



# Impact of Age on Locoregional and Distant Recurrence After Mastectomy for Ductal Carcinoma In Situ With or Without Microinvasion

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## ABSTRACT

**Background.** Locoregional recurrence (LRR) after breast-conserving surgery (BCS) for ductal carcinoma in situ (DCIS) is increased in young women. We examined the impact of age on LRR and distant disease after mastectomy for DCIS ± microinvasion.

**Methods.** We identified consecutive patients with DCIS ± microinvasion treated with mastectomy from 1995 to 2017. LRR was defined as recurrence at the ipsilateral chest wall or regional nodes.

**Results.** Overall, 3121 cases were identified, of which 421 (13.5%) had DCIS + microinvasion. Median age was 49 years and median follow-up was 6.4 years; 821 were followed for 10 or more years. Thirty-four LRRs were observed: 33 (97%) were invasive, and 23 (68%) were in the chest wall alone. Cumulative 10-year LRR incidence was 1.4%. Age < 50 years, high grade, and DCIS + microinvasion were associated with LRR ( $p \leq 0.001$ ); however, margin status was not ( $p = 0.14$ ). Adjusting for grade and DCIS + microinvasion, age < 50 years (hazard ratio [HR] 14.7, 95% confidence interval [CI] 3.5–61.5;  $p < 0.001$ ) was associated with LRR. Compared with

women  $\geq 50$  years of age, women age < 40 years had the highest risk (HR 27.0, 95% CI 6.0–121), and women age 40–49 years had intermediate risk (HR 11.8, 95% CI 2.8–50.5). The cumulative 10-year LRR incidence was 4.2% for women < 40 years of age, 2.0% for women 40–49 years of age, and 0.2% for women  $\geq 50$  years of age. Women age < 40 years had a 10-year distant disease rate of 1.6% versus women age 40–49 years (0.7%) and women age  $\geq 50$  years (0.7%) (log-rank  $p = 0.051$ ). Grade, DCIS + microinvasion, and margins were unassociated with distant disease.

**Conclusions.** LRR after mastectomy for DCIS ± microinvasion is uncommon, but is more frequent among women < 50 years of age, particularly in those < 40 years of age. The 10-year LRR rate in this youngest group remains low at 4.2%. Young age is an independent risk factor for LRR after BCS or mastectomy.

Ductal carcinoma in situ (DCIS) accounts for over 20% of newly diagnosed breast cancers as a result of increased detection with the widespread adoption of screening mammography.<sup>1</sup> Standard local treatment options include breast-conserving surgery (BCS) alone, BCS with adjuvant radiotherapy, and mastectomy. Survival is excellent with all options, with 20-year breast cancer-specific mortality rates of 3–4% after all surgical treatments,<sup>2,3</sup> but locoregional recurrence (LRR) rates vary widely.<sup>2,4,5</sup> Randomized trials of BCS with or without radiation found 10-year LRR rates of 20–30% after BCS alone; these rates decreased to 9–15% with the addition of radiation, a reduction of 50%.<sup>3,4,6–8</sup> In contrast, a meta-analysis of

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eight studies demonstrated a 10-year adjusted LRR rate of 2.6% (95% confidence interval [CI] 0.8–4.5%) among women with DCIS treated with mastectomy.<sup>9</sup>

