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EPIDEMIOLOGY

Survival after bilateral breast cancer: results from a population-based study

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Abstract
Background Controversy exists on the impact of bilaterality of breast cancer on survival. We used population-based data to compare survival of women with unilateral versus bilateral breast cancer.
Patients and methods At the Geneva cancer registry, we identified all 7,912 women diagnosed with invasive breast cancer between 1970 and 2002. Breast cancers were categorized as unilateral, synchronous bilateral (contralateral tumour diagnosed within six months after the first tumour) and metachronous bilateral (contralateral tumour diagnosed over six months after the first tumour). With multivariate modelling we compared characteristics and survival between women with unilateral and bilateral disease.
Results Patients with synchronous bilateral tumours (n = 155, 2.0%) had more often lobular histology and less frequently stage I disease than women with unilateral disease. Women with metachronous breast cancer (n = 219, 2.8%) received less often chemotherapy or hormone therapy for their first tumours. Ten-year disease-specific survival was similar (66%) after unilateral and metachronous bilateral breast cancer, but worse after synchronous bilateral cancer (51%). After adjustment, breast cancer mortality risks were not significantly increased for women with either synchronous or metachronous bilateral disease (Hazard ratios 1.1 (0.8–1.5) and 0.8 (0.5–1.4), respectively).
Conclusion This large population-based study indicates that bilaterality of breast cancer is not associated with impaired survival.

Keywords Bilateral · Breast cancer · Population-based · Survival

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Introduction

Bilateral breast cancer is relatively rare, but has an important emotional impact on the patient. Having two breast cancers instead of one requires more extensive locoregional treatment and is thought to carry a worse outcome. The causes and the prognostic consequences of bilateral breast cancer are far from being established.

Epidemiological studies on the risk factors for bilateral breast cancer are scarce [1, 2]. Women with bilateral breast cancer have more frequently a positive family history of breast cancer compared to women with unilateral disease [3–7]. Women who develop

breast cancer at young age also have an increased risk to develop a contralateral tumour [8]. This is explained by their longer overall life expectancy and by the fact that they more often belong to high-risk families [9, 10].

Female breast cancer patients who carry germ-line mutations in the *BRCA1* or *BRCA2* genes (the main genes involved in genetic predisposition to breast cancer) have an annual risk of 2–6% of developing contralateral breast cancer [11]. However, as the prevalence of *BRCA1* and *BRCA2* mutations is very low, most bilateral breast cancer patients do not carry *BRCA1* and *BRCA2* mutations [12].

It is unclear whether contralateral breast cancer occurrence, either synchronous or metachronous, has an impact on survival. Some studies found worse survival for patients with bilateral breast cancer [13–15], others showed similar survival rates for patients with unilateral and bilateral breast cancer [3–5, 13–21]. Unfortunately, many of these studies did not account for important prognostic factors such as systemic therapy.

The aim of this study is to evaluate the impact of contralateral breast cancer occurrence on survival.

Patients and methods

The Geneva cancer registry records all incident cancer cases occurring in the population of the canton (approximately 420,000 inhabitants) since 1970. It collects information from various sources and only less than 2% of cases are recorded from death certificates only [22]. All hospitals, pathology laboratories and private practitioners in the canton are requested to report every cancer case. Trained tumour registrars systematically abstract data from medical files. Physicians regularly receive questionnaires to complete missing clinical and therapeutic data. Recorded data include socio-demographic information, method of discovery, tumour characteristics (coded according to the International Classification of Diseases for Oncology, ICD-O) [23], stage of disease at diagnosis, hormone receptor status and treatment during the first 6 months after diagnosis. The registry regularly assesses survival, taking as reference date the date of confirmation of diagnosis or the date of hospitalization (if it preceded the diagnosis and was related to the disease). In addition to passive follow-up (standard examination of death certificates and hospital records), active follow-up is performed yearly using the files of the Cantonal Population Office. Cause of death is taken from clinical files.

We included all patients diagnosed with primary invasive breast cancer between 1970 and 2002, living in the canton of Geneva. We excluded women diagnosed at death/autopsy ($n = 95$) and women with contralateral in situ breast cancer ($n = 88$).

Bilateral breast cancer was classified as synchronous in patients with a second invasive breast cancer diagnosed within six months after the first breast cancer and as metachronous if the second breast cancer occurred more than six months after the first.

Variables of interest were age, social class (high, middle, low, unknown), sector of care (private vs. public) and period of diagnosis. Familial risk was available for breast cancer patients diagnosed after 1990 and categorized as low (no first-or second-degree relative with breast or ovarian cancer), high (either ≥1 first-degree relative with breast or ovarian cancer ≤50 years, ≥2 first-degree relatives with breast/ovarian cancer at any age, or ≥3 patient cases of breast/ovarian cancer among first-or second-degree relatives) or moderate (all other family histories of breast and/or ovarian cancer).

For staging, we used the pathologic pTNM (Tumour Node Metastasis) classification system or, when not available, the clinical cTNM classification [24]. Tumour differentiation (grade) was classified as well (grade 1), moderately (grade 2) or poorly differentiated (grade 3), or unknown. Information on oestrogen receptor status was available since 1995 and considered positive when ≥10% of the tumour cells expressed oestrogen receptors. Tumour histology was classified as ductal (ICD-O code 8500), lobular (ICD-O code 8520 or 8522) and other.

