Original Article

Magnitude of Reduction in Risk of Second Contralateral Breast Cancer With Bilateral Mastectomy in Patients With Breast Cancer: Data From California, 1998 Through 2015

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BACKGROUND: Increasingly, patients with breast cancer undergo bilateral mastectomy (BLM). To the authors' knowledge, the magnitude of benefit is unknown. **METHODS:** The authors used data from the Surveillance, Epidemiology, and End Results (SEER) program regarding all women diagnosed with American Joint Committee on Cancer stage 0 to stage III unilateral breast cancer in California from 1998 through 2015 and treated with BLM versus breast-conserving therapy including surgery and radiotherapy (BCT) or unilateral mastectomy (ULM). The authors measured relative risks of second contralateral breast cancer (CBC) and breast cancer death using Fine and Gray multivariable regression modeling adjusted for the competing risk of death and death from another cause, respectively, and potential confounding factors. Absolute excess risk of CBC was measured as the observed minus expected number of breast cancers in the general population divided by 10,000 person-years at risk. **RESULTS:** Among 245,418 patients with a median follow-up of 6.7 years, 7784 patients (3.2%) developed CBC. Relative risks were lower after BLM (hazard ratio [HR], 0.10; 95% CI, 0.07-0.14) and higher after ULM (HR, 1.07; 95% CI, 1.02-1.13) versus BCT. Absolute excess risks were higher after BCT and ULM (5.0 and 13.6 more cases, respectively) compared with BLM (28.6 fewer cases). BLM reduced risk more among older women (38.0 fewer cases for women aged ≥50 years vs 17.9 fewer cases among women aged <50 years) but provided similar risk reduction across categories of tumor grade and tumor hormone receptor status. Compared with BCT, the risk of breast cancer death was equivalent after BLM (HR, 1.03; 95% CI, 0.96-1.11) and higher after ULM (HR, 1.21; 95% CI, 1.17-1.25). **CONCLUSIONS:** BLM may reduce second breast cancer risk by 34 to 43 cases per 10,000 person-years compared with other surgical procedures, but is not associated with a lower risk of death. Second breast cancers are rare, and their reduction should be weighed against the harms associated with BLM. ***Cancer* 2020;126:958-970**. © *2019 American Cancer Society*.

KEYWORDS: absolute excess risk, bilateral mastectomy, breast cancer, cancer prevention, second contralateral breast cancer.

INTRODUCTION

The use of bilateral mastectomy (BLM) as a primary treatment for unilateral breast cancer has risen in the US population, despite several clinical trials and observational studies that have demonstrated no survival benefit from this invasive procedure.[1-3] BLM is uncommon outside of the United States. Moreover, BLM has greater morbidity than unilateral mastectomy (ULM) or breast-conserving surgery with radiotherapy (breast conserving therapy [BCT]), in terms of complications, body image, recovery time, and impact on employment.[4-8]

The choice to undergo BLM is complex. Although the probability of developing a contralateral second breast cancer has declined in the United States over time,[9] potentially due to the more widespread use of adjuvant endocrine therapy,[10] the majority of patients report that fear of a subsequent breast cancer was their primary motivation for choosing to undergo BLM.[11] Prior studies have reported that BLM confers a relative risk reduction in the range of 90% to 95% for second contralateral breast cancers among patients with a personal and family history of breast cancer.[12-15] However, to the best of our knowledge, there is no population-based evidence regarding the absolute reduction in second contralateral breast cancer risk conferred by BLM, particularly in patient subgroups defined by specific demographic and tumor characteristics. A better understanding of the effectiveness and absolute risk reduction from BLM across patient subgroups may guide shared decision making among women with breast cancer and their surgeons.

Leveraging the large, diverse population of California, we used data from the population-based California Cancer Registry (CCR) to estimate the risks of second contralateral breast cancers, risks of breast cancer-specific death, and

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absolute excess risks (AERs) (compared with the general population) among women with American Joint Committee on Cancer (AJCC) stage 0 to stage III breast cancer who were treated with BLM versus other surgical procedures from 1998 through 2015.

MATERIALS AND METHODS

The study population comprised all women who were residing in California when diagnosed with a first primary breast cancer (*International Classification of Diseases for Oncology, 3rd Edition* [ICD-O-3] site codes C.50.0-50.9 and ICD-O-3 histologic codes 8000, 8010, 8020, 8022, 8050, 8140, 8201-8230, 8255, 8260, 8401, 8453, 8480-8525, and 8575) of AJCC stages 0 to III between January 1, 1998, (study start date) and December 31, 2015 (study end date). Human subjects approval was covered under the Greater Bay Area Cancer Registry protocol approved by the institutional review boards of the Cancer Prevention Institute of California and the University of California at San Francisco.

Information from the CCR included demographic and clinical characteristics, tumor features, initial treatment course, occurrence of a subsequent ipsilateral or contralateral breast cancer, vital status, and cause of death as of December 31, 2015. Patients with subsequent ipsilateral cancers after >6 months were censored at the time of that event because it is possible that these were in-breast tumor recurrences rather than second primary breast cancers. Only contralateral breast cancers (invasive or in situ) were categorized as second breast cancers for the purpose of this analysis. To focus primarily on sequential rather than concurrent breast tumors, we excluded second breast tumors that were diagnosed <6 months after the first breast cancer diagnosis. In addition, we excluded women whose surgery occurred >6 months after the initial diagnosis. Second tumors reported within the first 6 months after the initial diagnosis may have been diagnosed before the treatment surgery or may have represented incidental diagnoses made on review of surgical pathology rather than true primary tumors. Surgeries that occurred >6 months after the initial diagnosis may reflect disease progression or recurrence, not treatment of the primary tumor. Patients were eligible for inclusion in the study if they had received 1 of 4 surgical treatments consistent with clinical practice guidelines within 6 months of the initial diagnosis: BLM, ULM, or breast-conserving treatment consisting of breast-conserving surgery (BCS) with radiotherapy (BCT)[16]; in women aged ≥70 years with AJCC stage I, hormone receptor-positive, and human epidermal growth factor receptor 2 (HER2)-negative breast cancer, BCS without radiotherapy also was included because this treatment is consistent with practice guidelines for such patients.[16] Women who received non-guideline-concordant surgical treatment were excluded from the analysis because they were considered to be nonrepresentative of the standard of care. Neighborhood socioeconomic status was measured using patients' residential census block group at the time of diagnosis using an established multicomponent scale.[17] Patient subgroups of <5 individuals were reported as n < 5 to preserve patient anonymity, in accordance with the practices of the CCR.[18] Tumors were considered negative for estrogen receptor (ER) and progesterone receptor (PR) if both receptors were negative. Tumors were considered ER positive and/or PR positive if either receptor was positive.

