RESEARCH COMMUNICATION

Survival From Synchronous Bilateral Breast Cancer: The Experience of Surgeons Participating in the Breast Audit of the Society of Breast Surgeons of Australia and New Zealand

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Abstract

Background: Previous studies generally indicate that synchronous bilateral breast cancers (SBBC) have an equivalent or moderately poorer survival compared with unilateral cases. The prognostic characteristics of SBBC would be relevant when planning adjuvant therapies and follow-up medical surveillance. The frequency of SBBC among early breast cancers in clinical settings in Australia and New Zealand was investigated, plus their prognostic significance, using the Breast Cancer Audit Database of the Society of Breast Surgeons of Australia and New Zealand, which covered an estimated 60% of early invasive lesions in those countries. Design: Rate ratios (95% confidence limits) of SBBC were investigated among 35,370 female breast cancer cases by age of woman, histology type, grade, tumour diameter, nodal status, lymphatic/vascular invasion and oestrogen receptor status. Univariate and multivariable disease-specific survival analyses were undertaken. Results: 2.3% of cases were found to be SBBC (i.e., diagnoses occurring within 3 months). The figure increased from 1.4% in women less than 40 years to 4.1% in those aged 80 years or more. Disease-specific survivals did not vary by SBBC status (p=0.206). After adjusting for age, histology type, diameter, grade, nodal status, lymphatic/vascular invasion, and oestrogen receptor status, the relative risk of breast cancer death for SBBC was 1.17 (95% CL: 0.91, 1.51). After adjusting for favourable prognostic factors more common in SBBC cases (i.e., histology type, grade, lymphatic/vascular invasion, and oestrogen receptor status), the relative risk of breast cancer death for SBBC was 1.42 (95% CL: 1.10, 1.82). After adjusting for unfavourable prognostic factors more common in SBBC cases (i.e., older age and large tumour diameter), the relative risk of breast cancer death for SBBC was 0.98 (95% CL: 0.76, 1.26). Conclusions: Results confirm previous findings of an equivalent or moderately poorer survival for SBBC but indicate that SBBC status is likely to be an important prognostic indicator for some cases.

Keywords: Synchronous bilateral breast cancer prevalence - prognosis survival - Australia - New Zealand

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Introduction

Evidence of the prognostic significance of synchronous bilateral compared with unilateral breast cancer is available from a number of studies (Gollamudi et al., 1997; Heron et al., 2000; Kollias et al., 2001; Newman et al., 2001; Jobsen et al., 2003; Polednak, 2003; Tousimis, 2005; Beckmann et al., 2011). While results vary, most indicate that synchronous bilateral breast cancers (SBBC) have either an equivalent or moderately poorer survival compared with unilateral cases. The prognostic characteristics of SBBC may be a relevant consideration when planning adjuvant therapies and frequency of follow-up medical surveillance, although generally accepted protocols that take account of bi-laterality are not yet available (Heron et al., 2000; Tousimis, 2005; Beckmann et al., 2011). The prevalence of SBBC in patient populations may also be a relevant factor when setting survival targets for clinical practices and health services that include relatively high numbers of these cases.

The Society of Breast Surgeons of Australia and New Zealand is developing models for predicting breast cancer survival according to socio-demographic and clinical risk factor data recorded on the Breast Cancer Audit database. By comparing observed survivals with survivals predicted by these models, shortfalls can be identified for guiding quality improvement initiatives. The relevance of including SBBC in such models is uncertain from the international evidence (Gollamudi et al., 1997; Heron et al., 2000; Kollias et al., 2001; Newman et al., 2001; Jobsen

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et al., 2003; Polednak, 2003; Tousimis, 2005; Beckmann et al., 2011) and is investigated in this study, using the Audit database.

An earlier Australian study of the prognostic significance of bilateral breast cancer in treatment centres in the Australian Capital Territory (ACT) and South Eastern New South Wales (SENSW) (Beckmann et al., 2011) indicated a more than two-fold risk of breast cancer death among SBBC than unilateral cases, although the elevation was not statistically significant after adjusting for age and conventional clinical risk factors (e.g., tumour size, grade, and nodal status). Characteristics found to be more common in SBBC than unilateral cases included positive family history, lobular histology type and larger tumour size at diagnosis (Beckmann et al., 2011). The study provided important evidence of comparative outcomes for SBBC and unilateral breast cancers in an Australian region, although statistical power would have been limited by the numbers of synchronous events available for analysis (52 cases and eight deaths) (Beckmann et al., 2011).

