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Impact of age on risk of recurrence of DCIS: Outcomes of 2996 women treated with breast-conserving surgery over 30 years

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Abstract

Background—Age is a known risk factor for recurrence for women with DCIS treated with breast-conserving surgery (BCS); we explored the relationship between age, other risk factors, and recurrence.

Methods—Using a prospectively maintained database of DCIS patients undergoing BCS from 1978–2010, the association of age and recurrence risk was analyzed using Kaplan–Meier estimates, multivariable analysis (MVA), and competing-risk MVA (CRMVA).

Results—2996 cases were identified. Median follow-up for those without recurrence was 75 mos; 732 had ≥10y follow-up. 363 (12%) had recurrence: 192 (53%) DCIS, 160 (44%) invasive, 11 (3%) unknown. Risk of recurrence decreased with age, even after adjustment for eight clinicopathologic variables on MVA (hazard ratios [HR] with <40y as reference: 40–49y[0.82, p=0.36], 50–59y[0.46, p=0.0005], 60–69y[0.50, p=0.003], 70–79y[0.56, p=0.02], ≥80y [0.21, p=0.0015]). This association persisted for cohorts with and without RT. Using CRMVA, the effect of age on invasive recurrence was empirically stronger than for DCIS recurrence. 10y invasive recurrence was 16% vs. 6.5% in women <40y vs. women ≥40y. Only 0.6% of the population ultimately developed distant disease; those <40y constituted 4.7% (141/2996) of the population but 21% (4/19) of those developing distant disease.

Conclusions—Risk of recurrence of DCIS decreases with age; this effect is particularly strong at the extremes of age, and is independent of other clinicopathologic factors. The oldest women are at low risk of recurrence; the youngest have a higher overall and especially invasive recurrence rate, although mortality remains low. These findings should be incorporated into risk/benefit discussions of treatment options.

Keywords

DCIS; breast-conserving surgery; age; recurrence; invasive recurrence; distant metastases

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INTRODUCTION

Widespread adoption of screening mammography over the last 30 years has led to an increased detection of ductal carcinoma in situ (DCIS), such that it now accounts for over 20% of breast cancers diagnosed in the U.S.[1, 2] Current treatment options for DCIS include breast-conserving surgery (BCS) alone, BCS with radiation (RT), BCS with endocrine therapy, BCS with both RT and endocrine therapy, mastectomy, and even bilateral mastectomy.[3, 4] There is currently concern about overtreatment of this lesion; however, while survival is excellent with all treatments, local recurrence rates vary widely with various treatment options.[5–11]

Both retrospective studies[12–14] and the randomized trials of RT[7–10] have shown that younger age is associated with a higher risk of local recurrence for DCIS treated with BCS. A recent analysis of DCIS patients from the Surveillance, Epidemiology, and End Results (SEER) registry found an increased risk of breast cancer mortality for those <35y of age.[11] However, the relationship between age and recurrence across the full spectrum of age, and the interaction between age and other clinicopathological and treatment factors has not been fully elucidated. The goal of this study was to explore the association of age with ipsilateral locoregional recurrence, both in situ and invasive, and development of distant disease.

METHODS

Following Institutional Review Board approval the outcomes of DCIS patients who underwent BCS at Memorial Sloan Kettering Cancer Center from 1978–2010 were analyzed from a prospectively maintained database. Bilateral cases of DCIS in patients with either synchronous (n=30) or metachronous (n=29) lesions were abstracted as separate cases.

Patients were grouped and analyzed according to age at the time of surgery (<40, 40–49, 50–59, 60–69, 70–79 or ≥80y). Other factors analyzed were: family history of breast cancer (defined as ≥1 first- or second-degree family member), presentation (radiological or clinical), nuclear grade (low/intermediate or high), necrosis, number of excisions required (≤2 or ≥3), margin status (positive/close (≤2mm) or negative (>2mm)), use of adjuvant RT and endocrine therapy, and treatment time period (≤1998 or ≥1999).[15]

The primary endpoint was time to first recurrence, categorized as DCIS or invasive recurrence. DCIS recurrence was defined as ipsilateral breast recurrence of DCIS without invasion. Invasive recurrence was defined as first recurrence as ipsilateral invasive breast cancer, ipsilateral axillary nodal recurrence without ipsilateral breast recurrence, or, in a single patient, distant recurrence in the absence of any ipsilateral recurrence or contralateral diagnosis of breast carcinoma. Time to event was defined as the interval between definitive surgery and date of first recurrence.

