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EPIDEMIOLOGY

Impact of microinvasion on breast cancer mortality in women with ductal carcinoma in situ

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Abstract
Background Ductal carcinoma in situ (DCIS) is a neoplastic proliferation of epithelial cells which is confined within the basement membrane of the mammary ductal–lobular system. It is of interest to determine to what extent the potential to metastasize increases for DCIS patients when the basement membrane is breached (i.e. microinvasion is present).
Methods We retrieved the records of 525,395 women who had either first primary DCIS or small (≤ 2.0 cm) node-negative invasive breast cancer in the Surveillance, Epidemiology and End Results (SEER) registries database (1990–2013). For each patient, we extracted information on year of diagnosis, age at diagnosis, tumour size, tumour grade, oestrogen receptor status, use of radiotherapy, type of surgery, cause of death and follow-up time. We classified patients into four groups, according to the size of the invasive component of the primary tumour. We estimated the actuarial rate of breast cancer-specific mortality at ten and 20 years for women in each size category.
Results We identified 161,394 women with pure DCIS, 13,489 women with microinvasive carcinoma (≤ 0.1 cm of invasion), 153,856 women with invasive cancer 0.2–1.0 cm in size and 196,656 women with invasive cancer 1.1–2.0 cm in size. The 20-year actuarial breast cancer-specific mortality rate was 3.8% for women with pure DCIS, was 6.9% for women with microinvasive carcinoma, was 6.8% for women with invasive cancer 0.2–1.0 cm in size and was 12.1% for women with invasive cancer 1.1–2.0 cm in size. The adjusted hazard ratio for death associated with microinvasive carcinoma (vs. pure DCIS) was 2.00 (95% CI 1.76–2.26; $p < 0.0001$).
Conclusions In terms of prognosis, microinvasive cancer more closely resembles small invasive cancer 0.2–1.0 cm) than pure DCIS. For invasive cancers under 1.0 cm, size has little impact on mortality.

Keywords Breast cancer · Microinvasion · DCIS · Survival

Introduction

Ductal carcinoma in situ (DCIS), or stage 0 breast cancer, is defined as a proliferation of ductal epithelial cells with all the morphological features of malignancy, but without evidence of invasion beyond the basement membrane into the surrounding breast tissue [1]. In some cases, DCIS may be associated with foci of microinvasion (one or more foci of stromal invasion, none exceeding 0.1 cm in size) [1, 2]. Such cases are classified as microinvasive carcinoma [1, 2]. An invasive tumour larger than 0.1 cm in size is classified as invasive carcinoma [1, 2].

Microinvasive carcinoma accounts for about 1% of all breast cancer cases and microinvasion is found in association with approximately 5–10% of cases of DCIS [3–5]. The vast majority of microinvasive lesions are found with DCIS lesions [5–10]; typically, with those DCIS that are large in extent, are high-grade and exhibit comedo histology [3–17]. Rarely, microinvasive cancer is seen in the absence of an

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adjacent in situ component [5–8]. This may be because it is difficult to visualize an isolated 1-mm lesion, but an adjacent in situ component greatly increases its detectability. For this reason, microinvasive carcinoma is commonly described as "DCIS with microinvasion" although the presence of DCIS is not mandatory. The American Joint Committee on Cancer (AJCC) and the World Health Organization (WHO) classify microinvasive carcinoma with invasive cancers, designated as "T1mic" (i.e. the earliest possible diagnosis of invasive breast cancer) [1, 2]. Under this classification, microinvasive carcinoma (≤ 0.1 cm of invasion) is presumed to be distinct from pure DCIS and from invasive tumours > 1 mm in size.

Current guidelines from the National Comprehensive Cancer Network (NCCN) recommend that patients with microinvasive carcinoma be treated the same as patients with small invasive cancers [18]. In general, this includes axillary node staging (which is not typically recommended for DCIS). Approximately 5–10% of patients with microinvasive carcinoma are node positive [19–26]. Adjuvant chemotherapy is generally recommended for patients with node-positive disease, but adjuvant chemotherapy is not routinely recommended for node-negative patients with invasive tumours 0.5 cm or less in size [18]. Whether or not some node-negative microinvasive patients should be considered for systemic therapy is unclear.

