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EPIDEMIOLOGY

Impact of a prior diagnosis of DCIS on survival from invasive breast cancer

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Abstract A diagnosis of invasive breast cancer after DCIS can be described as a new primary cancer or as a local invasive recurrence. It is of interest to determine if, among women with early-stage breast cancer, a past history of DCIS influences survival. We retrieved the records of 306,249 women diagnosed with stage I or stage II breast cancer between 2004 and 2012, in the surveillance, epidemiology, and end results registries database, of whom 5395 had a previous diagnosis of DCIS. For each patient, we extracted information on the year of diagnosis, age at diagnosis, tumor size, nodal status, grade, estrogen receptor status, type of surgery (lumpectomy/mastectomy), use of radiotherapy (no/yes), prior DCIS (no/yes), cause of death, and follow-up time. For each case with prior DCIS, we recorded information on the year of diagnosis of DCIS, laterality of DCIS, and treatments received for DCIS. We matched 3979 patients with a prior DCIS to 3979 patients without a prior DCIS, according to the various prognostic features of the invasive cancer. We estimated the risk of death from breast cancer for patients with invasive ductal carcinoma, with and without a prior diagnosis of DCIS. We identified 306,249 women with stage I/II breast cancer, of whom 2335 had a prior ipsilateral DCIS and 3060 had a prior contralateral DCIS. Breast cancer-specific survival at 9 years was 94.6 % for patients with a prior DCIS (ipsilateral or contralateral) and was 95.2 % for patients with no prior DCIS ($p = 0.32$). In a matched analysis (3979 matched pairs), the hazard ratio for death from breast cancer for patients with a prior ipsilateral DCIS, compared to patients with no prior DCIS, was 0.91 (95 % CI = 0.49–1.68; $p = 0.75$). A prior diagnosis of ipsilateral DCIS does not impact upon the prognosis of women with early-stage invasive breast cancer. This suggests that primary breast cancers and local invasive recurrences following DCIS are similar conditions and should be treated in the same way.

Keywords DCIS · Invasive breast cancer · Local recurrence · Survival

Introduction

The conventional view of breast cancer progression is that cancer first begins in the ducts (or lobules) as in situ disease, then invades the surrounding breast tissue prior to metastasizing to distant sites [1]. It is presumed that invasion within the breast (i.e., beyond the basement membrane) is a prerequisite for distant metastasis, and that following invasion, as cancers enlarge, they increase in their propensity to metastasize. In this model, ductal carcinoma in situ (DCIS) is as a nonlethal precursor lesion, whereas invasive breast cancer has acquired the propensity to grow and to metastasize [1]. An ipsilateral invasive breast cancer which is observed after DCIS may be described as either a new primary cancer or as an invasive local recurrence [2, 3]. In contrast, most ipsilateral in-breast events following invasive breast cancer are classified as local recurrences [4].

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In patients with invasive breast cancer, preventing the development of ipsilateral invasive recurrence (with radiotherapy or with mastectomy) does not prevent death from breast cancer [5, 6]. This is similar to the situation for local recurrences following DCIS [7–11], and suggests that an in-breast invasive event following a case of DCIS may be better characterized as an invasive local recurrence than as a new primary cancer. However, it is not clear if the distinction between invasive recurrences and invasive primary cancers is clinically relevant. In this study, we analyzed data from the SEER Registry and asked if, among all women with a stage I or II invasive breast cancer (either a first primary cancer or an in-breast malignant cancer following a diagnosis of DCIS), the history of DCIS influences survival.

Methods

Data source

We abstracted data from the most recent SEER18 registries research database (November 2013 submission). The SEER18 database contains data from the SEER9 registries (Atlanta, Connecticut, Detroit, Hawaii, Iowa, New Mexico, San Francisco-Oakland, Seattle-Puget Sound, and Utah), the SEER13 registries (SEER 9 plus Los Angeles, San Jose-Monterey, Rural Georgia, and the Alaska Native Tumor Registry), and the registries of Greater California, Kentucky, Louisiana, New Jersey, and Greater Georgia. In total, the SEER18 database covers approximately 28 % of the total US population (based on the 2010 Census). We submitted the Data Agreement Form to access the SEER data files.

The SEER registry does not routinely record cancer recurrences, but data coders are advised to consider cases of invasive breast cancer following DCIS to be new primaries and these are recorded. Because of this, it is possible to use the SEER database to determine whether or not the prognosis of a woman with an early-stage invasive breast cancer depends on whether or not she has a prior diagnosis of DCIS.

