The Breast 20 (2011) 158–164

Contents lists available at ScienceDirect

The Breast

journal homepage: www.elsevier.com/brst

Original article

Clinical characteristics and outcomes of bilateral breast cancer in an Australian cohort

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ARTICLE INFO

Article history:
Received 21 May 2010
Received in revised form
15 September 2010
Accepted 8 October 2010

Keywords:
Breast neoplasm
Bilateral
Epidemiology
Survival

ABSTRACT

Purpose: Uncertainty remains about the impact of bilateral breast cancer. Characteristics and outcomes of unilateral and bilateral breast cancer were compared within an Australian multi-institutional cohort.
Methods: Demographic, tumour and treatment characteristics were compared among unilateral ($n = 2336$) and bilateral cases (52 synchronous, 35 metachronous) using descriptive analyses. Disease-specific outcomes were investigated using Cox regression modelling to adjust for prognostic and treatment factors.
Results: Factors associated with increased risk of bilateral breast cancer included lobular histology ($p = 0.046$), family history ($p = 0.025$) and metropolitan residence ($p = 0.006$). Mastectomy was more common for bilateral cases ($p = 0.001$) while radiotherapy was less common ($p = 0.015$). Index metachronous cases were less likely to receive hormonal therapy ($p = 0.001$). Five-year survivals for metachronous, synchronous and unilateral cases were 79%, 88% and 94%, respectively. Poorer outcomes remained after adjusting for prognostic factors [HR = 2.26, 1.21–4.21].
Conclusion: Our results confirm international findings indicating worse outcomes from bilateral compared with unilateral breast cancer.

Introduction

Despite ongoing investigation, the epidemiology of bilateral breast cancer (BBC) remains controversial.[1] Questions remain about whether BBC represents increased susceptibility to breast cancer or simply a second occurrence of breast cancer. Factors identified as being associated with an increased risk of BBC include younger age at first diagnosis, a history of lobular carcinoma of the breast and family history of breast cancer.[2–4] Rather than reflecting increased breast cancer susceptibility, these associations could be explained through increased time to develop a second cancer (younger age), or increased surveillance (personal risk profiles or cancer type).[5]

The extent to which BBC impacts on survival is also unclear. Many studies that have found no difference in survival for women with BBC did not account for other prognostic factors (e.g. tumour stage, tumour grade, and age at diagnosis).[6–10] Recent studies that have adjusted for prognostic factors have produced varied results, showing either no statistically significant increased risk[11–14] or a moderately increased risk of death.[5,15–18] Since decisions about appropriate management of BBC will be influenced by perceptions of susceptibility and likely outcomes, understanding the clinical significance of BBC is important.

In this study we have examined the clinical characteristics, management patterns and survival outcomes, for unilateral, synchronous and metachronous BBC cases, within a cohort of Australian women with operable invasive breast cancer.

Materials and methods

Data were collected over a ten-year period on the demographics, tumour characteristics, treatments and outcomes of early breast cancer among patients treated in the Australian Capital Territory (ACT) or South Eastern New South Wales (SE NSW) through an ongoing prospective audit which began in 1997.[19] This audit was approved by the ACT Human Research Ethics Committee.

Enrolment was by patient consent and all persons treated for breast cancer in the region were eligible to participate. Based on estimates from the ACT cancer registry, participation was about

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doi:10.1016/j.breast.2010.10.004

90% for ACT patients, but data on participation for SE NSW residents were unavailable. Variables collected in the audit include patient demographics, tumour histology, tumour size, tumour grade, lymphovascular invasion, axillary nodal status, tumour hormone receptor status, familial cancer risk based on family history,[20] surgical procedures, the use of radiotherapy and systemic adjuvant therapies. Vital status was assessed through regular follow-up by clinicians, General Practitioners and death notifications. Diagnoses of second primary breast cancers were recorded as separate events. This study only included women with an initial diagnosis of invasive breast cancer. Males, women with in situ (index) cancers and women with a second primary in the same breast were excluded.

Bilaterality was classified according to the Royal Australasian College of Surgeons definition,[21] with cases diagnosed within 90 days of diagnosis of the first breast cancer classified as synchronous and cases diagnosed more than 90 days apart classified as metachronous. For synchronous BBC with identical diagnosis dates, the larger invasive tumour was assigned as the index tumour for analysis. If tumour sizes were similar, the higher grade tumour was

Table 1
Comparisons of demographic, tumour and treatment factors (of index tumours) for bilateral versus unilateral breast cancers, synchronous versus metachronous cases, and in situ versus invasive second cancers.

