Original Investigation

Breast Cancer Mortality After a Diagnosis of Ductal Carcinoma In Situ

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IMPORTANCE Women with ductal carcinoma in situ (DCIS), or stage 0 breast cancer, often experience a second primary breast cancer (DCIS or invasive), and some ultimately die of breast cancer.

OBJECTIVE To estimate the 10- and 20-year mortality from breast cancer following a diagnosis of DCIS and to establish whether the mortality rate is influenced by age at diagnosis, ethnicity, and initial treatment received.

DESIGN, SETTING, AND PARTICIPANTS Observational study of women who received a diagnosis of DCIS from 1988 to 2011 in the Surveillance, Epidemiology, and End Results (SEER) 18 registries database. Age at diagnosis, race/ethnicity, pathologic features, date of second primary breast cancer, cause of death, and survival were abstracted for 108 196 women. Their risk of dying of breast cancer was compared with that of women in the general population. Cox proportional hazards analysis was performed to estimate the hazard ratio (HR) for death from DCIS by age at diagnosis, clinical features, ethnicity, and treatment.

MAIN OUTCOMES AND MEASURES Ten- and 20-year breast cancer–specific mortality.

RESULTS Among the 108 196 women with DCIS, the mean (range) age at diagnosis of DCIS was 53.8 (15-69) years and the mean (range) duration of follow-up was 7.5 (0-23.9) years. At 20 years, the breast cancer–specific mortality was 3.3% (95% CI, 3.0%-3.6%) overall and was higher for women who received a diagnosis before age 35 years compared with older women (7.8% vs 3.2%; HR, 2.58 [95% CI, 1.85-3.60]; $P < .001$) and for blacks compared with non-Hispanic whites (7.0% vs 3.0%; HR, 2.55 [95% CI, 2.17-3.01]; $P < .001$). The risk of dying of breast cancer increased after experience of an ipsilateral invasive breast cancer (HR, 18.1 [95% CI, 14.0-23.6]; $P < .001$). A total of 517 patients died of breast cancer following a DCIS diagnosis (mean follow-up, 7.5 [range, 0-23.9] years) without experiencing an in-breast invasive cancer prior to death. Among patients who received lumpectomy, radiotherapy was associated with a reduction in the risk of ipsilateral invasive recurrence at 10 years (2.5% vs 4.9%; adjusted HR, 0.47 [95% CI, 0.42-0.53]; $P < .001$) but not of breast cancer–specific mortality at 10 years (0.8% vs 0.9%; HR, 0.86 [95% CI, 0.67-1.10]; $P = .22$).

CONCLUSIONS AND RELEVANCE Important risk factors for death from breast cancer following a DCIS diagnosis include age at diagnosis and black ethnicity. The risk of death increases after a diagnosis of an ipsilateral second primary invasive breast cancer, but prevention of these recurrences by radiotherapy does not diminish breast cancer mortality at 10 years.

Editorial

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Ductal carcinoma in situ (DCIS, or stage 0 breast cancer) accounts for approximately 20% of mammographically detected breast cancers.[1] Five percent of cases are diagnosed in women before age 40 years.[2] Some women with DCIS experience a second in-breast cancer event (DCIS or invasive), and a small proportion of patients with DCIS ultimately die of breast cancer.[3] It is not clear what factors predict mortality after a diagnosis of DCIS. In particular, the impact of patient characteristics, such as age at diagnosis and ethnic group, on breast cancer mortality has not been studied.

Women who have an ipsilateral invasive breast cancer recurrence experience a greatly increased risk of death from breast cancer from that time on.[4,5] Many patients who die of breast cancer after a diagnosis of DCIS experience an in-breast invasive recurrence prior to death, but some women die of breast cancer without first receiving a diagnosis of local invasive disease.[5-7] It is unclear to what extent mortality from breast cancer after DCIS is the direct consequence of an invasive recurrence or whether fatal cases of DCIS have high malignant potential from the outset. In particular, it has not been shown that preventing invasive recurrences by means of radiotherapy or extensive breast surgery (mastectomy) reduces the risk of breast cancer-specific mortality.

At a Glance

- The purpose of this study was to estimate the mortality from breast cancer following a diagnosis of ductal carcinoma in situ (DCIS) and to identify risk factors for death from breast cancer.
- The 20-year breast cancer–specific mortality rate following a diagnosis of DCIS was 3.3%.
- Young age at diagnosis and black ethnicity were significant predictors of breast cancer mortality.
- Prevention of invasive in-breast recurrence with either radiotherapy or mastectomy did not prevent death from breast cancer.
- The clinical course of women with DCIS is similar to that of women with small invasive breast cancers.

Methods

Data Source

We abstracted data from the most recent Surveillance, Epidemiology, and End Results (SEER) 18 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 US population (based on the 2010 Census). The research protocol was approved by the research ethics board of the Women's College Hospital, University of Toronto, Toronto, Ontario, Canada. Because patients cannot be identified, the research ethics board of the Women's College Hospital exempted this study from review.