The opportunity presents to complement the ACT/SENSW study with data for 35,370 Australian and New Zealand women with invasive breast cancers diagnosed in 1998-2005 and included in the Breast Cancer Audit (Roder et al., 2010). These women comprised all those on the Audit database for whom SBBC status had been recorded (96%).

Audit data were collected by participating surgeons and accounted for an estimated 60% of early breast cancers diagnosed in Australia and New Zealand during that period (Roder et al., 2010). Although these breast cancers were not selected to be representative of all early breast cancers, their characteristics appear to be similar, in that their survivals were similar to those recorded at a population level in New South Wales and the USA [Surveillance Epidemiology and End Results (SEER) data] (Tracey et al., 2007; Ries et al., 2008; Roder et al., 2010). In addition, differences in survival among Audit cases by conventional risk factors (e.g., tumour size, grade, nodal status and oestrogen receptor status) accorded with differences expected from population-based data (Tracey et al., 2007; Ries et al., 2008; Roder et al., 2010).

The objective of this study is to determine from the Breast Cancer Audit database the prevalence of SBBC among early breast cancers, whether survival differences exist by SBBC status after adjusting for age and conventional clinical risk factors, and based on results, to assess whether SBBC status should be included in statistical models for predicting survivals of women treated at participating Breast Cancer Audit practices. Ethics approval for this study was obtained from research ethics committees of the Australian Institute of Health and Welfare and Royal Australasian College of Surgeons.

Materials and Methods

Breast Cancer Audit data for Australian women with invasive cancer were linked to the National Death Index at the Australian Institute of Health and Welfare, using the first three digits of the surname, dates of birth and jurisdiction of residence for probabilistic matching (Roder et al., 2010). A pilot investigation had been undertaken in South Australia, in which data for 1,179 women treated by South Australian surgeons were linked with official death records. The accuracy and completeness of the death data so obtained were assessed by comparison with death information recorded on the South Australian Cancer Registry for the same women where full names were available for linkage purposes and resolution of doubtful links had been undertaken by Registry staff through active follow-up. The results showed a high accuracy of data linkage, with a sensitivity of breast-cancer death detection of 93.1%, a specificity of 99.9%, a predictive value positive of 96.4%, and a predictive value negative of 99.8% (Roder, et al., 2010).

Following the pilot, death data were obtained from the National Death Index using this same process for all Australian women recorded on the Audit database (Roder, et al., 2010). In New Zealand, a similar follow-up of deaths was undertaken through the National Mortality Collection by deterministic matching using the National Health Index. This Index comprises a unique alphanumeric identifying number for each New Zealander.

The date of censoring of live cases in the survival analysis was December 31st, 2007. Analyses were limited to cancers diagnosed in 1998-2005 to allow enough follow-up time for survival assessment. A total of 35,346 cases and 2,315 breast cancer deaths were included in the survival analysis, with a mean follow-up period of 58 months and a range from less than one to 119 months. The analysis excluded 24 cases of unilateral breast cancer for whom insufficient data were available to determine breast cancer survival.

Women were classified according to whether they had SBBC using criteria from the Breast Cancer Audit data set specification (RACS, 2011). The definition includes bilateral breast cancers diagnosed at the same time or where differences between times of diagnosis were three months or less. The cancer characteristics available from the database were those applying to the first lesion detected or when detection was at the same time, the more dominant of the lesions (usually the largest, or where the sizes were equivalent, the highest grade).

Variables entered in the survival analyses as potential co-variables included age at diagnosis, histology type, tumour size, histology grade, nodal status, lymphatic/vascular invasion and oestrogen receptor status, categorized as shown in Table 1. The associations of these variables with SBBC status first were investigated using the Pearson chi-square test for binary and nominal variables and the Mann-Whitney U test for ordinal variables (Armitage & Berry, 1987). Rate ratios for SBBC were analysed by variable category (Garlinger & Abramson, 1995).

These potential co-variables are all established predictors of survival (De Vita et al., 2008; Roder et al., 2010) and all except nodal status were associated in the Audit data with SBBC status ($p \leq 0.039$) and considered to have the potential to confound the observed relationships of SBBC with survival. System features such as case load and private health insurance status were also entered but

they were not associated with SBBC status (p≥0.187) and were not expected to confound relationships of SBBC status with survival. Although treatment protocols may affect relative outcomes by SBBC status, they were not included in this initial study which, like most previous studies (Gollamudi et al., 1997; Heron et al., 2000; Kollias et al., 2001; Newman et al., 2001; Jobsen et al., 2003; Polednak, 2003; Tousimis, 2005; Beckmann et al., 2011), focused on pre-treatment prognostic factors.