Statistical Analysis

We estimated associations with second contralateral breast cancer risk among patients undergoing BCT compared with those receiving other treatments using a Fine and Gray competing risk regression model, with follow-up beginning 6 months after the initial diagnosis. We selected Fine and Gray as the primary analytic method because it employs a multivariable model that reduces bias due to informative censoring. This method estimates the hazard rate ratio (HR) and 95% CI by modeling the hazard of the cumulative incidence function while controlling for the competing risk of death and adjusting for the variables shown in Table 1 as potential confounders. Fine and Gray regression was used to estimate associations with the risk of breast cancer death, controlling for the competing risk of death from other causes, among patients undergoing BCT compared with those receiving other treatments,[19-21] and Cox regression was used to estimate associations with risk of death from all causes.

The proportional hazards assumption was tested for all 3 outcomes using Cox regression by examining the correlation between time and scaled Schoenfeld residuals for surgical procedure and all covariates. The proportional hazards assumption was not violated for the subsequent contralateral breast cancer outcome, but was violated for the breast cancer-specific mortality outcome for AJCC stage, tumor size, grade (ICD-O-3), and ER/PR status and for all-cause mortality for age, AJCC stage, tumor size, lymph node involvement, grade, and ER/PR status. When stage of disease was included as an underlying stratifying variable in the Cox breast cancer-specific

TABLE 1. Patient and Tumor Characteristics Among 245,418 Patients With AJCC Stage 0 to III Breast Cancer in California, 1998 to 2015

	Surgical Procedures									
	BCS Without RT (in Patients Aged ≥70 Years, AJCC Stage I, ER/PR Positive, and HER2 Negative)		Breast-Conserving Therapy (Surgery With RT)		Unilateral Mastectomy		Bilateral Mastectomy		All Patients	
	No.	Column %	No.	Column %	No.	Column %	No.	Column %	No.	Column %
All	7015	100.0	127,766	100.0	92,062	100.0	18,575	100.0	245,418	100.0
Race/ethnicity										
NH white	5510	78.5	87,149	68.2	53,920	58.6	13,171	70.9	159,750	65.1
NH black	311	4.4	6964	5.5	5271	5.7	721	3.9	13,267	5.4
Hispanic	698	10.0	18,448	14.4	17,196	18.7	2662	14.3	39,004	15.9
Chinese	112	1.6	3773	3.0	3773	4.1	366	2.0	8024	3.3
Japanese	111	1.6	1774	1.4	1367	1.5	172	0.9	3424	1.4
Filipina	100	1.4	4260	3.3	5124	5.6	612	3.3	10,096	4.1
Other Asian/Pacific Islander	105	1.5	4414	3.5	4681	5.1	698	3.8	9898	4.0
Other or unknown	68	1.0	984	0.8	730	0.8	173	0.9	1955	0.8
Age at time of diagnosis, y										
<40	—	—	4407	3.4	5541	6.0	2470	13.3	12,418	5.1
40-49	—	—	22,195	17.4	18,138	19.7	6227	33.5	46,560	19.0
50-64	—	—	54,188	42.4	32,792	35.6	7101	38.2	94,081	38.3
≥65	7015	100.0	46,976	36.8	35,591	38.7	2777	15.0	92,359	37.6
Marital status at time of diagnosis										
Unmarried	3925	56.0	47,126	36.9	37,489	40.7	5954	32.1	94,494	38.5
Married	2838	40.5	77,404	60.6	52,012	56.5	12,173	65.5	144,427	58.8
Unknown	252	3.6	3236	2.5	2561	2.8	448	2.4	6497	2.6
Neighborhood SES, quintiles										
First (lowest)	675	9.6	11,561	9.0	12,638	13.7	1313	7.1	26,187	10.7
Second	1156	16.5	19,109	15.0	17,164	18.6	2467	13.3	39,896	16.3
Third	1479	21.1	25,536	20.0	19,445	21.1	3480	18.7	49,940	20.3
Fourth	1754	25.0	31,676	24.8	21,199	23.0	4717	25.4	59,346	24.2
Fifth (highest)	1951	27.8	39,884	31.2	21,616	23.5	6598	35.5	70,049	28.5
Insurance status										
No insurance	17	0.2	798	0.6	799	0.9	123	0.7	1737	0.7
Private only	2111	30.1	81,644	63.9	53,931	58.6	14,549	78.3	152,235	62.0
Medicare with or without private insurance	4109	58.6	27,606	21.6	20,437	22.2	1989	10.7	54,141	22.1
Any Medicaid, military, or other public insurance	707	10.1	13,283	10.4	15,045	16.3	1605	8.6	30,640	12.5
Unknown	71	1.0	4435	3.5	1850	2.0	309	1.7	6665	2.7
AJCC stage of disease										
0	—	—	19,545	15.3	9436	10.2	3022	16.3	32,003	13.0
I	7015	100.0	71,106	55.7	28,044	30.5	6570	35.4	112,735	45.9
II	—	—	33,906	26.5	40,242	43.7	6578	35.4	80,726	32.9
III	—	—	3209	2.5	14,340	15.6	2405	12.9	19,954	8.1
Tumor size, cm										
<1	2785	39.7	34,934	27.3	11,883	12.9	3450	18.6	53,052	21.6
1.0-1.9	3878	55.3	56,678	44.4	25,909	28.1	5692	30.6	92,157	37.6
2.0-2.9	352	5.0	23,845	18.7	21,802	23.7	4032	21.7	50,031	20.4
3.0-5.0	0	0.0	10,729	8.4	22,173	24.1	3480	18.7	36,382	14.8
>5	0	0.0	1580	1.2	10,295	11.2	1921	10.3	13,796	5.6