Cohort selection

We used the SEER*Stat version 8.2.1 to perform a case-listing session and retrieved cases of all women who were diagnosed with primary stage I or stage II breast cancer from 2004 to 2012. For each case, we retrieved information on the year of breast cancer diagnosis, age of diagnosis, tumor size, nodal status, estrogen receptor (ER) status, treatments received (type of surgery and use of radiotherapy), prior DCIS diagnosis, race/ethnicity, cause of death, and follow-up time in years. For patients with a prior diagnosis of primary DCIS, we recorded the date of diagnosis, the laterality (ipsilateral or contralateral to the invasive breast cancer), and the treatments received (type of surgery and use of radiotherapy).

We retrieved the vital status of patients at the time of last follow-up. Based on this information, we grouped all patients into three categories: (1) alive, (2) dead due to breast cancer, and (3) dead due to other causes. We extracted the information on survival time from the variable 'survival time months'. The SEER*Stat program estimates survival time by subtracting the date of diagnosis from the date of last contact (the study cut-off). The study cut-off date was December 31, 2012.

Statistical analyses

We compared the baseline characteristics of 306,249 women with primary stage I/II breast cancer, according to their history of DCIS (no prior DCIS vs. prior DCIS). We also compared the baseline characteristics of the 5395 women with a history of DCIS, according to the laterality of DCIS (ipsilateral vs. contralateral).

We defined breast cancer-specific survival as the time from diagnosis of invasive breast cancer to death from breast cancer. We performed a Cox-proportional hazards regression analysis to examine the influences of prior DCIS (no/yes/ipsilateral/contralateral), year of diagnosis, age of diagnosis, tumor size, nodal status, ER-status, tumor grade, type of surgery (lumpectomy/mastectomy), and use of radiotherapy (no/yes) on the risk of breast cancer death in women with stage I/II invasive ductal carcinoma. For patients with a prior DCIS, we examined the influence of the various DCIS treatments (radiotherapy use and type of surgery) and the time to recurrence (time from DCIS to invasive breast cancer) on the risk of breast cancer death. We performed univariable (unadjusted) and multivariable (adjusted) analyses. We excluded women treated without surgery (or for whom information on surgery was unknown) for the invasive breast cancer or the prior DCIS from the analysis.

To confirm the results of the multivariable regression and to adjust for the differences in the baseline characteristics of patients with and without a prior diagnosis of DCIS, we performed a matched prospective analysis. We matched one woman with a prior diagnosis of DCIS to one woman without a prior diagnosis of DCIS, according to the following characteristics: age of diagnosis, year of diagnosis, tumor size, ER-status, nodal status, type of surgery, and follow-up time. We used the Kaplan–Meier method to calculate 10-year breast cancer-specific survival for the 3797 matched pairs, according to DCIS history. We calculated the hazard ratio for death from the invasive ductal

Table 1 Baseline characteristics of women with early-stage breast cancer according to history of DCIS, 2004–2012 ($N = 306,249$)

