

Mortality Among Women With Ductal Carcinoma In Situ of the Breast in the Population-Based Surveillance, Epidemiology and End Results Program

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Background: Over 14% of breast cancers diagnosed in the United States annually are ductal carcinomas in situ (DCIS). There are no published population-based reports of the likelihood of breast cancer death among US women with DCIS.

Methods: We used data from the Surveillance, Epidemiology and End Results program to determine the likelihood of breast cancer death at 5 and 10 years among US women aged 40 and older diagnosed with DCIS from 1978 to 1983 (before screening mammography was common; n = 1525) and from 1984 to 1989 (when screening mammography became common; n = 5547). We also calculated standardized mortality ratios (SMRs) to compare observed deaths from breast cancer, cardiovascular disease, and all causes combined among women with DCIS with deaths expected based on general population mortality rates.

Results: Among women diagnosed with DCIS from 1978 to 1983, 1.5% died of breast cancer within 5 years and 3.4% within 10 years. Among women diagnosed from 1984 to 1989, 0.7% died of breast cancer within 5 years

and 1.9% within 10 years. Relative to the general population, risk of breast cancer death was greater for women diagnosed from 1978 to 1983 (SMR, 3.4; 95% confidence interval [CI], 2.5-4.5) than for women diagnosed from 1984 to 1989 (10-year SMR, 1.9; 95% CI, 1.5-2.3). Women diagnosed from 1984 to 1989 were significantly less likely than women in the general population to have died of cardiovascular diseases (10-year SMR, 0.6; 95% CI, 0.5-0.7) or of all causes combined (SMR, 0.8; 95% CI, 0.7-0.8).

Conclusions: Among women diagnosed with DCIS, risk of death from breast cancer was low, at least within the 10 years following diagnosis. This may reflect the effectiveness of treatment for DCIS, the "benign" nature of DCIS, or both. At 10 years, women diagnosed from 1984 to 1989 were less likely than women diagnosed from 1978 to 1983 to have died of breast cancer, and their risk of dying of all causes combined was lower than that in the general population.

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THERE HAS been a marked increase in reported cases of ductal carcinoma in situ (DCIS) of the breast since the early 1980s.¹ Since most DCIS lesions do not present as a breast lump but are often visible on mammographic films, the increase in detected cases is thought largely to be a result of increases in the prevalence of screening mammography. In 1983, based on data from the National Cancer Institute's Surveillance, Epidemiology and End Results (SEER) program, there were an estimated 4901 cases of DCIS in the United States compared with an estimated 28 958 cases in 1995. According to SEER data, 14.4% of all newly diagnosed breast cancers in the United States in 1993 were DCIS, compared with 2.8% in 1973 and 3.8% in 1983,² and reports suggest that a

much higher proportion of mammographically detected breast cancers are DCIS.^{3,4}

The natural history of DCIS is not clear,^{5,6} and given our current inability to predict which DCIS lesions will progress to invasive cancer, most DCIS cases are treated surgically, with or without radiation. In 1995, according to SEER data, 37.2% of DCIS cases were treated by mastectomy, 30.6% by lumpectomy plus radiation, and 30.4% by lumpectomy alone; only 1.8% received no surgical treatment beyond biopsy.²

There are no published population-based reports of the eventual likelihood of dying of breast cancer among US women diagnosed with and treated for DCIS, nor of their likelihood of dying of breast cancer or other causes relative to women in the general population. Owing to small numbers and/or limited follow-up time,

METHODS

We examined the mortality experience through 1995 of white and black women aged 40 and older who were newly diagnosed with DCIS from 1978 to 1989, using data from the SEER program. During the study period, the SEER program sites included approximately 10% of the total US population. The SEER program determines cancer survival rates by linkage of cancer cases to regional and national death registries and other means. In this way, data are collected on the causes of death for all patients in the program who have died. Our analysis was confined to white and black women with DCIS because breast cancer rates vary by race, and the number of DCIS cases among women of other racial groups was relatively small. Included were all cases of carcinoma in situ of the breast, with the following exclusions: cases of lobular carcinoma in situ; cases of DCIS for which SEER had a report of any previous invasive breast cancer or any invasive breast cancer within the 2 months following the index diagnosis; and DCIS cases (n = 8) diagnosed only at autopsy or only on the basis of a death certificate report. Almost all women were treated surgically, with or without radiation.