TABLE 1. *Continued*

	Surgical Procedures									
	BCS Without RT (in Patients Aged ≥70 Years, AJCC Stage I, ER/PR Positive, and HER2 Negative)		Breast-Conserving Therapy (Surgery With RT)		Unilateral Mastectomy		Bilateral Mastectomy		All Patients	
	No.	Column %	No.	Column %	No.	Column %	No.	Column %	No.	Column %
Tumor grade (ICD-O-3)										
1	3195	45.5	32,781	25.7	14,553	15.8	3142	16.9	53,671	21.9
2	3047	43.4	53,449	41.8	36,893	40.1	7555	40.7	100,944	41.1
3	554	7.9	36,376	28.5	35,575	38.6	6981	37.6	79,486	32.4
Unknown	219	3.1	5160	4.0	5041	5.5	897	4.8	11,317	4.6
Tumor histology										
Ductal	5758	82.1	110,403	86.4	78,103	84.8	15,500	83.4	209,764	85.5
Lobular	579	8.3	7866	6.2	8793	9.6	2162	11.6	19,400	7.9
Other	678	9.7	9497	7.4	5166	5.6	913	4.9	16,254	6.6
ER/PR										
Both negative	—	—	15,923	12.5	16,025	17.4	2956	15.9	34,904	14.2
Either positive	7015	100.0	101,100	79.1	65,036	70.6	14,250	76.7	187,401	76.4
Unknown or borderline	—	—	10,743	8.4	11,001	11.9	1369	7.4	23,113	9.4
HER2 status										
Negative	7015	100.0	76,400	59.8	48,090	52.2	11,254	60.6	142,759	58.2
Positive	—	—	12,527	9.8	13,435	14.6	2580	13.9	28,542	11.6
Unknown or borderline	—	—	38,839	30.4	30,537	33.2	4741	25.5	74,117	30.2
Lymph node involvement										
Negative	—	—	105,130	82.3	54,443	59.1	12,234	65.9	178,777	72.8
Positive	—	—	22,636	17.7	37,619	40.9	6341	34.1	66,641	27.2
Y of cancer diagnosis										
1998	8	0.1	5781	4.5	5691	6.2	252	1.4	11,732	4.8
1999	153	2.2	5949	4.7	5747	6.2	295	1.6	12,144	4.9
2000	185	2.6	6535	5.1	5834	6.3	375	2.0	12,929	5.3
2001	240	3.4	6767	5.3	5970	6.5	486	2.6	13,463	5.5
2002	257	3.7	7088	5.5	5739	6.2	507	2.7	13,591	5.5
2003	240	3.4	7112	5.6	5224	5.7	602	3.2	13,178	5.4
2004	272	3.9	7364	5.8	5369	5.8	724	3.9	13,729	5.6
2005	344	4.9	7984	6.2	5169	5.6	660	3.6	14,157	5.8
2006	447	6.4	7671	6.0	5199	5.6	830	4.5	14,147	5.8
2007	460	6.6	7948	6.2	5283	5.7	1028	5.5	14,719	6.0
2008	466	6.6	7837	6.1	5371	5.8	1223	6.6	14,897	6.1
2009	515	7.3	7561	5.9	5180	5.6	1443	7.8	14,699	6.0
2010	482	6.9	7749	6.1	5199	5.6	1574	8.5	15,004	6.1
2011	630	9.0	7941	6.2	5064	5.5	1748	9.4	15,383	6.3
2012	626	8.9	7660	6.0	4987	5.4	1856	10.0	15,129	6.2
2013	686	9.8	7443	5.8	4715	5.1	2115	11.4	14,959	6.1
2014	692	9.9	7421	5.8	4166	4.5	1930	10.4	14,209	5.8
2015	312	4.4	3955	3.1	2155	2.3	927	5.0	7349	3.0
Reporting hospital was an NCI-designated cancer center										
No	6734	96.0	120,670	94.4	87,958	95.5	17,284	93.0	232,646	94.8
Yes	281	4.0	7096	5.6	4104	4.5	1291	7.0	12,772	5.2