Patient and tumour characteristics	Unilateral ($n = 2336$)	Bilateral ($n = 89$)	p-value	Synchronous ($n = 52$)	Metachronous ($n = 37$)	p-value	In situ ($n = 26$)	Invasive ($n = 63$)	p-value
Age group									
Mean (years)	57.6	57.2	0.378	57.9	56.3	0.279	54.0	58.6	0.129
Residence									
Metropolitan (ACT)	1505 (64.4)	70 (78.7)	0.006	43 (82.7)	27 (73.0)	0.270	24 (92.3)	46 (73.0)	0.043
Rural (SE NSW)	831 (35.6)	19 (21.4)		9 (17.3)	10 (27.0)		2 (7.7)	17 (27.0)	
Family history									
Average risk	1880 (81.2)	64 (71.9)	0.025	36 (69.2)	28 (75.7)	0.541	19 (73.1)	45 (71.4)	0.482
Increased risk	236 (10.2)	12 (13.5)		8 (15.4)	4 (10.8)		2 (7.7)	10 (15.9)	
High risk	200 (8.6)	13 (14.6)		8 (15.4)	5 (13.5)		5 (19.2)	8 (12.7)	
Detection									
Breast screen	720 (30.8)	24 (27.0)	0.736	12 (23.1)	12 (32.4)	0.515	7 (26.9)	17 (27.0)	0.075
GP/specialist/other	437 (18.7)	18 (20.2)		10 (19.2)	8 (21.6)		9 (34.6)	9 (14.6)	
Patient	1179 (50.5)	47 (52.8)		30 (57.7)	17 (46.0)		10 (38.5)	37 (58.7)	
Tumour type									
Ductal	1873 (80.2)	64 (71.9)	0.046	35 (67.3)	29 (78.4)	0.394	17 (65.4)	47 (74.6)	0.533
Lobular	232 (9.9)	16 (18.0)		10 (19.2)	6 (16.2)		5 (23.1)	11 (17.5)	
Other	231 (9.9)	9 (10.1)		7 (13.5)	2 (5.4)		4 (15.4)	5 (7.9)	
Tumour size									
≥10 mm	492 (21.1)	11 (12.5)	0.013	4 (7.8)	7 (18.9)	0.131	6 (23.1)	5 (8.1)	0.010
11–20 mm	952 (40.8)	34 (38.6)		19 (37.3)	15 (40.5)		13 (50.0)	21 (33.9)	
21–50 mm[a]	768 (32.9)	35 (39.8)		23 (45.1)	12 (32.4)		7 (26.9)	36 (58.1)	
>50 mm	122 (5.2)	8 (9.1)		5 (9.8)	3 (8.1)		–	–	
Tumour grade									
1	669 (29.2)	18 (20.5)	0.142	8 (15.7)	10 (27.0)	0.337	6 (24.0)	12 (19.1)	0.594
2	903 (39.4)	39 (44.3)		24 (47.1)	15 (40.5)		11 (44.0)	28 (44.4)	
3	721 (31.4)	31 (35.2)		19 (37.3)	12 (32.4)		8 (32.0)	23 (36.5)	
Nodal status									
Negative	1343 (61.2)	49 (58.3)	0.592	29 (58.0)	20 (58.8)	0.940	15 (60.0)	34 (57.6)	0.840
Positive	850 (38.8)	35 (41.7)		21 (42.0)	14 (41.2)		10 (40.0)	25 (42.4)	
ER									
Negative	424 (18.3)	22 (25.0)	0.110	12 (23.1)	10 (27.8)	0.617	5 (19.2)	17 (27.4)	0.418
Positive	1896 (81.7)	66 (75.0)		40 (76.9)	26 (72.2)		21 (80.8)	45 (72.6)	
PgR									
Negative	698 (30.1)	30 (34.1)	0.427	14 (26.9)	16 (44.4)	0.088	8 (30.8)	22 (35.5)	0.670
Positive	1619 (69.9)	58 (65.9)		38 (73.1)	20 (55.6)		18 (69.2)	40 (63.5)	
LVI									
No	1687 (74.4)	62 (77.5)	0.534	32 (71.1)	30 (85.7)	0.121	19 (82.6)	43 (75.4)	0.487
Yes	580 (25.6)	18 (22.5)		13 (28.9)	5 (14.3)		4 (17.4)	14 (24.6)	
Mastectomy									
No	1140 (48.8)	27 (30.3)	0.001	11 (21.2)	16 (43.2)	0.025	9 (34.6)	18 (28.6)	0.573
Yes	1196 (51.2)	62 (69.7)		41 (78.8)	21 (56.8)		17 (65.4)	4 (71.4)	
Surgical margins									
<5 mm	640 (27.4)	24 (27.0)	0.929	15 (28.9)	9 (24.3)	0.636	8 (30.8)	16 (25.4)	0.604
≥5 mm	1696 (72.6)	65 (73.0)		37 (71.1)	28 (75.7)		18 (69.2)	47 (74.6)	
Axillary clearance[b]									
No	749 (32.1)	17 (19.1)	0.010	10 (19.2)	7 (18.9)	0.971	8 (30.8)	9 (14.3)	0.072
Yes	1587 (67.9)	72 (80.9)		42 (80.8)	30 (81.1)		18 (69.2)	54 (85.7)	
Radiotherapy									
No	859 (36.8)	44 (49.4)	0.015	27 (51.9)	17 (45.9)	0.578	9 (34.6)	35 (55.6)	0.072
Yes	1477 (63.2)	45 (50.6)		25 (48.1)	20 (54.1)		17 (65.4)	28 (44.4)	
Chemotherapy									
No	1211 (51.8)	39 (43.8)	0.137	20 (38.5)	19 (51.4)	0.227	12 (46.2)	27 (42.9)	0.776
Yes	1125 (48.2)	50 (56.2)		32 (61.5)	18 (48.7)		14 (53.8)	36 (57.1)	
Endocrine therapy									
No	568 (24.3)	24 (27.0)	0.568	7 (13.5)	17 (45.9)	0.001	10 (38.5)	14 (22.2)	0.116
Yes	1768 (75.7)	65 (73.0)		45 (86.5)	20 (54.1)		16 (61.5)	49 (77.8)	