Using the Kaplan-Meier life-table method, we first determined the estimated proportion of women with DCIS who died of breast cancer within 5 and 10 years following their DCIS diagnosis. Cox proportional hazards models, adjusted for age and race, were used to compare differences in survival for women diagnosed with DCIS from 1978 to 1983 (n = 1523) and those diagnosed from 1984 to 1989 (n = 5531). We found no indication of departure from the proportional hazards assumption when we tested it using

log minus log plots of the survivor function and plots of Schoenfeld residuals against time.

For women diagnosed with DCIS during the 2 time periods, we also compared the observed numbers of breast cancer deaths at 5 and 10 years following DCIS diagnosis with the numbers expected based on breast cancer mortality rates in the general population. Expected numbers were calculated by applying age-, race-, and year-specific breast cancer death rates in the general population of women in the SEER areas over the study periods (based on mortality counts provided by the National Cancer Institute) to the corresponding person-years at risk among the women with DCIS. The resultant measure is the standardized mortality ratio (SMR) and its 95% confidence interval (CI).¹³ We also calculated corresponding SMRs for CVD (*International Classification of Diseases, Ninth Revision* codes 410-414 for ischemic heart disease, 428-429 for heart failure, 430-438 for cerebrovascular disease, and 444 for arterial embolism and thrombosis) and SMRs for all causes combined.

For comparison, we examined the same outcomes for women in the SEER database diagnosed from 1978 to 1983 and 1984 to 1989 with the following types of invasive breast cancer: (1) invasive breast cancers smaller than 2 cm with no report of positive lymph nodes (ie, those considered consistent with screening¹⁴); (2) localized breast cancer (ie, invasive neoplasms confined to the breast regardless of tumor size); (3) regional breast cancer (ie, invasive neoplasms extending directly beyond the breast or into regional lymph nodes); and (4) distant (metastatic) disease. As collection of data on tumor size and lymph nodes in the SEER program only began in the early 1980s, localized invasive cancers smaller than 2 cm could be identified only for the later period (1984-1989).

most clinical series that have tracked women treated for DCIS have focused on the risk of breast cancer recurrence, rather than risk of death per se. The aggregate experience of the observational series and clinical trials, however, suggests that risk of breast cancer death in women treated for DCIS is quite low, with estimates ranging from 0% to 6% up to a decade or more following diagnosis.⁷⁻¹² However, most previous analyses have been based on small numbers of deaths, and therefore mortality estimates in those studies are associated with wide confidence intervals.

We analyzed data reported to the population-based registries of the SEER program for US white and black women aged 40 and older diagnosed with DCIS between 1978 and 1989 to (1) determine the proportion who died of breast cancer at 5 and 10 years following diagnosis, comparing results for women diagnosed with DCIS between 1978 and 1983 (before the use of screening mammography was common) and those diagnosed between 1984 and 1989 (when screening mammography became more common); (2) ascertain separately for women diagnosed with DCIS from 1978 to 1983 and 1984 to 1989 the risk of dying of breast cancer, cardiovascular diseases (CVDs), and of all causes combined relative to that expected based on rates in the general population; and (3) examine for comparison the same out-

comes for women diagnosed with localized, regional, and distant invasive breast cancer during the study period.

RESULTS

NUMBERS OF DEATHS

Among the 7072 DCIS cases diagnosed between 1978 and 1989 included in this analysis, a total of 1293 deaths occurred through 1995. Length of follow-up ranged from 0 to 215 months, with a median of 99 months. **Table 1** shows the distribution by age at diagnosis of DCIS cases and of subsequent deaths due to breast cancer, CVD, and all causes combined within each age-at-diagnosis group. A total of 145 women died of breast cancer, 414 of CVD, and 734 from all other causes combined. Thus, most deaths that occurred were due to causes other than breast cancer.

