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Equivalent survival after nipple-sparing compared to non-nipple-sparing mastectomy: data from California, 1988–2013

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Abstract

Purpose—Nipple-sparing mastectomy, which may improve cosmesis, body image, and sexual function in comparison to non-nipple-sparing mastectomy, is increasingly used to treat early-stage breast cancer; however, long-term survival data are lacking. We evaluated survival after nipple-sparing mastectomy versus non-nipple-sparing mastectomy in a population-based cancer registry.

Methods—We conducted an observational study using the California Cancer Registry, considering all stage 0–III breast cancers diagnosed in California from 1988 to 2013. We compared breast cancer-specific and overall survival time after nipple-sparing versus non-nipple-sparing mastectomy, using multivariable analysis.

Results—Among 157,592 stage 0–III female breast cancer patients treated with unilateral mastectomy from 1988–2013, 993 (0.6 %) were reported as having nipple-sparing and 156,599 (99.4 %) non-nipple-sparing mastectomies; median follow-up was 7.9 years. The proportion of mastectomies that were nipple-sparing increased over time (1988, 0.2 %; 2013, 5.1 %) and with neighborhood socioeconomic status, and decreased with age and stage. On multivariable analysis, nipple-sparing mastectomy was associated with a lower risk of breast cancer-specific mortality compared to non-nipple-sparing mastectomy [hazard ratio (HR) 0.71, 95 % confidence interval (CI) 0.51–0.98]. However, when restricting to diagnoses 1996 or later and adjusting for a larger set of covariates, risk was attenuated (HR 0.86, 95 % CI 0.52–1.42).

Conclusions—Among California breast cancer patients diagnosed from 1988–2013, nipple-sparing mastectomy was not associated with worse survival than non-nipple-sparing mastectomy. These results may inform the decisions of patients and doctors deliberating between these surgical approaches for breast cancer treatment.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical standards All research complied with current laws of the United States of America.

Keywords

Breast cancer; Mastectomy; Skin-sparing; Nipple-sparing; Survival

Introduction

Despite randomized clinical trials demonstrating equivalent survival after breast conserving therapy versus mastectomy [1], use of mastectomy (specifically, contralateral prophylactic mastectomy) has risen recently [2]. This coincided with increased uptake of genetic testing for cancer risk assessment [3, 4], and with reports that prophylactic mastectomy reduces breast cancer risk among women with an inherited *BRCA1/2* mutation [5]. Given evidence that mastectomy rates are rising, interest has grown in less invasive procedures such as nipple-sparing mastectomy (NSM) [6]. Compared to non-nipple-sparing mastectomy (non-NSM), NSM may improve cosmesis, body image, and sexual function [7]. However, concerns remain about NSM's safety with regard to breast cancer recurrence and survival. Randomized clinical trials do not exist and are unlikely to be initiated, and existing observational studies were limited to single centers or short follow-up time. We took advantage of the large population-based California Cancer Registry (CCR) to compare survival of stage 0–III female breast cancer patients treated with NSM versus non-NSM from 1988 to 2013.

Methods

The study population consisted of all female California residents diagnosed with a first primary breast cancer (International Classification of Disease for Oncology, 3rd Edition, site codes C50.0–50.9 and histologic codes: 8000, 8010, 8020, 8022, 8050, 8140, 8201–8230, 8255, 8260, 8401, 8453, 8480–8525, and 8575), of American Joint Commission on Cancer stages 0–III, from January 1, 1988 to December 31, 2013. The analysis was overseen by the Institutional Review Board of the Cancer Prevention Institute of California. We obtained CCR information regarding patient and tumor characteristics, initial treatment course and patient vital status through December 31, 2013. We used an established measure of neighborhood socioeconomic status (SES) based on patients' residence when diagnosed [8]. An initial surgical procedure of subcutaneous mastectomy, also called nipple-sparing mastectomy, was coded as NSM. Procedures of total (simple) mastectomy, modified radical mastectomy, radical mastectomy, or extended radical mastectomy (all without removal of uninvolved contralateral breast) and mastectomy NOS were coded as non-NSM. Survival time was measured in days from diagnosis to death. We used Cox proportional hazards regression to model associations with overall and breast cancer-specific mortality. Minimally adjusted models were stratified by stage and adjusted for age. Fully adjusted models were stratified by stage and histology; adjusted for age, race/ethnicity, tumor size, lymph node involvement, adjuvant chemotherapy and/or radiation, neighborhood SES, marital status, hospital characteristics (SES composition of patients and National Cancer Institute-designated cancer center status), and diagnosis year; and adjusted for clustering by hospital. In secondary analyses limited to diagnoses in 1996 or later, for which more covariates were available, models were additionally adjusted for grade, estrogen receptor (ER)/progesterone