Characteristic	Value	Prior DCIS		*P*
		No $N = 300,845$ (98.2 %)	Yes $N = 5395$ (1.8 %)	
Year of diagnosis	Mean	2008.2 (2004–2012)	2008.6 (2004–2012)	<0.0001
Age at DCIS dx	Mean	N/A	57.6 (24–95)	<0.0001
Age at BC diagnosis		60.3 (2–114)	63.4 (26–98)	
Age of BC diagnosis	>50	221,263 (73.5 %)	4461(82.7 %)	<0.0001
	40–50	60,392 (20.1 %)	846 (15.7 %)	
	Less than 40	19,190 (6.4 %)	88 (1.6 %)	
Stage at diagnosis	Stage I	172,195 (57.2 %)	3844 (71.3 %)	<0.0001
	Stage IIA	88,926 (29.6 %)	1198 (22.2 %)	
	Stage IIB	39,724 (13.2 %)	353 (6.5 %)	
Laterality of prior DCIS	Ipsilateral	N/A	2335 (43.3 %)	N/A
	Contralateral		3060 (56.7 %)	
Histology	Ductal	257,327 (85.5 %)	4519 (83.8 %)	0.0002
	Nonductal	43,518 (14.5 %)	876 (16.2 %)	
Tumor size (mm)	Mean	18.4 (0–800)	14.6 (0–400)	<0.0001
Tumor size by group	Less than 10	72,617 (24.1 %)	2159 (40.0 %)	<0.0001
	10–19	119,028 (39.6 %)	2025 (37.5 %)	
	20–50	103,470 (34.4 %)	1129 (20.9 %)	
	>50	5611 (1.9 %)	77 (1.4 %)	
	Unknown	119 (0.04 %)	5 (0.1 %)	
Tumor grade	I	69,705 (23.2 %)	1423 (26.4 %)	<0.0001
	II	123,783 (41.1 %)	2376 (44.0 %)	
	III/IV	92,820 (30.8 %)	1250 (23.2 %)	
	Unknown	14,537 (4.8 %)	346 (6.4 %)	
Nodal status	Negative	248,279 (82.5 %)	4794 (88.9 %)	<0.0001
	Positive	52,566 (17.5 %)	601 (11.1 %)	
Estrogen receptor status	Negative	53,409 (17.8 %)	753 (14.0 %)	<0.0001
	Positive	235,405 (78.2 %)	4382 (81.2 %)	
	Unknown	12,031 (4.0 %)	260 (4.8 %)	
Current radiation	No	139,768 (46.5 %)	3511 (65.1 %)	<0.0001
	Yes	152,333 (50.6 %)	1764 (32.7 %)	
	Unknown	8744 (2.9 %)	120 (2.2 %)	
Past radiation (for DCIS)	No	N/A	3446 (63.9 %)	N/A
	Yes		1854 (34.4 %)	
	Unknown		95 (1.8 %)	
Current surgery	No	6761 (2.3 %)	86 (1.6 %)	<0.0001
	Lumpectomy	186,188 (61.9 %)	2313 (42.9 %)	
	Mastectomy	107,472 (35.7 %)	2987 (55.3 %)	
	Unknown	424 (0.1 %)	9 (0.2 %)	
Past surgery (for DCIS)	No	N/A	214 (4.0 %)	N/A
	Lumpectomy		3928 (72.8 %)	
	Mastectomy		1241 (23.0 %)	
	Unknown		12 (0.2 %)	

Table 1 continued

Characteristic	Value	Prior DCIS		*P*
		No $N = 300,845$ (98.2 %)	Yes $N = 5395$ (1.8 %)	
Race	White	244,102 (81.1 %)	4337 (80.4 %)	<0.0001
	Black	29,542 (9.8 %)	547 (10.1 %)	
	Chinese	4374 (1.4 %)	86 (1.6 %)	
	Japanese	3231 (1.1 %)	105 (1.9 %)	
	South Asian	1986 (0.7 %)	28 (0.5 %)	
	Other Asian	12,639 (4.2 %)	236 (4.4 %)	
	Others	4971 (1.6 %)	56 (1.0 %)	
End-status	Alive	275,629 (91.6 %)	5019 (93.0 %)	0.0007
	BC death	10,039 (3.4 %)	140 (2.6 %)	
	Other death	15,177 (5.0 %)	236 (4.4 %)	

carcinoma for patients with no prior DCIS compared to those with any prior DCIS (ipsilateral or contralateral), prior ipsilateral DCIS, or prior contralateral DCIS. All statistical analyses were done using Statistical Analysis Software version 9.4 (SAS Institute Inc., Cary, NC, USA). A p value of 0.05 or less was taken for statistical significance.

Results

We identified 306,249 women who were diagnosed with primary stage I or stage II breast cancer from 2004 to 2012. There were 300,845 women with no prior DCIS (98.2 %) and 5395 women with a prior DCIS (1.8 %). Table 1 summarizes the baseline characteristics of these women. Compared to women with no prior DCIS, invasive breast cancers in women with a prior diagnosis of DCIS were, on average, smaller (mean 14.6 vs. 18.4 mm for no prior DCIS; $p < 0.0001$) and were less likely to be node-positive (11.1 vs. 17.5 % for no prior DCIS; $p < 0.0001$). After a mean of 4.1 years of follow-up from the date of invasive cancer, fewer women with a prior DCIS had died of breast cancer than women with no prior DCIS (2.6 vs 3.4 %; $p < 0.001$).

