70	287	3	0.47	0.15–1.51	0.53	0.16–1.68
Family history of breast cancer						
None	3609	89	1.00	Reference	1.00	Reference
2nd or 3rd degree	383	8	0.82	0.40–1.69	0.83	0.40–1.71
1st degree	533	16	1.26	0.74–2.14	1.23	0.72–2.11
1st and 2nd degree	102	5	2.09	0.85–5.15	2.06	0.83–5.08
Menopausal status						
Post-menopausal	1974	37	1.00	Reference	1.00	Reference
Pre-menopausal	2596	80	1.77	1.20–2.61	1.10	0.61–1.97
Full-term pregnancy						
⩾1	3630	88	1.00	Reference	1.00	Reference
Nulliparous	855	27	1.24	0.81–1.91	1.23	0.80–1.90
Primary tumour characteristics						
Clinical tumour size (cm)						
⩽2	1423	43	1.00	Reference	1.00	Reference
>2–5	2706	64	0.74	0.50–1.08	0.79	0.53–1.17
>5	499	11	0.68	0.35–1.33	0.69	0.35–1.35
Number of positive lymph nodes						
None	1839	31	1.00	Reference	1.00	Reference
1–3	1634	45	1.51	0.96–2.39	1.42	0.89–2.27
4–9	617	20	1.59	0.90–2.80	1.66	0.93–2.96
⩾10	537	22	1.94	1.12–3.37	2.03	1.15–3.57
Histological grade						
1	1707	35	1.00	Reference	1.00	Reference
2	1429	33	1.69	0.83–3.44	1.66	0.81–3.40
3	840	22	1.41	0.87–2.29	1.42	0.87–2.32
Histological type						
Ductal	2518	56	1.00	Reference	1.00	Reference
Lobular	363	5	0.60	0.24–1.50	0.69	0.28–1.75
ER status						
Positive	2115	39	1.00	Reference	1.00	Reference
Negative	650	18	1.43	0.82–2.51	1.42	0.80–2.52
PR status						
Positive	1635	32	1.00	Reference	1.00	Reference
Negative	1131	25	1.08	0.64–1.83	1.18	0.69–2.00
Her2 status						
Positive	422	10	1.00	Reference	1.00	Reference
Negative	1620	42	1.13	0.57–2.26	1.01	0.50–2.02
Treatment of primary tumour						
Surgery						
Mastectomy	2928	77	1.00	Reference	1.00	Reference
Breast conservation	1651	40	0.95	0.65–1.40	1.45	0.92–2.29
Radiotherapy						
No	1050	25	1.00	Reference	1.00	Reference
Yes	3529	92	1.30	0.91–1.87	1.92	1.28–2.86
Chemotherapy						
No	1056	25	1.00	Reference	1.00	Reference
Yes	3603	93	0.81	0.52–1.27	0.74	0.46–1.20
Endocrine therapy						
No	1068	25	1.00	Reference	1.00	Reference
Yes	3560	93	0.77	0.49–1.20	1.67	0.96–2.89

* Multivariate models are adjusted for age at diagnosis of first primary breast cancer (continuous), period of diagnosis of the first primary breast cancer (5-year categories), family history of breast cancer (yes/no), tumour size (continuous), lymph node status (yes/no) and endocrine treatment (yes/no).

CBC, regardless of prior recurrence. The majority of studies found that younger age increases the risk of CBC as did having affected family members,[3] and this can be explained by a higher susceptibility to breast cancer that may give rise to cancer developing in both breasts. Although it has been suggested that both age and family history interact,[15] we did not find such an effect here.

We did not observe any an association between invasive lobular histology of the primary cancer and increased CBC risk. Lobular type has been reported as a risk factor for CBC,[2,4,16–18] but associations have also been found to be borderline[19,20] or limited to patients who were young when diagnosed with a primary cancer[21] and to patients with synchronous CBC.[22]

Studies that analyse risk factors for CBC usually adjust for stage, while the risk of stage itself is generally not reported. A few studies that assessed stage of the initial breast cancer did not find an association with CBC.[5,6,17,20] In addition to the decreased incidence of CBC coinciding with the increased use of Tamoxifen and other endocrine therapies after 1980, over the same time period, the proportion of stage III cancers dropped compared to stage I and II cancers ($p < 0.0001$, χ^2 test). Although we did not find a clearly increased risk of CBC with composite stage, we did find associations with large tumour size, a high number of positive lymph nodes and high grade morphology, which all point towards higher disease load and/or more aggressive tumours. Our results, therefore, imply that a proportion of contralateral tumours could be metastatic recurrences. A few studies assessing the clonal relationship between primary and contralateral tumours based on molecular markers found that some tumours share a genetic profile,[23–25] also inferring that CBC may represent metastatic disease. Moreover, there is evidence that in a small proportion of patients who had received treatment, drainage to the contralateral axilla occurred,[26] which supports the possibility of an anatomical route for cancer cells.

5. Conclusion

Our results suggest that lymph node positivity is as important a risk factor for CBC as family history or age in patients who develop recurrent disease first, implying that some CBCs may be metastases from the primary tumour. Although the majority of contralateral tumours are assumed to be new primaries, this could lead to patients in whom it is a sign of metastatic disease receiving inadequate staging investigations and treatment that would be inappropriate in an advanced disease rather than early breast cancer context.

Conflict of interest statement

None declared.

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