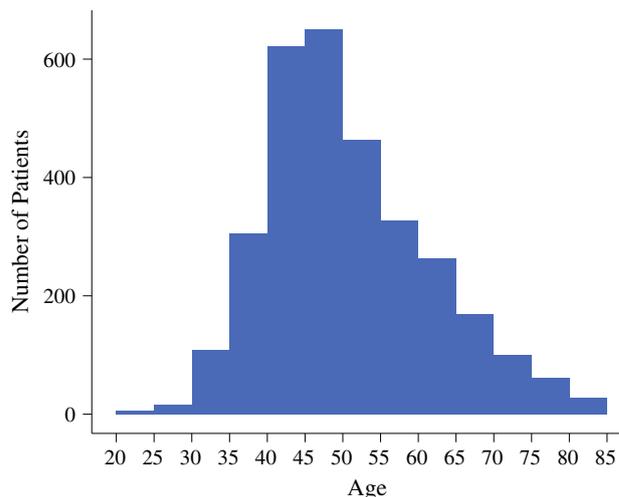
Young age, high nuclear grade, and inadequate margins are known risk factors for LRR after BCS,<sup>3,6,7,10,11</sup> but studies of their association with LRR after mastectomy have had variable results.<sup>12–18</sup> Clarifying the association of LRR with age is of particular importance in an era of increasing rates of mastectomy for DCIS, especially among young women,<sup>19,20</sup> as concerns about recurrence have been shown to greatly influence patient decision making.<sup>21</sup> We sought to define the effect of age on the risk of LRR and distant disease in the current era by examining a large population of consecutive patients treated at two cancer centers.

## METHODS

Following Institutional Review Board approval, we identified consecutive women treated with mastectomy for DCIS with or without microinvasion (DCIS ± microinvasion) at Memorial Sloan Kettering Cancer Center (MSKCC) from 1995 to 2017, and at Brigham and Women's Hospital/Dana-Farber Cancer Institute (DFCI) from 2000 to 2015. Microinvasion was defined as invasive tumor foci measuring ≤ 1 mm. Patients with node-positive disease, as well as those with prior or synchronous invasive cancer, were excluded. Bilateral cases of DCIS were abstracted as separate cases.

Standard clinicopathologic data were collected, including age at surgery, nuclear grade, margin status, and presence of microinvasion. Margins were categorized as negative (> 2 mm), close (≤ 2 mm), or positive (tumor at ink). The primary outcome of interest was LRR, defined as a biopsy-proven DCIS or invasive recurrence in the ipsilateral chest wall or ipsilateral regional lymph nodes, including axillary, supraclavicular, or internal mammary. Disease at any other site (other than the contralateral breast) was categorized as a distant recurrence.

Initially, an exploratory analysis grouped women by 5-year intervals of age (Fig. 1). Due to the limited number of patients and events, further analyses categorized patients into three age cohorts: < 40, 40–49, or ≥ 50 years. Categorical variables were compared using the Chi square test. Kaplan–Meier methods were used to estimate the time to LRR and distant recurrence, and 1 minus the Kaplan–Meier estimate was used for the 5- and 10-year cumulative incidence estimates by age. Patients were censored for distant recurrence at the date of contralateral invasive cancer. Multivariable Cox regression analysis was applied to assess the relationship between age group and recurrence, after adjusting for other factors. A *p* value < 0.05 was



**FIG. 1** Age distribution of women who underwent mastectomy for ductal carcinoma in situ ± microinvasion

considered statistically significant. All statistical analyses were conducted using R software version 3.5.0 (R Core Development Team, Vienna, Austria).

## RESULTS

Overall, 3121 mastectomies for DCIS ± microinvasion were identified; 2395 were performed at MSKCC and 726 at DFCI. Microinvasion was present in 421 (13.5%) cases. Axillary staging was performed in 2779 (89.0%) of all patients, including 410 (97.4%) of those with microinvasion. Median patient age was 49 years (interquartile range 43–58); the age distribution of the study population is shown in Fig. 1. Characteristics by age cohort and institution are summarized in Table 1. Women age < 40 years more often had high nuclear grade (*p* = 0.001) and close/positive margins (*p* = 0.004) compared with women age 40–49 years and ≥ 50 years.

The median follow-up time among survivors was 6.4 years (range 0–23); 821 were followed for ≥ 10 years. There were 34 LRRs—23 in the chest wall, 8 in the axillary nodes, and 3 in both. Of the 34 LRRs, 33 (97%) were invasive and 1 (3%) was in situ. Distant disease developed in 20 patients: 14 (70%) patients developed distant disease without LRR or contralateral carcinoma, 2 had a synchronous invasive LRR, 1 occurred 4 years after an invasive LRR, 2 occurred after the diagnosis of contralateral invasive cancer in the absence of ipsilateral LRR, and 1 was synchronous with contralateral invasive cancer diagnosis. The 3 patients with contralateral invasive cancer were censored for analysis of distant disease, for a total of 17 evaluable distant disease events. The cumulative 10-year incidence of LRR was 1.4% (95% CI 0.9–1.9%) and that of distant disease was 0.8% (95% CI 0.4–1.2%).

