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Bilateral Mastectomy and Breast Cancer Mortality

Vasily Giannakeas, PhD, MPH; David W. Lim, MDCM, MEd, PhD; Steven A. Narod, MD

IMPORTANCE The benefit of bilateral mastectomy for women with unilateral breast cancer in terms of deaths from breast cancer has not been shown.

OBJECTIVES To estimate the 20-year cumulative risk of breast cancer mortality among women with stage 0 to stage III unilateral breast cancer according to the type of initial surgery performed.

DESIGN, SETTINGS, AND PARTICIPANTS This cohort study used the Surveillance, Epidemiology, and End Results (SEER) Program registry database to identify women with unilateral breast cancer (invasive and ductal carcinoma in situ) who were diagnosed from 2000 to 2019. Three closely matched cohorts of equal size were generated using 1:1:1 matching according to surgical approach. The cohorts were followed up for 20 years for contralateral breast cancer and for breast cancer mortality. The analysis compared the 20-year cumulative risk of breast cancer mortality for women treated with lumpectomy vs unilateral mastectomy vs bilateral mastectomy. Data were analyzed from October 2023 to February 2024.

EXPOSURES Type of breast surgery performed (lumpectomy, unilateral mastectomy, or bilateral mastectomy).

MAIN OUTCOMES AND MEASURES Contralateral breast cancer or breast cancer mortality during the 20-year follow-up period among the groups treated with lumpectomy vs unilateral mastectomy vs bilateral mastectomy.

RESULTS The study sample included 661 270 women with unilateral breast cancer (mean [SD] age, 58.7 [11.3] years). After matching, there were 36 028 women in each of the 3 treatment groups. During the 20-year follow-up, there were 766 contralateral breast cancers observed in the lumpectomy group, 728 contralateral breast cancers in the unilateral mastectomy group, and 97 contralateral cancers in the bilateral mastectomy group. The 20-year risk of contralateral breast cancer was 6.9% (95% CI, 6.1%-7.9%) in the lumpectomy-unilateral mastectomy group. The cumulative breast cancer mortality was 32.1% at 15 years after developing a contralateral cancer and was 14.5% for those who did not develop a contralateral cancer (hazard ratio, 4.00; 95% CI, 3.52-4.54, using contralateral breast cancer as a time-dependent covariate). Deaths from breast cancer totaled 3077 women (8.54%) in the lumpectomy group, 3269 women (9.07%) in the unilateral mastectomy group, and 3062 women (8.50%) in the bilateral mastectomy group.

CONCLUSIONS AND RELEVANCE This cohort study indicates that the risk of dying of breast cancer increases substantially after experiencing a contralateral breast cancer. Women with breast cancer treated with bilateral mastectomy had a greatly diminished risk of contralateral breast cancer; however, they experienced similar mortality rates as patients treated with lumpectomy or unilateral mastectomy.

Editorial

Supplemental content

Author Affiliations: Women's College Research Institute, Women's College Hospital, Toronto, Ontario, Canada (Giannakeas, Lim, Narod); Women's Age Lab, Women's College Hospital, Toronto, Ontario, Canada (Giannakeas); Dalla Lana School of Public Health, University of Toronto, Toronto, Ontario, Canada (Giannakeas, Narod); Department of Surgery, Women's College Hospital, Toronto, Ontario, Canada (Lim); Department of Surgery, Division of General Surgery, University of Toronto, Toronto, Ontario, Canada (Lim); Institute of Medical Science, Temerty Faculty of Medicine, University of Toronto, Toronto, Ontario, Canada (Lim, Narod).

Corresponding Author: Steven A. Narod, MD, Women's College Research Institute, Women's College Hospital, 76 Grenville St, 6th Floor, Toronto, ON M5S 1B2, Canada (steven.narod@wchospital.ca).

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Many women with cancer in 1 breast, including those with ductal carcinoma in situ (DCIS), opt for bilateral mastectomy as their initial treatment.[1] The rationale for choosing bilateral mastectomy includes reducing the risk of a second primary cancer with the hope that this will reduce the chance of death.[1-6] For some women, undergoing reconstruction after bilateral mastectomy is expected to produce a more symmetrical appearance.[1-6]

It is established that removal of the unaffected breast reduces the incidence of second primary cancers,[1] but studies to date have not shown a decline in breast cancer mortality.[7,8] The lack of survival benefit may be due to contralateral breast cancer being too rare an event to see an effect and/or that it is caught early through screening. In theory, the expected benefit of contralateral mastectomy can be predicted by the risk of developing contralateral breast cancer and the extent to which experiencing a contralateral breast cancer increases breast cancer mortality.