Cohort Selection

We used SEER*Stat, version 8.1.5, to generate a case listing. We extracted cases of first primary female breast cancer (stage 0) diagnosed from 1988 to 2011. We selected women who had a diagnosis of histologically confirmed stage 0 breast cancer before age 70 years. We generated a case listing with information on the following variables: year and month of diagnosis, age at diagnosis, race/ethnicity, and median household income per year. The median household income was estimated from the Census 2007-2011 American Community Survey, based on the county of residence.[8] The technical documentation for the 2007-2011 American Community Survey files is available from the Census Bureau at http://www2.census.gov/acs2011_5yr/summaryfile/ACS_2007-2011_SF_Tech_Doc.pdf. We classified median annual household income into 4 categories: (1) no more than $53 900, (2) $53 901 to $60 810, (3) $60 811 to $71 519, and (4) $71 520 or more. We recorded ethnicity as non-Hispanic white, Hispanic white, black, Asian, and other, according to a method described in our previous publication.[9]

We extracted data on treatment of the index cases, including radiotherapy (yes, no, or unknown) and surgery (lumpectomy, unilateral mastectomy, bilateral mastectomy, none, or unknown). Information on hormonal therapy or chemotherapy was not provided.

Second primary cancers are recorded in the SEER database. For patients with DCIS, a second breast cancer is recorded as a new primary breast cancer (stage 0-IV). We recorded the date of second breast cancer, the stage of second breast cancer (American Joint Committee on Cancer pathological stage), and the laterality (ipsilateral or contralateral to the index case).

We identified 163 387 women with first primary stage 0 breast cancer, diagnosed from 1988 to 2011 (eTable 1 in the Supplement). We excluded cases in women who received a diagnosis at or after age 70 years (31 456 cases [19.3%]). We excluded 15 970 women with lobular carcinoma in situ. We excluded 3439 other women with the following histologic subtypes: 8070/2, 8140/3, 8200/2, 8211/2, 8240/2, 8246/2, 8255/2, 8310/2, 8401/2, 8453/2, 8480/2, 8481/2, 8500/2, 8502/2, 8510/2, 8540/2, 8540/3, 8541/2, 8541/3, 8542/2, 8543/2, 8543/3, 8550/2, 8571/2, and 8573/2 because these are nonepithelial cancers or are nonspecific categories. We excluded 1470 women with DCIS with microinvasion because these are often classified as invasive breast cancers. We excluded 7 women with Paget disease and 174 women with diffuse DCIS. We excluded 2582 women who experienced a second primary cancer within 6 months of the DCIS diagnosis because of the difficulty of distinguishing early cancers from cancers present at baseline. We excluded 13 women who died of breast cancer within the first 6 months of the DCIS diagnosis because this is uncharacteristic of DCIS and we question the accuracy of the diagnosis. We excluded 80 women who were missing details on key variables. This leaves 108 196 patients eligible for the study.

Vital Status

We used the "cause of death (COD) to site recode" variable in SEER18 to extract the status of patients at the time of last fol-

low-up. On the basis of this information, we grouped all patients into 3 categories: (1) alive, (2) dead due to breast cancer, and (3) dead due to other causes. We used the variable "survival time months" to extract information on the time from the date of diagnosis to the date of last follow-up. The SEER*stat program estimates survival time in months by subtracting the date of diagnosis from the date of last contact (the study cutoff). The study cutoff date was December 31, 2011.

Statistical Analyses

Descriptive Statistics

Descriptive statistics were performed to examine the baseline characteristics of the 108 196 women with stage 0 breast cancer.

Cumulative Incidence

We defined breast cancer–specific survival as the time from diagnosis of stage 0 breast cancer to death from breast cancer. We used the Kaplan-Meier method to calculate 20-year breast cancer–specific survival for stage 0 breast cancers, according to year of diagnosis, age at diagnosis, and ethnicity.

Standardized Mortality Ratio

We compared the risk of dying of breast cancer for women in the cohort of patients with DCIS to that of all women in the US population. Age-specific population-based mortality rates were derived from the SEER database. We divided the cohort of 108 196 patients with stage 0 breast cancer into 8 subgroups based on age at diagnosis (5-year intervals). For each patient we identified the age at diagnosis and the duration of follow-up. We assigned the years of follow-up for that patient to the appropriate age bins (eg, 30-34, 35-39, 40-44 years). We calculated the expected number of cancer deaths by multiplying the summed person-years for a given age bin by the age-specific mortality rate for that age group derived from the SEER data. We then divided the total number of deaths observed by the total number of deaths expected for all bins combined to calculate the standardized mortality ratio (SMR). An SMR was created for each age group, from 30 to 34 until 65 to 69 years.

Hazard Ratio of Death and Survival of Stage 0 Breast Cancer

We defined breast cancer–specific survival as the time from diagnosis of stage 0 breast cancer to death from breast cancer. We performed univariable (unadjusted) and multivariable (adjusted) analyses. We used the Kaplan-Meier method to calculate 20-year breast cancer–specific survival for stage 0 breast cancers, according to year of diagnosis, age at diagnosis, and ethnicity. We divided second primary breast cancers into stage 0 (noninvasive) and stage I to IV (invasive).