Of the 5395 women with a prior diagnosis of DCIS, 2335 had DCIS in the ipsilateral breast (43.3 %) and 3060 had DCIS in the contralateral breast only (56.7 %). Table 2 compares the baseline characteristics of the women with invasive breast cancer and a prior diagnosis of DCIS, according to the laterality of DCIS. The mean time from DCIS to invasive breast cancer was 6.6 years for patients with prior ipsilateral DCIS, compared to 5.1 years for patients with contralateral DCIS ($p < 0.0001$). The mean time from DCIS to invasive breast cancer for patients with a prior ipsilateral DCIS treated without radiotherapy was 6.0 years versus 5.1 years for contralateral DCIS; $p < 0.0001$. Patients with a prior ipsilateral DCIS were more likely to have high-grade invasive breast cancer (26.3 %) compared to patients with prior contralateral DCIS (20.8 %; $p < 0.0001$), and were also more likely to have ER-negative invasive breast cancer (15.7 %) compared to patients with prior contralateral DCIS (12.6 %; $p < 0.001$). After a mean of 5.8 years from the diagnosis of invasive breast cancer, 71 (3.0 %) of the women with prior ipsilateral DCIS had died of breast cancer compared to 69 (2.3 %) of the women with prior contralateral DCIS.

We examined the impact of various factors on the risk of death from breast cancer for all patients in the cohort (Table 3). In an adjusted analysis, there was no difference in the risk of death from breast cancer for patients with invasive ductal carcinoma and a prior diagnosis of DCIS (ipsilateral or contralateral) compared to those with no prior DCIS (adjusted HR = 1.08; 95 % CI = 0.89–1.31; $p = 0.46$). This was true for patients with prior ipsilateral DCIS compared to no prior DCIS (adjusted HR = 1.22; 95 % CI = 0.92–1.62; $p = 0.17$), and was true for patients with prior contralateral DCIS compared to no prior DCIS (adjusted HR = 1.04; 95 % CI = 0.81–1.34; $p = 0.77$).

We examined the prognostic impact of prior DCIS, according to the time from DCIS to invasive breast cancer (Table 3). Compared to patients with no prior DCIS, the adjusted hazard ratio for death for patients with a prior ipsilateral DCIS within 5 years of the invasive breast cancer was 1.81 (95 % CI = 1.30–2.51; $p = 0.0004$). The adjusted hazard ratio for death for patients with a prior ipsilateral DCIS more than 5 years from the invasive breast cancer was 0.64 (95 % CI = 0.37–1.11; $p = 0.11$). There was no difference in the risk of death from breast cancer for patients with a prior contralateral DCIS within 5 years of the invasive breast cancer, compared to patients with no prior DCIS (adjusted HR = 0.97; 95 % CI = 0.70–1.34; $p = 0.86$), or for patients with a prior contralateral DCIS more than 5 years from the invasive breast cancer,

Table 2 Baseline characteristics of women with early-stage breast cancer and a history of DCIS, according to the laterality of DCIS ($N = 5395$)