**TABLE 1** Characteristics of women undergoing mastectomy for DCIS with or without microinvasion, for the entire population and stratified by age group and institution

Characteristic	All		< 40 years		40–49 years		≥ 50 years		<i>p</i> value
	(n = 3121)		(n = 333)		(n = 1256)		(n = 1532)		
	<i>n</i>	%	<i>n</i>	%	<i>n</i>	%	<i>n</i>	%	
Entire population									
Microinvasion									0.065
Present	421	13.5	56	16.8	152	12.1	213	13.9	
Not present	2700	86.5	277	83.2	1104	87.9	1319	86.1	
Nuclear grade									0.001
Low/intermediate	1609	51.6	143	42.9	689	54.9	777	50.7	
High	1386	44.4	175	52.6	524	41.7	687	44.8	
Unknown	126	4.0	15	4.5	43	3.4	68	4.4	
Margins									0.004
Negative	2608	83.6	269	80.8	1055	84.0	1284	83.8	
Close/positive	82	2.6	17	5.1	35	2.8	30	2.0	
Unknown	431	13.8	47	14.1	166	13.2	218	14.2	
MSKCC population									
All	(n = 2395)		< 40 years		40–49 years		≥ 50 years		
(n = 2395)			(n = 270)		(n = 985)		(n = 1140)		
	<i>n</i>	%	<i>n</i>	%	<i>n</i>	%	<i>n</i>	%	
Microinvasion									0.076
Present	354	14.8	50	18.5	130	13.2	174	15.3	
Not present	2041	85.2	220	81.5	855	86.8	966	84.7	
Nuclear grade									0.005
Low/intermediate	1158	48.4	109	40.4	509	51.7	540	47.4	
High	1111	46.4	146	54.1	433	44.0	532	46.7	
Unknown	126	5.3	15	5.6	43	4.4	68	6.0	
Margins									0.014
Negative	1882	78.6	206	76.3	784	79.6	892	78.2	
Close/positive	82	3.4	17	6.3	35	3.6	30	2.6	
Unknown	431	18.0	47	17.4	166	16.9	218	19.1	
DFCI population									
All	(n = 726)		< 40 years		40–49 years		≥ 50 years		
(n = 726)			(n = 63)		(n = 271)		(n = 392)		
	<i>n</i>	%	<i>n</i>	%	<i>n</i>	%	<i>n</i>	%	
Microinvasion									0.723
Present	67	9.2	6	9.5	22	8.1	39	9.9	
Not present	659	90.8	57	90.5	249	91.9	353	90.1	
Nuclear grade									0.113
Low/intermediate	451	62.1	34	54.0	180	66.4	237	60.5	
High	275	37.9	29	46.0	91	33.6	155	39.5	
Margins									NA
Negative	726	100	63	100	271	100	392	100	