p-values <0.05 are considered statistically significant; GP – General Practitioner; PgR –progesterone; ER – oestrogen; LVI – lymphovascular invasion.
[a] In situ vs invasive tumour size category >20 mm.
[b] Axillary clearance is with or without sentinel node biopsy.

taken to be the index tumour. Sensitivity analyses using randomly selected index cases, where diagnosis dates were equivalent, produced very similar results to those using the largest tumour as index, with one exception which is reported in the text.

Comparisons of demographic and tumour characteristics were made between unilateral and index bilateral cases using Pearson's Chi-squared tests for differences in proportions for categorical variables, Mann–Whitney *U* tests for ordinal variables and *t*-tests for differences in means for continuous variables. Similar analyses were undertaken comparing characteristics of index synchronous and metachronous cancers and in situ and invasive second cancers.

The average annual incidence of BBC was determined using the actuarial life tables method, with person-time calculated from the date of diagnosis of the first cancer to the date of diagnosis of the second cancer, date of death or June 30, 2009, which ever arose first.

Disease-specific survivals were determined using Kaplan–Meier product-limit estimates, with Log-rank tests used to estimate differences in survivor fractions according to laterality. Cox proportional hazards regression analysis was undertaken to estimate the risk of breast cancer among women with bilateral cancers, adjusting for all prognostic and treatment factors that were found to be independent predictors of risk through backwards stepwise modelling. Survival was measured from the date of diagnosis of breast cancer, in months, up until the date of death or date of censoring, June 30, 2009, if patients were still alive. For bilateral cases, survival was measured from the date of diagnosis of the second breast cancer, with adjustments being made for prognostic indicators pertaining to the second tumour. In synchronous cases where diagnosis dates were identical, adjustments were made for factors relating to the index tumour (tumour with worst prognosis). Only cases with complete data were included in these analyse. [Note: Data were missing for nodal status and/or lymphovascular invasion 154 cases. If these cases were included by creating a 'missing' category for each of these variables, risk estimates for bilateral breast cancer were slightly higher than when cases were excluded.] Adjusted hazard ratios are reported for all bilateral cancers combined, and separately for synchronous and metachronous BBC, and for in situ and invasive BBC, compared with unilateral cases. These were derived from separate models. Data were analysed using STATA version10 software.[22]