receptor (PR) status, and insurance status. We tested the proportional hazards assumption for each covariate using correlation tests of time versus scaled Schoenfeld residuals. The assumption was violated for stage and histology; thus, we conducted stratified Cox regression models allowing the baseline hazard to vary by these variables. We used SAS version 9.4 for all analyses.

Results

A total of 547,893 women were diagnosed with a first primary breast cancer in California from 1988 to 2013. Patients were excluded from analysis as follows: stage other than 0–III (69,078); diagnosis by death certificate or autopsy (80) or not microscopically confirmed (369); ineligible histologic type (8166); tumor size unknown, microscopic, diffuse, Paget's or mammographic report only (42,118); surgery other than unilateral NSM or unilateral non-NSM (262,789); subsequent breast tumor within 2 months of diagnosis (6174); bilateral synchronous breast cancer (20); invalid follow-up (37); or unknown cause of death (1470). After exclusions, 157,592 women were available for analysis, of whom 156,599 (99.4 %) underwent unilateral non-NSM and 993 (0.6 %) unilateral NSM. NSM use increased over time (1988, 0.2 %; 2013, 5.1 %) and with neighborhood SES, and decreased with age (Table 1). The median follow-up was 7.9 years (interquartile range, 3.6–14.0 years) for all patients and for those who had non-NSM, compared to 1.9 years (interquartile range, 0.7–5.5 years) for patients who had NSM (Supplemental Table).

In both minimally and fully adjusted models, NSM was associated with lower breast cancer-specific mortality than non-NSM (hazard ratio, HR 0.71, 95 % confidence interval, CI 0.51–0.98 fully adjusted, Table 2). In a secondary analysis limited to diagnoses in 1996 or later, a decreased risk with NSM was seen in the minimally adjusted model (HR 0.61, 95 % CI, 0.38–0.98), but the effect was attenuated in the fully adjusted model (HR 0.79, 95 % CI, 0.48–1.30, data not shown), and further attenuated after adjusting for grade, ER/PR status, and insurance (HR 0.86, 95 % CI, 0.52–1.42).

In both minimally and fully adjusted models, NSM was not associated with overall mortality (Table 2). In a subset with diagnoses in 1996 or later, NSM was associated with lower overall mortality compared with non-NSM in a minimally adjusted model, but the effect was no longer significant after adjustment for all covariates.

Discussion

To the best of our knowledge, this is the largest population-based study of mortality among breast cancer patients treated with NSM compared to non-NSM, with longer median follow-up (7.9 years) than previously reported. Consistent with prior studies [6, 9–14], we found no evidence of worse survival after NSM in this "real world" setting. In fact, NSM was associated with better survival than non-NSM; however, this association did not persist in a multivariable model adjusting for all clinical and sociodemographic factors, including grade, ER/PR status, and insurance status. NSM use increased over time, and was more prevalent among younger women who had earlier-stage cancer and/or resided in higher-SES neighbor-

hoods. Thus, the better survival associated with NSM in the minimally adjusted model may reflect confounding by neighborhood SES.