Disease-specific survivals from breast cancer were calculated, defining breast-cancer deaths as those where breast cancer was recorded as a cause on the death certificate (Armitage & Berry, 1987). Disease-specific survivals have been shown to correspond closely with relative survival in population-based studies in Australia (SACR, 1999; SACR, 2007). For example, breast cancer survivals in South Australia for 1977-2003 diagnoses were found to be 80% at five years from diagnosis when using both disease-specific and relative survivals, and 70% and 69% respectively at 10 years from diagnosis (SACR, 2007). Disease-specific survivals are often preferred in clinical studies like the present one where due to referral practices, patients may not have risks of alternative causes of death that are equivalent to population norms (a required assumption in relative survival).

Survival times were calculated from diagnosis to December 31st, 2007 or date of death, whichever occurred first. Relative risks of case fatality from breast cancer (i.e., hazards ratios) and their 95% confidence intervals were calculated using Cox proportional hazards regression (Armitage & Berry, 1987). Assumptions of proportionality and lack of co-linearity were checked and found to be satisfied.

Results

Univariate analyses

A total of 837 women (2.3%) had a SBBC. Five year survival was 93.4% overall and did not differ significantly by SBBC status (p=0.206). The relative risk (95% confidence limits) of breast cancer death for SBBC compared with unilateral cases was 1.18 (0.91, 1.51).

Table 1 shows the proportion of cases with SBBC by age and other descriptor variables, rate ratios for SBBC and associated "p values". The following differences are evident:

- Rate ratios increased with age (MW p<0.001) with cases aged 80 years or more having a ratio of 3.03 (2.02, 4.53) compared with the reference category of less than 40 years.
- Rate ratios differed by histology type (chi-square p=0.014) with lobular cases having a ratio of 1.29 (1.06, 1.58) compared with the reference category of ductal lesions.
- Rate ratios varied with diameter (MW p<0.001) with a ratio of 1.59 (1.27, 1.99) applying for diameters of 40mm or more compared with the reference category of less than 10mm.
- Rate ratios reduced with increasing tumour grade (MW p<0.001) with high grade cancers having a ratio of 0.58 (0.48, 0.70) compared with low grade lesions.
- The rate ratio was lower for cases with lymphatic/vascular invasion (chi-square p=0.039), the ratio being 0.83 (0.70, 0.99).
- The rate ratio was lower for oestrogen receptor negative cases (chi-square p<0.001), the ratio being 0.50 (0.40, 0.62).

By comparison, statistically significant rate ratios were not found by nodal status, surgeon case load or private health insurance (chi-square p≥0.187).

Multivariable analyses

All characteristics in Table 1 that were associated with SBBC were entered as candidate predictors into a proportional hazards regression model, retaining those in Table 2 that were significant predictors (p<0.05). Predictors of higher risk of breast cancer death included:

Table 1. Rate ratios (95% Confidence Limits) of Invasive Synchronous Bilateral Compared with Other Breast Cancers by Age, Cancer and Service Characteristics: Australia and New Zealand Breast Cancer Audit, 1998–2005 Diagnoses*