A secondary endpoint was development of distant disease at any time, in the absence of contralateral invasive breast cancer.

Differences in patient characteristics by age were assessed using χ^2 test. Five- and 10-year Kaplan–Meier recurrence estimates by age were calculated for the entire population, as well as the cohorts with and without RT. Multivariable Cox regression analysis was used to assess the relationship between age and recurrence after adjustment for clinicopathological and treatment factors. Competing risk analysis was used to assess risk of invasive or in situ recurrence according to age univariately, and competing risk multivariable analysis was used to adjust for other factors. Women in whom the type of recurrence (invasive or DCIS) was not known were excluded from the competing risk analysis. All analyses were performed in SAS version 9.4 and R version 3.1.1.

RESULTS

2996 cases of DCIS managed with BCS were identified from 1978 to 2010. Characteristics of the entire population and the cohorts stratified by decade of age at the time of surgery are shown in Table 1. The median patient age was 57y (range 20–92). The distribution of the study population by age is shown in Supplemental Fig. 1.

The median follow-up was 75 months (range 0–30y) in patients without recurrence; 732 were followed for ≥10 years. There were 363 recurrences; 192 patients developed a DCIS ipsilateral breast recurrence. Of the 160 invasive recurrences, 147 were ipsilateral breast recurrence, 10 were concurrent breast and regional nodal recurrence, 2 had evidence of axillary recurrence only, and one had distant recurrence without evidence of locoregional recurrence or contralateral invasive disease. There were 11 cases of recurrence of unknown type. Distant disease developed in 19 patients; 16/19 occurred after an invasive locoregional recurrence.

Differences in patient, tumor and treatment characteristics by age

Women <40y constituted a smaller proportion of the population after 1999 as compared to the earlier years of the study (3.8% vs. 7.1%). Comparison across the age categories demonstrated that patients <40y more frequently presented clinically than their older counterparts, and less frequently received adjuvant endocrine therapy. Women ≥70y less frequently had ≥3 excisions, more frequently had positive or close margins, and less commonly received adjuvant RT or endocrine therapy.

Differences in recurrence rates by age

With increasing age there was a significant decrease in 10-year recurrence rates, ranging from 7.5% in women ≥80y to 27.3% in women <40y ($p<0.0001$) (Fig. 1a). After stratification by use of radiation, the association of decreasing recurrence rates with increasing age persisted in those not receiving and those receiving radiation (Fig. 1b and 1c).

Our population included only women undergoing BCS. To exclude the possibility that the observed relationship between age and recurrence risk is due to treatment selection bias toward BCS among young women, we examined the proportion of patients undergoing BCS and mastectomy by age (Supplemental Fig. 2). The proportion of women undergoing BCS was correlated with age, with younger women more frequently undergoing mastectomy,

thereby demonstrating that the observed association of young age and higher risk of recurrence is not due to underutilization of mastectomy in younger women.

Multivariable analysis

Multivariable analysis of 2,634 patients with complete data was performed, adjusting for presentation, family history, necrosis, number of excisions, margin status, adjuvant RT, adjuvant endocrine therapy, and treatment period. Grade was not significantly associated with age (p=0.4), nor with recurrence on either univariate (p=0.4) or multivariable (p=0.9) analysis; therefore it was not included in the final multivariable model (Table 2).

After adjustment for 8 clinicopathologic and treatment variables, risk of recurrence remained significantly lower in older age groups, with decreasing HRs with increasing age category (HRs with <40y as reference: 40–49y [0.82, p=0.36], 50–59y [0.46, p=0.0005], 60–69y [0.50, p=0.003], 70–79y [0.56, p=0.02], ≥80y [0.21, p=0.0015]) (Table 2).