TABLE 1. *Continued*

	Surgical Procedures									
	BCS Without RT (in Patients Aged ≥70 Years, AJCC Stage I, ER/PR Positive, and HER2 Negative)		Breast-Conserving Therapy (Surgery With RT)		Unilateral Mastectomy		Bilateral Mastectomy		All Patients	
	No.	Column %	No.	Column %	No.	Column %	No.	Column %	No.	Column %
SES of hospital's patient distribution										
Low: ≥50% in lowest 2 quintiles, <50% in highest 2 quintiles	1039	14.8	19,554	15.3	20,401	22.2	2636	14.2	43,630	17.8
Medium: neither low nor high	2102	30.0	36,918	28.9	29,909	32.5	4812	25.9	73,741	30.0
High: ≥50% in highest 2 quintiles, <50% in lowest 2 quintiles	3871	55.2	71,275	55.8	41,744	45.3	11,124	59.9	128,014	52.2
Fewer than 5 cancer patients at facility	<5		19	0.0	8	0.0	<5		33	0.0
Adjuvant chemotherapy										
No	6939	98.9	90,238	70.6	54,318	59.0	10,255	55.2	161,750	65.9
Yes	76	1.1	37,528	29.4	37,744	41.0	8320	44.8	83,668	34.1
Adjuvant RT										
No	7015	100.0	0	0.0	75,201	81.7	15,419	83.0	97,635	39.8
Yes	0	0.0	127,766	100.0	16,861	18.3	3156	17.0	147,783	60.2
Breast cancer outcomes										
Subsequent contralateral BC	143	2.0	4213	3.3	3384	3.7	44	0.2	7784	3.2
Subsequent ipsilateral BC	88	1.3	2387	1.9	310	0.3	93	0.5	2878	1.2
Subsequent bilateral BC	0	0.0	<5		0	0.0	<5		<5	
Subsequent BC, laterality unknown	0	0.0	19	0.0	28	0.0	<5		51	0.0
Died of breast cancer	152	2.2	5296	4.1	10,178	11.1	983	5.3	16,609	6.8
Died of other cause	1905	27.2	12,346	9.7	13,519	14.7	575	3.1	28,345	11.5
Died of unknown cause	24	0.3	446	0.3	602	0.7	40	0.2	1112	0.5
Lost to follow-up before 12/31/2015 (study end)	538	7.7	10,090	7.9	8987	9.8	1474	7.9	21,089	8.6
Followed until 12/31/2015	4165	59.4	92,968	72.8	55,054	59.8	15,361	82.7	167,548	68.3

Abbreviations: AJCC, American Joint Committee on Cancer; BC, breast cancer; BCS, breast-conserving surgery; ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; NCI, National Cancer Institute; NH, non-Hispanic; PR, progesterone receptor; RT, radiotherapy; SES, socioeconomic status.

mortality model, additionally stratifying by tumor size and diagnosis year changed the HR for the main effect of surgical procedure somewhat, but additionally stratifying by tumor grade or by ER/PR status did not. Thus, AJCC stage (stage 0, I, II, or III), tumor size (<1.0 cm, 1.0-1.9 cm, 2.0-2.9 cm, 3.0-4.9 cm, or >5.0 cm), and year of diagnosis (1998-2003, 2004-2009, or 2010-2015) were included as underlying stratifying variables in the fully adjusted Fine and Gray mortality models, which allowed the baseline hazard to vary by these factors, but tumor grade and ER/PR status were simply adjusted for in fully adjusted models. For all-cause mortality, age and disease stage were included as underlying stratification variables in the fully adjusted Cox regression model, and the other factors simply were adjusted for because stratifying by them did not change the main effect. Wald tests for interaction between surgical procedure and age, tumor grade, and ER/PR status were computed using cross-product terms in models adjusted for all statistically significant ($P < .05$) interactions with the stratification variable.

Based on evidence that absolute risk estimates are most easily understood and useful for patient decision making,[22,23] we calculated the AER of a second contralateral breast cancer as the number of observed breast cancer cases minus the expected number of incident breast cancers for the general California population. The expected number was calculated by multiplying age group-specific and calendar period-specific breast cancer incidence rates for California women by the corresponding person-years of follow-up in the current study cohort in jointly defined 5-year age groups and 3-year calendar periods and summing over all groups. The difference between the number of observed minus expected breast cancer cases was divided by person-years at risk. We presented AER estimates per 10,000 person-years at risk.

All analyses were performed using SAS statistical software (version 9.4; SAS Institute Inc, Cary, North Carolina) and all statistical tests were 2-sided. A $P < .05$ was used to denote statistical significance and no adjustment was made for multiple comparisons.

RESULTS

A total of 421,643 women were diagnosed with a first primary breast cancer in California from 1998 through 2015. Patients were excluded from analysis hierarchically as follows: age at diagnosis <20 years (37 patients); AJCC stage other than 0 to III (35,057 patients); diagnosis by death certificate or autopsy only (43 patients) or diagnosis not microscopically confirmed (278 patients); ineligible histologic type (5652 patients); tumor size unknown (19,739 patients), no tumor noted (445 patients), microscopic (6576 patients), diffuse (854 patients), Paget disease (n < 5 patients), or mammographic diagnosis only (1209 patients); unknown lymph node status (1986 patients); surgery other than ULM, BLM, or BCT except among women aged ≥70 years with AJCC stage I, ER/PR-positive, and HER2-negative breast cancer (59,602 patients undergoing lumpectomy without radiotherapy and not meeting the age, AJCC stage, ER/PR, and HER2 criteria above; 8912 patients with no surgery, other surgery, or surgery not otherwise specified; and 51 patients with unknown surgery); date of surgery >6 months after the initial diagnosis (11,404 patients); unknown surgery date (5190 patients); bilateral tumors at the time of initial diagnosis (11 patients); subsequent breast tumor diagnosed <6 months after the first tumor (8187 patients); and follow-up <6 months (10,991 patients). After exclusions, a total of 245,418 women remained, 7784 of whom (3.2%) developed a contralateral second breast cancer >6 months after the diagnosis of their first breast cancer. The median follow-up was 6.7 years.

Of the 245,418 women analyzed, 127,766 (52.1%) underwent BCT, 92,062 (37.5%) underwent ULM, and 18,575 (7.6%) underwent BLM. There were 7015 women (2.9%) aged ≥70 years with AJCC stage I, ER/PR-positive, HER2-negative disease who received BCS without radiotherapy. The majority of patients undergoing BCT were classified as having stages 0 to I disease (71.0%), compared with those undergoing ULM (40.7%) and BLM (51.7%) (Table 1).