A precise estimate of breast cancer mortality associated with microinvasion is required in order to determine the clinical significance of this early lesion and to guide the appropriate management strategy in patients with node-negative microinvasive carcinoma. Many studies suggest that microinvasive carcinoma has a prognosis and a natural history that closely resembles that of pure DCIS [6, 10, 11, 19–21]. However, these studies have been based on small numbers of patients and include none or a few deaths (low power). In the current study, we analysed cases of pure DCIS, of microinvasive breast cancer (≤ 0.1 cm) and of small invasive breast cancer (0.2–1.0 cm) diagnosed in the Surveillance, Epidemiology and End Results (SEER) database from 1990 to 2013, and we asked if (a) microinvasion increases the risk of breast cancer mortality in patients with DCIS and (b) the prognosis of microinvasive carcinoma is akin to that of pure DCIS or to that of small invasive breast cancer.

Methods

Study population

We used the SEER*Stat version 8.2.1 to perform a case-listing session and retrieved all cases of first primary female DCIS or small (≤ 2.0 cm), node-negative invasive breast cancer, diagnosed between 1990 and 2013 in the SEER18 registries database (November 2013 submission). Eligible cases included those with the AJCC classifications 'Tis' (carcinoma in situ; no evidence of an invasive component), 'T1mic' (microinvasive carcinoma; primary tumour ≤ 0.1 cm in size), 'T1a' (primary tumour > 0.1 cm but ≤ 0.5 cm in size), 'T1b' (primary tumour > 0.5 cm but ≤ 1.0 cm in size), 'T1c' (primary tumour > 1.0 cm but ≤ 2.0 cm in size), 'N0' (no regional lymph node metastasis histologically) and 'M0' (no clinical or radiographic evidence of distant metastases). Among the cases classified as 'Tis' (carcinoma in situ), we excluded those associated with lobular carcinoma in situ (LCIS), non-epithelial histologies, Paget's disease of the nipple and diffuse DCIS.

For each case, we retrieved information on the year of breast cancer diagnosis, age of diagnosis, tumour size, ethnicity, tumour grade, oestrogen receptor (ER) status, progesterone receptor (PR) status, use of radiotherapy, type of surgery, cause of death and follow-up time in years. Tumour size for the DCIS (Tis) lesions refers to the size (extent) of DCIS, and is an estimation of the volume of breast tissue occupied by DCIS. Tumour size for the invasive (T1) tumours refers to the greatest dimension (usually the diameter) of the largest contiguous area of stromal invasion and does not include adjacent DCIS.

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 31 December 2013.

Statistical analyses

We classified the patients into four groups, according to the size of the invasive component of the primary tumour (AJCC 'T' classification): (1) pure DCIS (no invasive component; Tis), (2) microinvasive carcinoma (≤ 0.1 cm of invasion; T1mic), (3) invasive cancer 0.2–1.0 cm in size (T1a or T1b) and (4) invasive cancer 1.1–2.0 cm in size (T1c).

To identify factors associated with the presence of microinvasion in DCIS, we compared the patients with pure DCIS and with microinvasive carcinoma for a range of factors, using the Student *T* test.

We defined breast cancer-specific survival as the time from diagnosis of breast cancer to death from breast cancer. Patients were censored at the date of last follow-up or of death from another cause. We used the Kaplan–Meier method to estimate the actuarial rates of breast cancer-specific survival at ten and 20 years for women in each of the four size categories (defined above).

Among the subgroup of patients with pure DCIS or microinvasive carcinoma, we performed a Cox proportional hazards regression analysis to examine the impact of microinvasion (vs. pure DCIS) on the risk of death from breast cancer. Covariates included year of diagnosis, age of diagnosis, ethnicity, ER status, PR status, tumour grade, use of radiotherapy and type of surgery.

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 a total of 525,395 women diagnosed with either first primary DCIS or small (≤ 2.0 cm) node-negative invasive breast cancer between 1990 and 2013. Table 1 summarizes the baseline characteristics of these women, according to the size of the invasive component of the primary tumour; 161,394 women had pure DCIS (no evidence of invasion), 13,489 women had microinvasive carcinoma (≤ 0.1 cm of invasion), 153,856 women had invasive cancer 0.2–1.0 cm in size (mean 0.72 cm) and 196,656 women had invasive cancer 1.1–2.0 cm in size (mean 1.53 cm). After a mean follow-up of 7.7 years, a total of 15,613 women had died of breast cancer, including 1837 women with pure DCIS (1.1%), 323 women with microinvasive carcinoma (2.4%), 3661 women with invasive cancer 0.2–1.0 cm in size (2.4%) and 9792 women with invasive cancer 1.1–2.0 cm in size (5.0%).