We have recently shown that the risk of contralateral breast cancer is approximately 0.4% per year for 20 years postdiagnosis.[9] Personalized knowledge of the risk of contralateral cancer and the benefit of bilateral mastectomy may facilitate counseling for women who are considering a bilateral mastectomy for the treatment of unilateral breast cancer.[10-12] We studied a large US-based cohort of women with a stage 0 to stage III breast cancer (per the *American Joint Committee on Cancer Staging Manual, eighth edition*) to estimate the cumulative risk of contralateral breast cancer and breast cancer mortality from diagnosis until 20 years postdiagnosis and compared outcomes according to the initial type of surgery.

Key Points

Question Does bilateral mastectomy for treatment of unilateral breast cancer reduce the 20-year risk of breast cancer mortality?

Findings This cohort study including 661 270 women with unilateral breast cancer who were closely matched by treatment type (lumpectomy, unilateral mastectomy, or bilateral mastectomy) and followed up for 20 years found that bilateral mastectomy was associated with a statistically significant reduction of contralateral breast cancer risk but not breast cancer mortality.

Meaning These findings indicating that contralateral mastectomy for unilateral breast cancer is an effective means of cancer prevention but does not reduce the risk of dying of breast cancer call into question the metastatic potential of a de novo contralateral cancer.

Methods

This cohort study was approved by the Women's College Hospital Ethics Board (Canada). Patient informed consent was not required because the study did not include identifiable data. The study was performed in accordance with the Declaration of Helsinki and adhered to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline.[13]

Study Cohort

Using SEERStat statistical software version 8.4.2, we performed a case-listing session of women diagnosed with a primary breast cancer in the SEER 17 registry (November 2021 submission). We included women with in situ or invasive breast cancer diagnosed from 2000 through 2019. We excluded women with any prior cancer; women who were diagnosed when they were younger than 30 years or 80 years or older; breast cancers with missing clinical information (eg, tumor stage, size, nodal status, laterality) or with stage not between 0 and IIIC; invasive or in situ breast cancers with histologic findings that were not of ductal, lobular, or mixed subtype; and missing or no follow-up months (eTables 1 and 2 in Supplement 1). We also excluded women who had no recorded surgery, unknown surgery, or had a mastectomy with an unspecified laterality. To avoid immortal time bias from treatment, we left-truncated our follow-up at 6 months postdiagnosis, and excluded women with any cancer events within 6 months of the initial diagnosis (eTable 3 in Supplement 1).

For each patient with unilateral breast cancer, we retrieved data on age at diagnosis, race and ethnicity, marital status, rurality, and median (county-level) household income from the SEER records. We also collected tumor data: year of diagnosis, laterality, tumor behavior (in situ or invasive), histologic subtype (ductal, lobular, or mixed), grade, stage, size, spread to the lymph nodes (N stage), and receptor status (estrogen receptor [ER], progesterone receptor, and human epidermal growth factor receptor 2 [*ERBB2*, formerly *HER2*]); and treatment data: type of breast surgery (lumpectomy, unilateral mastectomy, or bilateral mastectomy), chemotherapy (yes, no/unknown), and radiotherapy (yes, no, unknown). Information on endocrine therapy was not available in the SEER database.

Patients were followed up beginning at 6 months postdiagnosis (of the first breast cancer) until death from any cause, loss to follow-up, or the end of the study period (November 2021). We collected information on cause of death for those who died. We captured contralateral breast cancer events in the follow-up period by identifying invasive breast cancers that occurred in the opposite breast, and we recorded the time from the primary diagnosis to the diagnosis of the contralateral breast cancer. We also recorded clinical and treatment characteristics of the contralateral breast cancer.

Propensity Scores

We estimated generalized propensity scores for the 3 breast surgery groups: lumpectomy, unilateral mastectomy, and bilateral mastectomy. To accommodate nonlinear relationships and interactions among predictor variables, we used generalized boosted multinomial regression trees from the TWANG (Toolkit for Weighting and Analysis of Nonequivalent Groups,[14] version 2.5) in R (The R Foundation for Statistical Computing). The features incorporated into the classification model included patient demographics, clinical information, and treatment variables (eTable 4 in Supplement 1). We ran 20 000 gradient boosted machine iterations and retained the optimal model for

deriving our propensity score estimates. Subsequently, 3 generalized propensity score estimates were generated for each patient in our cohort, corresponding to each potential surgical approach.