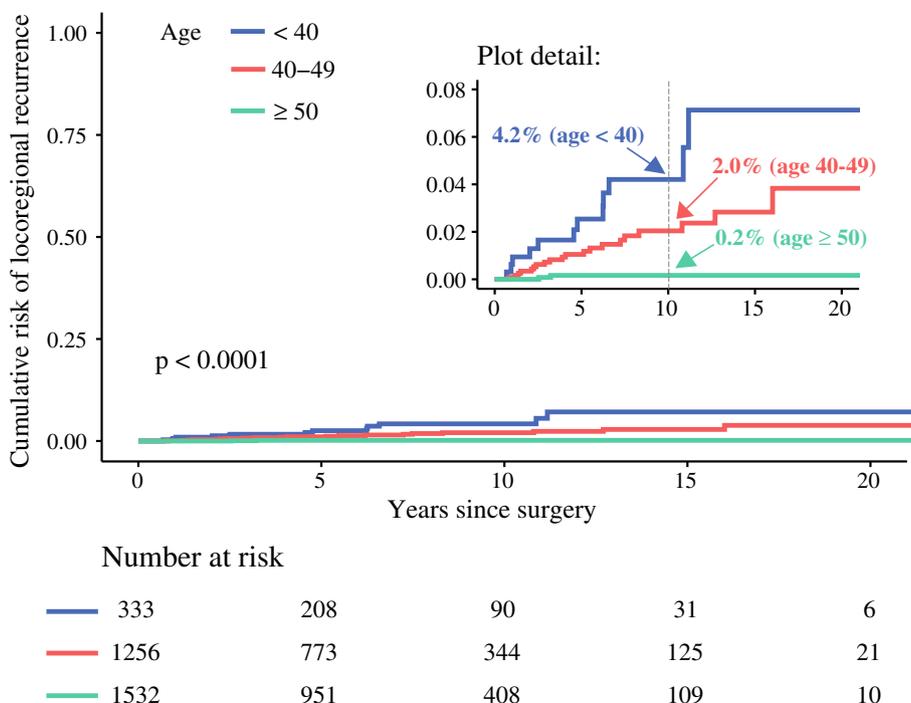
DCIS ductal carcinoma in situ, MSKCC Memorial Sloan Kettering Cancer Center, DFCI Dana-Farber Cancer Institute, NA not applicable

Effect of Age on Locoregional Recurrence (LRR)

On univariable analysis, age < 50 years at surgery (hazard ratio [HR] 15.0, 95% CI 3.58–62.4;  $p < 0.001$ ), presence of microinvasion (HR 3.35, 95% CI 1.66–6.77;  $p < 0.001$ ) and high nuclear grade (HR 3.56, 95% CI 1.60–7.88;  $p = 0.001$ ) were significantly associated with LRR, while close or positive margin status was not (HR 2.83, 95% CI 0.67–12.0;  $p = 0.14$ ). Younger age was associated with LRR, both when assessed as a continuous variable (HR 0.9 per year of age, 95% CI 0.86–0.94;  $p < 0.001$ ) and when categorized as three age groups (compared with women age  $\geq 50$  years: HR 11.8 [95% CI 2.8–50.5] for women age 40–49 years; HR 27.0 [95% CI 6.0–121] for women age < 40 years;  $p < 0.001$ ). On multivariable analysis, after adjusting for microinvasion (HR 2.88, 95% CI 1.40–5.92;  $p = 0.004$ ) and high nuclear grade (HR 3.09, 95% CI 1.38–6.94;  $p = 0.006$ ), age < 50 years (HR 14.7, 95% CI 3.5–61.5;  $p < 0.001$ ) remained significantly associated with an increase in LRR. The cumulative 10-year incidence of LRR was 4.2% for women age < 40 years, 2.0% for women age 40–49 years, and 0.2% for women age  $\geq 50$  years (Fig. 2).

Among women with both high-grade DCIS and microinvasion ( $n = 177$ ), the 10-year cumulative incidence of LRR was 17.3% (95% CI 1.6–30.5) for women age < 40 years, compared with 1.7% (95% CI 0–4.1) for women age  $\geq 50$  years. With neither microinvasion nor high grade, 10-year cumulative incidence of LRR was  $\leq 1.2\%$  for all age groups (Fig. 3).

**FIG. 2** Locoregional recurrence, by age (< 40, 40–49, or  $\geq 50$  years) at mastectomy, for ductal carcinoma in situ  $\pm$  microinvasion