Among the subgroup of 173,883 women with pure DCIS or microinvasive carcinoma, 13,489 of the women (7.7%) also had evidence of microinvasion (i.e. DCIS with microinvasion) and 161,394 women (92.3%) had pure DCIS. We compared the women with pure DCIS and microinvasive carcinoma (i.e. DCIS with microinvasion) for various patient and tumour-related factors (Table 2). Patients with ER-negative disease were more likely to have microinvasion compared to those with ER-positive disease (17.1% vs. 8.7%; $p < 0.0001$). Patients with PR-negative disease were more likely to have microinvasion compared to those with PR-positive disease (15.6% vs. 8.4%; $p < 0.0001$). Year of diagnosis, age at diagnosis, ethnicity and use of radiotherapy were not associated with the presence of microinvasion. Patients treated with microinvasion were more likely to be treated with mastectomy than those with pure DCIS (41% vs. 28%, respectively).

The breast cancer-specific survival curves for women in each of the four size categories are presented in Fig. 1. At 20 years, the actuarial rate of breast cancer mortality was 3.8% for patients with pure DCIS, was 6.9% for patients with microinvasive carcinoma (≤ 0.1 cm), was 6.8% for patients with invasive cancer 0.2–1.0 cm in size and was 12.1% for women with invasive cancer 1.1–2.0 cm in size.

In univariate analysis, the hazard ratio for death associated with microinvasion (vs. pure DCIS) was 2.01 (95% CI 1.78–2.26; $p < 0.0001$). In a multivariate analysis which included year of diagnosis, age at diagnosis, ethnicity, tumour grade, ER status, PR status, use of radiotherapy and type of surgery, the hazard ratio associated with microinvasion (vs. pure DCIS) was 2.00 (95% CI 1.76–2.26; $p < 0.0001$). Other factors independently associated with breast cancer mortality among patients with pure DCIS or microinvasive carcinoma include age at diagnosis (< 40 years and > 70 years vs. 51–70 years), black ethnicity, high tumour grade, ER positivity and the use of radiotherapy (Table 3).

We next examined the impact of the primary tumour size on the risk of death from breast cancer among women with small invasive cancers. In univariate analysis, compared to patients with microinvasive carcinoma (≤ 0.1 cm in size), the hazard ratio for death from breast cancer for patients with invasive cancer 0.2–1.0 cm in size was 1.02 (95% CI 0.91–1.14; $p = 0.73$) and for patients with invasive cancer 1.1–2.0 cm in size was 2.13 (95% CI 1.91–2.38; $p < 0.0001$). To examine in close detail the relationship between tumour size and breast cancer mortality, we compared the ten-year rates of breast cancer-specific mortality for women with small invasive cancers (≤ 2.0 cm in size), stratified according to tumour size by 1-mm intervals (Fig. 2). The ten-year breast cancer mortality rate was 2.8% for microinvasive cancers (≤ 1 mm in size); this remained constant (below 3.0%) until tumour size reached 8 mm. From 8 mm to 20 mm, ten-year breast cancer mortality increased from 3.3 to 9.8%.

Discussion

In this study, we found a similar risk of breast cancer mortality for patients with microinvasive carcinomas (≤ 0.1 cm) and those with small invasive cancers (0.2–1.0 cm). Moreover, patients with microinvasive carcinoma have an approximately two-fold increased risk of death from breast cancer compared to patients with pure DCIS. At 20 years, the actuarial rate of breast cancer-specific mortality was 3.8% for patients with pure DCIS, was 6.9% for patients with microinvasive carcinoma and was 6.8% for patients with small invasive breast cancer. These results suggest that the presence of microinvasion is an adverse prognostic factor in patients with DCIS and that, in terms of prognosis, microinvasive carcinoma (≤ 0.1 cm) is similar to small invasive cancer (0.2–1.0 cm). To our knowledge, this is the largest study of microinvasive carcinoma to date and the first study to compare microinvasive cancer with pure DCIS and with small invasive cancers using the SEER database.

Table 1 Characteristics of patients with pure DCIS or small (≤ 2.0 cm) node-negative invasive breast cancer (Tis—T1, N0, M0), according to the size of the invasive component of the primary tumour