Matching

We performed 1:1:1 matching of patients with lumpectomy vs unilateral mastectomy vs bilateral mastectomy. Each of the 3 observations were matched on year of diagnosis (within 2 years), age at diagnosis (within 2 years), histologic subtype, stage, estrogen-receptor status, and propensity score. For the propensity score matching criteria, we used a caliper of 0.6 times the SD of the logit of the propensity score among patients in each of the cohort's treatment groups.[15,16] Thus, we obtained 3 caliper values corresponding to each treatment level. Triplets were considered as a potential match if they met all of the matching criteria and absolute differences in propensity score between each observation were less than the caliper values (for each treatment level). Among potential triplets that met these criteria, we selected the group with the smallest sum of the Euclidean distance between observations of the propensity score values. Participants in the cohort were matched without replacement. A standardized difference of 0.1 or greater was considered to be a meaningful imbalance between groups.[17]

Statistical Analysis

We calculated the cumulative risk of contralateral breast cancer for the 20-year period after the breast cancer diagnosis for all women and by initial surgery performed. We followed up all participants for breast cancer–specific death from 6 months postdiagnosis to date of death, loss to follow-up, or end of the follow-up period (November 30, 2021). We used the Kaplan-Meier method to estimate the survival of patients with breast cancer at 20 years postdiagnosis by surgery type. We estimated the subdistribution hazard ratio (HR) for breast cancer outcomes using a Fine and Gray survival model while treating other causes of death as a competing risk. We treated contralateral breast cancer as a time-dependent variable when evaluating the association with breast cancer mortality. Furthermore, we estimated annual rates of our outcomes by dividing the number of events by the total number of person-years for each year of follow-up. *P* values were 2-tailed with a level of significance set at < .05. Statistical analyses were performed from October 2023 to February 2024 using SAS statistical software, version 9.4 (SAS Institute).

Results

There were 661 270 eligible women with breast cancer (mean [SD] age, 58.7 [11.3]) in the study cohort; 564 062 cases of invasive breast cancer (85.3%) and 97 208 cases of DCIS (14.7%). Descriptive details of the entire cohort are shown in eTable 5 in Supplement 1. Most of the cohort (70.6%) had undergone breast-conserving surgery, 23.4% had a unilateral mastectomy, and 6.0% had a bilateral mastectomy. Most of the participants had received radiotherapy (61.9%) and 37.1% were known to have received chemotherapy. Patients who had undergone mastectomy were younger than those who underwent lumpectomy, were more likely to have a lobular or mixed breast cancer, and were more likely to have advanced clinical features (high tumor grade, larger size, and greater nodal involvement) (eTable 5 in Supplement 1).

We successfully matched 90.7% of the patients with bilateral mastectomy to generate 3 surgical groups of equal size based on the criteria described in the Methods section. After matching, there were 36 028 women in each of the 3 treatment groups. After matching, groups were similar across demographic, clinical, treatment variables, and propensity scores (**Table 1**; eTable 6 and eFigures 1 and 2 in Supplement 1). Patients with bilateral mastectomy who were not successfully matched had an earlier age at diagnosis, were more likely to have unfavorable tumor characteristics, and were more likely to have received chemotherapy and radiotherapy (eTable 7 in Supplement 1).

Breast cancer outcomes of the 3 matched groups are shown in **Table 2**. There were 766 patients (2.1% of cohort) with contralateral invasive breast cancer in the lumpectomy group; 728 patients (2.0%) with contralateral cancer in the unilateral mastectomy group; and 97 patients (0.3%) with contralateral breast cancer in the bilateral mastectomy group. Breast cancer characteristics and treatments used for contralateral cancer are shown in eTable 8 in Supplement 1. The median (IQR) time-elapsed between the primary cancer and the contralateral cancer was 5.0 (2.3-8.6) years. The annual risk of contralateral breast cancer for the lumpectomy and unilateral mastectomy groups combined over the 20-year follow-up period was 0.3% per year and the 20-year cumulative incidence of contralateral invasive breast cancer was 6.9% (eTable 9 in Supplement 1; **Figure**, A). The cumulative risk of contralateral breast cancer for patients with DCIS was slightly higher than that for patients with invasive cancer (8.2% vs 6.8%, respectively). The 20-year cumulative risk of contralateral breast cancer was 6.7% for ductal patients, 7.1% for lobular breast cancer patients, and 8.0% for those with mixed histologic findings.

In the lumpectomy and unilateral mastectomy groups combined, the cumulative breast cancer mortality at 15 years was 32.1% for those who developed contralateral cancer and 14.5% for those who did not (Figure, B). The HR for dying of breast cancer after experiencing a contralateral breast cancer for these patients was 4.00 (95% CI, 3.52-4.54). The HR was higher for women initially treated for DCIS (HR, 10.30; 95% CI, 5.17-20.49) than for women initially treated for invasive cancer (HR, 4.04; 95% CI, 3.54-4.60). For all matched patients, the HR for breast cancer mortality was similar for time from primary diagnosis to contralateral cancer. After experiencing a contralateral breast cancer in the first 5 years, the HR was 3.89 (95% CI, 3.36-4.49); in 5 to 10 years, the HR was 4.12 (95% CI, 3.24-5.23); in 10 to 15 years, the HR was 4.48 (95% CI, 2.73-7.35). The HR for breast cancer mortality declined slightly with increasing age at diagnosis of the contralateral cancer (30-39 years: HR, 5.16; 95% CI, 3.17-8.39; 40-64 years: HR, 4.19; 95% CI, 3.62-4.84; ≥65 years: HR, 3.25; 95% CI, 2.55-4.14) (eTable 10 in Supplement 1).