Locoregional therapy was categorized as breast-conserving surgery followed by radiotherapy, mastectomy with or without radiotherapy, and other (i.e. tumorectomy without radiotherapy and no surgery). Use of chemotherapy and hormone therapy was categorized as yes versus no/unknown.

For the comparison of tumour characteristics between women with synchronous bilateral breast cancer and those with unilateral disease, we considered the tumour with the most advanced stage and the highest grade. The oestrogen receptor status was considered negative if either one or both tumours were oestrogen receptor negative. Patients with at least one lobular tumour were categorized as having lobular histology.

To compare tumour and treatment characteristics of patients with metachronous bilateral breast cancer with those with unilateral disease, we used the characteristics of the first metachronous tumour.

With unconditional logistic regression analysis we identified all variables significantly associated with

synchronous or metachronous breast cancer. To determine which variables were both independently and significantly associated with synchronous or metachronous bilateral disease, we used multivariate logistic regression analysis, adjusting for all variables that were significant in univariate analysis.

Disease-specific survival rates were calculated with Kaplan–Meier analysis. With Cox proportional hazards analysis we identified the variables significantly linked to prognosis. Finally, we calculated breast cancer mortality risks (hazard ratio's [HR]) for patients with synchronous and metachronous bilateral breast cancer compared with patients with unilateral disease cancer and adjusted these risks for other prognostic factors. For women with metachronous breast cancer we calculated survival from the date of diagnosis of the second tumour.

Results

This study included 7,912 patients of whom 155 (2.0%) had synchronous bilateral breast cancer and 219 (2.8%) developed metachronous bilateral breast cancer after a median follow-up of 6.7 years. In univariate analysis, patients with synchronous bilateral breast cancer were significantly older, belonged more often to lower social class and were more often treated in the public sector (Table 1). These patients reported more frequently a strong family history of breast and/or ovarian cancer, but this difference was not statistically significant. They presented with later stage at diagnosis and had more often lobular histology. There were no significant differences in grade and oestrogen receptor status.

After adjustment for age, social class, sector of care, stage, and histologic subtype, both higher stage and histology (lobular subtype) remained independently and significantly associated with synchronous breast cancer. Compared with patients with stage I disease, patients with stage II disease had a twofold increased risk of synchronous bilateral breast cancer (Odds Ratio [OR], 2.2; 95% CI, 1.4–3.5), and those with stage III disease had a threefold increased risk (OR, 2.9; 95% CI, 1.7–5.1). Lobular histology increased the risk for synchronous bilateral disease more than threefold (OR, 3.5; 95% CI, 2.3–5.4). Patients with synchronous bilateral breast cancer were significantly more often treated with mastectomy (71% vs. 49% of unilateral patients, $P < 0.001$) and received significantly more often chemotherapy (36% vs. 28% of unilateral patients, $P = 0.035$) and hormone therapy (47% vs. 36% of unilateral patients, $P = 0.001$).

Patients who developed metachronous breast cancer were significantly younger at the time of their first breast cancer and were more often diagnosed during the early years of the study (Table 2). We observed no differences in social class or sector of care. Patients with metachronous bilateral breast cancer had more often a highly increased familial risk, but this difference was not significant. Also, they had less often distant metastases at the time of diagnosis of their first tumour. The proportions of stage I, II, and III disease were not significantly different from women with unilateral disease. There were no significant differences in tumour grade. Women with metachronous bilateral disease had significantly more often oestrogen receptor negative disease at the time of diagnosis of their first tumour and less often histology other than ductal or lobular. Women who developed metachronous bilateral breast cancer underwent more often mastectomy for their first tumour, and had less often chemotherapy or hormone therapy. After adjustment for all variables univariately linked to metachronous bilateral cancer, women with oestrogen receptor positive tumours had a lower risk of developing contralateral breast cancer than women with oestrogen receptor negative disease (OR, 0.2; 95% CI, 0.1–0.7). Breast cancer treatment regimens not including systemic chemotherapy or hormone therapy were also significantly and independently associated with contralateral breast cancer occurrence (OR, 1.8; 95% CI, 1.2–2.6, and OR, 2.0; 95% CI, 1.2–3.4, respectively). Patients with histology other than ductal or lobular for their first tumours remained at significantly decreased risk of developing contralateral disease (OR, 0.3; 95% CI, 0.2–0.5).

Five-year disease-specific survival rates for women with unilateral breast cancer, synchronous bilateral breast cancer and (second) metachronous bilateral breast cancer were 78% (95% CI, 77–79%), 77% (95% CI, 69–85%) and 80% (95% CI, 74–86%), respectively (Fig. 1). Ten-year disease-specific survival rates were 66% (95% CI, 65–67%), 51% (95% CI, 39–63%) and 66% (95% CI, 58–74%), respectively.

In univariate analysis, recognized prognostic variables, such as lower social class, advanced stage, poor differentiation, negative oestrogen receptor status, extensive locoregional therapy, use of chemotherapy and hormone therapy, but also breast cancer diagnosed in the earlier years of the study, and non-ductal or non-lobular histology, significantly increased the risk of death from breast cancer (data not shown).