Characteristics of Patients Who Developed LRR

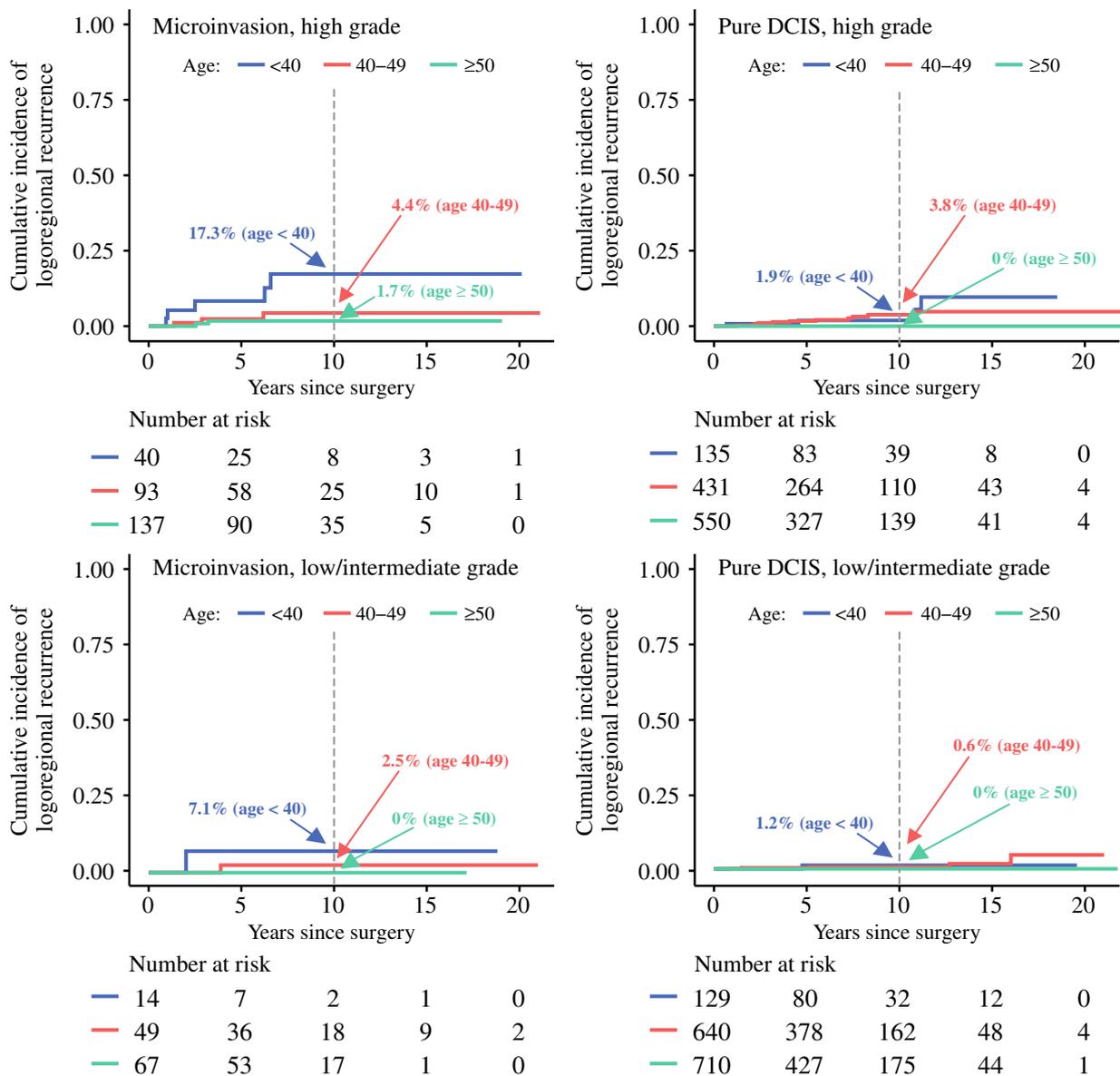
Characteristics of the 34 patients who developed LRR and pathologic features of initial disease are summarized in Table 2. Median age was 42 years (range 24–59), with only two women age  $\geq 50$  years. There were no patients with positive margins, while two (6%) patients had close margins. Thirty (88%) LRRs were treated with wide excision; 27 also received radiotherapy. Two patients with LRR had synchronous distant disease, and one patient developed distant disease 4 years later.