Characteristic	Value	Pure DCIS, no invasion $N = 161,394$	Microinvasive (≤ 0.1 cm) $N = 13,489$	Invasive 0.2–1.0 cm $N = 153,856$	Invasive 1.1.2.0 cm $N = 196,656$
Year of diagnosis	Mean	2005.0 (90–13)	2004.5 (90–13)	2004.5 (90–13)	2004.1 (90–13)
	1990–2000	35,330 (21.9%)	3360 (24.9%)	38,899 (25.3%)	54,207 (27.6%)
	2001–2013	126,064 (78.1%)	10,129 (75.1%)	114,957 (74.4%)	142,449 (72.4%)
Age at diagnosis (years)	Mean	58.8 (15–105)	58.8 (20–100)	62.3 (2–103)	61.5 (17–114)
	< 40	5739 (3.6%)	593 (3.4%)	3955 (2.6%)	8470 (4.3%)
	40–50	41,133 (25.5%)	3194 (23.7%)	26,073 (17.0%)	38,194 (19.4%)
	51–70	82,561 (51.3%)	7132 (52.9%)	80,592 (52.4%)	95,442 (48.5%)
	> 70	31,962 (19.8%)	2570 (19.1%)	43,236 (28.1%)	54,550 (27.7%)
Ethnicity	White	126,962 (78.7%)	10,589 (78.5%)	131,527 (85.5%)	164,762 (83.8%)
	Black	16,708 (10.4%)	1382 (10.3%)	10,289 (6.7%)	15,688 (8.0%)
	Other/unknown	17,724 (11.0%)	1518 (11.3%)	12,040 (7.8%)	16,205 (8.2%)
Tumour size (mm)	Microscopic	7204 (6.3%)	13,489 (100%)	0	0
	2–10	52,753 (45.9%)	0	153,856 (100%)	0
	11–20	28,711 (25.0%)	0	0	196,656 (100%)
	21–50	18,883 (16.4%)	0	0	0
	> 50	7280 (6.3%)	0	0	0
	Unknown	46,563	0	0	0
	Mean (range)	15.6 (0–888)	N/A	7.2 (2–10)	15.2 (11–20)
Tumour grade	I	17,752 (14.3%)	2058 (23.9%)	56,020 (39.8%)	42,991 (23.7%)
	II	51,118 (41.2%)	3291 (38.2%)	60,911 (43.3%)	84,409 (46.5%)
	III/IV	55,327 (44.5%)	3269 (37.9%)	23,769 (16.9%)	54,009 (29.8%)
	Unknown	37,197	4871	13,156	15,247
ER status	Negative	14,361 (15.6%)	2968 (28.7%)	17,110 (12.3%)	30,376 (16.8%)
	Positive	77,730 (84.4%)	7386 (71.3%)	122,406 (87.7%)	150,297 (83.2%)
	Unknown	69,303	3135	14,340	15,783
PR status	Positive	22,161 (25.5%)	4085 (40.7%)	31,974 (23.3%)	47,908 (26.9%)
	Negative	64,743 (74.5%)	5962 (59.3%)	105,151 (76.7%)	130,379 (73.1%)
	Unknown	74,490	3442	16,731	18,369
Radiation	No	88,601 (56.0%)	7439 (56.2%)	63,232 (41.9%)	90,384 (47.1%)
	Yes	69,570 (44.0%)	5799 (43.8%)	87,513 (58.1%)	101,449 (52.9%)
	Unknown	3223	251	3111	4823
Surgery	No surgery	3900 (2.7%)	124 (1.1%)	1497 (1.0%)	2298 (1.4%)
	Lumpectomy	98,051 (69.1%)	6653 (57.7%)	95,620 (62.9%)	111,799 (68.5%)
	Mastectomy	39,892 (28.1%)	4745 (41.2%)	33,674 (22.2%)	49,196 (30.1%)
	Unknown	19,551	1967	23,065	33,363
End-status	Alive	142,024 (88.0%)	11,485 (85.1%)	126,360 (82.1%)	153,457 (78.0%)
	BC death	1837 (1.1%)	323 (2.4%)	3661 (2.4%)	9792 (5.0%)
	Other death	17,533 (10.9%)	1681 (12.5%)	23,835 (15.5%)	33,407 (17.0%)
Follow-up (years)	Mean (range)	7.7 (0–23)	7.9 (0–33)	7.7 (0–23)	7.8 (0–23)

We identified eight single-institution studies which report on breast cancer death in patients with microinvasive carcinoma [11, 12, 19, 21–25]. Some studies found that patients with microinvasive carcinoma have a worse prognosis than patients with pure DCIS [12, 22, 23] and other studies have concluded that the natural history of microinvasive carcinoma closely resembles that of pure DCIS [11,19,21,24). These studies are based on small numbers of cases (37–414 cases) and few deaths (0–12 deaths) and they employ varying definitions of microinvasion.