Characteristic	Value	Ipsilateral DCIS		Contralateral DCIS ($N = 3060$)	p value (all ipsi vs. contra)
		All patients ($N = 2335$)	No RT ($N = 1487$)		
Year of diagnosis	Mean	2008.6 (2004–2012)	2008.5 (2004–2012)	2008.6 (2004–2012)	0.26
Age at DCIS	Mean	55.7 (24–95)	56.9 (24–95)	59.1(26–94)	<0.0001
Age at BC		62.2 (2–114)	62.9 (28–98)	63.4(20–98)	<0.0001
Age of BC diagnosis	>50	1853 (79.4 %)	1182 (79.5)	2608 (85.2 %)	<0.0001
	40–50	419 (17.9 %)	256 (17.4)	427 (14.0 %)	
	<40	63 (2.7 %)	46 (3.1)	25 (0.8 %)	
Stage at diagnosis	Stage I	1677 (71.8 %)	1041 (70.0)	2167 (70.8 %)	0.65
	Stage IIA	512 (21.9 %)	341 (22.9)	686 (22.4 %)	
	Stage IIB	146 (6.3 %)	105 (7.1)	207 (6.8 %)	
Histology	Ductal	1975 (84.6 %)	1205 (81.0)	2544 (83.1 %)	0.15
	Nonductal	360 (15.4 %)	282 (19.0)	516 (16.9 %)	
Tumor size	Mean (mm)	14.8 (0–400)	14.9 (0–400)	14.4 (0–400)	0.38
Tumor size by group	<10	975 (41.8 %)	590 (39.7)	1184 (38.7 %)	0.004
	10–19	826 (35.4 %)	550 (37.0)	1199 (39.2 %)	
	20–50	487 (20.9 %)	318 (21.4)	642 (21.0 %)	
	>50	55 (1.9 %)	28 (1.9)	32 (1.1 %)	
	Unknown	2 (0.1 %)	1 (0.1)	3 (0.1 %)	
Tumor grade	I	522 (22.4 %)	370 (24.9)	901 (29.4 %)	<0.0001
	II	1015 (43.5 %)	626 (42.1)	1361 (44.5 %)	
	III/IV	613 (26.3 %)	371 (25.0)	637 (20.8 %)	
	Unknown	185 (7.9 %)	120 (8.1)	161 (5.3 %)	
Nodal status	Negative	2089 (89.5 %)	1299 (87.4)	2705 (88.4 %)	0.22
	Positive	246 (10.5 %)	188 (12.6)	355 (11.6 %)	
Estrogen receptor status	Negative	367 (15.7 %)	193 (13.0)	386 (12.6 %)	0.002
	Positive	1846 (79.1 %)	1221 (82.1)	2536 (82.9 %)	
	Unknown	122 (5.2 %)	73 (4.9)	138 (4.5 %)	
Current radiation	No	1694 (72.6 %)	915 (61.5)	1817 (59.4 %)	<0.0001
	Yes	597 (25.6 %)	540 (36.3)	1167 (38.1 %)	
	Unknown	44 (1.9 %)	32 (2.2)	76 (2.5 %)	
Past radiation (for DCIS)	No	1487 (63.7 %)	1487 (100)	1959 (64.0 %)	0.75
	Yes	810 (34.7 %)		1044 (34.1 %)	
	Unknown	38 (1.6 %)		57 (1.9 %)	
Current surgery	No	49 (2.1 %)	34 (2.3)	37 (1.2 %)	<0.0001
	Lumpectomy	839 (35.9 %)	725 (48.8)	1474 (48.2 %)	
	Mastectomy	1442 (61.8 %)	723 (48.6)	1545 (50.5 %)	
	Unknown	5 (0.2 %)	5 (0.3)	4 (0.1 %)	
Past surgery (for DCIS)	No	140 (6.0 %)	132 (8.8)	74 (2.4 %)	<0.0001
	Lumpectomy	1978 (84.7 %)	1160 (78.0)	1950 (63.7 %)	
	Mastectomy	209 (9.0 %)	187 (12.6)	1032 (33.7 %)	
	Unknown	8 (0.3 %)	8 (0.5)	4 (0.1 %)	

Table 2 continued

Characteristic	Value	Ipsilateral DCIS		Contralateral DCIS ($N = 3060$)	p value (all ipsi vs. contra)
		All patients ($N = 2335$)	No RT ($N = 1487$)		
Time from DCIS to BC	≤5years	1133 (48.5 %)	804 (54.1 %)	1205 (39.4 %)	<0.0001
	>5years	1202 (51.5 %)	683 (45.9 %)	1855 (60.6 %)	
Race	White	1840 (78.8 %)	1187 (79.8)	2497 (81.6 %)	0.02
	Black	278 (11.9 %)	179 (12.0)	269 (8.8 %)	
	Chinese	36 (1.5 %)	25 (1.7)	51 (1.7 %)	
	Japanese	45 (1.9 %)	21 (1.4)	60 (2.0 %)	
	South Asian	12 (0.5 %)	5 (0.3)	16 (0.5 %)	
	Other Asian	99 (4.2 %)	54 (3.6)	137 (4.5 %)	
	Others	26 (1.1 %)	16 (1.1)	30 (1.0 %)	
End-status	Alive	2116 (92.8 %)	1368 (92.0)	2853 (93.2 %)	0.18
	BC death	71 (3.0 %)	45 (3.0)	69 (2.3 %)	
	Other death	98 (4.2 %)	74 (5.0)	138 (4.5 %)	

compared to patients with no prior DCIS (adjusted HR = 1.16; 95 % CI = 0.78–1.74; $p = 0.46$).