Compared with BCT recipients in a Fine and Gray multivariable adjusted model (Table 2), BLM recipients had a significantly lower risk of contralateral breast cancer (HR, 0.10; 95% CI, 0.07-0.14), whereas ULM recipients had a higher risk (HR, 1.07; 95% CI, 1.02-1.13) and those who underwent BCS without radiotherapy (aged ≥70 years with AJCC stage I, ER/PR-positive, HER2-negative disease) had equivalent risk (HR, 0.91; 95% CI, 0.77-1.08). Results were similar in a model minimally adjusted for age and disease stage (BLM HR, 0.10 [95% CI, 0.07-0.13]; ULM HR, 1.10 [95% CI, 1.05-1.15]; and BCS HR, 0.85 [95% CI, 0.71-1.00]). Stratified analyses in multivariable adjusted models demonstrated similar risk reductions associated with BLM in younger and older women (aged <50 years: HR, 0.09 [95% CI, 0.05-0.15] vs aged ≥50 years: HR, 0.11 [95% CI, 0.07-0.18]; *P* for interaction for BLM, .48) and by hormone receptor status (ER/PR negative: HR, 0.13 [95% CI, 0.07-0.23] vs ER/PR positive: HR, 0.09 [95% CI, 0.06-0.15]; *P* for interaction for BCS = .35), and greater risk reduction in

TABLE 2. Associations Between Risk of Second Contralateral Breast Cancer With 95% CIs Among Patients With AJCC Stage 0 to III Breast Cancer in California: 1998 to 2015[a]

	HR	Lower 95% CI	Upper 95% CI	*P*
Surgical procedure				
BCS (reference: BCT)	1.00	—	—	—
BCS without RT: restricted to age ≥70 y, AJCC stage I, ER/PR positive and HER2 negative	0.91	0.77	1.08	.30
ULM	1.07	1.02	1.13	.0081
BLM	0.10	0.07	0.14	<.0001
Race/ethnicity				
NH white (reference)	1.00	—	—	—
NH black	1.23	1.13	1.35	<.0001
Hispanic	1.00	0.94	1.07	.97
Chinese	1.12	0.97	1.30	.13
Japanese	1.00	0.81	1.22	.97
Filipina	1.30	1.17	1.44	<.0001
Other Asian/Pacific Islander ethnicity	1.02	0.90	1.16	.77
Age at time of diagnosis, y				
<40	1.16	1.05	1.29	.0034
40-49	0.96	0.91	1.02	.20
50-64 (reference)	1.00	—	—	—
≥65	0.90	0.84	0.96	.0024
Marital status at time of diagnosis				
Married (reference)	1.00	—	—	—
Unmarried	1.01	0.96	1.06	.71
Neighborhood SES, quintiles				
First (lowest) (reference)	1.00	—	—	—
Second	0.94	0.85	1.04	.23
Third	0.93	0.84	1.02	.14
Fourth	1.00	0.91	1.10	.99
Fifth (highest)	0.97	0.88	1.06	.48
Insurance status				
Private only (reference)	1.00	—	—	—
No insurance	1.08	0.85	1.36	.54
Medicare with or without private insurance	0.98	0.91	1.04	.46
Any Medicaid, military, or other public insurance	0.92	0.85	1.00	.06
AJCC stage of disease				
0	1.41	1.29	1.54	<.0001
I (reference)	1.00	—	—	—
II	0.92	0.86	0.98	.02
III	0.99	0.88	1.11	.81
Tumor size (per cm increase)	1.01	1.00	1.02	.06
Tumor grade				
1 (reference)	1.00	—	—	—
2	0.97	0.91	1.02	.23
3	0.93	0.86	0.99	.04
Tumor histology				
Ductal (reference)	1.00	—	—	—
Lobular	1.00	0.91	1.10	.94
Other	0.99	0.91	1.07	.75
ER/PR status				
Either positive (reference)	1.00	—	—	—
Both negative	1.30	1.21	1.39	<.0001
Lymph node involvement				
Negative (reference)	1.00	—	—	—
Positive	0.94	0.88	1.02	.14
Y of diagnosis (per 1-y increase)	0.97	0.97	0.98	<.0001
Reporting hospital an NCI-designated cancer center				
No (reference)	1.00	—	—	—
Yes	0.98	0.85	1.12	.72
SES of hospital's patient distribution				
High: ≥50% in highest 2 quintiles, <50% in lowest 2 quintiles (reference)	1.00	—	—	—
Low: ≥50% in lowest 2 quintiles, <50% in highest 2 quintiles	0.99	0.91	1.07	.73
Medium: neither low nor high	0.98	0.92	1.04	.45
Adjuvant therapy (chemotherapy and/or RT)				
No (reference)	1.00	—	—	—
Yes	0.93	0.88	0.99	.03

TABLE 2. *Continued*

	HR	Lower 95% CI	Upper 95% CI	*P*
Stratified models				
Surgical procedures by age category at time of diagnosis[b]				
Age <50 y				
BCT (reference)	1.00	—	—	—
ULM	0.99	0.89	1.09	.77
BLM	0.09	0.05	0.15	<.0001
Age ≥50 y				
BCS: age ≥70 y, AJCC stage I, ER/PR positive, HER2 negative	0.88	0.74	1.04	.14
BCT (reference)	1.00	—	—	—
ULM	1.11	1.05	1.18	.0003
BLM	0.11	0.07	0.18	<.0001
Surgical procedures by grade categories[c]				
Grade 1 or 2				
BCS: age ≥70 y, AJCC stage I, ER/PR positive, HER2 negative	0.86	0.71	1.05	.13
BCT (reference)	1.00	—	—	—
ULM	1.10	1.03	1.18	.003
BLM	0.07	0.04	0.13	<.0001
Grade 3				
BCS: age ≥70 y, AJCC stage I, ER/PR positive, HER2 negative	1.10	0.63	1.91	.73
BCT (reference)	1.00	—	—	—
ULM	1.02	0.93	1.10	.72
BLM	0.14	0.09	0.22	<.0001
Surgical procedures by ER/PR categories[d]				
ER/PR negative				
BCT (reference)	1.00	—	—	—
ULM	1.02	0.90	1.15	.78
BLM	0.13	0.07	0.23	<.0001
ER/PR positive				
BCS: age ≥70 y, AJCC stage I, ER/PR positive, HER2 negative	0.92	0.77	1.09	.34
BCT (reference)	1.00	—	—	—
ULM	1.11	1.04	1.18	.002
BLM	0.09	0.06	0.15	<.0001

Abbreviations: AJCC, American Joint Committee on Cancer; BCS, breast-conserving surgery; BCT, breast-conserving surgery with radiotherapy; BLM, bilateral mastectomy; ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; HR, hazard ratio; NCI, National Cancer Institute; NH, non-Hispanic; PR, progesterone receptor; RT, radiotherapy; SES, socioeconomic status; ULM, unilateral mastectomy.