Results

Cohort characteristics

Of the 2425 women who had surgery for invasive breast cancer over the 10-year period, 52 presented with synchronous BBC and 37 developed metachronous bilateral breast cancers during the follow-up period. This represents 2.1% and 1.5% of the patient cohort, respectively. A large proportion of the second cancers were ductal carcinoma in situ (DCIS); 17 synchronous cases (33%) and 9 metachronous cases (24%). The mean interval between the first and the second cancer was eight days for synchronous cases (35 cases [67%] were diagnosed simultaneously) and 1046 days (2 years and 10 months) for metachronous cases. Overall, 80% of second cancers (71 cases) were diagnosed within three years of the index case. The average annual incidence of BBC (including synchronous cases) was 0.61% (95%CI 0.49–0.74%), while the annual incidence of metachronous BBC was 0.25% (95% CI 0.18–0.35%), or 0.19% (95% CI 0.13–0.28%) when considering invasive second cancers only.

The follow-up period (from date of diagnosis of the index cancer) was greater for women who developed metachronous BBC (mean = 83 months) than for unilateral (74 months) or synchronous cases (69 months) as would be expected since metachronous cancers are more likely to be observed among women who have longer follow-up. However the follow-up period from the date of the second cancer for metachronous cases was considerably shorter than for unilateral cases (mean = 49 months).

A total of 7% of women diagnosed with unilateral breast cancer died from their cancer (167 cases), whereas 15% of those with synchronous BBC and 21% of those with metachronous BBC died from breast cancer during the observed period (8 cases each).

Comparisons between women with unilateral and bilateral breast cancer

Women from the metropolitan area (ACT) were more likely to be diagnosed with BBC than women from rural areas (SE NSW) ($p = 0.006$). However, there were no statistically significant differences in whether the cancers were symptomatic at diagnosis or in the mode of cancer detection. Women with BBC were more likely to have a moderate or high breast cancer risk based on family history compared with women with unilateral cancers ($p = 0.025$). Age at first diagnosis was not significantly different between women with unilateral and bilateral breast cancer (Table 1).

Lobular histology was more common among women who developed BBC than those with unilateral cancers ($p = 0.046$) while index bilateral cancers were larger in diameter than unilateral cancers ($p = 0.013$).

If index cases were chosen at random for synchronous cancers where diagnosis dates were identical, rather than choosing the larger tumour as the index, no association was found in relation to diameter (results not shown). No statistically significant associations were found with other clinical factors.

Differences were noted in the management of bilateral cancers. Mastectomy was more common in women with BBC ($p = 0.001$), whereas radiotherapy was less common ($p = 0.015$). Women with BBC were also more likely to have complete clearance of axillary nodes ($p = 0.010$). There were no significant differences with respect to the use of systemic adjuvant chemotherapy, adjuvant endocrine therapy, or surgical margins.

Comparisons of synchronous and metachronous cancers (based on the characteristics of first tumour)

No statistically significant differences in demographic or clinical characteristics were observed between the index tumours for synchronous and metachronous cases. However, the small number of cases in each group limited the power to detect significant differences. Non-significant differences suggest that the first tumour in synchronous cases was more likely to be symptomatic and self-detected rather than screen detected compared with metachronous index cancers. Index synchronous cancers tended to be larger, higher grade and progesterone positive compared with index metachronous cancers. However, these differences may simply reflect random variation.

Significant differences were seen in the treatment provided for index synchronous and metachronous cancers, with mastectomy ($p = 0.025$) and adjuvant endocrine therapy ($p = 0.001$) being more likely for synchronous cases.

Comparisons of in situ and invasive bilateral cancer cases (based on the characteristics of first tumour)

Factors which differed significantly between women who developed in situ versus invasive BBC include place of residence and size of the index tumour. In situ second cancers were likely among metropolitan residents ($p = 0.043$). The index tumour was

Table 2
Disease-specific survival and risk of breast cancer death derived from Cox proportional hazards regression, with survival time calculated from date of second cancer for bilateral breast cancers.