Age and Risk of Distant Disease

The cumulative 10-year distant disease rate was 0.8% (95% CI 0.4–1.2). Women younger than age 40 years had a 10-year distant disease rate of 1.6% compared with women age 40–49 years (0.7%) and  $\geq 50$  years (0.7%) (log-rank  $p = 0.051$ ). Presence of microinvasion (HR 1.84, 95% CI 0.60–5.65;  $p = 0.28$ ) and high nuclear grade (HR 0.76, 95% CI 0.27–2.14,  $p = 0.60$ ) were not associated with the development of distant disease. No women who developed distant disease had positive margins.

DISCUSSION

In this large consecutive cohort of women treated in the contemporary era with mastectomy for DCIS  $\pm$  microinvasion, including over 1500 women under the age of 50 years, the overall cumulative 10-year incidence of LRR



	Age < 40 years		Age 40-49 years		Age ≥ 50 years	
	Proportion with LRR	10-year cumulative incidence LRR (95% CI)	Proportion with LRR	10-year cumulative incidence LRR (95% CI)	Proportion with LRR	10-year cumulative incidence LRR (95% CI)
DCIS + microinvasion High grade	5/40	17.3% (1.6%-30.5%)	3/93	4.4% (0%-9.2%)	2/137	1.7% (0%-4.1%)
DCIS + microinvasion Low/intermediate grade	1/14	7.1% (0%-19.7%)	1/49	2.5% (0%-7.2%)	0/67	0% (0%-0%)
Pure DCIS High grade	4/135	1.9% (0%-4.5%)	11/431	3.8% (1.3-6.2%)	0/550	0% (0%-0%)
Pure DCIS Low/intermediate grade	1/129	1.2% (0%-3.4%)	5/640	0.6% (0-1.3%)	0/710	0% (0%-0%)

**FIG. 3** Ten-year cumulative incidence of locoregional recurrence after mastectomy for ductal carcinoma in situ ± microinvasion, by age group and stratified by nuclear grade and presence of

microinvasion. DCIS ductal carcinoma in situ, LRR locoregional recurrence, CI confidence interval

**TABLE 2** Clinicopathologic features of patients who developed locoregional recurrence ( $n = 34$ ) after undergoing mastectomy for DCIS with or without microinvasion

	Patients with LRR ( $n = 34$ )	
	<i>n</i>	%
<i>Characteristics of initial DCIS</i>		
Age (years) at mastectomy		
Median (range)	42 (24–59)	
< 40 ( $n = 333$ )	12	35.3
40–49 ( $n = 1256$ )	20	58.8
≥ 50 ( $n = 1532$ )	2	5.9
Family history <sup>a</sup>		
Strong	9	26.5
Weak	11	32.4
None	14	41.2
Primary method of diagnosis		
Imaging	13	38.2
Physical finding	21	61.8
Microinvasion present	12	35.3
Axillary staging performed	33	97.1
Distribution of disease		
Single quadrant	6	17.6
Multiple quadrants	26	76.5
Unknown	2	5.9
Nuclear grade		
Low/intermediate	8	23.5
High	25	73.5
Unknown	1	2.9
Presence of necrosis	32	94.1
Margins		
Negative	26	76.5
Close	2	5.9
Positive	0	0
Unknown	6	17.6
<i>Characteristics of locoregional recurrence</i>		
Month to recurrence [median (range)]	47 (8–191)	
LRR histology		
DCIS	1	2.9
Invasive	33	97.1
LRR location		
Chest wall only	23	67.6
Axilla only	8	23.5
Both chest wall and axilla	3	8.8
Developed distant disease	3	8.8

LRR locoregional recurrence, DCIS ductal carcinoma in situ

<sup>a</sup>A 'strong' family history was defined as at least one first-degree relative with breast cancer before age 50 years, or two or more relatives with breast cancer; a lesser degree of family history was defined as 'weak'

was 1.4%, with younger age being independently associated with a higher risk of LRR even after adjusting for other known risk factors.