[a]Fine and Gray regression model with death as a competing risk, adjusted for the variables in the table.

[b]*P* for interaction of .09 for the global test of an interaction between age and surgical procedure from a fully adjusted model additionally adjusted for statistically significant interactions with age (race, insurance type, AJCC stage of disease, hormone receptor status, year of diagnosis, and adjuvant treatment). Individual interaction terms were *P* = .03 for ULM and *P* = .48 for BLM.

[c]*P* for interaction of .06 for the global test of an interaction between grade and surgical procedure from a fully adjusted model additionally adjusted for statistically significant interactions with grade (race and lymph node involvement). Individual interaction terms were *P* = .57 for BCS, *P* = .20 for ULM, and *P* = .03 for BLM.

[d]*P* for interaction of .15 for the global test of an interaction between ER/PR status and surgical procedure from a fully adjusted model additionally adjusted for statistically significant interactions with ER/PR status (race and AJCC stage of disease). Individual interaction terms were *P* = .11 for ULM and *P* = .35 for BLM.

those with tumors of lower grade (grade 1-2: HR, 0.07 [95% CI, 0.04-0.13] vs grade 3: HR, 0.14 [95% CI, 0.09-0.22]; *P* for interaction for BLM = .03). Supporting Figure 1 shows unadjusted cumulative incidence function plots for the development of contralateral breast cancer by surgical procedure stratified by age and hormone receptor status, which control for the competing risk of death.

AER of second contralateral breast cancer differed among surgical procedures (Table 3). BLM recipients had 28.6 fewer cases per 10,000 person-years at risk compared with the general California population, whereas BCT recipients had 5.0 more cases and ULM recipients had 13.6 more cases. AER reduction after BLM was somewhat greater for women aged ≥50 years at the time of the initial diagnosis (38.0 fewer cases per 10,000 person-years at risk) versus those aged <50 years (17.9 fewer cases), with lower grade (31.4 fewer cases) versus higher grade (23.9 fewer cases) tumors, and with ER/PR-positive (29.5 fewer cases) versus ER/PR-negative (23.4 fewer cases) tumors. AER increases were notable in BCT recipients aged <50 years (21.2 more cases per 10,000 person-years at risk) with grade 3 (11.3 more cases) or ER/PR-negative (19.2 more cases) tumors, with a similar pattern noted after ULM.

Compared with BCT recipients in a Fine and Gray multivariable adjusted model (Table 4), BLM recipients had a similar risk of breast cancer death as BCT recipients (HR, 1.03; 95% CI, 0.96-1.11). Risk of breast cancer death was slightly higher among ULM recipients (HR, 1.21; 95% CI, 1.17-1.25) and recipients of BCS without radiotherapy who were aged ≥70 years with AJCC stage I, ER/PR-positive, HER2-negative disease (HR,

TABLE 3. AER of Second Contralateral Breast Cancer, Shown as Excess Cases per 10,000 Person-Years Among Patients With AJCC Stage 0 to III Breast Cancer Compared With the General Population in California: 1998 to 2015[a]

	Observed	Expected	Total Person-Years	Absolute Excess Risk
Surgical procedure				
BCS without RT: restricted to age ≥70 y, AJCC stage I, ER/PR positive and HER2 negative	143	145	32,384	−0.7
BCT	4213	3755	918,682	5.0
ULM	3384	2517	639,370	13.6
BLM	44	327	99,017	−28.6
Age at first breast cancer diagnosis, y				
<50	1905	1066	436,687	19.2
≥50	5879	5678	1,252,767	1.6
Tumor grade				
1 or 2	4675	4349	1,059,270	3.1
3	2641	1999	534,040	12.0
ER/PR status				
Both negative	1320	858	228,891	20.2
Either positive	5229	4979	1,236,805	2.0
Surgical procedures by age category at time of diagnosis				
Age <50 y				
BCT	976	531	210,551	21.2
ULM	911	435	179,820	26.5
BLM	18	101	46,315	−17.9
Age ≥50 y				
BCS: age ≥70 y, AJCC stage I, ER/PR positive, HER2 negative	143	145	32,384	−0.7
BCT	3237	3224	708,131	0.2
ULM	2473	2082	459,550	8.5
BLM	26	226	52,702	−38.0
Surgical procedures by grade categories				
Grade 1 or 2				
BCS: age ≥70 y, AJCC stage I, ER/PR positive, HER2 negative	121	128	28,568	−2.5
BCT	2706	2570	614,130	2.2
ULM	1832	1456	359,800	10.4
BLM	16	194	56,772	−31.4
Grade 3				
BCS: age ≥70 y, AJCC stage I, ER/PR positive, HER2 negative	13	12	2556	5.8
BCT	1285	993	258,663	11.3
ULM	1319	886	237,151	18.3
BLM	24	109	35,670	−23.9
Surgical procedures by ER/PR categories				
ER/PR negative				
BCT	649	431	113,063	19.2
ULM	660	381	101,009	27.7
BLM	11	46	14,819	−23.4
ER/PR positive				
BCS: age ≥70 y, AJCC stage I, ER/PR positive, HER2 negative	143	145	32,384	−0.7
BCT	2950	2871	696,214	1.1
ULM	2109	1723	435,820	8.9
BLM	27	240	72,387	−29.5

Abbreviations: AJCC, American Joint Committee on Cancer; AER, absolute excess risk; BCS, breast-conserving surgery; BCT, breast-conserving surgery with radiotherapy; BLM, bilateral mastectomy; ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; PR, progesterone receptor; RT, radiotherapy; ULM, unilateral mastectomy.
[a]Adjusted for age and calendar period.