Prognostic factors		Breast ca. deaths	5 year survival (95%CI)	Crude HR (95%CI)	Adjusted HR[a] (95%CI)
Total		183	93.4 (92.3–94.4)	–	–
Age group	<50 years	54	94.1 (92.6–95.3)	1.15 (0.82–1.61)	0.68 (0.48–0.96)
	50–69 years	95	93.7 (91.4–95.4)	1.00	1.00
	70 + years	34	90.7 (87.0–93.4)	1.39 (0.94–2.05)	1.62 (1.06–2.48)
Tumour size	≤10 mm	11	97.7 (95.8–98.8)	1.00	1.00
	11–20 mm	45	95.6 (93.9–96.8)	1.71 (0.92–3.18)	1.15 (0.59–2.23)
	>20 mm	127	88.8 (86.5–90.8)	5.85 (3.31–10.3)	1.94 (1.03–3.67)
Tumour grade	1	16	98.5 (97.2–99.8)	1.00	1.00
	2	56	95.1 (93.3–96.4)	3.01 (1.71–5.32)	1.78 (0.96–3.31)
	3	111	86.2 (83.3–88.7)	8.24 (4.81–14.1)	3.09 (1.67–5.74)
Nodal status	Negative	49	96.9 (95.7–97.7)	1.00	1.00
	Positive	128	87.7 (85.1–89.9)	4.54 (3.26–6.31)	2.68 (1.80–3.99)
LVI	Negative	78	96.2 (95.1–97.0)	1.00	1.00
	Positive	105	85.9 (82.7–94.1)	4.24 (3.14–5.73)	1.82 (1.27–2.61)
Mastectomy	No	51	96.5 (95.1–97.5)	1.00	1.00
	Yes	132	90.7 (88.8–92.3)	2.59 (1.87–3.59)	1.51 (1.04–2.20)
Endocrine therapy	No	77	87.7 (84.7–90.3)	1.00	1.00
	Yes	106	95.3 (94.1–96.3)	0.41 (0.31–0.55)	0.44 (0.31–0.62)
Laterality	Unilateral	167	93.7 (92.6–94.8)	1.00	1.00
	Bilateral:	16	84.2 (74.3–90.5)	3.04 (1.82–5.08)	2.26 (1.21–4.21)
	Synchronous	8	87.7 (74.6–94.3)	2.31 (1.14–4.69)	1.60 (0.64–3.86)
	Metachronous	8	79.3 (60.7–89.5)	4.47 (2.19–9.11)	3.56 (1.54–8.17)
	Invasive 2nd ca.	13	82.9 (70.4–90.5)	3.45 (1.97–6.08)	2.74 (1.43–5.28)
	In situ 2nd ca.	3	87.6 (66.2–95.8)	2.00 (0.64–6.27)	0.82 (0.11–5.94)

Analysis includes only cases with complete data ($n = 2171$), no co-linearity observed.
LVI – lymphovascular invasion.
[a] HR – Hazard ratios from Cox proportional hazards modelling adjusting for independent predictors of death from breast cancer.

also more likely to be smaller in diameter among those with in situ compared with invasive second cancers ($p = 0.015$). No other statistically significant differences were found.

Survival outcomes

Table 2 shows the survival fractions by demographic, clinical and treatment factors five years after diagnosis. The five-year survival for the whole cohort was 93.6% while the 10-year survival was 89.0%.

Univariate analyses of survival indicated significant differences in survival in relation to tumour size ($p < 0.001$), tumour grade ($p < 0.001$), oestrogen and progesterone receptor status ($p < 0.001$), nodal status ($p < 0.001$), lymphovascular invasion ($p < 0.001$) and histological type ($p = 0.005$). However, differences in age at diagnosis were not statistically significant. Similarly, there were no statistically significant differences in survival according to place of residence or family history of breast cancer. Having a mastectomy (as opposed to a local excision) and receiving systemic adjuvant chemotherapy were both associated with poorer outcomes ($p < 0.001$ for both), while receiving adjuvant endocrine therapy was associated with improved survival ($p < 0.001$).

Women with BBC had significantly worse survival from diagnosis of their second cancer compared with women with unilateral breast cancer ($p < 0.001$). The proportions surviving at 5 years were 79.3%, 87.7% and 93.7% for metachronous, synchronous and unilateral cases, respectively. The Kaplan–Meier survival curves for the different groups are shown in Fig. 1.