Young age confers an increased risk of local recurrence for DCIS treated with BCS with or without radiotherapy, with reported 10-year rates of invasive recurrence of 16–31% among women age < 50 years.<sup>3,4,6,7,10</sup> The EORTC 10853 trial randomized those treated with BCS for DCIS to radiation or not, and found that those age ≤ 40 years had a higher risk of recurrence than those age > 40 years (HR 1.94;  $p = 0.009$ ) at 15.7 years of follow-up.<sup>7</sup> Similarly, in a combined analysis of the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-17 and B-24 randomized trials with 16.8 and 13.6 years of follow-up, respectively, the youngest women were also demonstrated to have a higher risk of both invasive (with age ≥ 65 years as the reference: HR 2.1 among women age < 45 years, 1.8 among women age 45–54 years, and 1.5 among women age 55–64 years,  $p = 0.003$ ) and DCIS recurrence (HR 2.9 among women age < 45 years, 1.8 among women age 45–54 years, and 1.7 among women age 55–64 years;  $p < 0.001$ ).<sup>6</sup> In the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) combined analysis of 3729 women treated in the four randomized trials of adjuvant radiotherapy following BCS for DCIS, among women receiving radiotherapy, younger women had a higher 10-year absolute risk of ipsilateral breast events compared with older women (18.5% age < 50 years vs. 10.8% age ≥ 50 years), and radiotherapy resulted in a smaller proportional risk reduction in women age < 50 years (HR 0.69 for age < 50 years vs. HR 0.38 for age ≥ 50 years;  $p = 0.0004$ ).<sup>4</sup> Comparing recurrence risk by decade of age, Cronin et al.<sup>10</sup> found that the youngest women (age < 40 years) had the highest risk of both invasive and DCIS recurrence, with or without radiotherapy, and that this finding persisted after adjusting for numerous confounding clinicopathologic factors (with age ≥ 80 years as the reference; HR 7.1 for invasive recurrence, HR 4.2 for DCIS recurrence).

However, young women with DCIS are increasingly being treated with mastectomy. In a study of the Surveillance, Epidemiology and End Results (SEER) data of 3648 patients age < 40 years with unilateral DCIS treated between 1998 and 2011, 25.8% underwent unilateral mastectomy and 15.8% underwent bilateral mastectomy, with a significant increase in mastectomy rates after 2005.<sup>20</sup> Similar trends were reported in a National Cancer Database study of 212,936 women with DCIS. Mastectomy was performed significantly more frequently among women age < 50 years (39.9 vs. 29.5%), with an upward trend between 2004 and 2011.<sup>19</sup> There are no prospective

randomized trials evaluating outcomes of mastectomy for DCIS, and young women with DCIS comprised a minority in past studies.<sup>12,14–16</sup>

The low 10-year overall cumulative incidence of LRR of 1.4% among patients undergoing mastectomy for DCIS  $\pm$  microinvasion in this study is consistent with previously reported rates of 1–3%.<sup>9,12</sup> We found young age to be independently associated with LRR, even after adjusting for the presence of microinvasion and high nuclear grade, which are more prevalent in younger women. The cumulative 10-year incidence of LRR was 4.2% among women age < 40 years, 2.0% among women age 40–49 years, and 0.2% among women age  $\geq$  50 years. Similar results on the impact of age were reported by Owen et al., who examined 637 subjects with pure DCIS treated with mastectomy between 1990 and 1999 and found a higher 10-year LRR rate of 7.5% for women age  $\leq$  40 years ( $n = 55$ ), compared with 1.5% among those age > 40 years ( $p = 0.003$ ).<sup>14</sup> Other retrospective studies have found no association of age with LRR,<sup>12,13</sup> but are limited by small study populations with yet smaller numbers of young women. The largest of these was a consecutive cohort of 1546 women with DCIS treated with mastectomy from 1994 to 2003, but only 16% ( $n = 248$ ) were younger than age 45 years.<sup>12</sup> The current series with 909 women younger than age 45 years has substantially more power to examine this association.