Before adjustment, patients with synchronous bilateral breast cancer had a 40% excess risk of death as a result of their disease (Hazard ratio [HR], 1.4; 95% CI, 1.1–1.8) (Table 3). After adjustment for the

Table 1 Comparison of characteristics of patients with synchronous bilateral breast cancer and unilateral breast cancer

	Synchronous bilateral breast cancer		Unilateral breast cancer	Unadjusted odds ratio	Multiadjusted odds ratio[a]
Age					
> 75	37(24%)		1,528 (20%)	1[b]	1[b]
51–75	90 (58%)		4,132 (55%)	0.9(0.3–1.3)	0.9 (0.6–1.4)
41–50	24 (16%)		1,402 (19%)	0.7(0.4–1.2)	0.7 (0.4–1.3)
< 41	4 (3%)		476 (6%)	0.3 (0.1–1.0)	0.4 (0.1–1.1)
Civil status					
Single	24 (16%)		1,038 (14%)	1[b]	1[b]
Married	63 (41%)		3,838 (51%)	0.7 (0.4–1.1)	0.7 (0.4–1.1)
Widowed	45 (29%)		1,645 (22%)	1.2 (0.7–2.0)	1.1 (0.6–1.9)
Separated	23 (15%)		1,017 (14%)	1.0 (0.5–1.7)	1.0 (0.5–1.7)
Social class					
High	16 (10%)		1,232 (16%)	1[b]	1[b]
Middle	75 (48%)		3,701 (49%)	1.6 (0.9–2.7)	1.5 (0.9–2.6)
Low	49 (32%)		1,926 (26%)	2.0 (1.1–3.5)	1.7 (0.9–3.1)
Unknown	15 (10%)		679 (9%)	–	–
Sector of care					
Private	61 (39%)		3,695 (49%)	1[b]	1[b]
Public	94 (61%)		3,843 (51%)	1.5 (1.1–2.1)	1.3 (0.9–1.8)
Period of diagnosis					
1970–1979	27(17%)		1,751 (23%)	1[b]	1[b]
1980–1989	49 (32%)		2,028 (27%)	1.6 (1.0–2.5)	1.2 (0.7–2.0)
1990–2002	79 (51%)		3,759 (50%)	1.4 (0.9–2.1)	1.0 (0.6–1.5)
Familial risk					
Low (not increased)	52 (34%)		2,297 (31%)	1[b]	1[b]
Moderate	11 (7%)		643 (9%)	0.8 (0.4–1.5)	0.7 (0.4–1.4)
High	6 (4%)		170 (2%)	1.6 (0.7–3.7)	1.5 (0.6–3.6)
Not available[c]	86 (56%)		4,428 (59%)	–	–
Stage[d]	Most advanced tumour	Less advanced tumour			
I	26 (17%)	85 (54%)	2,260 (30%)	1[b]	1[b]
II	82 (53%)	53 (34%)	3,171 (42%)	2.2 (1.4–3.5)	2.2 (1.4–3.5)
III	30 (19%)	5 (3%)	857 (11%)	3.0 (1.8–5.2)	2.9 (1.7–5.1)
IV	9 (6%)	4 (3%)	451 (6%)	1.7 (0.8–3.7)	1.7 (0.8–3.8)
Unknown	8 (5%)	8 (5%)	799 (11%)	–	–
Differentiation[e]	Tumour with highest grade	Tumour with lowest grade			
Well	27 (17%)	43 (28%)	1,118 (15%)	1[b]	1[b]
Moderate	39 (25%)	41 (27%)	1,798 (24%)	0.9 (0.5–1.5)	0.7 (0.5–1.2)
Poor	26 (17%)	8 (5%)	998 (13%)	1.1 (0.6–1.9)	1.0 (0.6–1.8)
Unknown	63 (41%)	63 (41%)	3,624 (48%)	–	–
Oestrogen receptor status					
Positive	36 (23%)		1,871 (25%)	1[b]	1[b]
Negative	9 (6%)		400 (5%)	1.2 (0.6–2.4)	1.4 (0.7–3.0)
Unknown	110 (71%)		5,267 (70%)	–	–
Histology					
Ductal (both)	98 (63%)		4,969 (66%)	1[b]	1[b]
Lobular (at least one)	32 (21%)		494 (7%)	3.3 (2.2–4.9)	3.5 (2.3–5.4)
Other	25 (16%)		2,075 (28%)	0.6 (0.4–1.0)	0.5 (0.3–0.8)
Locoregional therapy					
BCS + radiotherapy	23 (15%)	22 (14%)	2,206 (29%)	$P < 0.0001$	
Mastectomy +/– radiotherapy	109 (71%)	110 (71%)	3,726 (49%)		
Other	23 (15%)	23 (15%)	1,606 (21%)		

Table 1 continued

	Synchronous bilateral breast cancer	Unilateral breast cancer	Unadjusted odds ratio	Multiadjusted odds ratio[a]
Chemotherapy				
Yes	56 (36%)	2,140 (28%)	$P = 0.035$	
No/unknown	99 (64%)	5,398 (72%)		
Tamoxifen				
Yes	73 (47%)	2,719 (36%)	$P = 0.005$	
No/unknown	82 (53%)	4,819 (63%)		