Characteristic	All cases	Bilateral (%)	Rate ratios	P value**
Age at diag. (yrs):				MW p< 0.001
<40#	2,203	30 (1.4)	1.00	
40-49	7,010	131 (1.9)	1.37 (0.93,2.03)	
50-69	18,339	434 (2.4)	1.74 (1.20,2.51)	
70-79	5,291	140 (2.6)	1.94 (1.31,2.87)	
≥80	2,474	102 (4.1)	3.03 (2.02,4.53)	
Histology type:				$X^2(2)$ p = 0.014
Ductal#	26,801	575 (2.2)	1.00	
Lobular	3,902	111 (2.8)	1.29 (1.06,1.58)	
Other	3,739	1010 (2.7)	1.23 (0.99,1.51)	
Pathology grade:				MW p < 0.001
Low#	8,372	240 (2.9)	1.00	
Intermediate	14,434	359 (2.5)	0.87 (0.74,1.02)	
High	10,111	168 (1.7)	0.58 (0.48,0.70)	
Tumour diameter (mm):				MW p < 0.001
<10#	7,674	169 (2.2)	1.00	
10-14	5,252	113 (2.2)	0.98 (0.77,1.24)	
15-19	6,355	126 (2.0)	0.90 (0.72,1.13)	
20-29	7,665	161 (2.1)	0.95 (0.77,1.18)	
30-39	3,166	83 (2.6)	1.10 (0.92,1.54)	
≥40	3,804	133 (3.5)	1.59 (1.27,1.99)	
Nodal status:				$X^2(1)$ p = 0.566
Ve-#	19,110	416 (2.2)	1.00	
Ve+	11,820	269 (2.3)	1.05 (0.90,1.22)	
Lymphatic/vascular invasion:				$X^2(1)$ p = 0.039
Ve-#	21,968	537 (2.4)	1.00	
Ve+	8,136	166 (2.0)	0.83 (0.70,0.99)	
Oestrogen receptor status:				$X^2(1)$ p < 0.001
Ve+#	25,641	666 (2.6)	1.00	
Ve-	7,095	92 (1.3)	0.50 (0.40,0.62)	
Private insurance:				$X^2(1)$ p = 0.939
Yes#	7,844	156 (2.0)	1.00	
No	6,728	135 (2.0)	1.01 (0.80, 1.27)	
Surgeon case load per annum:				MW p = 0.187
Up to 20#	3,928	95 (2.4)	1.00	
20-100	20,605	463 (2.2)	0.93 (0.75,1.16)	
>100	10,837	279 (2.6)	1.06 (0.85,1.34)	

*Rate ratios for synchronous bilateral compared with other cancers, **MW: Mann-Whitney U test; X^2(df): Pearson's chi-square test, #Reference

increasing age at diagnosis from 70 years; larger tumour diameter; higher grade; positive nodal status; lymphatic/vascular invasion; negative oestrogen receptor status; and possibly ductal histology type. After adjusting for these predictors, the relative risk of breast cancer death for SBBC was 1.17 (0.91, 1.51) (Table 2).

Table 1 indicates that SBBC had: (1) an excess of some unfavourable prognostic indicators for breast cancer death (i.e., older age at diagnosis and large tumour diameter); but also (2) an excess of some favourable prognostic indicators (i.e., non-ductal histology types, lower tumour grades, absence of lymphatic/vascular invasion, and positive oestrogen receptor status).

When the regression modelling was repeated, including as co-variables only favourable prognostic indicators more commonly found in SBBC, the relative risk of breast cancer death for SBBC was higher at 1.42 (1.10, 1.82) (Table 3). Conversely, when including as co-variables only unfavourable prognostic indicators more commonly found in SBBC, the relative risk of breast cancer death for SBBC was 0.98 (0.76, 1.26) (Table 4).

Table 2. Multivariate Proportional Hazards Regression Relative Risk (95% Confidence Limits) of Death from Breast Cancer by Invasive Synchronous Bilateral Breast Cancer Status, Age and Cancer Characteristics: Australia and New Zealand Breast Cancer Audit, 1998–2005 Diagnoses*

Characteristic	Cases	Deaths[a]	Relative risk
Synchronous bilateral cancers:			
No[#] 34,509	2,252	1.00	
Yes	837	63	1.17 (0.91,1.51)
Age at diag. (yrs):			
<40[#]	2,203	221	1.00
40-49	7,009	406	0.73 (0.62,0.86)
50-69	18,331	929	0.87 (0.75,1.01)
70-79	5,282	423	1.49 (1.26,1.76)
≥80	2,468	336	2.03 (1.70,2.43)
(unknown)	(53)	(0)	(0.00 (0.00,>1.00))
Histology type:			
Ductal[#]	26,064	1,785	1.00
Lobular	3,900	224	0.93 (080,1.07)
Other	3,735	181	0.83 (0.71,0.97)
(unknown)	(1,647)	(125)	(0.53 (0.42,0.66))
Pathology grade:			
Low[#]	8,366	160	1.00
Intermediate	14,421	673	1.65 (1.38,1.97)
High	10,107	1,214	2.83 (2.36,3.39)
(unknown)	(2,452)	(268)	(2.74 (2.19,3.43))
Tumour diam. (mm):			
<10[#]	7,668	180	1.00
10-14	5,249	176	1.29 (1.04,1.59)
15-19	6,350	286	1.42 (1.17,1.71)
20-29	7,659	550	1.83 (1.53,2.18)
30-39	3,165	348	2.38 (1.97,2.88)
≥40	3,803	609	3.46 (2.89,4.14)
(unknown)	(1,452)	(166)	(2.43 (1.93,3.05))
Nodal status:			
Ve-[#]	19,096	599	1.00
Ve+	11,815	1,231	2.03 (1.82,2.26)
(unknown)	(4,435)	(485)	(2.69 (2.36, 3.08))
Lymphatic/vascular invasion:			
Ve-[#]	21,954	831	1.00
Ve+	8,131	998	1.73 (1.56, 1.91)
(unknown)	(5,261)	(486)	(1.58 (1.39, 1.80))
Oestrogen receptor status:			
Ve-[#]	7,091	937	1.00
Ve+	25,623	1,142	0.48 (0.43,0.52)
(unknown)	(2,632)	(236)	(0.63 (0.53,0.75))