Separate multivariable analyses of the 1163 women treated without RT and the 1471 who received RT were performed. Age was significantly associated with recurrence risk in both groups, but the effect was most evident in women receiving radiation (Table 2).

Invasive versus in situ recurrences

Because the implications of invasive and in situ recurrence differ, we examined them as competing risks according to age (Fig. 2). Women <40y were empirically at higher risk for invasive recurrence than DCIS recurrence (10-year invasive vs. DCIS risk: 15.8% vs. 11.5%). In contrast, in all other age groups the risk of DCIS recurrence was at least as high as the risk of invasive recurrence. 10-year risk estimates for invasive recurrence were 15.8% vs. 6.5% for those <40 vs. ≥40y.

We also built a competing risk multivariable model to adjust for other clinicopathologic factors which vary by age or are associated with recurrence (Table 3). The effect of age on risk of invasive recurrence was greater than the effect of age on overall recurrence or in situ recurrence. For both invasive and in situ recurrences, the use of radiation was associated with an approximate 50% reduction in the risk of recurrence (p≤0.00004).

Age and risk of distant disease

19 (0.6%) patients ultimately developed distant disease (without contralateral invasive breast cancer). Women <40y accounted for 21% of these but constituted only 4.7% of our population. This suggests that young women may be at higher risk of developing distant disease, which is consistent with the finding that younger women were at particularly high risk for invasive recurrence. Yet, even among the youngest women <40y, only 2.8% developed distant metastases.

DISCUSSION

It has been recognized for almost two decades that age is associated with risk of recurrence for DCIS treated with BCS. In 1999, Van Zee et al. found that 6-year recurrence rates varied by age (47% [<40y], 14% [40–69y], 11% [≥70y], p=0.05), and that the differences persisted

when stratified by radiation use.[12] In 2000, Vicini et al. also reported that young age was a risk factor for recurrence among women who underwent BCS and RT; 10-year recurrence rates were 26% in women <45 vs. 8.6% in women ≥45y (p=0.03).[13] Cutuli et al. found that young age was associated with higher 7-year recurrence rates, but only in those treated with RT (29% [≤40y], 13% [41–60y], 8% [≥61y], p<0.001).[14]

As results of the randomized studies of adjuvant RT or tamoxifen for DCIS became available, these findings were confirmed with prospective data. In 2001, Bijker et al. reported EORTC 10853 results at median follow-up of 5.4y; age ≤40 compared to >40 was associated with a two-fold increased risk of recurrence (HR=2.14, p=0.02) on multivariable analysis.[16] With 15.7 years of follow-up, Donker et al. confirmed these findings with women ≤40y having a higher risk of recurrence than those >40y (HR=1.94, p=0.009).[9] While NSABP B-17 found no difference in recurrence rates between age groups (≤49, 50–59, ≥60y) at a median follow-up of 7.5 years,[17] in NSABP B-24 older women were found to have a lower risk of recurrence at a median follow-up of 6.2 years (relative risk for ≥50 vs. ≤49y = 0.43 [95% CI 0.31–0.59]).[18] In a combined analysis of B-17 and B-24 with long-term follow-up (16.8 and 13.6 years, respectively), age was a significant risk factor for both invasive and DCIS recurrence.[8] In that analysis, with ≥65y as the reference, younger women had a higher risk of invasive recurrence (HRs: 2.1 [<45y], 1.8 [45–54y], 1.5 [55–64y], p=0.003) and a higher risk of DCIS recurrence (HRs: 2.9 [<45y], 1.8 [45–54y], 1.7 [55–64y], p<0.001).