Table 1. Differences in Demographic, Clinical, and Treatment Characteristics Among Surgical Treatment Groups in Matched Cohort

Characteristic	Treatment group, No. (%)			Standardized difference		
	(1) Lumpectomy	(2) Unilateral mastectomy	3-Bilateral mastectomy	1 vs 2	1 vs 3	2 vs 3
Participants	36 028 (33.3)	36 028 (33.3)	36 028 (33.3)			
Year of diagnosis						
Mean (SD)	2010.8 (4.9)	2010.7 (4.9)	2010.8 (5.0)	0	0.01	0.01
Median (IQR)	2011 (2007-2015)	2011 (2007-2015)	2011 (2007-2015)			
Age at diagnosis, y						
Mean (SD)	53.4 (10.9)	53.4 (10.9)	53.3 (11.0)	0	0.01	0.01
Median (IQR)	53.0 (45.0-61.0)	53.0 (45.0-61.0)	52.0 (45.0-61.0)			
Race						
American Indian/Alaska Native	230 (0.6)	228 (0.6)	282 (0.8)	0	0.02	0.02
Black	3094 (8.6)	3031 (8.4)	2872 (8.0)	0.01	0.02	0.02
East Asian	718 (2.0)	693 (1.9)	724 (2.0)	0.01	0.01	0
Pacific Islander	213 (0.6)	258 (0.7)	235 (0.7)	0.02	0.01	0.01
South Asian	265 (0.7)	271 (0.8)	253 (0.7)	0	0.01	0
Southeast Asian	938 (2.6)	938 (2.6)	949 (2.6)	0	0	0
White	29 951 (83.1)	30 000 (83.3)	30 120 (83.6)	0	0.01	0.01
Other or unknown[a]	619 (1.7)	609 (1.7)	593 (1.6)	0	0	0.01
Ethnicity						
Non-Hispanic	31 895 (88.5)	31 785 (88.2)	32 280 (89.6)	0.01	0.04	0.03
Hispanic	4133 (11.5)	4243 (11.8)	3748 (10.4)	0.01	0.04	0.03
Marital status						
Married	22 759 (63.2)	22 712 (63.0)	22 859 (63.4)	0	0.01	0.01
Never married	5462 (15.2)	5493 (15.2)	5242 (14.5)	0	0.02	0.02
Divorced	4352 (12.1)	4383 (12.2)	4530 (12.6)	0	0.01	0.02
Widowed	2119 (5.9)	2090 (5.8)	2074 (5.8)	0	0	0.01
Unknown	1336 (3.7)	1350 (3.7)	1323 (3.7)	0	0	0
Median county-level household income, $						
<35 000	425 (1.2)	483 (1.3)	479 (1.3)	0.01	0	0.01
35 000-39 999	779 (2.2)	789 (2.2)	740 (2.1)	0	0.01	0.01
40 000-44 999	1385 (3.8)	1423 (3.9)	1342 (3.7)	0.01	0.01	0.01
45 000-49 999	1864 (5.2)	1865 (5.2)	1785 (5.0)	0	0.01	0.01
50 000-54 999	2917 (8.1)	3023 (8.4)	3121 (8.7)	0.01	0.01	0.02
55 000-59 999	2682 (7.4)	2682 (7.4)	2830 (7.9)	0	0.02	0.02
60 000-64 999	6138 (17.0)	6078 (16.9)	6008 (16.7)	0	0.01	0.01
65 000-69 999	5675 (15.8)	5635 (15.6)	5801 (16.1)	0	0.01	0.01
70 000-74 999	3101 (8.6)	3134 (8.7)	3193 (8.9)	0	0.01	0.01
>75 000	11 062 (30.7)	10 915 (30.3)	10 728 (29.8)	0.01	0.01	0.02
Unknown	0	1 (0)	1 (0)	0.01	0	0.01
Rurality						
Large metropolitan	21 954 (60.9)	21 738 (60.3)	21 542 (59.8)	0.01	0.01	0.02
Medium metropolitan	7174 (19.9)	7280 (20.2)	7181 (19.9)	0.01	0.01	0
Small metropolitan	2915 (8.1)	2915 (8.1)	2968 (8.2)	0	0.01	0.01
Suburb	2359 (6.5)	2475 (6.9)	2501 (6.9)	0.01	0	0.02
Rural	1584 (4.4)	1585 (4.4)	1780 (4.9)	0	0.03	0.03
Unknown	42 (0.1)	35 (0.1)	56 (0.2)	0.01	0.02	0.01
Behavior						
In situ	3451 (9.6)	3451 (9.6)	3451 (9.6)	0	0	0
Invasive	32 577 (90.4)	32 577 (90.4)	32 577 (90.4)	0	0	0
Tumor type						
Ductal	30 283 (84.1)	30 283 (84.1)	30 283 (84.1)	0	0	0
Lobular	3473 (9.6)	3473 (9.6)	3473 (9.6)	0	0	0
Mixed	2272 (6.3)	2272 (6.3)	2272 (6.3)	0	0	0