We next examined the impact of treatments received for DCIS and the time to recurrence on survival from invasive breast cancer among the subgroup of patients with a prior DCIS. Among patients with any prior DCIS (ipsilateral or contralateral), there was no difference in the risk of death from invasive breast cancer associated with the prior use of radiotherapy (adjusted HR = 1.21; 95 % CI = 0.78–1.87; $p = 0.40$). There was also no significant difference in the risk of death for those treated with mastectomy for DCIS compared to those treated with lumpectomy (adjusted HR = 0.64; 95 % CI = 0.37–1.12; $p = 0.12$). These results were similar when restricted to women with a prior ipsilateral DCIS; the adjusted hazard ratio for death from invasive breast cancer associated with radiotherapy for prior ipsilateral DCIS was 1.28 (95 % CI = 0.65–2.55; $p = 0.48$), and with mastectomy for prior ipsilateral DCIS (vs. mastectomy) was 0.52 (95 % CI = 0.12–2.34; $p = 0.62$).

Because of the observed differences in the baseline characteristics of women with invasive ductal carcinoma according to their history of DCIS (Table 1), we also performed a matched analysis of 3979 pairs of patients with and without a prior DCIS. The characteristics of the patients in the matched analysis are compared in Table 4. In the matched analysis, breast cancer-specific survival was 94.6 % for those with a prior DCIS compared to 95.2 % for those with no prior DCIS ($p = 0.32$) (Fig. 1). After matching, the odds ratio for breast cancer-specific death for patients with a prior ipsilateral DCIS (vs. no prior DCIS) was 0.91 (95 % CI = 0.49–1.68; $p = 0.75$), and for patients with a prior contralateral DCIS (vs. no prior DCIS) was 1.55 (95 % CI = 0.88–2.72; $p = 0.13$) (Table 5).

Discussion

Approximately 15 % of women with DCIS will develop an invasive ipsilateral breast cancer within 15 years of diagnosis of the DCIS, and approximately 5 % of cases of new invasive breast cancer have a prior history of DCIS in the same breast [12]. Under the conventional view of breast cancer progression, the invasive cancer which follows DCIS is described as a new primary cancer [1]. However, the same lesion is also referred to as an invasive local recurrence after DCIS—this description is analagous to a local recurrence following an invasive breast cancer [7]. It is not clear which of these two is the more accurate description or if the distinction between the two has clinical relevance, either for predicting prognosis or for choosing optimal treatment.

Of the 306,249 women with stage I/II breast cancer in the SEER cohort, 1.8 % had a prior diagnosis of DCIS (0.8 % in the same breast and 1.0 % in the contralateral breast). Invasive breast cancers in women with a prior ipsilateral DCIS were smaller, on average (14.8 versus 18.4 mm), and were more likely to be lymph node-negative (89.5 vs. 82.5 %) compared to those in women with no prior DCIS. After adjusting for these prognostic factors, there was no difference in the risk of death from invasive breast cancer for women with or without a prior ipsilateral DCIS (adjusted HR = 1.22; 95 % CI = 0.92–1.62; $p = 0.17$). In the matched analysis, breast cancer-specific survival at 9 years was 95 % for patients with a prior DCIS

Table 3 Relative risk (RR) of breast cancer-specific death for all patients with invasive ductal carcinoma