However, based on this literature it is challenging to fully understand the relationship of age and recurrence risk because age categories have been variably defined and the extremes of age are under-represented. Both retrospective and prospective randomized trials have used widely varying age categorization schemes. In the randomized trials, the youngest cohort was defined as ≤40 (similar to our dataset) in the EORTC 10853 trial[9]; in contrast it was defined as <52y in the SweDCIS study.[7] The definition of the oldest age category has ranged from >40y to ≥65y.[8, 9] In addition, screening patterns limited the evaluation of the extremes of age; the SweDCIS and UK/ANZ trials primarily recruited from a screen-detected population ≥50y. Overall, few younger women were included in the trials: SweDCIS, 35 women <40y; EORTC 10853, 51 women ≤40y; UK/ANZ, 160 women <50y; and NSABP B-17, 138 women <45y. There were also relatively few older patients included: UK/ANZ, 181 women ≥65y; NSABP B-17, 159 women ≥65y, SweDCIS, 180 women ≥67y, and EORTC 10853, only 11 women >70y.[19]

We sought to examine the relationship of age and recurrence across the full spectrum of age. Because of the large size of our series and the lack of exclusions, we were able to systematically describe recurrence rates by decade of age, thereby reflecting the actual age distribution of patients presenting with DCIS and undergoing BCS. Women <40 and ≥70y constituted 4.7% and 18% of our population, respectively.

Our data demonstrate not only that the risk of recurrence after BCS for women with DCIS significantly decreases with age, but that it appears to do so in a non-linear fashion. Those in the youngest group (<40y) are at particularly high risk, while the eldest (≥80y) are at

particularly low risk. These findings persisted when the cohorts that did not and did receive radiation were analyzed separately.

Numerous clinicopathologic factors have been found to influence the risk of recurrence of DCIS and many of them vary by age, thereby potentially confounding the association of age and recurrence. Because our population is large, well-characterized, and has significant follow-up, we were able to adjust for many factors that vary with age at diagnosis, thereby enabling us to assess the independent effect of age on recurrence. The relationship between age and recurrence risk persisted after controlling for other factors with multivariable analysis.

The overview of the randomized trials of radiation for DCIS noted that RT resulted in a larger proportional reduction in risk for women ≥50y as compared to women <50y (HR 0.38 vs. 0.69, p=0.0004).[6] Updated results from the SweDCIS and UK/ANZ trials confirmed that there are age-related differences in the responsiveness to RT with smaller proportional and absolute risk reduction from RT in younger women.[7, 10] We found that after stratification for RT use, the hazard ratio for recurrence decreased with age in both RT and no RT cohorts, with the effect being more marked in the RT cohort; this observation is consistent with the finding of a greater benefit of RT with age.

The long-term outcome following an invasive recurrence is worse than after an in situ recurrence.[7–9] Data from EORTC 10853, SweDCIS, and pooled data from NSABP B-17 and B-24 trials showed that young age was associated with higher risk for an invasive recurrence.[7–9] In our population, recurrences in women <40y were more likely invasive than DCIS, in contrast to all other age groups in whom DCIS recurrences were at least as frequent as invasive recurrence (Fig. 2). Further, we found that the relationship between age and invasive recurrence risk was much stronger than that between age and DCIS recurrence. As compared to women with ages ≥80 or 50–79, women <40y had a 7-fold or 3-fold higher risk of developing an invasive recurrence, respectively.

Narod et al. recently reported SEER data showing that women with DCIS had a 3.3% 20-year breast cancer-specific mortality (including those who developed contralateral breast cancer), with women <35y having a higher risk of breast cancer-specific mortality than older women (HR=2.58, p<0.001).[11] Our population also had an excellent distant-disease free survival, with only 19 (0.6%) women, without contralateral invasive cancer, ultimately developing distant metastasis. While the number of distant events in our population is too small to perform a formal analysis, our finding that women <40y are at particularly high risk for invasive recurrence and are over-represented among those who did ultimately develop distant disease (4 of 19), is consistent with the observation of higher mortality among young women with DCIS. It is important to note that there were only 3 cases (0.1%) of distant metastases in the absence of invasive local recurrence or contralateral invasive breast cancer, supporting the importance of maintaining local control in these patients.