[a] Adjusted for age, social class, sector of care, stage, and morphology

[b] Reference category

[c] Family history was only recorded for women diagnosed after 1990

[d] For comparison of stage, the stage of the most advanced bilateral tumour was taken into account

[e] Differentiation was only recorded for women diagnosed after 1985

Table 2 Comparison of characteristics of patients with synchronous bilateral breast cancer and unilateral breast cancer

	Metachronous bilateral breast cancer		Unilateral breast cancer	Unadjusted odds ratio	Multiadjusted odds ratio[a]
Age category	First tumour	Second tumour			
76+	14 (6%)	42 (19%)	1,528 (20%)	1[b]	1[b]
51–75	102 (47%)	126 (58%)	4,132 (55%)	2.6 (1.5–4.7)	2.7 (1.5–4.8)
41–50	77 (35%)	43 (20%)	1,402 (19%)	6.0 (3.4–10.6)	5.7 (3.1–10.5)
<41	26 (12%)	8 (4%)	476 (6%)	6.0 (3.0–11.5)	5.4 (2.7–10.7)
Civil status					
Single	31 (14%)		1,038 (14%)	1[b]	1[b]
Married	129 (59%)		3,838 (51%)	1.1 (0.8–1.7)	1.0 (0.6–1.5)
Widowed	32 (15%)		1,645 (22%)	0.7 (0.4–1.1)	1.1 (0.6–1.8)
Separated	27 (12%)		1,017 (14%)	0.9 (0.5–1.5)	0.9 (0.5–1.6)
Social class					
High	32 (15%)		1,232 (16%)	1[b]	1[b]
Middle	121 (55%)		3,701 (49%)	1.3 (0.8–1.9)	1.4 (0.9–2.1)
Low	47 (22%)		1,926 (26%)	0.9 (0.6–1.5)	1.0 (0.6–1.6)
Unknown	19 (9%)		679 (9%)	–	–
Sector of care	First tumour	Second tumour			
Private	114 (52%)	101 (46%)	3,695 (49%)	1[b]	1[b]
Public	105 (48%)	118 (54%)	3,843 (51%)	0.9 (0.7–1.2)	1.0 (0.7–1.3)
Period	First tumour	Second tumour			
1970–1979	92 (42%)	31 (14%)	1,751 (23%)	1[b,c]	1[b,c]
1980–1989	86 (39%)	70 (32%)	2,028 (27%)	0.8 (0.6–1.1)	0.9 (0.6–1.2)
1990–2002	41 (19%)	118 (54%)	3,759 (50%)	0.2 (0.1–0.3)	0.4 (0.2–0.6)
Familial risk[d]					
Not increased	85 (39%)		2,297 (31%)	1[b]	
Moderately increased	20 (9%)		643 (9%)	0.8 (0.5–1.4)	1.0 (0.4–2.1)
Highly increased	8 (4%)		170 (2%)	1.3 (0.6–2.7)	1.8 (0.6–5.3)
Unknown	106 (48%)		4,428 (59%)	–	–
Stage	First tumour	Second tumour			
I	72 (33%)	101 (46%)	2,260 (30%)	1[b]	1[b]
II	102 (47%)	72 (33%)	3,171 (42%)	1.0 (0.7–1.4)	1.0 (0.7–1.4)
III	18 (8.2%)	16 (7%)	857 (11%)	0.7 (0.4–1.1)	0.8 (0.4–1.3)
IV	3 (1%)	10 (5%)	451 (6%)	0.2 (0.1–0.7)	0.4 (0.1–1.3)
Unknown	24 (11%)	20 (9%)	799 (11%)	–	–
Differentiation[e]	First tumour	Second tumour			
Well	17 (13%)	35 (16%)	1,118 (15%)	1[b]	1[b]
Moderate	26 (19%)	65 (30%)	1,798 (24%)	1.0 (0.5–1.8)	0.9 (0.5–1.8)

Table 2 continued

	Metachronous bilateral breast cancer		Unilateral breast cancer	Unadjusted odds ratio	Multiadjusted odds ratio[a]
Poor	22 (16%)	22 (10%)	998 (13%)	1.5 (0.8–2.7)	1.5 (0.8–2.9)
Unknown	71 (52%)	97 (44%)	3,624 (48%)	–	–
Oestrogen receptor[f]	First tumour	Second tumour			
Negative	8 (4%)	13 (6%)	400 (5%)	1[b]	1[b]
Positive	8 (4%)	62 (28%)	1,871 (25%)	0.2 (0.1–0.6)	0.2 (0.1–0.7)
Unknown	203 (93%)	144 (66%)	5,267 (70%)	–	–
Histology	First tumour	Second tumour			
Ductal	168 (77%)	164 (75%)	4,969 (66%)	1[b]	1[b]
Lobular	9 (4%)	25 (11%)	494 (7%)	0.5 (0.3–1.1)	0.8 (0.4–1.6)
Other	42 (19%)	30 (14%)	2,075 (28%)	0.6 (0.4–0.8)	0.3 (0.2–0.5)
Locoregional therapy	First tumour	Second tumour			
BCS + radiotherapy	33 (15%)	39 (18%)	2,206 (29%)	1[b]	1[b]
Mastectomy +/– radiotherapy	166 (76%)	134 (61%)	3,726 (49%)	3.0 (2.0–4.3)	1.5 (0.9–2.3)
Other	20 (9%)	36 (22%)	1,606 (21%)	0.8 (0.5–1.5)	1.1 (0.6–2.1)
Chemotherapy					
With	39 (18%)	48 (22%)	2,140 (28%)	1[b]	1[b]
Without/unknown	180 (82%)	171 (78%)	5,398 (72%)	1.8 (1.3–2.6)	1.8 (1.2–2.6)
Tamoxifen					
With	22 (10%)	88 (40%)	2,719 (36%)	1[b]	1[b]
Without/unknown	197 (90%)	131 (60%)	4,819 (64%)	5.1(3.2–7.9)	2.0 (1.2–3.4)