Variables	Univariate RR (95 % CI) p	Multivariate* RR (95 % CI) p
Age at diagnosis (trend)	1.01 (1.01–1.01) < 0.0001	1.03 (1.03–1.03) < 0.0001
Year of diagnosis (trend)	0.95 (0.94–0.96) < 0.0001	0.96 (0.95–0.97) < 0.0001
Prior DCIS		
No	1	1
Yes	0.84 (0.69–1.02) 0.08	1.08 (0.89–1.31) 0.46
Yes, ipsilateral	0.94 (0.71–1.25) 0.67	1.22 (0.92–1.62) 0.17
Yes, contralateral	0.82 (0.64–1.06) 0.13	1.04 (0.81–1.34) 0.77
Yes, within 5 years	0.94 (0.75–1.19) 0.63	1.22 (0.96–1.54) 0.42
Yes, after more than 5 years	0.69 (0.50–0.97) 0.03	0.87 (0.63–1.22) 0.10
Yes, ipsilateral within 5 years	1.34 (0.97–1.86) 0.08	1.81 (1.30–2.51) 0.0004
Yes, ipsilateral >5 years	0.51 (0.30–0.88) 0.02	0.64 (0.37–1.11) 0.11
Yes, contralateral within 5 years	0.77 (0.56–1.06) 0.11	0.97 (0.70–1.34) 0.86
Yes, contralateral >5 years	0.93 (0.62–1.38) 0.71	1.16 (0.78–1.74) 0.46
Tumor size by group		
Less than 10	1	1
10–19	2.40 (2.18–2.65) < 0.0001	1.99 (0.80–2.19) 0.35
20–50	8.07 (7.37–8.84) < 0.0001	4.56 (4.16–5.02) < 0.0001
>50	11.5 (9.98–13.3) < 0.0001	7.38 (6.38–8.52) < 0.0001
Nodal status		
Negative	1	1
Positive	2.53 (2.42–2.65) < 0.0001	1.86 (1.78–1.95) < 0.0001
Estrogen receptor status		
Negative	1	1
Positive	0.28 (0.26–0.29) < 0.0001	0.46 (0.43–0.48) < 0.0001
Tumor grade		
I	1	1
II	3.14 (2.81–3.51) < 0.0001	2.22 (1.98–2.48) < 0.0001
III/V	9.38 (8.44–10.4) < 0.0001	4.11 (3.68–4.59) < 0.0001
Current radiation		
No	1	1
Yes	0.58 (0.56–0.61) < 0.0001	0.76 (0.72–0.80) < 0.0001
Surgery		
P. mastectomy	1	1
Mastectomy	1.81 (1.73–1.89) < 0.0001	1.08 (1.02–1.14) 0.005
Radiation for DCIS**		
No	1	1
Yes	1.15 (0.77–1.72) 0.49	1.21 (0.78–1.87) 0.40
Surgery for DCIS**		
P. mastectomy	1	1
Mastectomy	0.63 (0.38–1.05) 0.07	0.64 (0.37–1.12) 0.12

* All variables used in the multivariate regression except radiation for DCIS and surgery for DCIS

** Limited to subjects with prior DCIS, all variables used in the multivariate regression

and was 95 % for patients with no prior DCIS. This suggests that a prior diagnosis of DCIS in the same breast is not a prognostic factor for women with invasive breast cancer. This observation is consistent with the position that an invasive ipsilateral breast cancer following DCIS is similar to a new primary invasive breast cancer.

If the invasive ipsilateral breast cancer following DCIS were an invasive local recurrence, we might expect patients

Table 4 Comparison of the baseline characteristics of 3979 matched pairs

Characteristic	Value	No DCIS $N = 3979$	DCIS $N = 3979$	p
Year of diagnosis	Mean	2008.7 (2004–12)	2008.7 (2004–12)	Matched
Age at DCIS diagnosis	Mean	N/A	56.9 (24–92)	Matched
Age at BC diagnosis		62.9 (28–96)	62.9 (28–96)	
Follow-up time (years)	Mean	3.68 (0–8.9)	3.58 (0–8.9)	0.06
Tumor size (mm)	Less than 10	1539 (40.0 %)	1539 (40.0 %)	Matched
	10–19	1553 (39.0 %)	1553 (39.0 %)	
	20–50	804 (20.2 %)	804 (20.2 %)	
	>50	29 (0.73 %)	29 (0.73 %)	
Nodal status	Negative	3553 (89.2 %)	3553 (89.2 %)	Matched
	Positive	426 (10.7 %)	426 (10.7 %)	
Estrogen receptor status	Negative	609 (15.3 %)	609 (15.3 %)	Matched
	Positive	3370 (84.7 %)	3370 (84.7 %)	
Current surgery	Lumpectomy	1736 (43.6 %)	1736 (43.6 %)	Matched
	Mastectomy	2243 (56.4 %)	2243 (56.4 %)	
End-status	Alive/other	3922 (98.6 %)	3913 (98.3 %)	0.41
	BC death	57 (1.4 %)	66 (1.7 %)	

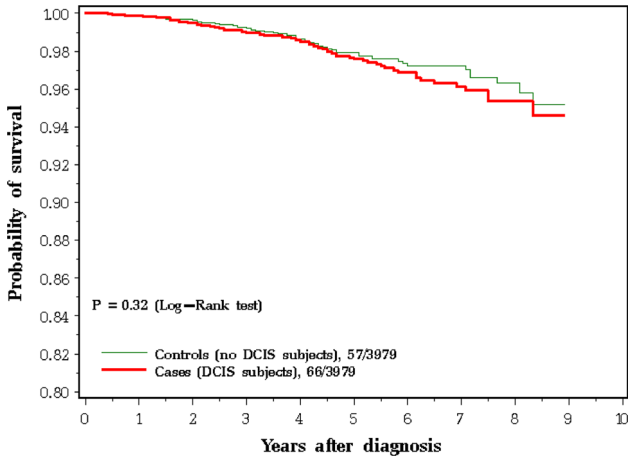

Fig. 1 Breast cancer-specific survival for 3979 matched pairs of invasive breast cancer patients with a history of DCIS (cases) and without a history of DCIS (controls)