*Date of censoring of live cases: December 31st 2007, [a]Number of breast cancer deaths, [#]Reference

Table 3. Multivariate Proportional Hazards Regression Relative Risk (95% Confidence Limits) of Death from Breast Cancer by Invasive Synchronous Bilateral Breast Cancer Status, After Adjusting for Favourable Prognostic Indicators More Commonly Found in Synchronous Bilateral Cases: Australia and New Zealand Breast Cancer Audit, 1998–2005 Diagnoses*

Characteristic	Cases	Deaths[a]	Relative risk
Synchronous bilateral cancers:			
No[#]	34,509	2,252	1.00
Yes	837	63	1.42 (1.10,1.82)
Histology type:			
Ductal[#]	26,064	1,785	1.00
Lobular	3,900	224	1.19 (1.03,1.38)
Other	3,735	181	0.93 (0.79,1.09)
(unknown)	(1,647)	(125)	0.60 (0.48,0.76)
Pathology grade:			
Low[#]	8,366	160	1.00
Intermediate	14,421	673	1.94 (1.63,2.31)
High	10,107	1,214	3.60 (3.02,4.30)
(unknown)	(2,452)	(268)	(4.04 (3.25,5.03))
Lymphatic/vascular invasion:			
Ve-[#]	21,954	831	1.00
Ve+	8,131	998	2.61 (2.37, 1.86)
(unknown)	(5,261)	(486)	(2.06 (1.82, 2.33))
Oestrogen receptor status:			
Ve-[#]	7,091	937	1.00
Ve+	25,623	1,142	0.50 (0.45,0.54)
(unknown)	(2,632)	(236)	(0.73 (0.62,0.87))

*Date of censoring of live cases: December 31st 2007, [a]Number of breast cancer deaths, [#]Reference

Table 4. Multivariate Proportional Hazards Regression Relative Risk (95% Confidence Limits) of Death from Breast Cancer by Invasive Synchronous Bilateral Breast Cancer Status, After Adjusting for Unfavourable Prognostic Indicators More Commonly Found in Synchronous Bilateral Cases: Australia and New Zealand Breast Cancer Audit, 1998–2005 Diagnoses*

Characteristic	Cases	Deaths[a]	Relative risk
Synchronous bilateral cancers:			
No[#]	34,509	2,252	1.00
Yes	837	63	0.98 (0.76,1.26)
Age at diag. (yrs):			
<40[#]	2,203	221	1.00
40-49	7,009	406	0.61 (0.52,0.72)
50-69	18,331	929	0.63 (0.54,0.73)
70-79	5,282	423	1.02 (0.86,1.20)
≥80	2,468	336	1.61 (1.36,1.91)
(unknown)	(53)	(0)	(0.00(0.00,>1.00))
Tumour diam. (mm):			
<10[#]	7,668	180	1.00
10-14	5,249	176	1.43 (1.17,1.77)
15-19	6,350	286	1.89 (1.57,2.28)
20-29	7,659	550	3.04 (2.57,3.60)
30-39	3,165	348	4.75 (3.97,5.69)
≥40	3,803	609	7.49 (6.33,8.86)
(unknown)	(1,452)	(166)	(5.26 (4.26,6.50))

*Date of censoring of live cases: December 31st 2007, [a]Number of breast cancer deaths, [#]Reference

Discussion

The five-year disease-specific survival of 93% for all breast cases in this study equates with the 93% reported for the ACT/SENSW (Beckmann et al., 2011). It is higher than the 88% reported by the Australian Institute of Health and Welfare for all female breast cancers diagnosed in Australia in 1998-2004, which is understandable since the latter cancers included both early and late diagnoses (AIHW, 2010). In the breast screening target age range of 50-69 years, where the proportion comprising early breast cancers is likely to have been higher than for other age groups, the Australian Institute of Health and Welfare reported a five-year survival of 90% (AIHW, 2010).