1.36; 95% CI, 1.16-1.59). Risk of breast cancer death was found to be statistically significantly associated with all factors included in the multivariable model (Table 4). Supporting Figure 2 shows unadjusted cumulative incidence function plots for breast cancer death by surgical procedure stratified by age and hormone receptor status, which control for the competing risk of death from other causes. Similarly for all-cause mortality, risk was increased for ULM and BCS compared with BCT, but was similar for BLM (BLM HR, 0.98 [95% CI, 0.93-1.04]; ULM HR, 1.36 [95% CI, 1.33-1.39]; and BCS HR, 2.24 [95% CI, 2.14-2.35]).

DISCUSSION

We took advantage of the large, diverse, population-based CCR to examine associations with second contralateral breast cancer and estimate the number of breast cancers potentially prevented by BLM. Among >240,000

TABLE 4. Associations Between Risk of Breast Cancer Death With 95% CIs Among Patients With AJCC Stage 0 to III Breast Cancer in California: 1998 to 2015[a]

	HR	Lower 95% CI	Upper 95% CI	*P*
Surgical procedure				
BCS with RT (BCT; reference)	1.00	—	—	—
BCS without RT: restricted to age ≥70 y, AJCC stage I, ER/PR positive and HER2 negative	1.36	1.16	1.59	.0001
ULM	1.21	1.17	1.25	<.0001
BLM	1.03	0.96	1.11	.35
Age at time of first breast cancer diagnosis, y				
<40 (reference)	1.00	—	—	—
40-49	0.78	0.73	0.83	<.0001
50-64	0.79	0.74	0.84	<.0001
≥65	0.93	0.87	0.99	.03
Race/ethnicity				
NH white (reference)	1.00	—	—	—
NH black	1.21	1.14	1.28	<.0001
Hispanic	0.92	0.88	0.96	.0004
Chinese	0.84	0.75	0.93	.0006
Japanese	0.81	0.69	0.94	.0062
Filipina	0.86	0.79	0.93	.0003
Other Asian/Pacific Islander ethnicity	0.86	0.79	0.93	.0003
Marital status at time of diagnosis				
Married (reference)	1.00	—	—	—
Unmarried	1.09	1.06	1.13	<.0001
Neighborhood SES, quintiles				
First (lowest) (reference)	1.00	—	—	—
Second	1.02	0.97	1.08	.41
Third	0.97	0.92	1.03	.33
Fourth	0.95	0.89	1.00	.06
Fifth (highest)	0.87	0.82	0.93	<.0001
Insurance status				
Private only (reference)	1.00	—	—	—
No insurance	1.20	1.04	1.39	.013
Medicare with or without private insurance	1.25	1.19	1.32	<.0001
Any Medicaid, military, or other public insurance	1.30	1.24	1.36	<.0001
Tumor grade				
1 (reference)	1.00	—	—	—
2	1.79	1.68	1.90	<.0001
3	2.73	2.55	2.91	<.0001
Tumor histology				
Ductal (reference)	1.00	—	—	—
Lobular	1.06	1.00	1.12	.06
Other	0.73	0.68	0.79	<.0001
ER/PR status				
Either positive (reference)	1.00	—	—	—
Both negative	1.55	1.49	1.61	<.0001
Lymph node involvement				
Negative (reference)	—	—	—	—
Positive	1.97	1.88	2.06	<.0001
Reporting hospital was an NCI-designated cancer center				
No (reference)	1.00	—	—	—
Yes	0.89	0.83	0.97	.005
SES of the hospital's patient distribution				
High: ≥50% in highest 2 quintiles, <50% in lowest 2 quintiles (reference)	1.00	—	—	—
Medium: neither low nor high	1.09	1.05	1.13	<.0001
Low: ≥50% in lowest 2 quintiles, <50% in highest 2 quintiles	1.08	1.03	1.14	.0016
Adjuvant therapy (chemotherapy and/or RT)				
No (reference)	1.00	—	—	—
Yes	1.12	1.08	1.17	<.0001

Abbreviations: AJCC, American Joint Committee on Cancer; BCS, breast-conserving surgery; BCT, breast-conserving surgery with radiotherapy; BLM, bilateral mastectomy; ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; HR, hazard ratio; NCI, National Cancer Institute; NH, non-Hispanic; PR, progesterone receptor; RT, radiotherapy; SES, socioeconomic status; ULM, unilateral mastectomy.

[a]Fine and Gray regression model with death from another cause as a competing risk, stratified by AJCC stage of disease, tumor size, and year of diagnosis and adjusted for the variables in the table. A total of 1150 patients with an unknown cause of death were excluded.

patients diagnosed with unilateral breast cancer over an 18-year period, approximately 3.2% developed a second contralateral breast cancer. The AER reduction after BLM was 29 fewer cases of second contralateral breast cancer per 10,000 person-years at risk versus an excess risk of 5 more cases after BCT. This can be interpreted as an absolute difference of 34 fewer cases per 10,000 person-years at risk after BLM compared with BCT. Similarly, we estimated an excess risk of 14 more cases after ULM, or an absolute difference of 43 fewer cases per 10,000 person-years at risk after BLM compared with ULM. It is interesting to note that the results of the current study confirm those of several prior analyses,[24-28] including our own,[1] that found no improvement in the risk of death from breast cancer associated with BLM versus BCT. One possible explanation is that survivors of breast cancer undergo more intensive secondary surveillance than before their diagnosis, and thus a second contralateral breast cancer is likely to be discovered at an earlier, more curable stage; therefore, the risk of death from breast cancer is more likely to be determined by the first breast cancer diagnosis than by the second. Another possibility is unmeasured confounders in the selection of surgical treatment, which might result in patients with tumors with a worse prognosis being more likely to undergo BLM than BCT. Regardless of its cause, the repeatedly demonstrated absence of a survival benefit associated with BLM should be a crucial consideration in any discussion regarding BLM for secondary cancer prevention.