(continued)

Table 1. Differences in Demographic, Clinical, and Treatment Characteristics Among Surgical Treatment Groups in Matched Cohort (continued)

Characteristic	Treatment group, No. (%)			Standardized difference		
	(1) Lumpectomy	(2) Unilateral mastectomy	3-Bilateral mastectomy	1 vs 2	1 vs 3	2 vs 3
Cancer stage[b]						
0	3451 (9.6)	3451 (9.6)	3451 (9.6)	0	0	0
I	11 760 (32.6)	11 760 (32.6)	11 760 (32.6)	0	0	0
IIA	8734 (24.2)	8734 (24.2)	8734 (24.2)	0	0	0
IIB	6089 (16.9)	6089 (16.9)	6089 (16.9)	0	0	0
IIIA	4177 (11.6)	4177 (11.6)	4177 (11.6)	0	0	0
IIIB	373 (1.0)	373 (1.0)	373 (1.0)	0	0	0
IIIC	1444 (4.0)	1444 (4.0)	1444 (4.0)	0	0	0
Tumor grade[b]						
I	5021 (13.9)	5290 (14.7)	5274 (14.6)	0.02	0	0.02
II	14 772 (41.0)	14 881 (41.3)	14 633 (40.6)	0.01	0.01	0.01
III	14 817 (41.1)	14 521 (40.3)	14 679 (40.7)	0.02	0.01	0.01
Unknown	1418 (3.9)	1336 (3.7)	1442 (4.0)	0.01	0.02	0
Size, cm						
Mean (SD)	2.4 (1.6)	2.5 (1.6)	2.5 (1.7)	0.01	0.01	0.03
Median (IQR)	2.0 (1.3-3.1)	2.0 (1.3-3.2)	2.0 (1.2-3.2)			
Tumor stage[b]						
Tis	3452 (9.6)	3451 (9.6)	3454 (9.6)	0	0	0
T1	16 101 (44.7)	15 814 (43.9)	15 941 (44.2)	0.02	0.01	0.01
T2	13 680 (38.0)	13 798 (38.3)	13 417 (37.2)	0.01	0.02	0.02
T3	2463 (6.8)	2620 (7.3)	2851 (7.9)	0.02	0.02	0.04
T4	332 (0.9)	345 (1.0)	365 (1.0)	0	0.01	0.01
N stage[b]						
N0	19 946 (55.4)	20 240 (56.2)	20 153 (55.9)	0.02	0	0.01
N1	11 471 (31.8)	11 193 (31.1)	11 313 (31.4)	0.02	0.01	0.01
N2	3154 (8.8)	3111 (8.6)	3090 (8.6)	0	0	0.01
N3	1457 (4.0)	1484 (4.1)	1472 (4.1)	0	0	0
ER status						
Negative	7304 (20.3)	7304 (20.3)	7304 (20.3)	0	0	0
Positive	27 275 (75.7)	27 275 (75.7)	27 275 (75.7)	0	0	0
Unknown	1449 (4.0)	1449 (4.0)	1449 (4.0)	0	0	0
PR status						
Negative	10 575 (29.4)	10 593 (29.4)	10 784 (29.9)	0	0.01	0.01
Positive	23 530 (65.3)	23 488 (65.2)	23 358 (64.8)	0	0.01	0.01
Unknown	1923 (5.3)	1947 (5.4)	1886 (5.2)	0	0.01	0
ERBB2 (*HER2*) status						
Not applicable	13 888 (38.5)	13 878 (38.5)	13 772 (38.2)	0	0.01	0.01
Negative	15 722 (43.6)	15 794 (43.8)	15 751 (43.7)	0	0	0
Positive	3857 (10.7)	3758 (10.4)	3864 (10.7)	0.01	0.01	0
Unknown	2561 (7.1)	2598 (7.2)	2641 (7.3)	0	0	0.01
Radiotherapy						
No	25 267 (70.1)	25 283 (70.2)	25 239 (70.1)	0	0	0
Yes	9947 (27.6)	9932 (27.6)	9949 (27.6)	0	0	0
Unknown	814 (2.3)	813 (2.3)	840 (2.3)	0	0.01	0
Chemotherapy						
No or unknown	15 820 (43.9)	15 915 (44.2)	15 539 (43.1)	0.01	0.02	0.02
Yes	20 208 (56.1)	20 113 (55.8)	20 489 (56.9)	0.01	0.02	0.02

Abbreviations: ER, estrogen receptor; PR, progesterone receptor.