Results of multivariate modelling indicated an increased risk of death from breast cancer in women with BBC, after adjusting for differences in prognostic indicators and treatments provided (Hazard Ratio [HR] bilateral = 2.26, 95% CI 1.21–4.21). When bilateral cases were categorised as synchronous or metachronous within the multivariate model, both categories were found to have elevated HRs compared with unilateral cases (HR synchronous = 1.60, 95% CI 0.64–3.86 and HR metachronous = 3.56, 95% CI 1.54–8.17) although the difference was only statistically significant for metachronous BBC (Table 2).

When bilateral cancers were categorised as either in situ and invasive second cancers, only women with invasive second cancer had a statistically significant elevated risk of death from breast cancer (HR invasive = 2.74; 95% CI 1.43–5.28). Women who had in situ second cancers had no increased risk compared with women with unilateral breast cancer (HR in situ = 0.82; 95% CI 0.11–5.94).

Discussion

Previous estimates of the annual incidence of metachronous BBC range from 0.1% to 1.0%[3,4,23] with the majority in the region of 0.5–0.6%. Estimates of the proportion of synchronous breast cancer range from 0.3% to 3%,[2,5] with some variation being explained by differing definitions of synchronicity. Just over 2.1% of our cohort was diagnosed with synchronous BBC, which is consistent with recently reported findings from Sweden.[23] On the other hand, the average annual incidence of metachronous bilateral breast cancer in our study population was 0.25%, which is at the lower end of the range. Hartman et al.[24] reported a 30% decrease in the incidence of metachronous BBC over the last 30 years, along with a 40% increase in the incidence of synchronous BBC. These authors attribute this to increased use of bilateral mammography as a routine part of diagnostic work up. Given that our study populations is a relatively recent cohort who have been exposed to population-based mammography and would have had quite intensive diagnostic work up, the high proportion of synchronous cases and relatively low metachronous incidence rate would be expected.

We found that the risk of BBC was greater for women with lobular histology, those with moderate or strong family history, and for metropolitan residents. While our findings relating to histological type and personal risk profile are consistent with other studies,[23,25–28] they do not exclude the possibility that these associations are due to enhanced surveillance, rather than increased susceptibility. Women considered at greater risk of developing breast cancer because of family history are likely to undergo more intensive surveillance, which in turn increases the likelihood of a diagnosis of BBC. Recent population-based studies

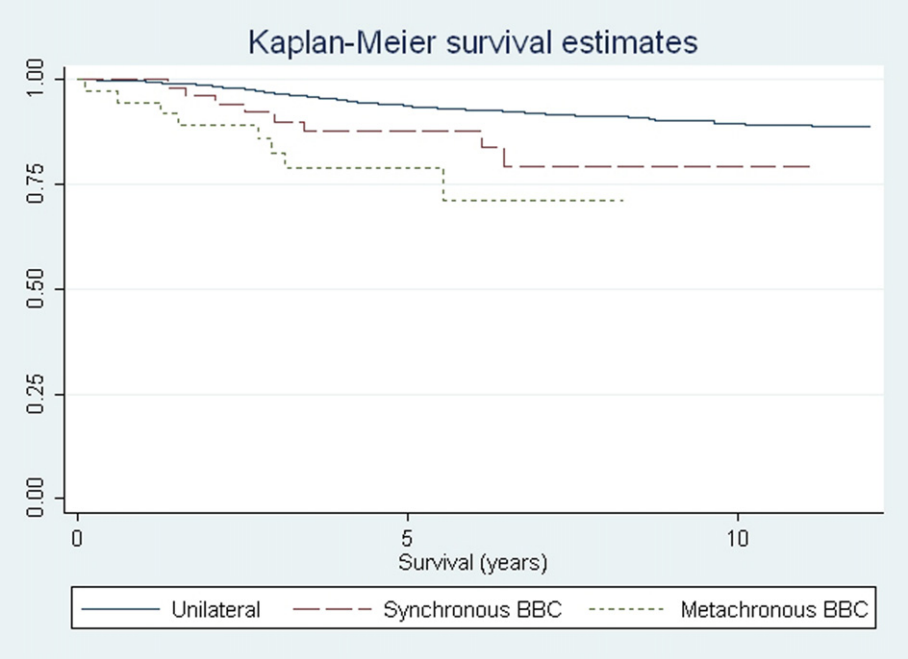

Fig. 1. Survival curves for patients with unilateral, synchronous bilateral and metachronous bilateral breast cancer. (Log likelihood ratio p-value<0.001).