We performed a Cox proportional hazards regression analysis to examine the influences of year of diagnosis, age at diagnosis, ethnicity, income, estrogen receptor (ER) status, tumor size, histologic subtype, and grade on the hazard ratio (HR) of death in patients with stage 0 breast cancer. We conducted sensitivity analyses to evaluate the impact of including or excluding women with DCIS with microinvasion and those who had a breast cancer recurrence or death within 6 months of the DCIS diagnosis.

We estimated the impact of experiencing a second primary breast cancer (invasive or DCIS, ipsilateral or contralateral) on 20-year mortality from breast cancer (HR). In this analysis, second primary breast cancer was considered as a time-dependent covariate in the Cox proportional hazards regression analyses. In 4 separate subanalyses, second primary cancers were divided into ipsilateral invasive, ipsilateral noninvasive, contralateral invasive, and contralateral noninvasive.

We performed a Cox proportional hazards regression analysis to examine the influence of treatment on the HR for death in patients with stage 0 breast cancer. Radiotherapy was coded as ever or never. Surgery was coded as lumpectomy or unilateral mastectomy. Information on type of surgery has been recorded in SEER from 1998 onward, and survival was estimated at 10 years. Women who had a bilateral mastectomy, who did not receive surgery, or for whom the use of radiotherapy or type of surgery was not recorded were excluded from this analysis. To estimate the impact of radiotherapy on mortality from breast cancer, we included only those patients who were treated with breast-conserving surgery. All statistical analyses were performed using Statistical Analysis Software, version 9.4 (SAS Institute Inc). $P \leq .05$ (2 sided) was taken for statistical significance.

Results

A total of 108 196 women with DCIS qualified for the study (eTable 2 in the Supplement). The mean (range) age at diagnosis of DCIS was 53.8 (15-69) years, and the mean (range) duration of follow-up was 7.5 (0-23.9) years. For the entire cohort, at 20 years the breast cancer–specific mortality was 3.3% (95% CI, 3.0%-3.6%). The risk of death from breast cancer among all women who received a diagnosis of DCIS was 1.8 times greater than that of the US population (SMR, 1.8 [95% CI, 1.7-1.9]). The SMR decreased with increasing age at diagnosis, from 17.0 for women with DCIS before age 35 years to 1.4 for women older than 65 years (**Table 1**).

In a multivariable analysis, age at diagnosis and ethnicity were significant predictors of breast cancer mortality (**Table 2**). Women who received a diagnosis before age 35 years had a higher risk of death from breast cancer at 20 years than older women (7.8% vs 3.2%; HR, 2.58 [95% CI, 1.85-3.60]; $P < .001$). The 20-year breast cancer–specific survival curves by age at diagnosis are shown in eFigure 1 in the Supplement. Black women had a higher risk of death from stage 0 breast cancer than white, non-Hispanic women (7.0% vs 3.0%; adjusted HR, 2.42 [95% CI, 2.05-2.87]; $P < .001$) (Table 2). This was also true for black women compared with women from other ethnic groups (**Figure 1**) and for black women treated with each modality (eFigures 2-4 in the Supplement). The increased risk of death from stage 0 breast cancer in black vs white women was similar in models that did and did not adjust for income. Other factors that predicted breast cancer mortality included tumor size (eFigure 5 in the Supplement), grade (eFigure 6 in the Supplement), ER status (**Figure 2**), and comedonecrosis (Table 2). The results of the multivariable analysis did not change substantially when we included patients with micro-

Table 1. Standardized Mortality Ratios (SMRs) of Breast Cancer Following a Diagnosis of Ductal Carcinoma In Situ, by Age at Diagnosis

Age at Diagnosis, y	Person-years	Follow-up, Mean (SD), y	Deaths, No.		SMR (95% CI)
			Observed	Expected	
30-34	8 830.1	9.0 (6.2)	22	1.3	17.0 (10.9-25.3)
35-39	35 503.3	8.9 (6.0)	62	8.5	7.3 (5.6-9.3)
40-44	103 719.2	8.0 (5.7)	112	35.7	3.1 (2.6-3.8)
45-49	142 083.6	7.7 (5.5)	144	67.4	2.1 (1.8-2.5)
50-54	149 541.9	7.5 (5.4)	157	91.7	1.7 (1.4-2.0)
55-59	138 475.9	7.3 (5.2)	145	103.9	1.4 (1.2-1.6)
60-64	120 619.5	7.1 (5.3)	138	107.3	1.3 (1.1-1.5)
65-69	113 118.3	7.3 (5.3)	162	118.0	1.4 (1.2-1.6)
All	811 891.8	7.5 (5.4)	942	533.8	1.8 (1.7-1.9)

invasion (model 2, eTable 3 in the Supplement) or patients with a breast cancer death or recurrence within 6 months of the DCIS diagnosis (model 3, eTable 3 in the Supplement), indicating that our results are not sensitive to these assumptions.