To our knowledge, this is the first large study of mastectomy patients with DCIS that includes those with microinvasion and that finds microinvasion to also be associated with an increased incidence of LRR on multivariable analysis. Prior studies of DCIS with microinvasion, in which the majority of patients underwent BCS, have demonstrated no definite association of microinvasion with LRR.<sup>22–24</sup> Our results indicate that women age < 40 years who have both microinvasion and high grade harbor the majority of excess risk (10-year cumulative incidence 17.3%) compared with women age 40–49 and  $\geq$  50 years who had 10-year cumulative incidence of LRR of only 4.4% and 1.7%, respectively. Individualized counseling on the risk of LRR based on the presence of these factors when known preoperatively may be of particular value among women motivated toward mastectomy by a desire to minimize recurrence.

Several studies have suggested that close or positive margins are associated with LRR after mastectomy for pure DCIS,<sup>16–18</sup> while others have found no association,<sup>12–15</sup> similar to our results. Fitzsullivan et al.<sup>16</sup> observed a 10-year LRR rate of 5% with margins  $\leq$  1 mm, 3.6% with margins 1.1–2.9 mm, and 0.7% for margins  $\geq$  3 mm ( $p < 0.001$ ) among 803 patients with DCIS treated with mastectomy between 1996 and 2009. In a retrospective analysis of 574 patients treated between 1994 and 2002,

Rashtian et al.<sup>18</sup> similarly noted a significantly higher LRR rate with margins  $\leq$  2 mm at mastectomy. Conversely, Klein et al.<sup>12</sup> demonstrated no difference in the rates of 10-year LRR with either high-grade or close/positive margins in a consecutive population of 1546 DCIS patients, reporting rates of 3% among those with positive margins, 1.4% among those with  $\leq$  2 mm margins, 1.5% among those with > 2 mm margins, and 2.8% among those with unknown margin status ( $p = 0.5$ ). Interpretation and applicability of results are made difficult by differing margin width categories and variable protocols of pathologic assessment across studies.

Overall survival after DCIS is excellent, with SEER analyses showing a 3.3% 20-year breast cancer-specific mortality, although rates are higher among women age < 35 years (HR 2.58;  $p < 0.001$ ) compared with older women.<sup>2</sup> While the 10-year distant disease rate of 1.6% among women age < 40 years in this study was slightly higher than rates among older women, this did not reach statistical significance. The majority of recurrences in our population were invasive and occurred in the chest wall in women age < 50 years, consistent with previously reported patterns.<sup>14,18</sup> While not well-studied among mastectomy patients, long-term outcomes following an invasive recurrence after BCS are known to be worse than after an in situ recurrence.<sup>6,7</sup>

Limitations of our study include its retrospective nature, the small number of LRRs, possible changes in pathologic assessment of margins over the study period, a small number of patients with positive margins, and the inability to include size or extent of DCIS in our analysis due to variable reporting and inconsistent parameters for quantification. However, this study includes a large consecutive population of women widely distributed over the full spectrum of age seen in practice, and treated in the contemporary era. While overall rates of LRR after mastectomy for DCIS  $\pm$  microinvasion are low, we have demonstrated an increased risk among young women. Awareness of this risk is of key importance in an era of increasing utilization of mastectomy for DCIS, especially among the young. Appropriate preoperative discussion and counseling, with an accurate understanding of estimated risk, is an essential element of optimal disease management.

## CONCLUSIONS

Distant disease-free survival after mastectomy for DCIS  $\pm$  microinvasion is excellent among all age groups, with 10-year rates of 98% among women age < 40 years, and 99% among women age  $\geq$  40 years. Overall rates of LRR after mastectomy for DCIS with or without

microinvasion are low. Young age, microinvasion, and high grade are associated with an increased risk; after adjustment for these factors, young age is independently predictive of LRR. Women under age 40 years had the highest risk, yet their cumulative 10-year LRR incidence remains low at 4.2%. The majority of excess risk occurred in those with all three risk factors (age < 40 years, microinvasion, high grade).

Young age is a risk factor for LRR after mastectomy or BCS for DCIS. Appropriate discussion with careful and evidence-based LRR risk estimation is warranted.

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