by Hartman, however, suggest genetic susceptibility does play an independent role (particularly for metachronous BBC).[23,24] Similarly, lobular cancers are often more difficult to detect[29,30] which may reflect more intense diagnostic procedures and/or surveillance resulting in a greater chance of detecting cancer in the other breast. The higher incidence of BBC noted in those residing in the metropolitan area suggests better access to screening and diagnostic services leading to increased detection of bilateral cancers.

Tumour size was the only other feature that differed significantly between index bilateral cases and unilateral cases. However, the larger tumour size in bilateral cases is likely to be an artefact of selecting the index synchronous cancer, when diagnosed simultaneously. No difference in tumour size was found when index cases were selected at random for synchronous cases with identical diagnosis dates.

Patient and tumour characteristics did not differ significantly between index synchronous and metachronous cases, suggesting no difference in risk profiles although the statistical power was limited due to the small number of cases. Differences observed in relation to whether the second cancer was in situ or invasive at diagnosis (i.e. place of residence and size of the first tumour) suggest thorough diagnostic work up has contributed to earlier detection in our population. Also in the ACT it is routine to recommend annual mammography after the diagnosis of breast cancer.

Findings relating to the management of bilateral cancers, as a group, are influenced predominantly by treatment choices made in relation to synchronous cases. Increased likelihood of mastectomy and complete clearance of axillary nodes indicates a more radical treatment protocol compared with unilateral breast cancer, despite evidence suggesting conservative treatment is equally effective for BBC.[1] When synchronous and (index) metachronous cases were compared, significant differences were observed for surgery type and adjuvant endocrine therapy. Mastectomy use for index metachronous cases was similar to that for unilateral cases. The use of adjuvant endocrine therapy in the treatment of index metachronous cases was significantly less frequent than for synchronous cases and also lower than in unilateral cases, with 30% not receiving adjuvant endocrine therapy despite the index case being oestrogen and/or progesterone receptor positive. Ensuring that guidelines are followed in relation to the use of adjuvant endocrine therapy in the treatment of breast cancer may be an important strategy for reducing BBC incidence, given several other studies have indicated reduced risk following endocrine therapy.[3]

Our results clearly indicate an increased risk of death from breast cancer in women with BBC, about twice that for unilateral breast cancer. Worse survival was independent of differences in the clinical features or management of tumours in these women, but only applied where the second cancer was invasive. Results were strongest in relation to metachronous BBC, with a non-significant increased risk being observed for synchronous BBC. While the results of previous series are mixed, the majority of studies that accounted for differences in prognostic and treatment factors between groups using multivariate methods have suggested worse survival outcomes for BBC (Table 3). Significant increases in the risk of death from BBC have been reported by several groups,[5,15–18] while non-significant trends toward increased risk have been reported by others.[10,12,31] The small number of bilateral cases in two of the latter studies is the likely reason for their non-significant findings. A recent study using data from the Geneva cancer registry[14] was the only multivariate, population-based study to find no difference in outcomes, with survival being measured from the date of diagnosis of the second tumour. In contrast, a nationwide study undertaken in Sweden,[24] which examined mortality rates rather than survival, found breast cancer mortality was significantly higher in women with synchronous or metachronous BBC diagnosed within ten years. Furthermore, this research showed that variations in clinical and treatment characteristics did not account for the increased mortality.

The fact that we observed statistically significant differences in survival, despite the relatively small number of cases (i.e. low power), suggests a true underlying difference in outcomes. Our

Table 3
Summary of bilateral breast cancer survival studies that used Cox proportional hazards regression.