PROPORTION OF WOMEN DYING OF BREAST CANCER

The likelihood of breast cancer death among women diagnosed with DCIS was low. Moreover, women diagnosed with DCIS between 1984 and 1989 were less likely to die of breast cancer than women diagnosed between

Table 1. Age-Specific Numbers of Women Diagnosed With DCIS* From 1978 to 1989 and Numbers of Deaths by Cause†

Age, y	DCIS Cases	Breast Cancer Deaths	Cardiovascular Disease Deaths	Other Causes of Death	All Causes of Death
40-49	1567	30	6	37	73
50-59	1743	21	20	92	133
60-69	1933	43	86	177	306
70+	1829	51	302	428	781
Total	7072	145	414	734	1293

*DCIS indicates ductal carcinoma in situ. Unless otherwise indicated, data are number of cases.

†Included are cases of carcinoma in situ of the breast diagnosed from 1978 to 1989 in white and black women aged 40 or older and reported to the Surveillance, Epidemiology and End Results (SEER) program, excluding cases of lobular carcinoma in situ, cases for which SEER had a report of any previous breast cancer or any invasive breast cancer within the 2 months following the index DCIS diagnosis, and cases diagnosed only at autopsy or based only on the death certificate report. Of the total of 7072 cases, 532 were black women, among whom there were 9 breast cancer deaths, 50 cardiovascular disease deaths, and 76 deaths from other causes. Deaths are tabulated by age group at diagnosis, which is often not the age group at death. Median length of follow-up, 99 months.

Table 2. Percentage of Women With DCIS by Age and by Year of Diagnosis* Who Died of Breast Cancer at 5 and 10 Years Following DCIS Diagnosis

	No. of DCIS Cases	Total Breast Cancer Deaths	Percentage Dying of Breast Cancer (95% CI)†	
			At 5 Years	At 10 Years
Age at Diagnosis, y				
40-49	1567	30	0.5 (0.2-0.9)	2.1 (1.3-2.9)
≥50	5505	115	1.0 (0.7-1.3)	2.4 (1.9-2.9)
Year of Diagnosis				
1978-1983	1525	64	1.5 (0.9-2.1)	3.4 (2.5-4.4)
1984-1989	5547	81	0.7 (0.5-0.9)	1.9 (1.5-2.4)
Total	7072	145	0.9 (0.7-1.1)	2.3 (1.9-2.7)

*DCIS indicates ductal carcinoma in situ.

†CI indicates confidence interval. Data are Kaplan-Meier estimates.

1978 and 1983. As detailed in **Table 2**, the Kaplan-Meier estimate of the proportion of women with DCIS who died of breast cancer was 0.9% within 5 years following DCIS diagnosis, and 2.3% within 10 years. Results were similar for women aged 40 to 49 years and those aged 50 years or older. However, results differed by diagnostic period; 3.4% of women diagnosed with DCIS from 1978 to 1983 died of breast cancer within 10 years, compared with 1.9% of women diagnosed from 1984 to 1989. Using a Cox proportional hazards model adjusted for age and race, we found that the relative risk of death from breast cancer for women diagnosed with DCIS between 1984 and 1989 was 0.6 (95% CI, 0.4-0.8) compared with that for women diagnosed between 1978 and 1983.

For comparison, the proportion of women in the SEER database diagnosed with localized invasive breast cancer between 1978 and 1989 who died of breast cancer was 7.3% (95% CI, 7.1%-7.6%) at 5 years following diagnosis and 14.2% (95% CI, 13.9%-14.5%) at 10

Table 3. Standardized Mortality Ratios (SMRs) Among Women Diagnosed With Breast Cancer, by Stage of Disease and Year of Diagnosis (1978-1983 and 1984-1989), Compared With Women in the General Population*