It is important to note that the results of the current study join those of earlier studies in offering reassurance that second contralateral breast cancer is uncommon.[30] Previous studies have shown that the incidence of second contralateral breast cancer varies according to patient characteristics, with greater risk reported among younger women with ER/PR-negative tumors.[31-34] This likely reflects the higher prevalence of hereditary pathogenic variants in *BRCA1/2* and other DNA repair genes within this patient subpopulation[33-36]; however, a recent study also reported a high risk of second contralateral breast cancers among women with a family history of breast cancer, even when genetic testing was negative.[37] Unlike survivors of ER/PR-positive cancers, survivors of ER/PR-negative tumors do not undergo adjuvant endocrine therapy, which has the beneficial side effect of reducing their risk of a second breast cancer.[38] As in prior studies,[30,32-34,37] we found a significant increase in the risk of second breast cancer among women aged <50 years at the time of initial diagnosis and/or with ER/PR-negative disease. These findings are consistent with clinical practice guidelines that advise genetic counseling and testing among women diagnosed at age <50 years or with triple-negative breast cancer.[39]

Our AER estimates have enabled the comparison of surgical options. For example, our AER estimate for survivors of ER/PR-negative disease suggested 19 (for BCT) or 28 (for ULM) more second contralateral breast cancers per 10,000 person-years at risk (compared with the population average) versus 23 fewer cases after BLM; this might be interpreted as 42 or 51 fewer second contralateral breast cancers after BLM compared with BCS or ULM. With regard to survivors of ER/PR-positive disease, the difference was more modest, at 31 or 38 fewer second contralateral breast cancers after BLM compared with BCS or ULM. However, caution is needed when extrapolating aggregate data to individuals. Moreover, patients differ in numeracy and in the valence they place on risk estimates. What one patient might consider to be a negligible benefit of BLM, weighed against its potential harms of greater pain, recovery time, and impact on body image and employment,[4-6] might appear worthwhile to another. These estimates can help benchmark the benefits of BLM according to patient characteristics.

The current study has some limitations. Most important, we were unable to discount the possibility that the observed risk reductions may reflect confounding. We adjusted for available known confounders for the development of contralateral breast cancer and breast cancer death using a Fine and Gray multivariable regression model. However, we could not exclude the influence of unmeasured confounders, particularly inherited cancer susceptibility. Because the Surveillance, Epidemiology, and End Results program does not routinely collect germline genetic testing information, we could not distinguish pathogenic variant carriers who might benefit the most from BLM, and this was a limitation of the study. Ongoing efforts to link genetic testing data to Surveillance, Epidemiology, and End Results records should facilitate re-evaluation of this question in the future.[40,41] Another limitation was the relatively short median follow-up of 6.7 years. The current study focused on women with first primary breast cancers but it is possible that these women differed from those who pursue BLM after being diagnosed with a second or third primary breast cancer. Our AER estimates were based on a standardized incidence ratio approach that compares with breast cancer rates in the general population, which is an accepted way with which to derive such estimates,[31,42] but were not adjusted for confounders other than age and calendar year, and differed from the Fine and Gray method we used elsewhere in the current study. Although the study sample

size was very large, it still is possible that smaller, possibly important, differences may not have been detected. A P value <.05 was used to denote statistical significance, and no adjustment was made for multiple comparisons; the chance of falsely rejecting a null hypothesis may exceed .05. The study was limited to residents of California and may not fully represent other populations. However, the notable strengths of the current study included the size and diversity of California's population and a registry that is stringently audited for quality.

Implications for Patient Care

Among patients with breast cancer, BLM is estimated to reduce the risk of developing a second contralateral breast cancer substantially compared with BCT or ULM, and to a level well below the average woman's risk of developing a first breast cancer. However, to the best of our knowledge, there is no evidence that BLM reduces the risk of death from breast cancer. Second contralateral breast cancers are uncommon, and the absolute risk reduction with BLM varies according to patient age and tumor characteristics. Absolute risk estimates often are more comprehensible to patients, and therefore their presentation is recommended.[22,23] These results may be used to guide shared decision making regarding the surgical prevention of second contralateral breast cancers.

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CONFLICT OF INTEREST DISCLOSURES

Allison W. Kurian has received research funding to her institution from Myriad Genetics for work performed outside of the current study. Alison J. Canchola has received grants from the National Institutes of Health and the California Department of Public Health for work performed as part of the current study. Christina A. Clarke is employed by and holds equity in GRAIL Inc, a life sciences company developing tests for early cancer detection, for work performed outside of the current study. Scarlett L. Gomez has received grants from the National Institutes of Health and the California Department of Public Health for work performed as part of the current study. Cindy S. Ma made no disclosures.

AUTHOR CONTRIBUTIONS

Allison W. Kurian: Conceptualization, analysis and interpretation of the results, writing–original draft, and writing–review and editing. **Alison J. Canchola:** Formal data analysis, methodology, and writing–review and editing. **Cindy S. Ma:** Interpretation of the results and writing–original draft. **Christina A. Clarke:** Conceptualization, data curation, analysis and interpretation of the results, and writing–review and editing. **Scarlett L. Gomez:** Conceptualization, data curation, analysis and interpretation of the results, and writing–review and editing.

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