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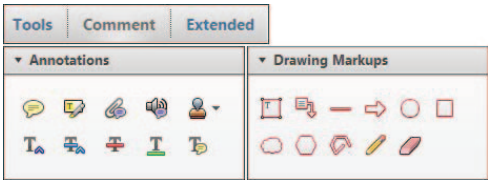

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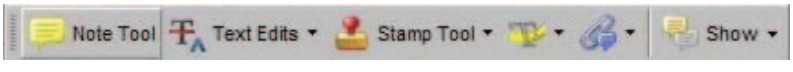

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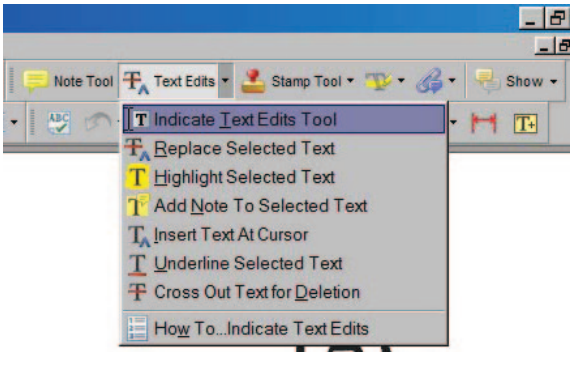

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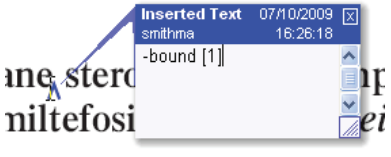

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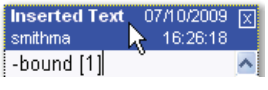

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Trends in Treatment Patterns and Outcomes for Ductal Carcinoma In Situ

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Abstract

Background: Impact of contemporary treatment of pre-invasive breast cancer (ductal carcinoma in situ [DCIS]) on long-term outcomes remains poorly defined. We aimed to evaluate national treatment trends for DCIS and to determine their impact on disease-specific (DSS) and overall survival (OS).

Methods: The Surveillance, Epidemiology, and End Results (SEER) registry was queried for patients diagnosed with DCIS from 1991 to 2010. Treatment pattern trends were analyzed using Cochran-Armitage trend test. Survival analyses were performed using inverse probability weights (IPW)–adjusted competing risk analyses for DSS and Cox proportional hazard regression for OS. All tests performed were two-sided.

Results: One hundred twenty-one thousand and eighty DCIS patients were identified. The greatest proportion of patients was treated with lumpectomy and radiation therapy (43.0%), followed by lumpectomy alone (26.5%) and unilateral (23.8%) or bilateral mastectomy (4.5%) with significant shifts over time. The rate of sentinel lymph node biopsy increased from 9.7% to 67.1% for mastectomy and from 1.4% to 17.8% for lumpectomy. Compared with mastectomy, OS was higher for lumpectomy with radiation (hazard ratio [HR] = 0.79, 95% confidence interval [CI] = 0.76 to 0.83, $P < .001$) and lower for lumpectomy alone (HR = 1.17, 95% CI = 1.13 to 1.23, $P < .001$). IPW-adjusted ten-year DSS was highest in lumpectomy with XRT (98.9%), followed by mastectomy (98.5%), and lumpectomy alone (98.4%).

Conclusions: We identified substantial shifts in treatment patterns for DCIS from 1991 to 2010. When outcomes between locoregional treatment options were compared, we observed greater differences in OS than DSS, likely reflecting both a prevailing patient selection bias as well as clinically negligible differences in breast cancer outcomes between groups.

Ductal carcinoma in situ (DCIS) of the breast is a clonal proliferation of cells that appear morphologically malignant by microscopy but are contained within the lumen of the mammary ducts by the basement membrane. DCIS is commonly identified by microcalcifications on mammography, with detection by palpation accounting for less than 10% of cases (1). The incidence of DCIS has increased in parallel with the widespread adoption of mammography for breast cancer screening; while DCIS was rarely diagnosed prior to 1980, it currently accounts for over 20% of all new breast cancer diagnoses in the United States, with more than 60 000 new cases annually (2,3).

DCIS is widely considered to be a nonobligate precursor lesion of invasive ductal breast cancers. However, reliable prognostic markers to identify those DCIS likely to progress to invasive cancer remain elusive. Estimates of the proportion of DCIS that will progress to invasive cancer vary widely, but it has been AQ2 estimated that 20% to 30% of DCIS progress to invasive breast cancer estimated within 10 years without treatment (4–6). Because of this, detection and treatment of DCIS is routinely

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recommended in an effort to reduce long-term breast cancer–specific mortality.