[a] Other includes other Asian, unknown, and missing data.

[b] Per the *American Joint Committee on Cancer Staging Manual, eighth edition*.

The number of deaths from breast cancer in each group was 3077 women in the lumpectomy group, 3269 women (9.07%) in the unilateral mastectomy group, and 3062 women (8.50%) in the bilateral mastectomy group (Table 2). The 20-

Table 2. Breast Cancer Outcomes Among Matched Participants, by Surgery Type[a]

Outcome	Participants, No.	Events, No.	PY	Rate/100 PY	20-y Cumulative incidence (95% CI)	HR (95% CI)	*P* value
Contralateral invasive breast cancer							
Lumpectomy	36 028	766	252 623.5	0.3	7.8 (6.3-9.5)	1.00 [Reference]	NA
Unilateral mastectomy	36 028	728	252 284.8	0.29	6.1 (5.3-7.0)	0.93 (0.87-1.01)	.08
Bilateral mastectomy	36 028	97	259 473.7	0.04	0.7 (0.5-0.9)	0.12 (0.10-0.15)	<.001
Breast cancer death							
Lumpectomy	36 028	3077	256 156.1	1.2	16.3 (15.4-17.1)	1.00 [Reference]	NA
Unilateral mastectomy	36 028	3269	255 542.6	1.28	16.7 (15.9-17.6)	1.07 (1.02-1.11)	.003
Bilateral mastectomy	36 028	3062	259 905.1	1.18	16.7 (15.7-17.7)	0.99 (0.95-1.03)	.57

Abbreviations: HR, hazard ratio; NA, not applicable; PY, person years.

[a] Survival estimates (20-year cumulative incidence, HR, and *P* value) were generated while accounting for competing risks. For contralateral invasive breast cancer, death was treated as a competing risk. For breast cancer–specific death, all other death categories were treated as a competing risk.

year cumulative mortality from breast cancer was 16.3% for those in the lumpectomy group, 16.7% for those in the unilateral mastectomy group, and 16.7% for those in the bilateral mastectomy group (Figure, C). Compared to women in the lumpectomy group, the HR for dying of breast cancer for those in the bilateral mastectomy group was 0.99 (95% CI, 0.95-1.03). Compared to women in the lumpectomy group, the HR for dying of breast cancer for those in the unilateral mastectomy group was 1.07 (95% CI, 1.02-1.11). In patients with lobular cancer, a bilateral mastectomy was associated with a significant reduction in breast cancer mortality compared with lumpectomy (HR, 0.80; 95% CI, 0.70-0.92; *P* = .002) (eTable 11 in Supplement 1). The 20-year mortality from lobular cancer was also higher than that for patients with ductal or mixed histologic findings and was higher for patients with ER-negative breast cancer than ER-positive breast cancers. The HR for dying of breast cancer by surgery type was stable by follow-up interval (eTable 12 in Supplement 1).

Discussion

Rates of contralateral prophylactic mastectomy and bilateral mastectomy are increasing among women with unilateral, sporadic breast cancer.[1,18,19] This is despite consensus guidelines discouraging the procedure in women of average risk.[20-24] It is possible that many women who chose bilateral mastectomy overestimate their risk of developing a contralateral breast cancer[1-6,24] and may overestimate the benefit in terms of reducing breast cancer deaths. This emphasizes the need to have accurate information on the risks to enable physician counseling and improve patient education.