[a] Adjusted for age, period of diagnosis, stage, locoregional therapy, chemotherapy, hormone therapy. Due to the high proportion of patients with unknown oestrogen receptor status, this variable was not incorporated in multivariate analysis

[b] Reference category

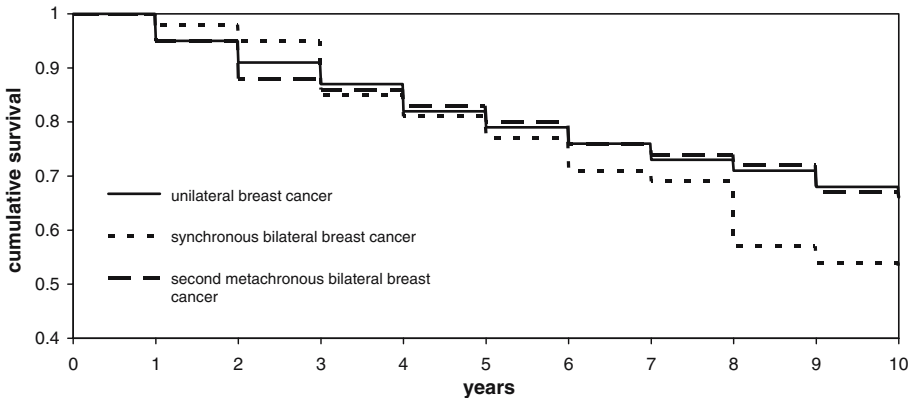
[c] In this comparison, period of diagnosis of the first bilateral tumour was taken into account

[d] Family history was only recorded for women diagnosed after 1990

[e] Tumour differentiation was only recorded for women diagnosed after 1985

[f] Oestrogen receptor status was only recorded for women diagnosed after 1995

other prognostic variables, the risk of death from breast cancer was no longer significantly increased for synchronous bilateral breast cancer patients (multiadjusted HR, 1.1; 95% CI, 0.9–1.5). Before adjustment, women with metachronous bilateral disease had a similar risk of death from breast cancer after their



Numbers at risk

Unilateral	7,538	6,645	5,802	5,032	4,380	3,793	3,310	2,887	2,529	2,214
Synchronous	155	138	124	99	85	72	61	54	42	32
Metachronous	219	190	159	147	120	104	92	79	70	60

Fig. 1 Disease-specific survival after unilateral, synchronous bilateral and second metachronous bilateral breast cancer

Table 3 Unadjusted and adjusted effect of bilaterality on breast cancer specific survival

	Unadjusted hazard ratios	Adjusted hazard ratios[a]
Unilateral breast cancer	1[b]	1[b]
Synchronous bilateral breast cancer	1.4 (1.1–1.8)	1.1 (0.9–1.5)
Metachronous bilateral breast cancer[c]	1.0 (0.8–1.3)	0.8 (0.5–1.4)

[a] Adjusted for age, social class, period of diagnosis, stage, grade, oestrogen receptor status, histology and treatment

[b] Reference

[c] For the calculation of breast cancer mortality risks after metachronous bilateral disease, the date of diagnosis of the second tumour was taken as starting point

second tumour as breast cancer patients who never had breast cancer before (HR, 1.0; 95% CI, 0.8–1.3) which remained similar after adjustment for all prognostic variables (multiadjusted HR, 0.8; 95% CI, 0.5–1.4). (Table 3).

Discussion

Patients with synchronous or metachronous bilateral breast cancer have the same risk of death from breast cancer as patients with unilateral disease. This means that having two breast cancers instead of one per se is not predictive of a worse prognosis. In addition, patients with synchronous and metachronous bilateral breast cancer do not share similar characteristics. The risk of synchronous bilateral cancer is three times higher in patients with stage III disease and in patients with lobular histology, while the risk of metachronous cancer is not influenced by these factors. Metachronous breast cancer, on the other hand, was more common in patients with oestrogen receptor negative disease and in women who did not receive adjuvant systemic treatment. The risk of metachronous cancer was higher in young women, while older women had an increased risk of synchronous bilateral breast cancer.