Among all patients, the risk of ipsilateral invasive recurrence at 20 years was 5.9% and the risk of contralateral invasive recurrence was 6.2%. The (mean) annual rate of contralateral invasive cancer was 0.31%. The second primary breast cancers are described in eTable 4 in the Supplement. We estimate the risk of ipsilateral invasive in-breast recurrence at 20 years to be 9.5% for patients with DCIS who had breast-conserving surgery without radiotherapy and 4.5% for those who had breast-conserving surgery and radiotherapy. The risk of dying from breast cancer increased after an ipsilateral invasive recurrence (HR, 18.1 [95% CI, 14.0-23.6]; $P < .001$) or a contralateral invasive recurrence (HR, 13.8 [95% CI, 11.5-16.6]; $P < .001$) but not after a DCIS recurrence (ipsilateral or contralateral) (eTable 5 in the Supplement).

Among the 42 250 women who were treated with lumpectomy and radiotherapy, 547 women developed an ipsilateral invasive recurrence in the follow-up period (1.3%) and 163 women (0.4%) died of breast cancer. Among the 19 762 women who were treated with lumpectomy without radiotherapy, 595 women developed an ipsilateral invasive recurrence (3.0%) and 102 women (0.5%) died of breast cancer. Among the 25 527 women treated with a mastectomy (unilateral or bilateral), 200 women experienced an ipsilateral invasive recurrence (0.8%) and 154 (0.6%) women died of breast cancer. Characteristics of patient groups according to treatment received are presented in eTable 6 in the Supplement.

Of the 956 women who died of breast cancer in the follow-up period, 395 (41.3%) experienced an in-breast invasive recurrence prior to death (210 ipsilateral, 165 contralateral, and 20 laterality unknown) and 517 (54.1%) did not experience an in-breast invasive recurrence prior to death. Among the 163 women who were treated with lumpectomy and radiotherapy and then died of breast cancer, 94 did not experience an in-breast invasive recurrence prior to death (57.7%). Among the 102 women treated with lumpectomy without radiotherapy who died of breast cancer, 51 did not experience an in-breast invasive recurrence prior to death (50.0%). Among the 154 women treated with a mastectomy (unilateral or bilateral) who died of breast cancer, 112 did not experience an in-breast invasive recurrence prior to death (72.7%).

After breast-conserving surgery, radiotherapy was associated with a significant reduction in the risk of ipsilateral invasive recurrence at 10 years (2.5% vs 4.9%; adjusted HR, 0.47 [95% CI, 0.42-0.53]; $P < .001$) and a nonsignificant reduction in breast cancer-specific mortality at 10 years (0.8% vs 0.9%; adjusted HR, 0.81 [95% CI, 0.63-1.04]; $P = .10$) (**Table 3** and eFigure 7 in the Supplement). The risk of ipsilateral invasive recurrence at 10 years was lower for patients treated with unilateral mastectomy than for patients treated with lumpectomy (1.3% vs 3.3%; adjusted HR, 0.81 [95% CI, 0.73-0.90]; $P < .001$). Breast cancer mortality at 10 years was higher for women who underwent unilateral mastectomy than for women who underwent lumpectomy (1.3% vs 0.8%; unadjusted HR, 1.45 [95% CI, 1.18-1.79]; $P < .001$) (eFigure 8 in the Supplement), but after adjusting for age at diagnosis, year of diagnosis, income, ER status, tumor size, grade, and ethnic group, the difference was not significant (HR, 1.20 [95% CI, 0.96-1.50]; $P = .11$) (Table 3).

Discussion

We estimate the 10-year breast cancer-specific mortality rate after a diagnosis of DCIS to be 1.1% and the rate at 20 years to be 3.3%. Compared with women in the US general population, the risk of dying of breast cancer for a woman who had received a diagnosis of DCIS was increased by 1.8 times. The excess risk was notable for women who received a diagnosis before age 35 years; only 1.2% of the women in this study received a diagnosis before 35 years, but for them, mortality was approximately 17 times greater than expected in the 9 years following diagnosis. The mortality rate reported here is lower than rates reported in the past.[3,7,10] In the 20-year follow-up report of the Sweden DCIS randomized trial (1046 women who received a diagnosis of DCIS between 1987 and 1999), the breast cancer-specific mortality rate was 1.8% at 10 years and was 3.9% at 20 years.[10] In a previous study of DCIS cases from the SEER program, the 10-year breast cancer mortality rate was 3.4% for women who received a diagnosis from 1978 to 1983 and 1.9% for women who received a diagnosis from 1984 to 1989.[3] In our updated analysis, the 10-year mortality rate continues to decline; for women who received a diagnosis from 1988 to 2011, it was 1.1%. The reason for the decline may be better distinction between DCIS and invasive

Table 2. Breast Cancer–Specific Mortality and Hazard Ratios (HRs) for Breast Cancer Mortality After Ductal Carcinoma In Situ