Period of Diagnosis and Length of Follow-up, y	SMR (95% CI)		
	Breast Cancer	Cardiovascular Disease	All Causes
DCIS			
1978-1983			
5	3.1 (1.9-4.8)	0.9 (0.7-1.1)	1.1 (0.9-1.2)
10	3.4 (2.5-4.5)	0.8 (0.7-1.0)	1.0 (0.9-1.1)
1984-1989			
5	1.6 (1.1-2.1)	0.6 (0.5-0.7)	0.7 (0.7-0.8)
10	1.9 (1.5-2.3)	0.6 (0.5-0.7)	0.8 (0.7-0.8)
Subset of Localized Invasive Disease†			
1984-1989			
5	6.2 (5.7-6.7)	0.7 (0.6-0.7)	1.0 (1.0-1.0)
10	6.7 (6.3-7.1)	0.7 (0.6-0.7)	1.1 (1.0-1.1)
All Localized Invasive Disease			
1978-1983			
5	17.8 (17.0-18.6)	1.0 (1.0-1.1)	1.7 (1.7-1.8)
10	16.8 (16.2-17.3)	1.0 (1.0-1.0)	1.7 (1.6-1.7)
1984-1989			
5	11.8 (11.3-12.3)	0.8 (0.7-0.8)	1.3 (1.3-1.3)
10	11.4 (11.0-11.8)	0.8 (0.8-0.8)	1.3 (1.3-1.3)
Regional Invasive Disease			
1978-1983			
5	64.3 (62.6-66.0)	1.1 (1.0-1.1)	3.8 (3.7-3.9)
10	55.5 (54.3-56.7)	1.0 (1.0-1.1)	3.4 (3.4-3.5)
1984-1989			
5	50.5 (49.1-51.9)	1.1 (1.0-1.1)	3.2 (3.2-3.3)
10	45.1 (44.0-46.2)	1.0 (1.0-1.1)	2.9 (2.9-3.0)
Distant Disease			
1978-1983			
5	290.4 (279.7-301.3)	1.3 (1.1-1.5)	12.8 (12.3-13.2)
10	254.2 (245.3-263.4)	1.3 (1.1-1.4)	11.1 (10.7-11.4)
1984-1989			
5	258.3 (249.0-267.8)	1.4 (1.2-1.6)	12.3 (11.9-12.7)
10	232.8 (224.8-241.0)	1.3 (1.1-1.5)	10.9 (10.6-11.2)

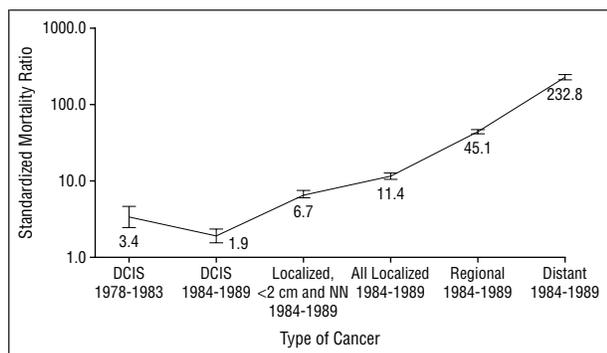
*DCIS indicates ductal carcinoma in situ; CI, confidence interval. The DCIS cases and general population data are all from Surveillance, Epidemiology and End Results (SEER) program areas.

†Defined as breast cancers smaller than 2 cm and node negative; since data on tumor size and nodal status have only been collected by the SEER programs since 1983, the mortality experience of cases consistent with screening could be examined for women diagnosed from 1984 to 1989 but not for the earlier period.

years. The proportion of women with regional invasive breast cancer who had died of breast cancer was 25.6% (95% CI, 25.2%-26.0%) at 5 years and 40.2% (95% CI, 39.7%-40.7%) at 10 years. Among women with distant disease, 77.3% (95% CI, 76.3%-78.3%) had died of breast cancer at 5 years and 88.2% (95% CI, 87.3%-89.1%) at 10 years.

STANDARDIZED MORTALITY RATIOS

Table 3 and the **Figure** give cause-specific SMRs for women diagnosed with breast cancer, by cancer type, compared with women in the general population. As indicated by the SMRs, women diagnosed with DCIS between 1978 and 1983 were more likely to die of breast



Ten-year standardized breast cancer mortality ratios for women diagnosed with ductal carcinoma in situ (DCIS) from 1978 to 1983 and 1984 to 1989, and for women diagnosed with invasive breast cancer from 1984 to 1989, compared with women in the general population. Brackets indicate 95% confidence intervals; NN, node negative.

cancer at both 5 and 10 years than women in the general population. Standardized mortality ratios were lower for women diagnosed between 1984 and 1989 (SMR, 1.9; 95% CI, 1.5-2.3) than for those diagnosed between 1978 and 1983 (10-year SMR, 3.4; 95% CI, 2.5-4.5). Women with DCIS were less likely than women in the general population to die of CVD, a finding that was more pronounced for those diagnosed with DCIS between 1984 and 1989 (SMR at 10 years, 0.6; 95% CI, 0.5-0.7) than for those diagnosed between 1978 and 1983 (SMR, 0.8; 95% CI, 0.7-0.99). Women diagnosed from 1984 to 1989, but not those diagnosed earlier, were also less likely than women in the general population to die of all causes combined (10-year SMR, 0.8; 95% CI, 0.7-0.8).