Our study has limitations. Most notably, we had to restrict our assessment to patients having unilateral mastectomy, because SEER and other registries do not capture the nipple-sparing status of bilateral mastectomies. Given the benefits of prophylactic bilateral mastectomy for patients with hereditary breast cancer [5] and the growing interest in bilateral NSM as a less invasive approach for primary breast cancer prevention in high-risk women [13], comparing outcomes of bilateral NSM versus bilateral non-NSM would be clinically valuable. This limitation should be addressed by adding detail about nipple-sparing status to routinely collected registry data items regarding bilateral mastectomy. Other gaps in registry data include family history and inherited genetic mutation status; however, we would not expect major differences in hereditary risk between the two groups that received unilateral mastectomy. Another potential concern is the possibly differential coding of NSM by hospital cancer registrars, which could result in misclassification of some NSM as non-NSM. There was differential follow-up time between patients who received non-NSM compared to NSM; however, the multivariable models that we used controlled for this difference. Moreover, results that included only the more recently diagnosed patients (1996–2013) were similar to those of the full cohort (1988–2013), which offers evidence that our findings are robust to differences in follow-up time. Despite these limitations, however, our study offers considerable strengths: it encompasses the full and diverse population of California, minimizes selection bias and provides results that can be generalized broadly. In the absence of randomized clinical trials, our comprehensive observational study of 157,592 breast cancer patients offers the best available evidence regarding the comparable survival between NSM and non-NSM.

Conclusion

Among California breast cancer patients diagnosed from 1988 to 2013, nipple-sparing mastectomy was not associated with worse survival than non-nipple-sparing mastectomy. These results may inform decisions of patients and doctors deliberating between these surgical approaches for breast cancer treatment.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Breast cancer patient characteristics by use of nipple-sparing and non-nipple-sparing unilateral mastectomy in California, 1998–2013

Variable	Unilateral mastectomy, non-nipple-sparing		Unilateral mastectomy, nipple-sparing		Total
	N	Column %	*N*	Column %	
All patients	156,599		993		157,592
Race/ethnicity					
Non-hispanic white	103,002	65.8	634	63.8	103,636
Non-hispanic black	8690	5.5	42	4.2	8732
Hispanic	24,368	15.6	140	14.1	24,508
Chinese	4423	2.8	19	1.9	4442
Japanese	2015	1.3	9	0.9	2024
Filipina	6202	4.0	22	2.2	6224
Other Asian/Pacific Islander	6645	4.2	111	11.2	6756
Non-hispanic American Indian/other/unknown	1254	0.8	16	1.6	1270
Age at diagnosis, years					
<40	10,537	6.7	128	12.9	10,665
40–49	30,174	19.3	327	32.9	30,501
50–64	52,090	33.3	382	38.5	52,472
65+	63,798	40.7	156	15.7	63,954
Marital status at diagnosis					
Not married	64,741	41.3	340	34.2	65,081
Married	88,040	56.2	626	63.0	88,666
Unknown	3818	2.4	27	2.7	3845
Neighborhood SES statewide quintile[a]					
Quintile (Q) 1 (lowest)	21,610	13.8	74	7.5	21,684
Q2	29,697	19.0	127	12.8	29,824
Q3	33,092	21.1	156	15.7	33,248
Q4	35,417	22.6	235	23.7	35,652
Q5 (highest)	36,783	23.5	401	40.4	37,184
Insurance status					
None	1330	0.8	5	0.5	1335

Variable	Unilateral mastectomy, non-nipple-sparing		Unilateral mastectomy, nipple-sparing		Total
	N	Column %	*N*	Column %	
Private only	65,849	42.0	621	62.5	66,470
Medicare only/Medicare and private	14,325	9.1	44	4.4	14,369
Any public/Medicaid/military	30,338	19.4	174	17.5	30,512
Unknown	44,757	28.6	149	15.0	44,906
American joint committee on cancer stage					
0	11,791	7.5	216	21.8	12,007
I	50,767	32.4	374	37.7	51,141
II	73,696	47.1	336	33.8	74,032
III	20,345	13.0	67	6.7	20,412
Tumor size, cm					
<1	18,206	11.6	197	19.8	18,403
1.0–1.9	46,494	29.7	311	31.3	46,805
2.0–2.9	37,838	24.2	211	21.2	38,049
3.0–4.9	33,361	21.3	170	17.1	33,531
5.0+	20,700	13.2	104	10.5	20,804
Grade					
I	19,675	12.6	149	15.0	19,824
II	55,522	35.5	396	39.9	55,918
III	56,995	36.4	345	34.7	57,340
Unknown	24,407	15.6	103	10.4	24,510
Histology					
Ductal	132,954	84.9	845	85.1	133,799
Lobular or with lobular component	14,125	9.0	92	9.3	14,217
Other	9520	6.1	56	5.6	9576
ER/PR status					
Negative (ER and PR both negative)	23,927	15.3	126	12.7	24,053
Positive (ER and/or PR-positive)	92,327	59.0	715	72.0	93,042
Unknown/borderline	40,345	25.8	152	15.3	40,497
Lymph node involvement					
Negative	91,755	58.6	735	74.0	92,490

Breast Cancer Res Treat. Author manuscript; available in PMC 2018 January 09.