Author	Study population	No. of cases	Hazard ratio	Methods
Healey et al.[31] 1993, USA	Harvard Medical School, Centre for Radiotherapy	Unilateral = 1624 Metachronous = 77	Met = 1.16 (0.50–2.28)	Adjusted for age, nodes, stage, and adjuvant therapy
Black et al.[15] 1996, USA	SEER database, 1973–1990	N = 138,962	Bilateral = 1.56	Adjusted for age and stage
Heron et al.[10] 2000, USA	Pennsylvania hospitals (2) 1960–1995	Unilateral = 1315 Synchronous = 47 Metachronous = 103	Sync = 1.32 (0.57–3.05) Met = 1.33 (0.57–3.20)	(sync ≤1 year) Adjusted for age and stage Survival from 2nd tumour
Abdalla et al.[16] 2000, USA	University of Chicago hospitals, 1927–1987	Unilateral = 2004 Synchronous = 23 Metachronous = 107	Bilateral = 1.4 (1.09–1.95)	(sync ≤1 month) Cox multivariate model with bilateral as time dependent covariate
Kollias et al.[17] 2001, UK	Nottingham City Hospital, 1975–1995	Unilateral = 3104 Synchronous = 26 Metachronous = 80	Bilateral = 1.67 (1.08–2.56)	Cox multivariate model with bilateral as time dependent covariate
Polednak[18] 2002, USA	Connecticut Tumour registry, 1995–1999	Unilateral = 13,495 Synchronous = 300	Sync = 1.43 (1.09–1.87)	(sync ≤3 months) Adjusted for age, stage and histology
Carmichael et al.[11] 2002, UK	William Harvey Hospital, Kent, 1963–1999	Unilateral = 1810 Synchronous = 43 Metachronous = 92	HR not reported (p = 0.25)	(sync≤3 months) Adjusted for age, nodes, grade and tumour size
Jobsen et al.[12] 2003, Netherlands	Medisch Spectrum Twente, Radiotherapy Dept.	Unilateral = 1679 Synchronous = 26	Sync = 2.2 (0.7–7.2)	(sync ≤3 months) Adjusted for clinical and treatment factors
Takahashi et al.[13] 2005, Japan	Hokkaido University Hospital, 1960–2001	Unilateral = 1168 Synchronous = 13 Metachronous = 33	Sync = 0.46 (0.06–3.3) Met = 1.84 (0.57–5.9)	(sync <6 months) Adjusted for clinical and treatment factors
McCaul[5]2006, USA	SEER database, 1973–2000	N380,000	Sync = 1.45 (1.27–1.66) Met = 1.8 (1.67–1.94)	(sync = same month) Adjusted for patient, histology and treatment (HRs for local disease only)
Verkooijen et al.[14] 2007, Switzerland	Geneva Cancer Registry, 1970–2002	Unilateral = 7558 Synchronous = 155 Metachronous = 219	Sync = 0.8 (0.5–1.4) Met = 1.1 (0.9–1.5)	(sync ≤6 months) Adjusted for patient, clinical and treatment factors Survival from 2nd tumour

Sync = synchronous; Met = metachronous; HR = Hazard ratio.

study population included all patients with operable breast cancer who received surgery in the ACT/SE NSW region over a ten year period. All cases were followed up at regular intervals to ascertain recurrence, vital status and cause of death. Survival at five years for our study group is almost identical to that reported for women across the state of NSW who had local or regional disease.[32] This provides assurance that ascertainment of vital status among women with unilateral breast cancer was accurate.

Worse outcomes for women with BBC were observed in our study, even after correction for known conventional prognostic factors. The worse outcome may simply reflect the increased burden of disease imposed by the second cancer, but differences in the biological behaviour of breast cancers in women with bilateral disease are possible. Research looking for differences in patterns of gene expression between unilateral and bilateral breast cancers may help resolve this issue.

Conclusion

The differences in survival observed in women with BBC and those with unilateral disease are clinically important. Consideration of the relatively poor outcome in this small group of women should inform decisions about systemic adjuvant therapy, where assessment of the underlying risk of relapse and breast cancer death is critical. In addition, this study confirms that adjuvant endocrine therapy for endocrine responsive early breast cancer has a clinically important benefit in reducing the risk of metachronous breast cancer. Results also support ongoing surveillance following the diagnosis of unilateral breast cancer to detect bilateral tumours at an early stage.

Conflict of interest statement

The authors have no conflict of interest.

Acknowledgements

Funding for the ACT and SE NSW Breast Cancer Treatment Group Quality Assurance Project has been provided by ACT Health and Bosom Buddies ACT. The authors wish to thank the women who have participated in the project over the past decade and the clinicians who have provided data for the Audit.

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