The association between age and risk of recurrence should be incorporated into a thorough discussion with a woman regarding the various treatment options, including the relative importance to that individual woman of the various risks and benefits of each option. Given

that there is no evidence of a survival advantage with or without RT, or with BCS or mastectomy, and given that the quality of life implications—both the psychological and the physical—of various treatment options will vary in different women, we believe that the optimal approach is to provide risk estimates that are as accurate as possible. We have previously developed a nomogram[20] (available at www.nomograms.org), now validated in at least 4 different independent populations,[21–24] that incorporates age and provides a risk estimate for an individual woman. A careful discussion with the patient can then help her weigh the risks and benefits and their relative value for her, so that she can make her best decision.

CONCLUSIONS

Risk of recurrence following BCS for DCIS decreases with age; this effect is particularly strong at the extremes of age, and persists even after controlling for other clinicopathologic and treatment factors. This finding remained true in cohorts that were treated with and without RT. The oldest women are at low risk of recurrence; the youngest have a higher overall and especially invasive recurrence rate, although mortality remains low. These findings should inform discussions in patients presenting with DCIS and be incorporated into risk/benefit considerations for surgical planning and adjuvant treatments.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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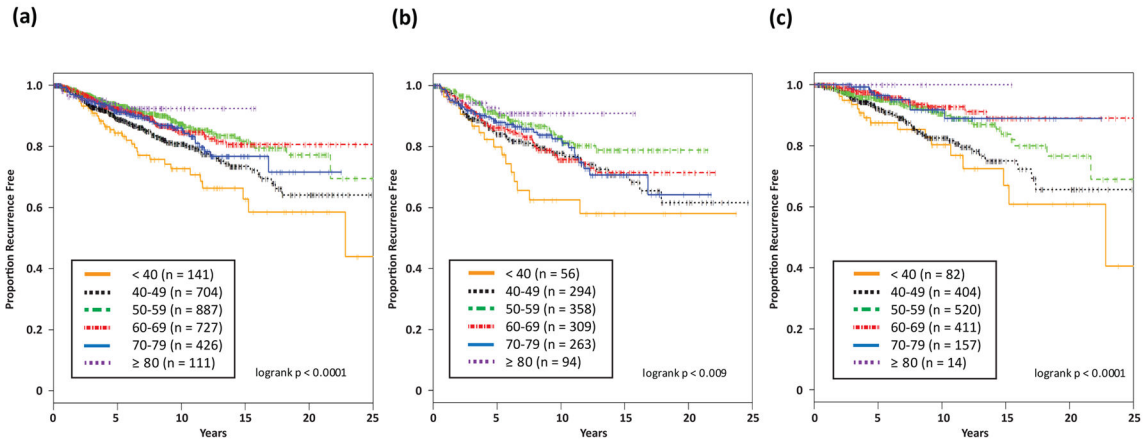
SYNOPSIS

Following breast-conserving surgery for DCIS, women ≥80y are at low risk for any recurrence, while those <40y are at higher risk of recurrence, especially invasive recurrence, even after adjustment for other clinicopathologic variables and use of adjuvant therapies.



At Risk: 2996 1755 732 234 71 6

Age	Recurrence Rate (95% Confidence Interval) 5-year, %	10-year, %	HR	p
< 40	15.6 (10.2–23.4)	27.3 (19.4–37.6)	1	---
40–49	11.0 (8.7–13.9)	19.2 (15.7–23.3)	0.68	0.05
50–59	6.5 (4.9–8.5)	12.5 (9.9–15.8)	0.41	< 0.0001
60–69	7.6 (5.8–10.0)	15.4 (12.2–19.3)	0.46	0.0002
70–79	8.8 (6.2–12.3)	13.9 (10.1–18.9)	0.54	0.006
≥ 80	6.0 (2.7–13.1)	7.5 (3.6–15.3)	0.34	0.01

At Risk: 1374 792 348 110 26

Age	Recurrence Rate (95% Confidence Interval) 5-year, %	10-year, %	HR	p
< 40	20.1 (11.3–34.3)	37.5 (24.4–54.6)	1	---
40–49	15.9 (11.8–21.2)	22.1 (16.9–28.7)	0.64	0.1
50–59	9.3 (6.5–13.2)	16.9 (12.5–22.7)	0.40	0.001
60–69	13.8 (10.2–10.0)	24.3 (18.9–31.0)	0.58	0.05
70–79	12.1 (8.4–17.2)	17.5 (12.4–24.3)	0.55	0.04
≥ 80	7.2 (3.3–15.6)	9.1 (4.3–18.4)	0.29	0.007