with a prior ipsilateral DCIS to have a worse prognosis than patients with no prior DCIS. Invasive local recurrences are believed to represent the emergence of cancer cells either not removed by surgery or not killed by radiotherapy, and therefore are generally thought to carry a less favorable prognosis than primary invasive cancers which arise in an untreated breast [13]. This was not the case; in fact in an unadjusted analysis case, fatality was lower for women with a prior history of DCIS.

Table 5 Odds ratio (OR) for breast cancer-specific death for the 3979 matched pairs

Prior DCIS?	Univariate OR (95 % CI) p
No	1
Yes	1.22 (0.81–1.84) 0.35
Yes ipsilateral	0.91 (0.49–1.68) 0.75
Yes contralateral	1.55 (0.88–2.72) 0.13

However, it could also be argued that the prognosis of women with an invasive local recurrence following DCIS would be expected to be similar to women with early-stage breast cancer. It is accepted that local recurrences are an indicator of the presence of distant metastases, and that survival after a local recurrence depends to a great extent on the prognosis of the primary tumor. In a recent study, we found that local recurrences following DCIS tend to have a similar prognosis as primary stage I breast cancers, local recurrences following stage I breast cancer have the prognosis of stage II breast cancer, and local recurrences following stage II breast cancer have the prognosis of stage III breast cancer [12]. Others have also reported that survival after local recurrence depends on the initial stage at diagnosis [14–17].

Interestingly, there was a significant increase in the risk of death from breast cancer associated with a prior ipsilateral DCIS if the invasive cancer occurred within 5 years (adjusted HR = 1.81; 95 % CI = 1.30–2.51; $p = 0.0004$) but no association with a prior ipsilateral DCIS five or more years from the invasive cancer (adjusted HR = 0.64 (95 % CI = 0.37–1.11; $p = 0.11$)). That is, the time from DCIS to invasive cancer was a significant prognostic factor. The 9-year mortality rate was 91.3 % for women who had a short interval from DCIS to cancer versus 96.5 % for women for whom the interval was between 6 and 24 years. This is analogous to the prognostic impact of the disease-free interval among patients

with an ipsilateral breast tumor recurrence following primary invasive breast cancer [18, 19], suggesting that invasive ipsilateral breast cancers following DCIS have characteristics of invasive local recurrences.

Our analysis has some limitations. There may be some misclassifications between the groups of patients with and without a prior DCIS. It is possible that some patients with invasive breast cancer in the 'no prior DCIS' group had a past history of DCIS that was not recorded in the SEER database, for example, if the patient had been diagnosed in a city that was not covered by SEER. Further, we expect that for most women with DCIS followed by breast cancer, the diagnosis is made prior to the diagnosis of invasive cancer. We did not have information on progesterone receptor (PR) status or HER2 status for the breast tumors. Information on the use of systemic therapies (chemotherapy, tamoxifen, Herceptin, etc.) was also not available.

In our recent study of women with DCIS in the SEER database, we also found that ipsilateral invasive breast cancers following DCIS are similar to invasive local recurrences [7]. In that study, treatment of DCIS with radiotherapy or mastectomy (compared to lumpectomy alone) reduced the risk of invasive ipsilateral breast cancer at 10 years by 50–75 %, but did not reduce breast cancer mortality. This is also the case for local recurrences following primary invasive breast cancer [5, 6]. This prompted us to consider DCIS as qualitatively the same as the invasive breast cancer and the ipsilateral invasive breast cancer following DCIS as an invasive local recurrence. Like local recurrences after primary invasive breast cancer, the invasive local recurrence after DCIS is only a marker for the presence of distant metastases, and does not influence the probability of metastases itself—if a 50–75 % reduction in the incidence of invasive ipsilateral recurrence after DCIS does not reduce the mortality, then the metastatic potential of the invasive recurrence must be very low and clinically irrelevant. Taken together, our results suggest that ipsilateral invasive breast cancers following DCIS have characteristics of both primary invasive breast cancers and invasive local recurrences.

Compliance with ethical standards

Conflict of interest The authors have no conflicts of interest to declare.

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