An earlier analysis of the SEER database studied 87,695 women with DCIS and 8863 women with microinvasive carcinoma diagnosed from 1990 to 2012 [26]. They report the 20-year breast cancer mortality rate to be 4.0%

Table 2 Comparison of women with a final diagnosis of pure DCIS and microinvasive carcinoma (i.e. DCIS with microinvasion) ($N = 174,883$)

Characteristic	Value	Pure DCIS $N = 161,394$ (92.3%)	DCIS with microinvasion $N = 13,489$ (7.7%)
Year of diagnosis	1990–2000	35,330 (91.3%)	3360 (8.7%)
	2001–2013	126,064 (92.6%)	10,129 (7.4%)
Age at diagnosis (years)	< 40	5739 (90.6%)	593 (9.4%)
	40–50	41,133 (92.8%)	3194 (7.2%)
	51–70	82,561 (92.0%)	7132 (8.0%)
	> 70	31,962 (92.6%)	2570 (7.4%)
Ethnicity	White	126,962 (92.3%)	10,589 (7.7%)
	Black	16,708 (92.4%)	1382 (7.6%)
	Other/unknown	17,724 (92.1%)	1518 (7.9%)
Tumour grade	I	17,752 (89.6%)	2058 (10.4%)
	II	51,118 (94.0%)	3291 (6.0%)
	III/IV	55,327 (94.0%)	3269 (6.0%)
	Unknown	37,197 (88.4%)	4871 (11.6%)
ER status	Negative	14,361 (82.9%)	2968 (17.1%)
	Positive	77,730 (91.3%)	7386 (8.7%)
	Unknown	69,303 (95.7%)	3135 (4.3%)
PR status	Positive	22,161 (84.4%)	4085 (15.6%)
	Negative	64,743 (91.6%)	5962 (8.4%)
	Unknown	74,490 (95.6%)	3442 (4.4%)
Radiation	No	88,601 (92.3%)	7439 (7.7%)
	Yes	69,570 (92.3%)	5799 (7.7%)
	Unknown	3223 (92.8%)	251 (7.2%)
Surgery	No surgery	3900 (96.9%)	124 (3.1%)
	Lumpectomy	98,051 (93.6%)	6653 (6.4%)
	Mastectomy	39,892 (89.4%)	4745 (10.6%)
	Unknown	19,551 (90.9%)	1967 (9.1%)
End-status	Alive	142,024 (92.5%)	11,485 (7.5%)
	BC death	1837 (85.0%)	323 (15.0%)
	Other death	17,533 (91.3%)	1681 (8.7%)

Assuming 100% of patients with a diagnosis of microinvasive carcinoma have an associated DCIS component (SEER does not report information on the in situ component of invasive tumours)

for patients with DCIS and 9.7% for patients with microinvasive carcinoma. The multivariate hazard ratio of death associated with microinvasion was 1.92 (95% CI 1.64–2.24; $p < 0.001$). Although overlapping, our cohorts had a few key differences. We included women of all ages, whereas Wang et al. restricted the analysis to women diagnosed between the ages of 20 and 69. We excluded about 7.0% of the microinvasive cohort because they were node positive, whereas Wang et al. retained these patients. We restricted our analysis to node-negative microinvasive carcinoma, because SEER defines DCIS as having no evidence of lymph node metastasis (N0 or NX). (If there is evidence of nodal involvement reported for a tumour with in situ (Tis) pathology, SEER automatically classifies it as invasive cancer (T0 or T1mic), because "an in situ tumour theoretically cannot metastasize and apparently an area of invasion was missed by the pathologist".) In practice, about 3% of patients with a final diagnosis of pure DCIS are found to have lymph node metastases [27–30]. Nevertheless, the SEER DCIS cohort excludes those who are node positive, therefore it is necessary to exclude the microinvasive patients who are node positive for an accurate comparison.

By increasing the resolution and focusing on the metastatic potential of small lesions, we address competing theories about the early stages of breast cancer progression. Breast cancer progression is often described as a linear, multistep process through a series of pathological stages: hyperplastic benign lesions (with and without cellular atypia)—carcinoma in situ—invasive carcinoma and (ultimately) metastatic disease [31]. Microinvasive carcinoma is thought to represent an interim stage in the progression from in situ to invasive carcinoma [1, 2]. Almost always found in association with DCIS, it is often described as "DCIS with microinvasion" [4–8]. Histologically, the predominant