Tremendous variations in DCIS treatment patterns exist (7). Current National Comprehensive Cancer Network (NCCN) recommended treatment options include mastectomy, lumpectomy with radiation, or lumpectomy alone with the potential addition of tamoxifen for hormone receptor–positive DCIS. Randomized trials indicate that lumpectomy with radiation therapy results in lower rates of DCIS recurrence but were underpowered to detect a difference in overall or breast cancer–specific survival (4,8). Moreover, there are few data to indicate the magnitude of benefit to be derived from the currently recommended treatments compared with no treatment. Long-term active surveillance in well-selected patients is a potential alternative to surgical management, but largely because of concerns about an increased risk of invasive cancer at the time of delayed surgical excision and the lack of tools to predict which patients are most likely to progress, the acceptance rate for omission of surgery is very low (9,10). More precise estimates of the impact of contemporary treatment of DCIS on survival are needed to inform both future treatment recommendations and clinical trials of alternative management strategies. We therefore designed a population-based study to analyze treatment trends and survival in a large cohort of patients with DCIS undergoing contemporary treatment.

Methods

We conducted a retrospective cohort study of patients diagnosed with ductal carcinoma in situ (DCIS) using the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) database (11). SEER is one of the largest validated cancer registries of the United States, representing almost 30% of all new cancer diagnoses per year. The SEER database was queried from 1991 to 2010 identifying female breast cancer patients age 18 years or older with a behavior code in situ, excluding patients with ICD-O-3 codes of 8520/2 (lobular carcinoma in situ), 8522/2 (intraductal and lobular in situ carcinoma), and 8720/2 (melanoma in situ). Patients without microscopic confirmation of the diagnosis, those identified at autopsy or on death certificate only or whose surgery was unknown, and patients for whom DCIS was not the first cancer diagnosis were also excluded from analysis.

SEER Treatment Variables and Covariates

Patient-specific variables included age (in quartiles), race (white, black, others/unknown), Hispanic origin, marital status (married, not married, unknown), place of residence (rural, small urban, large urban), census tract based high school education (quartiles), and census tract based median household income (quartiles). Tumor-specific variables included: grade (low, intermediate, high, unknown), tumor size (≤15 mm, 16–40 mm, >40 mm, unknown), estrogen receptor (ER) status (positive, negative, unknown), progesterone receptor (PR) status (positive, negative, unknown), and number of lymph node examinations (none, 1–4 categorized as sentinel lymph node biopsy [SLNB], ≥5 categorized as axillary dissection [ALND]). Treatment characteristics included surgery (none, lumpectomy, unilateral mastectomy, bilateral mastectomy) and radiation therapy (yes, no). Systemic hormonal therapy was not reliably collected in SEER and was thus not included in the analysis. Patients age 91 years or older were recoded to age 90 years to fulfill HIPAA privacy regulations. The number of SEER registries increased over time; 1991: nine registries (Atlanta, Connecticut, Detroit, Hawaii, Iowa, New Mexico, San Francisco, Seattle, Utah); 1992–1999: 13 registries (SEER 9 plus Alaska Natives, Los Angeles, Rural Georgia, San Jose-Monterey); after 2000: 18 registries (SEER 13 plus California, Greater Georgia, Kentucky, Louisiana, New Jersey).

Cause of death was based on SEER-attributed primary cause of death, categorized as breast cancer, other malignant disease, cardiovascular disease, pulmonary disease, infectious disease, diabetes mellitus, and others/unknown. We grouped patients into five treatment categories: no treatment, lumpectomy without radiation, lumpectomy with XRT, unilateral mastectomy, and bilateral mastectomy excluding patients with other or unknown treatments.