Parameter	Patients, No.	20-Year Mortality (95% CI), %	Univariate HR (95% CI)	*P* Value	Multivariate HR[a] (95% CI)	*P* Value
All patients	108 196	3.3 (3.0-3.6)	N/A	N/A	N/A	N/A
Age at diagnosis, y						
<35	1 279	7.8 (4.5-11.1)	2.26 (1.60-3.20)	<.001	1.88 (1.32-2.66)	<.001
35-39	3 974	4.5 (3.3-5.6)	1.24 (0.94-1.63)	.13	1.15 (0.87-1.51)	.33
40-49	31 438	2.9 (2.4-3.3)	0.78 (0.66-0.93)	<.001	0.77 (0.65-0.91)	<.001
50-59	38 993	3.0 (2.5-3.4)	0.81 (0.69-0.95)	.01	0.81 (0.69-0.95)	.01
60-69	32 512	3.7 (3.1-4.3)	1 [Reference]		1 [Reference]	
Year of diagnosis						
1988-1989	1 961	3.4 (2.5-4.2)	1 [Reference]		1 [Reference]	
1990-1999	21 161	3.5 (3.1-3.8)	1.01 (0.77-1.33)	.92	0.98 (0.74-1.29)	.87
2000-2011	85 074	N/A	0.88 (0.66-1.18)	.40	0.84 (0.61-1.14)	.25
Ethnic group						
White, non-Hispanic	76 188	3.0 (2.6-3.3)	1 [Reference]		1 [Reference]	
White, Hispanic	8 840	3.2 (2.2-4.2)	1.09 (0.84-1.43)	.52	1.06 (0.81-1.39)	.67
Black	10 943	7.0 (5.3-8.7)	2.55 (2.17-3.01)	<.001	2.42 (2.05-2.87)	<.001
Asian	10 037	2.8 (1.8-3.8)	0.85 (0.65-1.10)	.21	0.85 (0.65-1.11)	.24
Other	2 188	4.1 (1.2-7.1)	1.48 (0.97-2.27)	.07	1.48 (0.96-2.26)	.07
Annual household income, $						
Q1 (≤53 900)	27 576	3.3 (2.7-3.9)	1 [Reference]		1 [Reference]	
Q2 (53 901-60 810)	26 571	4.1 (3.4-4.8)	1.01 (0.85-1.21)	.88	1.07 (0.89-1.28)	.47
Q3 (60 811-71 519)	26 879	2.8 (2.4-3.3)	0.83 (0.70-1.00)	.04	0.94 (0.78-1.12)	.48
Q4 (≥71 520)	27 170	3.3 (2.7-3.8)	0.86 (0.72-1.03)	.10	0.97 (0.18-1.17)	.77
Estrogen receptor status						
Negative	8 908	3.8 (2.5-5.1)	1 [Reference]		1 [Reference]	
Positive	46 002	4.0 (3.1-4.9)	0.53 (0.41-0.69)	<.001	0.61 (0.46-0.80)	<.001
Unknown	53 286	3.2 (2.9-3.5)	0.58 (0.46-0.73)	<.001	0.64 (0.51-0.81)	<.001
Grade						
Well differentiated	10 841	3.7 (1.5-5.9)	1 [Reference]		1 [Reference]	
Moderately differentiated	32 395	4.2 (2.0-6.4)	1.23 (0.89-1.70)	.21	1.22 (0.88-1.69)	.23
Poorly differentiated	36 765	2.5 (1.6-3.5)	1.88 (1.38-2.55)	<.001	1.73 (1.27-2.36)	<.001
Unknown	28 195	3.4 (3.1-3.8)	1.73 (1.28-2.33)	<.001	1.57 (1.16-2.13)	<.001
Size, cm						
<1.0	36 565	2.6 (2.1-3.0)	1 [Reference]		1 [Reference]	
1.0-1.9	19 778	3.3 (2.4-4.2)	1.34 (1.09-1.64)	<.001	1.28 (1.05-1.57)	.02
2.0-4.9	14 530	3.8 (2.6-5.0)	1.74 (1.41-2.16)	<.001	1.58 (1.27-1.96)	<.001
≥5.0	4 243	2.9 (1.7-4.1)	2.12 (1.52-2.95)	<.001	1.82 (1.30-2.54)	<.001
Unknown	33 080	4.0 (3.4-4.5)	1.66 (1.42-1.94)	<.001	1.56 (1.33-1.83)	<.001
Histologic subtype						
Intraductal, solid type	53 361	3.2 (2.8-3.6)	1 [Reference]		1 [Reference]	
Comedonecrosis	14 211	3.7 (3.1-4.4)	1.34 (1.15-1.57)	<.001	1.20 (1.02-1.42)	.02
Papillary	5 940	3.8 (2.4-5.1)	1.02 (0.78-1.33)	.89	1.00 (0.77-1.31)	.98
Cribriform	8 163	4.0 (0.5-7.6)	0.62 (0.43-0.90)	.01	0.75 (0.52-1.10)	.14
Other ductal, not otherwise specified	26 521	3.5 (2.3-4.7)	0.91 (0.74-1.11)	.33	0.92 (0.75-1.13)	.40

Abbreviations: NA, not applicable; Q, quartile.