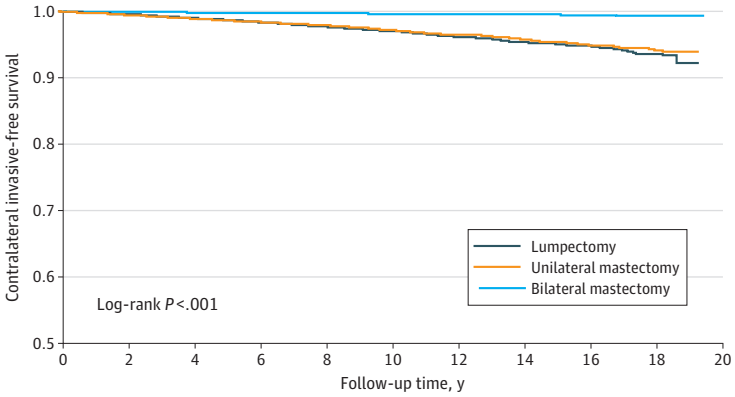
These study findings indicate that the risk of contralateral cancer is 6.9% at 20 years postdiagnosis and that the occurrence of a contralateral cancer increases the subsequent chance of death by 4-fold. However, prevention of contralateral cancer through preemptive surgery did not appear to reduce the risk of death in the 20-year period. This situation is analogous to that of ipsilateral invasive recurrence.[25,26] In the NSABP B-04 trial, Fisher et al[25] reported that the risk of distant disease was 3.4 times greater in patients in whom an ipsilateral recurrence occurred. However, neither mastectomy nor breast irradiation after lumpectomy lowered the risk of distant disease. These authors concluded in 1991 that an ipsilateral recurrence was a "'marker' for a risk already present"[25] and indicative of a failure of adjuvant chemotherapy to eradicate latent metastases. It is generally presumed that a contralateral breast cancer is a new primary tumor with the potential to metastasize. Our findings question this interpretation. If the increase in deaths after a contralateral breast cancer were due to metastasis of the second cancer, we would expect bilateral mastectomy to be beneficial.

It has been speculated that in most previous studies the numbers are too few to demonstrate a substantial mortality benefit from contralateral cancer. In the current study, there were 1591 cases of contralateral breast cancer among the 3 groups, and we were able to show that contralateral breast cancers increased the risk of dying (HR of 3.96 for all matched patients). This finding is inconsistent with the position that contralateral cancers are caught early and do not impact on survival. In the California Cancer Registry,[27] survival was compared for 377 176 women with unilateral breast cancer and 15 586 with contralateral breast cancer (women with bilateral mastectomy were excluded). The contralateral breast cancers were on average smaller than the first primary cancers and less likely to be node positive. Nevertheless, contralateral breast cancer was associated with worse survival compared with unilateral breast cancer. The findings of that study[27] and our study suggest that early detection of contralateral breast cancer may not be an effective means of reducing mortality. Furthermore, if preventing contralateral cancer is not an effective means of mortality reduction, it is unlikely that screening postdiagnosis would be effective.

Some have suggested that in previous studies[28,29] the various treatment groups had inherently different mortality risks. For this reason, we generated 3 closely matched groups with similar demographic characteristics and other prognostic factors. One might propose that the contralateral cancers represent metastases of the first cancer; this has been shown to be true in some cases.[28,29] However, the risk of contralateral cancer was the same for patients with DCIS as with invasive cancer, despite that those with DCIS have a much lower risk of metastases.[9] We have also shown previously that patients

Figure. Breast Cancer–Specific Outcomes Among Matched Participants, by Surgery Type[a]

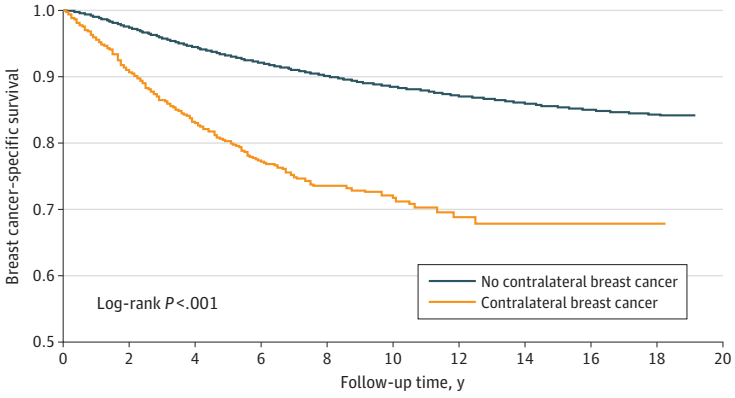
A 20-y Contralateral invasive-free survival



No. at risk

Lumpectomy	36028	30409	24450	18866	13987	9606	6032	3,634	1905	568	0
Unilateral mastectomy	36028	30207	24304	18858	13953	9598	6105	3723	1946	591	0
Bilateral mastectomy	36028	30631	24970	19419	14551	10059	6422	3904	2099	709	0