At Risk: 1588 949 381 123 44 6

Age	Recurrence Rate (95% Confidence Interval) 5-year, %	10-year, %	HR	p
< 40	12.5 (6.7–22.7)	19.7 (11.4–32.9)	1	---
40–49	7.8 (5.3–11.2)	17.4 (13.0–23.1)	0.74	0.3
50–59	4.6 (3.0–7.0)	9.4 (6.5–13.5)	0.43	0.003
60–69	2.9 (1.6–5.3)	7.3 (4.5–11.7)	0.28	0.0001
70–79	3.6 (1.4–9.3)	8.3 (3.9–17.2)	0.31	0.007
≥ 80	0 (–)	0 (–)	0	---

Fig. 1.

Proportion recurrence-free, by age at surgery, in (a) entire population, (b) in cohort *not* receiving radiation, and (c) in cohort receiving radiation.

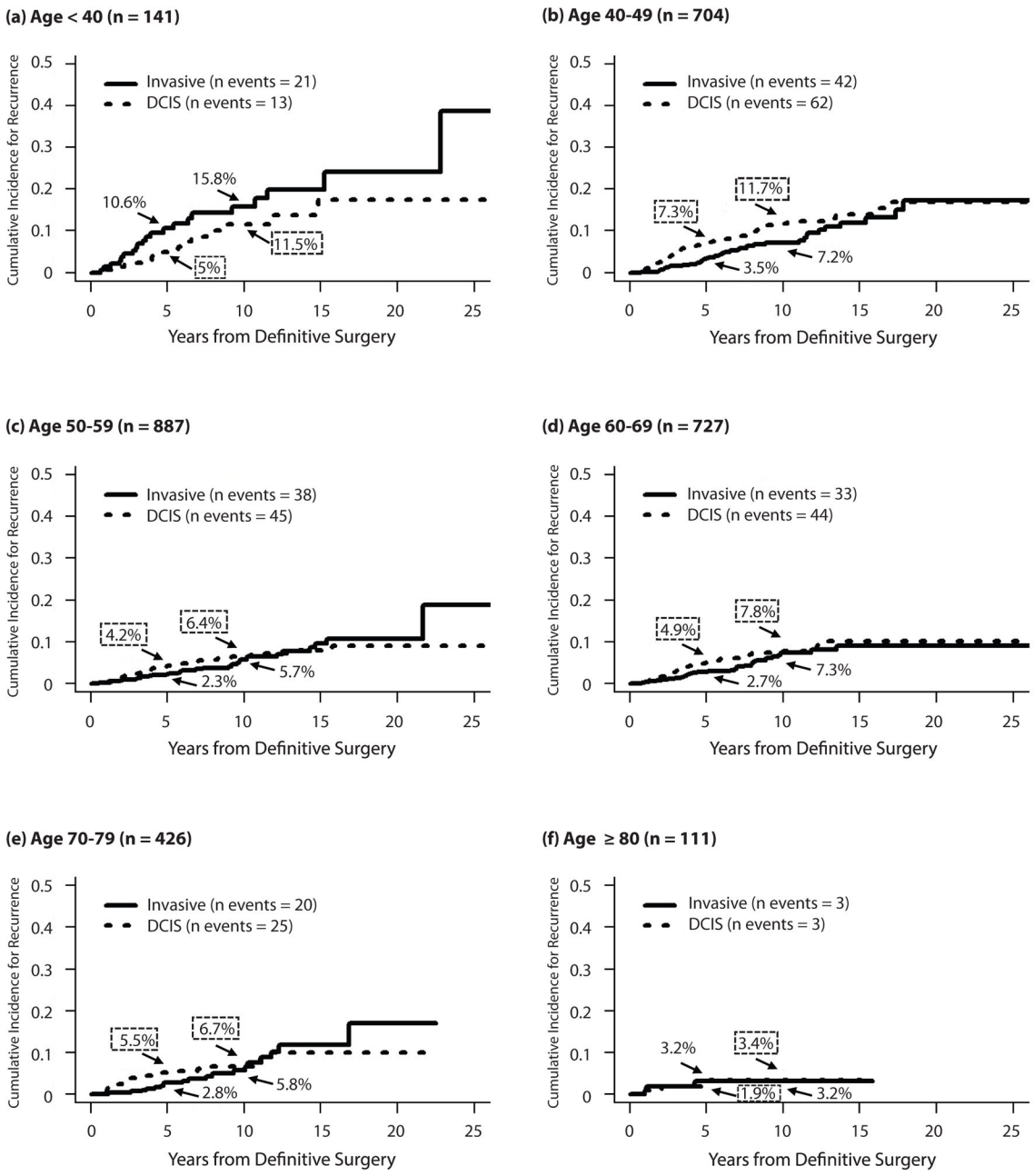


Fig. 2.

Competing risk curves for invasive vs. DCIS recurrence by age, for women age (a) <40y, (b) 40–49y, (c) 50–59y, (d) 60–69y, (e) 70–79y, and (f) ≥80y.

TABLE 1

Characteristics of the entire population, and by age group

Characteristic	Total population N=2996		<40 N=141		40 – 49 N=704		50 – 59 N=887		60 – 69 N=727		70 – 79 N=426		≥80 N=111		
	n	%	n	%	n	%	n	%	n	%	n	%	n	%	*p* value*
Presentation															
Clinical	386	13	43	30	99	14	91	10	83	11	52	12	18	16	<0.0001
Radiological	2606	87	98	70	605	86	795	90	644	89	371	87	93	84	
Unknown	4	0	0	0	0	0	1	0	0	0	3	1	0	0	
Family History															
No	1816	61	84	60	427	61	522	59	452	62	264	62	67	60	0.7
Yes	1163	39	54	38	266	38	358	40	262	36	154	36	42	38	
Unknown	44	1	3	2	11	2	7	1	13	2	8	2	2	2	
Nuclear Grade															