By comparison, women diagnosed with localized invasive cancers smaller than 2 cm from 1984 to 1989 were 6.7 times more likely to die of breast cancer in the 10 years following their diagnosis than women in the general population. Like women with DCIS, they had a significantly reduced risk of dying of CVD, but their overall risk of dying (all causes combined) was similar to that of women in the general population. Among the larger group of all women with localized invasive breast cancer (not limited to cancers smaller than 2 cm), and even more so among women with regional and distant invasive breast cancer, risk of breast cancer death was markedly elevated compared with women in the general population. However, breast cancer SMRs did decline between the 1978 to 1983 period and the 1984 to 1989 period (eg, the 10-year SMR declined from 16.8 to 11.4 for localized disease and from 55.5 to 45.1 for regional disease). Women with localized breast cancer diagnosed between 1984 and 1989 had significantly lower risks of death from CVD than women in the general population, as was seen for women with DCIS. However, women diagnosed with localized breast cancer between 1978 and 1983 and women with regional breast cancer diagnosed in both periods had risks of death from CVD similar to that of the general population. For women with all types of invasive breast cancer, the overall risk of dying (all causes combined) within 5 or 10 years following breast cancer diagnosis was significantly higher than among women in the general population. Nonetheless, all-cause SMRs declined between 1978 to 1983 and 1984 to 1989 for

women of every breast cancer type (eg, the 10-year all-cause SMR declined from 1.7 to 1.3 for localized disease, and from 3.4 to 2.9 for regional disease).

COMMENT

As suggested by earlier relatively small case series, the absolute risk of dying of breast cancer among women with DCIS is low, at least within the first 10 years following diagnosis and treatment. In the large population-based SEER series, we found that 3.4% of women diagnosed with DCIS from 1978 to 1983 and 1.9% of those diagnosed from 1984 to 1989 had died of breast cancer after 10 years. Because almost all women with DCIS are treated surgically, with or without radiation, it is impossible to know from these data the extent to which the low risk of death from breast cancer among women with DCIS results from effective treatment or reflects the relatively benign nature of the disease—or both. In any event, it should be emphasized that although a small proportion of women with DCIS will ultimately die of breast cancer, DCIS per se is not a life-threatening disease. Rather, deaths from breast cancer among women with DCIS are thought to result from an invasive component unrecognized at the time of the DCIS diagnosis: either the progression to invasive cancer of DCIS that was inadequately excised or unrecognized, or the development of an independent invasive breast cancer.

The degree to which the experience of DCIS cases diagnosed before the early 1980s (when the prevalence of screening mammography was low) can be generalized to cases diagnosed today is unclear. Presumably a smaller proportion of cases diagnosed from 1978 to 1983 was mammographically detected than has been true since the mid 1980s, when screening mammography became increasingly widespread. Lesions in the earlier period may have been larger or more likely to have some degree of invasiveness, albeit undiagnosed. Mammographically detected cases make up most of the DCIS detected today, and thus it will be of interest to follow the long-term experience of more recently diagnosed cases. Our finding that the percentage of women with DCIS who died of breast cancer within 10 years was lower for women diagnosed between 1984 and 1989 than for women diagnosed between 1978 and 1983 could be interpreted in several ways: (1) perhaps diagnostic precision has improved, such that DCIS cases diagnosed in the later period were less likely to be associated with unrecognized microinvasive breast cancer, which would reduce the chance of breast cancer death; (2) perhaps DCIS cases diagnosed in the later period have only an apparent survival advantage stemming from diagnosis earlier in the disease course, which has no real impact on eventual breast cancer mortality (lead-time bias); (3) perhaps mammography is increasing the proportion of detected DCIS cases with low malignant potential; or (4) perhaps mammographic detection actually is improving the prognosis for breast cancer survival among women diagnosed with DCIS. We do not know the extent to which any of these possible interpretations is correct.