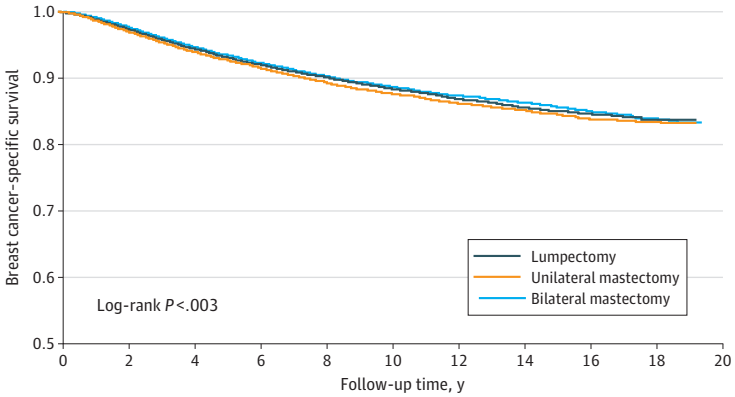
B 20-y Breast cancer-specific survival after contralateral invasive breast cancer



No. at risk

No contralateral breast cancer	72056	60616	48754	37724	27940	19204	12137	7357	3851	1159	0
Contralateral breast cancer	1494	1051	676	430	260	168	83	36	9	1	0

C 20-y Breast cancer-specific survival



No. at risk

Lumpectomy	36028	30532	24676	19148	14287	9879	6268	3821	2021	604	0
Unilateral mastectomy	36028	30349	24544	19132	14206	9847	6317	3866	2025	621	0
Bilateral mastectomy	36028	30662	25006	19449	14580	10088	6445	3922	2107	713	0

Twenty-year contralateral invasive breast cancer-free survival among matched participants, by surgery type (A); 20-year breast cancer–specific survival after experiencing a contralateral invasive breast cancer (B); 20-year breast cancer–specific survival among matched participants, by surgery type (C).

[a]Panel B includes only matched patients with lumpectomy or unilateral mastectomy.

with DCIS have similar risks of invasive ipsilateral recurrence as patients with invasive cancers.[30]

There have been several articles published on the impact of contralateral breast cancer on breast cancer survival. In a study from Sweden, Hartman et al[31] reported that the prognosis depended mostly on the time elapsed from first primary tumor to contralateral breast cancer. Women who developed contralateral cancer within 5 years of the first primary had a much higher mortality than those who experienced it 10 or more years from first diagnosis. We did not observe this in our study; using contralateral cancer as a time-dependent variable, the HR for death from breast cancer was approximately 4 for all time frames.

The strengths of our study were that we performed an analysis on the risks of contralateral breast cancer and breast cancer mortality using a contemporary population-based cohort. To our knowledge, this is the largest contemporary population-based study of bilateral mastectomy patients studied to date and with longer follow-up than prior survival analyses,[8,32,33] given that patients were followed up for an average of 7.1 years. We were able to examine the influence of patient, tumor, and treatment factors on the risk of contralateral cancer.

Limitations

The study had several limitations. We did not have data on the use of endocrine therapy, and this may have affected the risks of contralateral cancer among patients with ER-positive breast cancer (invasive and DCIS). We did not have data on family history or *BRCA1* or *BRCA2* variation status; these patients are at higher risk of contralateral breast cancer. We did not have cancer screening records, and many of the contralateral cancers may have been associated with intensified screening efforts. There are many risk factors for contralateral breast cancers, including use of tamoxifen, chemotherapy, gene variations, personalized risk scores, and family history that we did not consider.[34-41] It is also possible that there are several other unmeasured confounders that were not captured in our propensity score matching.

It is also important to note that this study compared contralateral invasive breast cancer and breast cancer mortality rates in a control sample of patients that resembled the bilateral mastectomy cohort in contrast to prior survival analyses on contralateral prophylactic mastectomy.[8,32,33,42,43] We restricted the cohort to patients with lobular, ductal, or mixed histologic findings. Therefore, the interpretation of these study findings is limited to this patient profile and should not be assumed to be representative of the entire population with breast cancer. Some prior survival analyses only examined ER-negative breast cancers specifically[42] or only compared unilateral vs bilateral mastectomy, excluding the lumpectomy group.[43]

Conclusions

The findings of this cohort study indicate that women with unilateral breast cancer should be advised that bilateral mastectomy greatly reduces the risk of a second cancer, but does not affect mortality. The risk of contralateral breast cancer in women with unilateral primary breast cancer is substantial and remains relatively constant throughout a patient's lifetime. Based on these data, we expect that 69 in 1000 women with breast cancer will develop a contralateral cancer within 20 years of diagnosis. After experiencing a contralateral breast cancer, the mortality rate increased 4-fold from the time of contralateral cancer until the end of follow-up among the study cohort. However, the patients treated with bilateral mastectomy for unilateral breast cancer experienced similar mortality rates as those treated with unilateral surgery.

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Acquisition, analysis, or interpretation of data: All authors.
Drafting of the manuscript: Giannakeas, Narod.
Critical review of the manuscript for important intellectual content: All authors.
Statistical analysis: Giannakeas, Narod.
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