Low/intermediate	1787	60	82	58	420	60	543	61	422	58	259	61	61	55	0.4
High	994	33	47	33	235	33	287	32	259	36	124	29	42	38	
Unknown	215	7	12	9	49	7	57	6	46	6	43	10	8	7	
Necrosis															
Absent	1029	34	46	33	270	38	308	35	228	31	139	33	38	34	0.1
Present	1802	60	84	60	395	56	533	60	465	64	256	60	69	62	
Unknown	165	6	11	8	39	6	46	5	34	5	31	7	4	4	
Number of excisions															
≤2	2775	93	130	92	634	90	820	92	676	93	406	95	109	98	0.01
≥3	217	7	11	8	67	10	67	8	50	7	20	5	2	2	
Unknown	4	0	0	0	3	0	0	0	1	0	0	0	0	0	
Margin status															
Close/positive	553	19	27	19	119	17	147	16	128	18	99	23	33	30	0.0003
Negative	2235	75	100	71	549	78	689	77	543	74	285	67	69	62	
Unknown	208	7	14	10	36	5	51	6	56	8	42	10	9	8	

Characteristic	Total population N=2996		<40 N=141		40 – 49 N=704		50 – 59 N=887		60 – 69 N=727		70 – 79 N=426		≥80 N=111		
	n	%	n	%	n	%	n	%	n	%	n	%	n	%	*p* value*
Radiation therapy															
Yes	1588	53	82	58	404	57	520	59	411	57	157	37	14	13	<0.0001
No	1374	46	56	40	294	42	358	40	309	43	263	62	94	85	
Unknown	34	1	3	2	6	1	9	1	7	1	6	1	3	3	
Endocrine therapy															
Yes	628	21	16	11	145	21	238	27	158	22	63	15	8	7	<0.0001
No	2321	77	122	87	553	79	636	72	556	76	356	84	98	88	
Unknown	47	2	3	2	6	1	13	1	13	2	7	2	5	5	
Year of surgery															
≤1998	785	26	56	40	181	26	214	24	179	25	128	30	27	24	0.0014
≥1999	2211	74	85	60	523	74	673	76	548	75	298	70	84	76	