The proportion of invasive breast cancer cases recorded on the Breast Cancer Audit database as being SBBC was 2.3%, which is close to the 2.1% reported for the ACT/SENSW (Beckmann et al., 2011). Proportions of SBBC reported in most studies have ranged from less than 1% to around 3%, although figures as high as 12% have been reported when periods between lesion detection of up to 12 months have been regarded as synchronous, as opposed to the three-month cut-off used here (Dawson et al., 1998; Tousimis, 2005; Beckmann et al., 2011).

The proportion of females with invasive breast cancers classified as SBBC in this study ranged from 1.4% in women under 40 years to 4.1% in those over 80 years of age. Results from previous studies have been inconsistent, with some providing confirmatory findings (Hartman et al., 2007), but others suggesting an opposite trend by age (Dawson et al., 1998; Chen et al., 1999). Potentially results would be affected by the duration allowed between lesion detection to qualify as SBBC, which was shorter at three months here than where the duration was allowed to extend up to 12 months (Tousimis, 2005).

The higher proportion of SBBC among lobular and potentially other non-ductal histology types is consistent with evidence from a number of studies (Horn & Thompson, 1988; Cook et al., 1996; Dawson et al., 1998; Chen et al., 1999; Hartman et al., 2007; Verkooijen et al., 2007). The higher proportion for large cancers is supported by previous studies (Verkooijen et al., 2007; Beckmann et al. 2011) with one study finding this to have resulted from using size of the more dominant lesion for cases detected at the same time (Beckmann et al., 2007). The increased proportion of SBBC among cases classified as lower grade and without lymphatic/vascular invasion may reflect less biologically aggressive tumour activity which may predispose to a longer pre-clinical phase, allowing more time for a second lesion to arise.

International evidence of the prognostic significance of SBBC is not consistent, although most studies suggest that these cancers have either an equivalent or moderately poorer survival compared with unilateral cases (Gollamudi et al., 1997; Heron et al., 2000; Kollias et al.2001; Newman et al. 2001; Jobsen et al., 2003; Polednak, 2003; Tousimis, 2005; Beckmann et al., 2011). Differences in results may reflect variations in definition of synchronicity or differences in patient risk profile (Tousimis, 2005). The present study suggested that SBBC had a moderately poorer survival that did not achieve statistical significance. However, statistical modelling also suggested the potential for the prognostic importance of SBBC to vary, depending on the concurrence of other prognostic factors. For example, when unilateral and bilateral cases were compared, adjusting for favourable prognostic indicators more commonly found in SBBC, SBBC cases had a risk of breast cancer death about 42% higher than unilateral cases. By comparison, the risk of breast cancer death was approximately the same for SBBC and unilateral cases when adjusting for unfavourable prognostic indicators more commonly found in bilateral cases.

A deficiency of this study was the lack of detail available on the second bilateral cancers. Features of these cancers, including whether invasive or in situ, could impact on survival. If advances in mammography and other imaging have led to more SBBC, the second ones may have tended to be very small and of low grade, which could have affected outcomes, but we could not investigate that possibility. Also despite the large number of breast cancers studied, there was limited statistical power due to high survivals and consequently few breast cancer deaths to study among synchronous cases (n=63). This restricted opportunities to investigate interactions by histology type and other prognostic variables. In addition, HER-2 status was not recorded for a sufficient period to be included.

The effect of differences in treatment on comparative survivals of SBBC and unilateral cases requires further investigation. Differences in clinical management have been found, with mastectomies, axillary clearances and systemic therapies observed to be more common and radiotherapy less common among SBBC than unilateral cases in the ACT/SENSW study (Beckmann et al., 2011). It is possible that comparative survivals of SBBC and unilateral cases would vary with differences in treatment protocol. Given complexities of classifying and interpreting effects of the many different treatment combinations, we chose to focus on pre-treatment risk factors in this study but intend to address treatment effects in a second study dedicated to this topic.

The present data suggest that when adjusting for all risk factors, both favourable and unfavourable, an increased risk of breast cancer death of about 17% applies to SBBC compared with unilateral cases, although the result was not statistically significant. Based on that estimate, a prevalence of 2.3% of synchronous bilateral lesions would be expected to increase risk of death by only about 0.4% when compared with a cohort of unilateral cases. Even if the prevalence were three-fold at 6.9%, the increase in risk would only be about 1.2% compared with unilateral cases. On this basis we consider it unnecessary to include SBBC status in the statistical models used to predict survival for most patient groups.

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