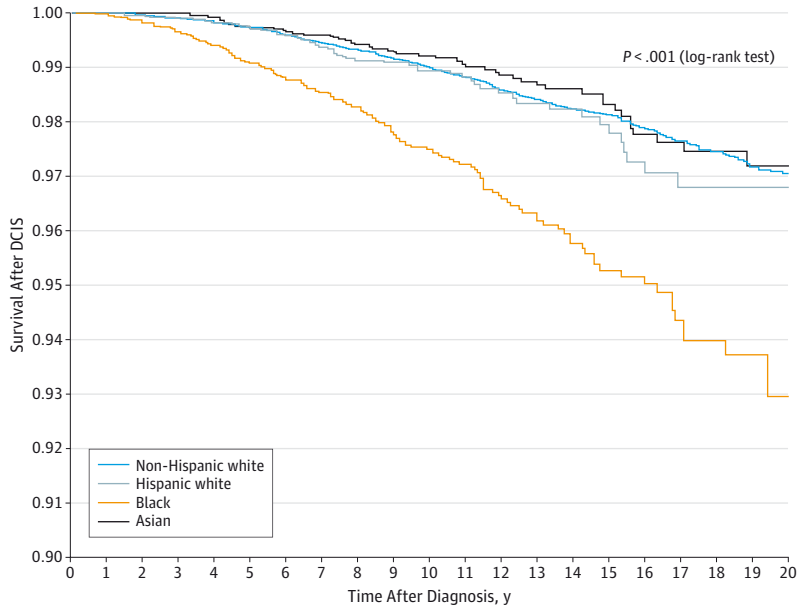
[a] Adjusted for year of diagnosis, age at diagnosis, ethnicity, income, estrogen receptor status, tumor size, and grade.

cancer, but overdiagnosis is likely, given that the incidence of DCIS has increased dramatically over the same period.[11] It is unlikely that the decline in mortality is due to more effective treatments because we show here that mortality rates did not vary with specific treatment.

Risk Factors for Mortality

In an adjusted analysis, DCIS before age 35 years was associated with an HR for mortality of 2.16 (95% CI, 1.54-3.02; $P < .001$) compared with all women who received a diagnosis at an older age. A relatively high mortality rate for stage 0 breast cancer

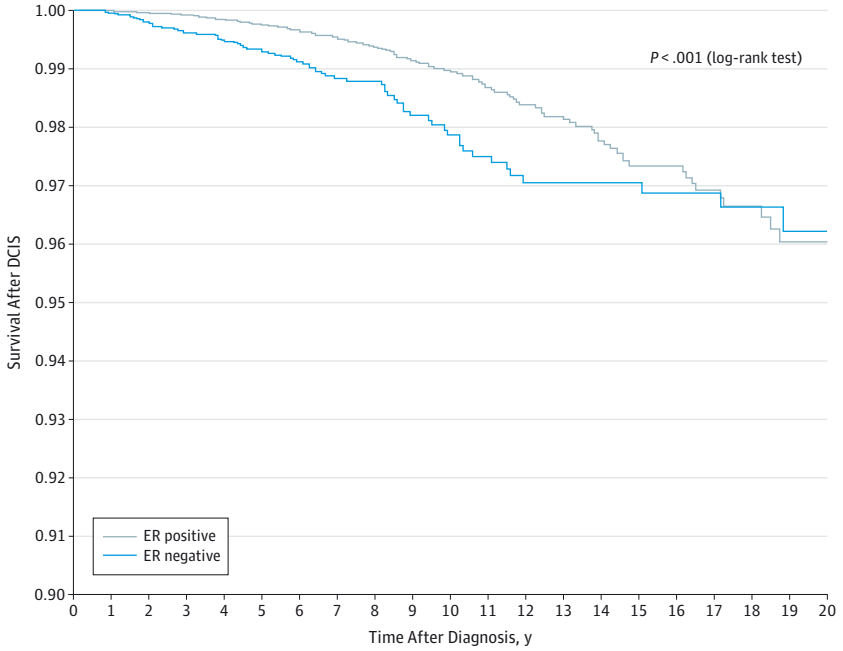
Figure 1. Twenty-Year Breast Cancer–Specific Survival After Ductal Carcinoma In Situ (DCIS) by Race/Ethnicity



No. at risk					
Non-Hispanic white	76 188	48 614	24 336	9199	2573
Hispanic white	8839	4738	1929	612	106
Black	10 943	6219	2673	852	188
Asian	10 036	5721	2756	977	231

Death occurred by 20 years after a diagnosis of DCIS for 623 of 76 188 whites, 59 of 8839 Hispanic whites, 185 of 10 943 blacks, and 61 of 10 036 Asians.

Figure 2. Twenty-Year Breast Cancer–Specific Survival After Ductal Carcinoma In Situ (DCIS) by Estrogen Receptor (ER) Status



No. at risk					
ER positive	46 002	16 573	3212	1236	189
ER negative	8908	4062	1124	567	115

Death occurred by 20 years after a diagnosis of DCIS for 82 of 8908 patients with ER-negative disease and 157 of 46 002 patients with ER-positive disease.

was also seen for black women. The unadjusted HR for black women (vs non-Hispanic white women) was 2.55 (95% CI, 2.17-3.01; $P < .001$), and this risk ratio was not attenuated when income, treatment, and tumor features were taken into consideration. It is improbable that black women had inferior survival because of less frequent screening or inadequate treatment.