Previous investigators have reported higher rates of lobular histology among women with synchronous breast cancer [18, 25, 26]. Among the 526 patients at the Geneva cancer registry diagnosed with lobular histology, 32 (6.1%) had synchronous bilateral disease versus 98 (1.9%) of the 5,067 patients with ductal cancer. This higher risk of synchronous contralateral disease opens the question whether patients diagnosed with lobular breast cancer should undergo contralateral breast MRI to rule out simultaneous malignancy. Interestingly, lobular histology was not associated with an increased risk of developing contralateral breast cancer later in life.

As already previously demonstrated, we found that women who received adjuvant systemic treatment had a lower risk of developing a second breast cancer later in life [27].

Some studies reported increased familial risks among women with bilateral breast cancer [4, 28]. Carmichael et al. [3] reported a significantly higher frequency of breast cancer family history among women with metachronous bilateral breast cancer, but not among women with synchronous bilateral cancer . Intra et al. [25] did not observe an increased familial risks among women with synchronous bilateral disease. Our study includes data on family history of cancer systematically collected since 1990, for over 3,300 breast cancer patients [29]. Women with highly increased familial risk tend to have more synchronous and metachronous bilateral breast cancer, but not significantly so. Nevertheless, the number of patients with unknown family history is rather important and we can therefore not draw any clear conclusions.

Bilateral breast cancer is not considered a major phenotype in carriers of *BRCA1* or *BRCA2* germ-line mutations [12, 30] and, according to recent recommendations, bilateral breast cancer patients who have no first- or second-degree relative with breast or ovarian cancer are not candidates for *BRCA1/2* evaluation [31, 32].

Our study also suggests that patients with oestrogen receptor negative tumours are at increased risk of developing contralateral breast cancer later in life compared with patients with oestrogen receptor positive tumours. This is probably due to the fact that the majority of patients with oestrogen receptor positive tumours received hormone therapy, which is known to reduce the risk of contralateral breast cancer. We realize that our study includes a quite large number of patients with missing information on hormone receptor status. However, subgroup analysis, including only patients diagnosed after 1995 (year when the Geneva cancer registry started recording hormone receptor status), showed similar results.

Table 4 lists previous studies that compared survival between women with bilateral and those with unilat-

Table 4 Literature overview of the studies comparing survival after bilateral versus unilateral breast cancer

	Study period	Breast cancer patients *N*	Bilateral breast cancer cases (%) *N*	Study design	5-year survival bilateral versus unilateral	10-year survival bilateral versus unilateral	Adjusted mortality risks	Survival statistically different	Remarks
Synchronous bilateral breast cancer									
Heron et al. [19]	1960–1995	1,465	47 (3.0%)	Hosp.-based	83% vs. 91%[a]	79% vs. 86%[a,b]	1.3 (0.6–3.1)	No	DCIS included; mortality risks not adjusted for treatment
Kollias et al. [33]	1975–1995	3,210	26 (0.8%)	Hosp.-based	–	54% vs. 60%	–	Yes, synchronous worse	
Carmichael et al. [3]	1963–1999	1,945	43 (2.0%)	Hosp.-based	67% vs. 83%[a]	–	–	No	No multivariate analysis
Jobsen et al. [17]	1983–2000	1,760	26 (1.5%)	Hosp.-based	82% vs. 91%[c]	41% vs. 84%[c]	2.2 (0.7–7.2)	No	
Levi et al. [15]	1974–1993	6,084	81 (1.3%)	Pop.-based	65% vs.73%[d]	51% vs.59%[d]	–	Yes, synchronous worse	No multivariate analysis
Polednak et al. [18]	1995–1999	15,542	300 (1.9%)	Pop.-based	64% vs.76%[a]	–	1.4 (1.1–1.9)	Yes, synchronous worse	DCIS included; limited follow-up; mortality risks not adjusted for treatment.
Takahashi et al. [34]	1960–2001	1,214	13 (1.1%)	Hosp.-based	86% vs.78%[c]	64% vs.72%[c]	0.6 (0.1–2.3)	No	
This study	1970–2002	7,912	155 (2.0%)	Pop.-based	77% vs.78%[c]	51% vs. 66%[c]	1.1 (0.9–1.5)	No	
Metachronous bilateral breast cancer									
Holmberg et al. [13]	1977–1978	1,349	67	Pop.-based	53% vs.69%[b,d]	–	2.1 (1.3–3.3)	Yes, metachronous worse	
Healey et al. [35]	1968–1985	1,624	77 (5%)	Hosp.-based	–	–	1.2 (0.6–2.3)	No	Only stage I and II breast cancer. Metachronous breast cancer patients had an increased risk for local or distant recurrence (HR 1.7, 95% CI, 1.0–2.7)
Heron et al. [19]	1960–1995	1,465	103 (7.1%)	Hosp.-based	91% vs. 91%[a]	86% vs. 86%[a,b]	1.3 (0.6–3.2)[g]	No	DCIS included; mortality risks not adjusted for treatment; survival evaluated after the first tumour in metachronous cases.
Kollias et al. [33]	1975–1995	3,210	86 (2.6%)	Hosp.-based	–	42% vs.60%	–	Yes, metachronous worse	
Carmichael et al. [3]	1963–1999	1,945	43 (2%)	Hosp.-based	77% vs. 83%[a]	–	–	No	No multivariate analysis