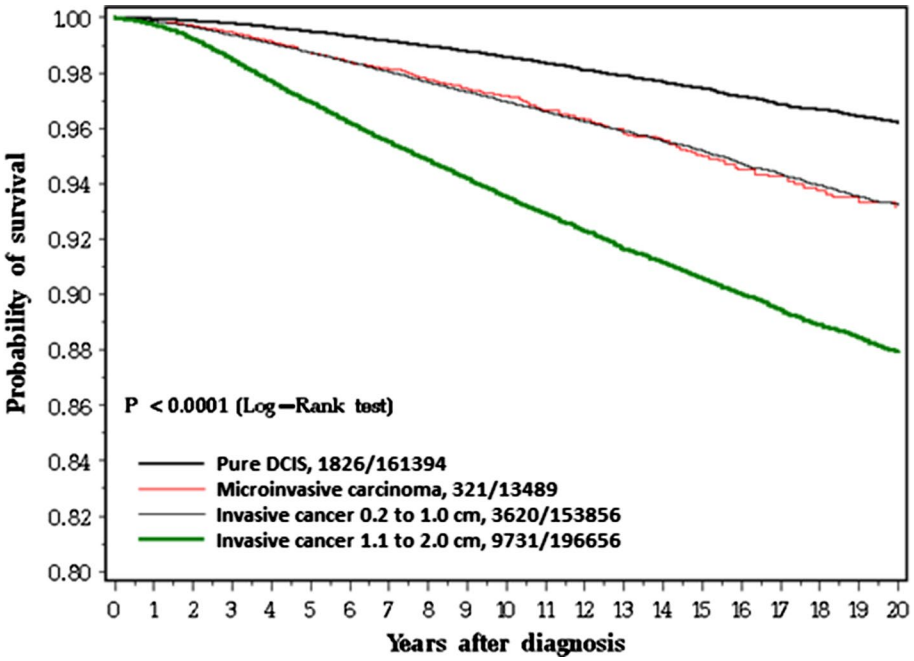

Fig. 1 20-year breast cancer-specific survival curves for patients with pure DCIS or small invasive breast cancer (Tis—T1, N0, M0), stratified according to the size of the invasive primary tumour

microinvasive pattern consists of single cells or clusters of cells immediately adjacent to a duct involved with DCIS, but which appear to be physically dissociated from the intraductal component [6, 7]. Less commonly, the microinvasive focus appears as a tongue-like projection of tumour through the basement membrane of a duct with DCIS, maintaining continuity with the in situ carcinoma [6, 7, 32]. In rare cases, a small isolated focus of invasion may be found without associated DCIS [5–8].

The natural history of cancer cell progression from DCIS to microinvasive carcinoma to invasive cancer remains a topic of speculation. It has been proposed that all invasive breast cancers arise from in situ carcinomas [31–33]. DCIS and invasive cancer frequently co-exist in the same breast; an associated DCIS component is found in about 45–85% of unselected invasive cancers [34–36]. The proportion of cases with a DCIS component is inversely related to the size of the invasive tumour; i.e. a DCIS component is present in about 95–100% of microinvasive tumours and in 20–45% of tumours larger than 5.0 cm in size [5–8, 34–36]. The observation of isolated microinvasive carcinomas indicates that there may be a pathway to invasion that does not involve an obligatory in situ stage. The high proportion of microinvasive tumours found in association with DCIS may simply be a function of the low detectability of microinvasive tumours in isolation, i.e. without being contiguous to a larger DCIS lesion. Alternatively, the low proportion of DCIS cases that exhibit microinvasion (7.7% in the current study) reflects perhaps on the short time interval between breaching of the basement membrane and growth of the invasive component to >1mm.

In the conventional (sequential) view of breast cancer progression, it is generally assumed that the metastatic potential of a tumour is directly proportional to the volume of the invasive component [37–39]. In this view, DCIS has no metastatic potential, whereas microinvasive carcinoma has acquired the potential to metastasize. As invasive carcinomas enlarge, they increase in their potential to metastasize. This model is largely based on the observation that the extent of stromal invasion present at the time of diagnosis (tumour size) in general is strongly correlated with the eventual probability of developing metastases [37–39]. From this it has been inferred that the number of cancer cells within the primary (invasive) tumour is the main determinant of whether or not metastatic dissemination will occur [39]. However, for very small cancers, the relationship between the extent of stromal invasion and the metastatic potential of a tumour raises doubts about this model. An alternate model states that the potential for metastasis is present from the outset—not once the cancer invades the breast stroma or reaches a particular size [40]. In this model, the presence and/or the extent of stromal invasion represent a marker of tumour aggressivity, rather than an indicator of the size of the pool of cancer cells that are the source of dissemination.