Variable	Unilateral mastectomy, non-nipple-sparing		Unilateral mastectomy, nipple-sparing		Total
	N	Column %	*N*	Column %	
Positive	63,369	40.5	238	24.0	63,607
Unknown	1475	0.9	20	2.0	1495
Received care at NCI-designated cancer center					
No	150,310	96.0	906	91.2	151,216
Yes	6289	4.0	87	8.8	6376
Patient SES quintile distribution[a] of reporting hospital					
>=50 % of patients in quintiles 4 or 5 (highest) and <50 % in quintiles 1 or 2	70,021	44.7	672	67.7	70,693
>=50 % of patients in quintiles 1 (lowest) or 2 and <50 % in quintiles 4 or 5	35,404	22.6	129	13.0	35,533
Mixed SES distribution	51,174	32.7	192	19.3	51,366
Received adjuvant treatment (chemotherapy and/or radiation)					
No	91,774	58.6	547	55.1	92,321
Yes	64,825	41.4	446	44.9	65,271
Vital status at the end of the study period					
Alive	93,815	59.9	875	88.1	94,690
Died of breast cancer	25,948	16.6	37	3.7	25,985
Died of another cause	36,836	23.5	81	8.2	36,917

Variable	Unilateral mastectomy, non-nipple-sparing		Unilateral mastectomy, nipple-sparing		Total
	N	Row %	*N*	Row %	
Year of diagnosis					
1988	5924	99.8	14	0.2	5938
2013	5114	94.9	276	5.1	5390

ER, estrogen receptor; NCI, National Cancer Institute; PR, progesterone receptor; SES, socioeconomic status

[a]Distribution based on statewide quintiles

Table 2

Breast cancer-specific and overall mortality among patients undergoing nipple-sparing and non-nipple-sparing unilateral mastectomy in California, 1988–2013

	Number of deaths	Total person-years	Age- and stage-adjusted[a]			Fully adjusted[b,c]		
			HR	95 % CI	*p* value	HR	95 % CI	*p* value
Breast cancer-specific mortality								
1988–2013 diagnoses								
Non-nipple-sparing	25,948	1451,617	1.0[a]			1.0[b]		
Nipple-sparing	37	4553	0.67	0.49–0.93	0.02	0.71	0.51–0.98	0.04
1996–2013 diagnoses								
Non-nipple-sparing	13,469	767,098	1.0[a]			1.0[c]		
Nipple-sparing	17	2518	0.61	0.38–0.98	0.04	0.86	0.52–1.42	0.55
Overall mortality								
1988–2013 diagnoses								
Non-nipple-sparing	62,784	1451,617	1.0[a]			1.0[b]		
Nipple-sparing	118	4553	0.91	0.76–1.09	0.31	0.92	0.76–1.12	0.41
1996–2013 diagnoses								
Non-nipple-sparing	29,707	767,098	1.0[a]			1.0[c]		
Nipple-sparing	32	2518	0.59	0.42–0.83	0.003	0.74	0.50–1.08	0.12

n = 157,592 for 1988–2013; *n* = 106,181 for 1996–2013

[a] Cox regression with time from diagnosis (days) as the time-scale; stratified by American Joint Committee on Cancer (AJCC) stage (0, I, II, III); and adjusted for age at diagnosis

[b] Cox regression with time from diagnosis (days) as the time-scale; stratified by AJCC stage (0, I, II, III) and histology (ductal, lobular or with lobular component, other); adjusted for age, race, tumor size, lymph node involvement, adjuvant treatment, neighborhood socioeconomic status (SES), marital status, patient SES distribution of reporting hospital, National Cancer Institute-designated cancer center, and year of diagnosis; and adjusted for clustering by hospital

[c] Same as the model in footnote b, but additionally adjusted for grade, estrogen and progesterone receptor status, and insurance status, which were not available before 1996

Breast Cancer Res Treat. Author manuscript; available in PMC 2018 January 09.