Table 3. Breast Cancer–Specific Mortality and Hazard Ratios (HRs) for Breast Cancer Mortality After Ductal Carcinoma In Situ, by Type of Treatment, 1998 to 2011

Treatment	Cases, No.	10-Year Mortality (95% CI), %	Univariate HR (95% CI)	*P* Value	Multivariate[a] HR (95% CI)	*P* Value
Lumpectomy						
Without radiotherapy	19 762	0.9 (0.7-1.1)	1 [Reference]		1 [Reference]	
With radiotherapy	42 250	0.8 (0.7-1.0)	0.86 (0.67-1.10)	.22	0.81 (0.63-1.04)	.10
All	63 319	0.8 (0.7-1.0)	1 [Reference]		1 [Reference]	
Unilateral mastectomy	19 515	1.3 (1.1-1.5)	1.45 (1.18-1.79)	<.001	1.20 (0.96-1.50)	.11

[a] Adjusted for year of diagnosis, age at diagnosis, ethnicity, income, estrogen receptor status, tumor size, and grade.

All cases were stage 0 at diagnosis, and the majority of these are diagnosed through mammography. The proportions of black and white women treated with mastectomy and radiotherapy were similar (eTable 5 in the Supplement), the effect was seen in women in all treatment groups (eFigures 2-4 in the Supplement), and income was not a risk factor for mortality (Table 2).

Other important risk factors for mortality following DCIS included ER status, high grade, tumor size, and comedonecrosis. In the first 10 years after diagnosis, the mortality rate for women with ER-negative cancers exceeded that for ER-positive cancers, but at 20 years, the mortality rates had reversed (Figure 2). Among the deaths from ER-negative DCIS, 13.4% occurred in years 10 to 19. In contrast, among the deaths of patients with ER-positive DCIS, 26.8% occurred in years 10 to 19. Interestingly, high-grade DCIS was not associated with an increased risk of ipsilateral invasive recurrence compared with low-grade DCIS (HR, 0.91 [95% CI, 0.78-1.07]; $P = .26$), but women with high-grade DCIS were 1.88 times more likely to die of breast cancer than women with low-grade DCIS (95% CI, 1.38-2.55; $P < .001$).

Impact of Recurrence on Mortality

The finding of greatest clinical importance was that prevention of ipsilateral invasive recurrence did not prevent death from breast cancer. Women with DCIS who developed an ipsilateral invasive in-breast recurrence were 18.1 times more likely to die of breast cancer than women who did not. For patients who had a lumpectomy, the use of radiotherapy reduced the risk of developing an ipsilateral invasive recurrence from 4.9% to 2.5% but did not reduce breast cancer-specific mortality at 10 years (0.9% vs 0.8%). Similarly, patients who underwent unilateral mastectomy had a lower risk of ipsilateral invasive recurrence at 10 years than patients who underwent lumpectomy (1.3% vs 3.3%) but had a higher breast cancer-specific mortality (1.3% vs 0.8%). Patients who had a mastectomy had cancers with a larger mean size and higher grade than patients who had a lumpectomy (eTable 5 in the Supplement). After adjustment for tumor size, grade, and other factors, the difference in survival for mastectomy vs lumpectomy was not significant (HR, 1.20 [95% CI, 0.96-1.50]; $P = .11$).

It has been stated that DCIS is a noninvasive precursor lesion that cannot metastasize or cause death in the absence of progression to an invasive breast cancer.[12] Several historical observations support this view. Only a fraction of treated DCIS lesions progress to invasive breast cancer,[13] but in the absence of treatment, the risk of invasive cancer is much higher.[14] Also, mortality from breast cancer in women with DCIS increases substantially following the development of an invasive local recurrence.[4,5] However, if DCIS were truly a (noninvasive) precursor of breast cancer, then a woman with DCIS should not die of breast cancer without first experiencing an invasive breast cancer (ipsilateral or contralateral), and the prevention of an invasive recurrence should prevent her death from breast cancer. Surprisingly, the majority of women with DCIS in the cohort who died of breast cancer did not experience an invasive in-breast recurrence (ipsilateral or contralateral) prior to death (54.1%). Furthermore, preventing the invasive in-breast recurrence (with mastectomy or radiotherapy) does not reduce mortality from breast cancer. This is in keeping with the findings of other studies.[5-7,10,15,16] In the Early Breast Cancer Trialists' Collaborative Group overview, assignment to radiotherapy was associated with an HR of 0.46 (standard error, 0.14) for ipsilateral breast cancer but with an HR of 1.22 (standard error, 0.11) for breast cancer mortality.[10] Among the 3729 women with DCIS in the study, there were 96 reported deaths from breast cancer (median follow-up, 8.9 years): 52 deaths among 1878 patients who had radiotherapy (2.8%) and 44 deaths among 1851 patients who did not have radiotherapy (2.4%). There were 54 patients with DCIS (1.4% of all patients) who experienced a distant or regional recurrence with no prior ipsilateral or contralateral cancer.[10] In a study of 2449 women with DCIS who were treated at the University of Texas MD Anderson Cancer Center, 25 women developed distant metastases (median follow-up, 4.5 years), of whom 16 had an intervening invasive recurrence and 9 did not.[16]