The underlying basis for the sequential model for invasive breast cancers is that an increase in the volume of the invasive component increases the risk of distant events [37–39]. This was not found in our study population. We estimated the 20-year breast cancer-specific mortality rate to be 6.9% for patients with microinvasive carcinoma and 6.8% for patients with small (0.2–1.0 cm) invasive cancer ($p = 0.73$). When we examined the impact of tumour size

Table 3 Univariate and multivariate hazard ratios for breast cancer mortality for patients with pure DCIS (Tis, N0, M0) or microinvasive carcinoma (T1mic, N0, M0)

Characteristic	Value	Univariate HR (95% CI)	*p*	Multivariate HR (95% CI)	*p*
Year of dx	1990–2000	1 [reference]		1 [reference]	
	2001–2013	0.83 (0.75–0.91)	0.0001	1.01 (0.89–1.15)	0.86
Age at dx	> 70 years	2.47 (2.23–2.73)	< 0.0001	2.43 (2.20–2.69)	< 0.0001
	51–70 years	1 [reference]		1 [reference]	
	40–50 years	0.93 (0.83–1.04)	0.21	0.93 (0.83–1.04)	0.20
	< 40 years	1.83 (1.53–2.18)	< 0.0001	1.63 (1.36–1.94)	< 0.0001
Ethnicity	White	1 [reference]		1 [reference]	
	Black	2.08 (1.86–2.33)	< 0.0001	2.13 (1.91–2.39)	< 0.0001
	Other/unknown	0.74 (0.62–0.87)	0.0003	0.77 (0.65–0.91)	0.002
Extent of DCIS[a]	≤ 1.0 cm	1 [reference]		1 [reference]	
	1.1–2.0 cm	1.25 (1.08–1.44)	0.002	1.22 (1.05–1.41)	0.008
	2.1–5.0 cm	1.45 (1.24–1.72)	< 0.0001	1.38 (1.17–1.63)	0.0002
	> 5.0 cm	1.69 (1.33–2.16)	< 0.0001	1.54 (1.20–1.97)	0.0007
	Unknown	1.56 (1.40–1.74)	< 0.0001	1.31 (1.17–1.47)	< 0.0001
Primary tumour	DCIS	1 [reference]		1 [reference]	
	Microinvasive	2.01 (1.78–2.26)	< 0.0001	2.00 (1.76–2.26)	< 0.0001
Tumour grade	I	1 [reference]		1 [reference]	
	II	1.21 (1.00–1.46)	0.05	1.32 (1.10–1.60)	0.004
	III/IV	1.56 (1.30–1.87)	< 0.0001	1.73 (1.44–2.08)	< 0.0001
	Unknown	1.69 (1.42–2.02)	< 0.0001	1.52 (1.27–1.82)	< 0.0001
ER status	Negative	1 [reference]		1 [reference]	
	Positive	0.58 (0.50–0.61)	< 0.0001	0.78 (0.64–0.95)	0.02
	Unknown	0.62 (0.54–2.06)	< 0.0001	0.86 (0.61–1.22)	0.40
PR status	Negative	1 [reference]		1 [reference]	
	Positive	0.62 (0.54–0.71)	< 0.0001	0.84 (0.69–1.02)	0.07
	Unknown	0.68 (0.60–0.77)	< 0.0001	0.79 (0.56–1.11)	0.17
Radiation	No	1 [reference]		1 [reference]	
	Yes	0.62 (0.57–0.68)	< 0.0001	0.76 (0.68–0.84)	< 0.0001
	Unknown	1.02 (0.75–1.39)	0.89	1.14 (0.84–1.55)	0.41
Surgery	Lumpectomy	1 [reference]		1 [reference]	
	Mastectomy	1.43 (1.27–1.60)	< 0.0001	1.12 (0.98–1.27) 0.10	
	No surgery	7.41 (6.28–8.75)	< 0.0001	6.47 (5.44–7.70)	< 0.0001
	Unknown	1.73 (1.55–1.94)	< 0.0001	1.53 (1.32–1.77)	< 0.0001

[a]DCIS patients only

on mortality in 1-mm size intervals (Fig. 2), breast cancer mortality at 10 years was relatively constant for patients with invasive tumours up to 7 mm in size. Above 7 mm, mortality increased with increasing tumour size. If metastatic potential is a function of the number of cancer cells in a tumour, then a 1-mm cancer, which has 1000 times as many cells as a 1-mm cancer, should have a *much* worse prognosis than a 1-mm cancer—however, there was no difference in crude mortality for invasive tumours 0.2–1.0 cm in size compared to those 0.1 cm or less in size. This uncoupling of tumour size and survival in small breast cancers under 1.0 cm in size is consistent with the alternate position that the in-breast tumour is a marker of cancer aggressiveness and not a source of metastases. In this sense, cancer within the breast is analogous to cancer within the lymph nodes; the greater the number of nodes involved the higher the risk of recurrence.