Table 4 continued

	Study period	Breast cancer patients *N*	Bilateral breast cancer cases (%) *N*	Study design	5-year survival bilateral versus unilateral	10-year survival bilateral versus unilateral	Adjusted mortality risks	Survival statistically different	Remarks
Takahashi et al. [34]	1960–2001	1,214	33 (2.7%)	Hosp.-based	65% vs.78%[c]	65% vs.72%[c]	2.2 (1.1–4.4)	Yes, metachronous worse	
This study	1970–2002	7,912	219 (2.8%	Pop.-based	80% vs.78%[c]	66% vs. 66%[c]	0.8 (0.5–1.4)	No	
Synchronous and metachronous bilateral cancer regrouped									
Wanebo et al. [14]	1969–1975	137	37 (NA)	Hosp.-based, case–control	61% vs.68%[e]	23% vs.54%[e]	–	No	DCIS included; no multivariate analysis.
Mose et al. [21]	1977–1982	498	28 (7.2%)	Hosp.-based	83% vs.73%[a]	56% vs.54%[a]	–	No	No multivariate analysis
Gajalakshmi et al. [5]	1960–1989	3,492	67 (2.1%)	Hosp.-based	47% vs.51%[d]	30% vs.41%[d]	1.8 (1.4–7.4)	Yes, bilateral worse	Mortality risk not significantly increased for women < 55 years
Abdalla et al. [20]	1927–1987	2,136	132 (6.2%)	Hosp.-based	–	53% vs. 48%[c,f]	1.5 (1.1–2.0)[g]	Yes, bilateral worse	No adjustment for treatment
Newman et al. [4]	1983–1994	140	70 (NA)	Hosp.-based, case–control	91 vs. 94[e]	73% vs. 83%[e]	–	No	DCIS included; no multivariate analysis

DCIS: ductal carcinoma in situ; Hosp.-based: hospital-based; *N*: number; NA: not applicable (for case–control studies, proportions of bilateral cancers were not calculated); Pop.-based: population-based

[a] Overall survival

[b] 8 years survival

[c] Disease specific survival

[d] Relative survival

[e] Disease free survival

[f] 20 years survival

[g] Mortality risk calculated taking first of metachronous breast cancer as index date

eral breast cancer. Some studies found no significant difference in survival rates between women with unilateral and women with synchronous bilateral breast cancer [3, 17, 19, 34], whereas other studies show significantly impaired survival rates for patients with synchronous disease [15, 18, 33]. For metachronous bilateral breast cancer, mortality risks were inconsistent between studies: some reported impaired survival after metachronous breast cancer [13, 33, 34], whereas others observed no difference in mortality risk [3, 19, 35]. Some authors did not differentiate between synchronous and metachronous bilateral breast cancer. They reported either similar mortality risks between unilateral and bilateral breast cancer patients [4, 14, 21] or impaired survival of women with bilateral disease [5, 20]. There are several explanations for the disagreement between studies. Bilateral breast cancer is a relatively rare event, often resulting in underpowered studies. In addition, several studies included patients with in situ cancer, which may have underestimated the effect of bilaterality on survival, as in situ breast cancer is associated with excellent prognosis. Finally, many studies did not adjust the mortality risks for important prognostic factors, such as age, stage at diagnosis, and type of treatment.

In this population-based study, we included all breast cancer patient cases occurring in a well-defined population and we accounted for most established prognostic factors, including treatment. We found similar breast cancer mortality risks for women with metachronous bilateral breast cancer, synchronous bilateral breast cancer and unilateral breast cancer.

We calculated mortality risks of patients with metachronous breast cancer taking the date of diagnosis of the second tumour as reference date. Thus, we avoided a healthy patient bias, i.e. only healthy, younger patients with good prognostic tumours live long enough to develop a second breast cancer. As a result, we could not draw any conclusions concerning the impact of second metachronous breast cancer occurrence on survival after breast cancer. However, we can conclude that for women diagnosed with breast cancer, the fact of having had breast cancer before does not seem to impair their outcome.

In conclusion, bilaterality of breast cancer was not associated with decreased survival, giving reassuring evidence to both women and clinicians that the presence of a second cancer per se is not a sign of more severe disease.