Strengths and Limitations

The mortality rate from breast cancer in women with DCIS is low, and it is necessary to study a large cohort for an extended period to generate a precise estimate of mortality (death from breast cancer after DCIS is too rare to use as an end point in randomized clinical trials). Due to its size, the SEER registry is unique in this respect. However, our study has several inherent limitations. We relied on the details of pathologic analysis supplied by SEER. It is possible that a formal pathology review would have found some cases of DCIS to be invasive (and vice versa). Collins et al[17] excluded 17% of cases after a central pathology review, but others report that after secondary pathological review of cases of DCIS, the proportion of women with a missed invasive cancer is as low as 2%.[18-20] The SEER database distinguishes between DCIS and

DCIS with microinvasion, and the 1470 cases with microinvasion were excluded. Also, the 10-year mortality rate reported here (1.1%) is lower than the 10-year mortality rates reported in the past,[3,7,10,15] contrary to what we would expect if invasive breast cancers were overrepresented in the sample. Furthermore, in an extended analysis of these data, the presence of microinvasion was not an adverse prognostic factor for mortality (eTable 3 in the Supplement).

We were unable to determine which cases of DCIS were screen detected and which were symptomatic. We did not have data on the margin status of the patients, and positive margins have been positively associated with the risk of in-breast recurrence.[21] We included household income in our statistical models, but this is an incomplete indicator of social class. It is possible that there may be undisclosed differences in access to care in the different racial groups, but we found that neither treatment (radiotherapy or surgery type) was predictive of mortality, and these therefore are unlikely to be confounders. Few women in the study would have received chemotherapy.

Some patients were treated with tamoxifen, and we did not have access to this information. Factors such as body mass index could influence survival, but these variables were not available in the SEER database. Data were missing for many individuals for key variables, including tumor size, grade, and ER status, but given the large size of the database (n = 108 196 patients), complete data were available for a large number of patients.

The SEER registry records multiple primary cancers but not recurrences. It is assumed that cancers in the opposite breast are new primary cancers and that a DCIS and an invasive cancer in the same breast are independent primaries, and therefore both are recorded routinely. However, in the event of 2 occurrences of DCIS in the same breast these may be coded as independent primaries or as a primary and a recurrence. As a result, the number of noninvasive recurrences in the ipsilateral breast is much less than expected (eTable 3 in the Supplement).

Interpretation

There are several similarities between the clinical course of women with DCIS and that of women with small invasive cancers. For both, tumor size and tumor grade are significant predictors of mortality.[22] For both, women with ER-positive cancers initially have a lower annual hazard for death and then the relationship between ER status and annual mortality reverses.[23] For both DCIS and invasive cancer, women who received a diagnosis before age 40 years have relatively poor survival[24,25] and black women do less well than white women.[9] For both DCIS and stage 1 cancer, mortality increases after an invasive in-breast recurrence.[4] However, although it is accepted that, for women with invasive breast cancer, prevention of in-breast recurrence does not prevent death,[26] this has not been widely accepted for women with DCIS. Also, for women with invasive cancers it is accepted that, in terms of survival, lumpectomy is equivalent to mastectomy,[27] even though patients who undergo mastectomy experience fewer local recurrences. For women with invasive cancer, radiotherapy is given to prevent in-breast recurrence, but the effect of radiotherapy on mortality is acknowledged to be small.[26] In the SEER database, these relationships between local recurrence and mortality hold equally well for patients with DCIS. These observations have been reported in other studies as well.[7,10,28]

It is often stated that DCIS is a preinvasive neoplastic lesion that is not lethal in itself.[11,29,30] The results of the present study suggest that this interpretation should be revisited. Cases of DCIS have more in common with small invasive cancers than previously thought. The current clinical paradigm focuses on risk factors for progression from DCIS to local (invasive) recurrence, and to study the impact of various prognostic factors or to compare treatments, invasive recurrence is the primary clinical end point.[31,32] For example, in the general population of patients with breast cancer, Oncotype DX is used to identify patients who are at low risk for death from breast cancer and who might not benefit from chemotherapy, but in the DCIS population, it is proposed that the test be used to identify patients who are at high risk for invasive recurrence (and not for death).[32] It is likely that the current paradigm was adopted because invasive recurrences after a diagnosis of DCIS are much more common than breast cancer deaths and are therefore amenable to study. Fewer than 1% of the patients in this 20-year study died of breast cancer (although the proportion is higher for young women and for black women).

Conclusions

Some cases of DCIS have an inherent potential for distant metastatic spread. It is therefore appropriate to consider these as de facto breast cancers and not as preinvasive markers predictive of a subsequent invasive cancer. The outcome of breast cancer mortality for DCIS patients is of importance in itself and potential treatments that affect mortality are deserving of study.

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