Other studies have also found that tumour size has a limited impact on prognosis among breast cancers under 1.0 cm (few studies have examined microinvasive tumours specifically) [25, 41–43]. The size–survival relationship is also attenuated in triple-negative breast cancer, in BRCA1-positive breast cancer and in small HER2-positive breast cancers [44]. Furthermore, for tumours above 6 cm in size, there appears to be little correlation between tumour size and prognosis [45, 46].

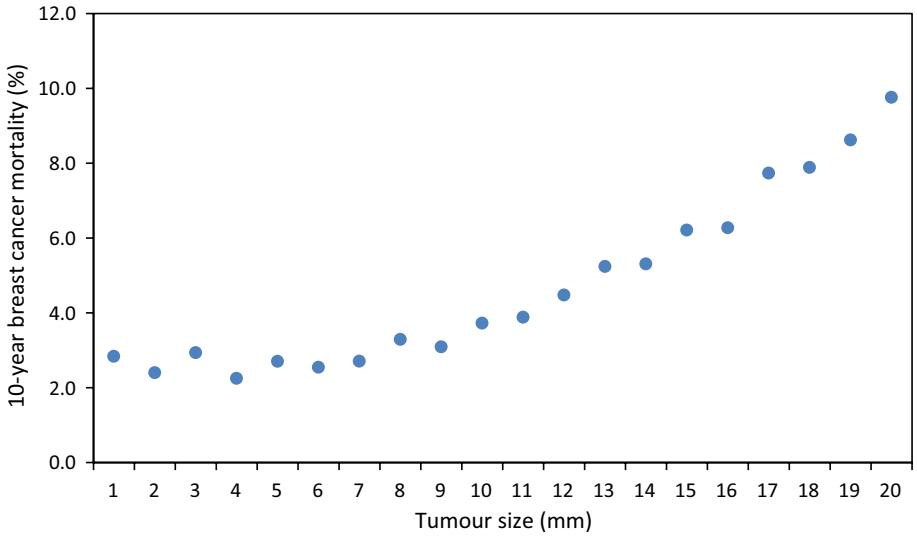

Fig. 2 Ten-year rates of breast cancer-specific mortality for women with invasive breast cancer ≤ 2.0 cm in size (T1, N0, M0), stratified according to tumour size by 1-mm intervals

Our analysis has several inherent limitations. We relied on the details of pathologic analysis supplied by SEER and it is possible that a formal pathology review would have found some cases of 'pure' DCIS to be microinvasive and vice versa. Another major limitation of the SEER database is that when both in situ and invasive components are present in a tumour, only the characteristics of the invasive component are recorded. We therefore have no information on the prognostic features of the DCIS lesions associated with the microinvasive tumours in our cohort. We also did not have any information on HER2 status or the use of chemotherapy, hormone therapy or targeted therapies for our cohort.

There are several implications of our finding that the relationship between tumour size and survival is attenuated in breast cancers under 1.0 cm. Most tumours smaller than one centimetre are detected by screening. Some of these tumours are thought to be incidental findings of screening, with such benign/indolent natural histories that they have no significant effect on survival (i.e. over-diagnosis). However, our results suggest that the likelihood of over-diagnosis does not increase with decreasing size for cancers under 8 mm. If a 1-mm cancer has the same risk of breast cancer mortality as a 7-mm cancer, then it is no more likely to have a benign/indolent natural history and should be considered equally relevant and clinically important. These results also challenge the limits of screening for cancers under 1.0 cm in terms of its potential for reducing mortality from breast cancer. For tumours smaller than 8 mm in size, further reductions in tumour size at diagnosis will not result in a reduction in the proportion of patients with occult metastases, therefore it is unclear how much can be gained from the use and development of more sensitive screening methods.

In conclusion, patients with microinvasive carcinoma have an increased risk of breast cancer mortality compared to patients with DCIS, but a similar risk of breast cancer mortality compared to patients with small invasive cancer (0.2–1.0 cm in size). Tumour size has a limited impact on mortality for invasive cancers under 1.0 cm. These results suggest that the relationship between tumour size and survival is not causal, but rather, that (like tumour grade and lymph node status) tumour size is a marker for breast cancer aggressiveness.

Compliance with ethical standards

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

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