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References

1. Dawson LA, Chow E, Goss PE (1998) Evolving perspectives in contralateral breast cancer. Eur J Cancer 34:2000–2009
2. Vaittinen P, Hemminki K (2000) Risk factors and age-incidence relationships for contralateral breast cancer. Int J Cancer 88:998–1002
3. Carmichael AR, Bendall S, Lockerbie L et al (2002) The long-term outcome of synchronous bilateral breast cancer is worse than metachronous or unilateral tumours. Eur J Surg Oncol 28:388–391
4. Newman LA, Sahin AA, Cunningham JE et al (2001) A case-control study of unilateral and bilateral breast carcinoma patients. Cancer 91:1845–1853
5. Gajalakshmi CK, Shanta V, Hakama M (1999) Survival from contralateral breast cancer. Breast Cancer Res Treat 58:115–122
6. Anderson DE, Badzioch MD (1985) Bilaterality in familial breast cancer patients. Cancer 56:2092–2098
7. Hemminki K, Vaittinen P (1999) Familial risks in second primary breast cancer based on a family cancer database. Eur J Cancer 35:455–458
8. Hartman M, Czene K, Reilly M (2005) Genetic implications of bilateral breast cancer: a population based cohort study. Lancet Oncol 6:377–382
9. Imyanitov EN, Hanson KP (2003) Molecular pathogenesis of bilateral breast cancer. Cancer Lett 191:1–7
10. Haffty BG, Harrold E, Khan AJ et al (2002) Outcome of conservatively managed early-onset breast cancer by BRCA1/2 status. Lancet 359:1471–1477
11. Chappuis PO, Stoppa-Lyonnet D, Asselain B et al (2002) The natural history of hereditary breast cancer. In: Morrison PJ, Hodgson SV, Haites NE (eds) Familial breast and ovarian cancer. Cambridge University Press, Cambridge
12. Steinmann D, Bremer M, Rades D et al (2001) Mutations of the BRCA1 and BRCA2 genes in patients with bilateral breast cancer. Br J Cancer 85:850–858
13. Holmberg L, Adami HO, Ekbom A et al (1988) Prognosis in bilateral breast cancer. Effects of time interval between first and second primary tumours. Br J Cancer 58:191–194
14. Wanebo HJ, Senofsky GM, Fechner RE et al (1985) Bilateral breast cancer. Risk reduction by contralateral biopsy. Ann Surg 201:667–677
15. Levi F, Randimbison L, Te VC et al (2003) Prognosis of bilateral synchronous breast cancer in Vaud, Switzerland. Breast 12:89–91
16. Kollias J, Ellis IO, Elston CW et al (1999) Clinical and histological predictors of contralateral breast cancer. Eur J Surg Oncol 25:584–589
17. Jobsen JJ, van der PJ, Ong F et al (2003) Synchronous, bilateral breast cancer: prognostic value and incidence. Breast 12:83–88
18. Polednak AP (2003) Bilateral synchronous breast cancer: a population-based study of characteristics, method of detection, and survival. Surgery 133:383–389
19. Heron DE, Komarnicky LT, Hyslop T et al (2000) Bilateral breast carcinoma: risk factors and outcomes for patients with synchronous and metachronous disease. Cancer 88:2739–2750
20. Abdalla I, Thisted RA, Heimann R (2000) The impact of contralateral breast cancer on the outcome of breast cancer patients treated by mastectomy. Cancer J 6:266–272
21. Mose S, Adamietz IA, Thilmann C et al (1997) Bilateral breast carcinoma versus unilateral disease. Review of 498 patients. Am J Clin Oncol 20:541–545

22. Bouchardy C (1997) Switzerland Geneva. In: Parkin DM, Whelan SL, Ferlay J et al (eds) Cancer incidence in five continents, vol VII. International Agency for Research on Cancer, Lyon
23. ICD-O International classification of diseases for oncology (1976) 1st edn. World Health Organization, Geneva
24. TNM classification of malignant tumours (2002) 6th edn. UICC, New York
25. Intra M, Rotmensz N, Viale G et al (2004) Clinicopathologic characteristics of 143 patients with synchronous bilateral invasive breast carcinomas treated in a single institution. Cancer 101:905–912
26. Mertens WC, Hilbert V, Makari-Judson G (2004) Contralateral breast cancer: factors associated with stage and size at presentation. Breast J 10:304–312
27. Early Breast Cancer Trialists' Collaborative Group (2005) Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: an overview of the randomised trials. Lancet 365:1687–1717
28. Gajalakshmi CK, Shanta V, Hakama M (1998) Risk factors for contralateral breast cancer in Chennai (Madras), India. Int J Epidemiol 27:743–750
29. Verkooijen HM, Fioretta G, Chappuis PO et al (2004) Set-up of a population-based familial breast cancer registry in Geneva, Switzerland: validation of first results. Ann Oncol 15:350–353
30. Gershoni-Baruch R, Dagan E, Fried G et al (1999) BRCA1 and BRCA2 founder mutations in patients with bilateral breast cancer. Eur J Hum Genet 7:833–836
31. Nelson HD, Huffman LH, Fu R et al (2005) Genetic risk assessment and BRCA mutation testing for breast and ovarian cancer susceptibility: systematic evidence review for the U.S. Preventive Services Task Force. Ann Intern Med 143:362–379
32. Hampel H, Sweet K, Westman JA et al (2004) Referral for cancer genetics consultation: a review and compilation of risk assessment criteria. J Med Genet 41:81–91
33. Kollias J, Ellis IO, Elston CW et al (2001) Prognostic significance of synchronous and metachronous bilateral breast cancer. World J Surg 25:1117–1124
34. Takahashi H, Watanabe K, Takahashi M et al (2005) The impact of bilateral breast cancer on the prognosis of breast cancer: a comparative study with unilateral breast cancer. Breast Cancer 12:196–202
35. Healey EA, Cook EF, Orav EJ et al (1993) Contralateral breast cancer: clinical characteristics and impact on prognosis. J Clin Oncol 11:1545–1552