The degree to which DCIS cases in the SEER data are misclassified is unknown. To the extent that cases coded as DCIS were actually early invasive breast cancers (about

5% to 15% of SEER DCIS cases by 1 estimate: Ann Coleman, PhD, personal communication, 1998), the risks of dying of breast cancer presented here for women with DCIS may be overestimated. Also, to the extent that women who truly had DCIS were misdiagnosed as having atypical hyperplasia or other benign diagnoses and therefore not included here, the risks of breast cancer death reported may be overestimated (assuming the excluded cases represent more benign types of DCIS). On the other hand, some women who actually had atypical hyperplasia may have been misclassified with the DCIS cases and erroneously included here, which would underestimate the risk of death from breast cancer for women with true DCIS.

We were unable to examine the effect of treatment type on differences between the 2 time periods, since the SEER program only began to collect data on DCIS treatment in 1983. Likewise we could not examine the effect of tumor size or histologic type on survival because tumor size is not recorded for about half of DCIS cases in the SEER data, and until recently histologic type was unspecified for most DCIS cases. However, it is noteworthy that the more favorable outcomes occurred among cases diagnosed in the later period despite declines in the use of mastectomy to treat DCIS over time.¹

It seems that women with DCIS represent a generally healthy subgroup of the population with respect to cardiovascular disease and, at least among those diagnosed more recently (1984-1989), possibly other causes of death as well. Women who present for mammographic screening (which is the mode of detection for most DCIS cases diagnosed today) may have healthier lifestyles and/or be more likely to use estrogens (which have been associated with a reduced risk of heart disease) than other women. Years ago it was shown that women in the Health Insurance Plan of Greater New York who were invited to undergo mammographic screening but refused to participate had much higher death rates from cardiovascular disease and from all causes combined than did women who chose to participate.¹⁵ Clinical trials of drugs have shown that women who are adherent to treatment, whether active drug or placebo, have lower risks of cardiovascular disease than poor adherers.^{16,17} Presumably, most women with DCIS and many with early localized invasive cancer are adherent to mammography, and such women may be healthier on average than other women. Recent studies suggest that women who undergo regular mammographic screening are more socioeconomically advantaged and practice more preventive health behaviors than women who do not.^{18,19} Moreover, having mammograms seems to be associated with estrogen use; in a cohort study of elderly upper middle class postmenopausal women, those who currently used estrogen were much more likely to report having had a mammogram than were those who never used estrogen (69.8% vs 45.3%, respectively).²⁰

Studies suggest that estrogen use may be associated with decreased risk of death from CVD^{21,22} and increased risk of breast cancer.^{22,23} Moreover, recent reports demonstrate a positive association between bone mineral density (a possible surrogate for cumulative estrogen exposure) and breast cancer risk.^{24,25} Thus, one might hypothesize that because of higher cumulative es-

trogen exposure, at least some women with breast cancer might be at lower risk of death from CVD. Our findings that women with DCIS and those with localized invasive breast cancers smaller than 2 cm are at lower risk of death from CVD are consistent with this possibility. However, we did not find a reduced risk of CVD for women diagnosed with regional invasive cancer—which is consistent with a case-control study that reported no association between history of coronary heart disease and risk of breast cancer.²⁶ Thus, the relatively lower risk of death from CVD among women with DCIS and early invasive breast cancers may largely reflect “healthy user” effects (eg, less smoking, lower weight, and better hypertension control) in women who present for screening compared with all women in the general population. That the SMR for CVD was not lower than expected for women with localized invasive breast cancer (regardless of size) who were diagnosed from 1978 to 1983 but was reduced for those who were diagnosed from 1984 to 1989 probably reflects a higher proportion of screen-detected cases in the later period.

Women treated for DCIS can be assured that their absolute risk of dying of breast cancer is low (an estimated 1.9% within 10 years of DCIS diagnosis for women diagnosed from 1984 to 1989). Risk may vary by histologic type or other disease characteristics, and results of ongoing studies designed to assess risk of recurrence by DCIS subtype will be of great interest.

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