*$\chi 2$ test of difference between age at time surgery

TABLE 2

Multivariable Cox models for recurrence, for entire population, and those without and with radiation

	Entire population (*n*=2634)				No-radiation cohort (*n*=1163)				Radiation cohort (*n*=1471)			
	n	**Events**	**HR**	**p value**	**n**	**Events**	**HR**	**p value**	**n**	**Events**	**HR**	**p value**
Age												
<40	119	29	1	--	46	15	1	--	59	14	1	--
40 – 49	625	99	0.82	0.36	247	52	0.83	0.54	378	47	0.89	0.71
50 – 59	791	75	0.46	0.0005	305	38	0.45	0.01	486	37	0.52	0.04
60 – 69	641	64	0.50	0.003	263	48	0.69	0.21	378	16	0.32	0.002
70 – 79	362	44	0.56	0.02	220	37	0.64	0.16	142	7	0.37	0.04
≥80	96	5	0.21	0.0015	82	5	0.24	0.006	14	0		
Presentation				0.008				0.02				0.25
Clinical	302	59	1		150	38	1		152	21	1	
Radiological	2332	257	0.67		1013	157	0.65		1319	100	0.75	
Family History				0.02				0.03				0.21
No	1614	180	1		713	109	1		901	71	1	
Yes	1020	136	1.31		450	86	1.37		570	50	1.26	
Necrosis				0.006				0.004				0.85
Absent	941	105	1		595	79	1		346	26	1	
Present	1693	211	1.42		568	116	1.54		1125	95	1.04	
Number of excisions				0.01				0.002				0.52
≤2	2433	284	1		1121	179	1		1312	105	1	
≥3	201	32	1.64		42	16	2.33		159	16	1.19	
Margin status				0.01				0.0004				0.82
Close/positive	522	81	1.39		202	50	1.81		320	31	0.95	
Negative	2112	235	1		961	145	1		1151	90	1	
Radiation therapy				<0.0001								
Yes	1163	195	0.42				NA				NA	

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	Entire population (*n*=2634)				No-radiation cohort (*n*=1163)				Radiation cohort (*n*=1471)			
	n	**Events**	**HR**	**p value**	**n**	**Events**	**HR**	**p value**	**n**	**Events**	**HR**	**p value**
No	1471	121	1									
Endocrine therapy				<0.0001				0.006				0.001
Yes	587	39	0.50		189	20	0.52		398	19	0.44	
No	2047	277	1		974	175	1		1073	102	1	
Year of surgery				0.005				0.001				0.91
≤1998	567	145	1		331	100	1		236	45	1	
≥1999	2067	171	0.7		832	95	0.61		1235	76	0.98	

TABLE 3

Competing risk multivariable model for invasive versus in situ recurrence

	Invasive recurrence		In situ recurrence	
	HR	**p value**	**HR**	**p value**
Age				
<40	1		1	
40 – 49	0.48	0.01	1.33	0.4
50 – 59	0.33	0.0002	0.69	0.3
60 – 69	0.29	0.00008	0.88	0.7
70 – 79	0.36	0.003	0.81	0.6
≥80	0.14	0.01	0.24	0.06
Presentation		0.8		0.02
Clinical	1.07		1.61	
Radiological	1		1	
Family History		0.3		0.04
No	1		1	
Yes	1.21		1.38	
Necrosis		0.2		0.02
Absent	1		1	
Present	1.27		1.5	
Number of excisions		0.8		0.007
≤2	1		1	
≥3	1.1		1.92	
Margin status		0.2		0.1
Close/positive	1.31		1.33	
Negative	1		1	
Radiation therapy		0.00004		<0.00001
Yes	0.43		0.45	
No	1		1	
Endocrine therapy		0.02		0.003
Yes	0.53		0.49	
No	1		1	
Year of surgery		0.9		0.0005
≤1998	1		1	
≥1999	1.03		0.56	