Statistical Analysis

Demographic and tumor-related characteristics were compared between the different treatment groups using Pearson's Chi-square test for categorical (counts, percentage) and analysis of variance for continuous (mean+/-standard deviation) variables. To assess treatment changes over time, the Cochrane Armitage trend test was used. Subset analyses were performed to assess changes among patient characteristics in use of radiation after lumpectomy; trends within specific SEER registries were displayed using heat maps. For the purpose of survival analysis, we a priori restricted the analysis to locoregional treatments recommended for DCIS according to NCCN treatment guidelines: mastectomy (uni- or bilateral), lumpectomy with XRT, and lumpectomy alone. Cox proportional hazard regression analysis and competing risk survival models were used to assess overall (OS) and disease-specific survival (DSS), respectively. Patients lost to follow-up were right censored in the survival analysis. Because the treatment assignment for those patients was not random, multivariable analysis as well as inverse probability weighting (IPW) based on propensity scores was applied to adjust for potential confounding by indication (covariates: age, race, hispanic origin, marital status, place of residence, laterality, tumor grade, tumor size, ER status, PR status, high school education and household income level, and year of diagnosis) (Supplementary Table 1, available online) (12). This method aims to reduce effect of treatment selection, creating a pseudo-randomized study design based on all measured potential confounders in the dataset (12). The effects of individual variables on DSS and OS with and without weighting were calculated. To assess whether five-year DSS changed over time, we included year of diagnosis as predictor to the unadjusted and multivariable-adjusted competing risk model. Further, IPW-adjusted survival curves were drawn after generalization of the method described by Cole et al. (13), and these IPW-adjusted curves were compared using the log-rank test. Additional stratified analyses were performed using three age groups (age 18–49, 50–69, and ≥70 years).

All statistical analyses were performed using STATA/SE version 13.1 (Stata Corporation, College Station, TX) or SAS version 9.2 (SAS Institute, Inc, Cary, NC). All *P* values were calculated as two-sided, with significance declared for *P* values below .05.

Results

Trends in DCIS Treatment

We identified 121 080 patients with DCIS who met the eligibility criteria. The largest proportion of patients underwent lumpectomy with XRT (43.0%), followed by lumpectomy alone (26.5%), unilateral mastectomy (23.8%), bilateral mastectomy (4.5%), and no surgical treatment (2.3%) (Table 1). Patients undergoing

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Table 1. Patient characteristics of SEER cohort diagnosed with DCIS* from 1991–2010 (n = 121 080 patients)*

Characteristic	No surgery or radiation therapy No. (%)	Lumpectomy without radiation therapy No. (%)	Lumpectomy with radiation therapy No. (%)	Unilateral mastectomy No. (%)	Bilateral mastectomy No. (%)	P†
Number of patients	2782 (2.3)	32 076 (26.5)	52 026 (43.0)	28 779 (23.8)	5417 (4.5)	
Age, y, mean, SD	61.6 (14.5)	61.8 (13.4)	58.1 (11.4)	58.4 (13.0)	50.9 (10.5)	<.001
Race						
White	1981 (71.2)	25 751 (80.3)	41 790 (80.3)	22 186 (77.1)	4736 (87.4)	
Black	357 (12.8)	3092 (9.6)	4960 (9.5)	3149 (10.9)	321 (5.9)	<.001
Other/unknown	444 (16.0)	3233 (10.1)	5276 (10.1)	3444 (12.0)	360 (6.7)	
Hispanic						
Yes	264 (9.5)	2731 (8.5)	4071 (7.8)	2261 (7.9)	355 (6.6)	<.001
No	2518 (90.5)	29 345 (91.5)	47 955 (91.2)	26 518 (92.1)	5062 (93.5)	
Married						
Yes	1116 (40.1)	17 645 (55.0)	33 193 (63.8)	17 608 (61.2)	3767 (69.5)	
No	1015 (36.5)	12 645 (39.4)	17 221 (33.1)	10 288 (35.8)	1480 (27.3)	<.001
Unknown	651 (23.4)	1786 (5.6)	1612 (3.1)	883 (3.1)	170 (3.1)	
Laterality						
Left	1390 (50.0)	16 409 (51.2)	26 652 (51.2)	14 845 (51.6)	2740 (50.6)	
Right	1355 (48.7)	15 641 (48.8)	25 371 (48.8)	13 920 (48.4)	2674 (49.4)	<.001
Unknown/other	37 (1.3)	26 (0.1)	3 (0)	14 (0.1)	3 (0.1)	
Tumor grade						
Low	304 (10.9)	4839 (15.1)	5299 (10.2)	2100 (7.3)	431 (8.0)	
Intermediate	769 (27.6)	10 562 (32.9)	16 362 (31.5)	7044 (24.5)	1677 (31.0)	
High	640 (23.0)	7100 (22.1)	19 387 (37.3)	11 293 (39.2)	2500 (46.2)	<.001
Unknown	1069 (38.4)	9575 (29.9)	10 978 (21.1)	8342 (29.0)	809 (14.9)	
Tumor size, mm						
≤15	596 (21.4)	17 839 (55.6)	29 214 (56.2)	10 140 (35.2)	2012 (37.1)	
16–40	153 (5.5)	3444 (10.7)	7899 (15.2)	6091 (21.2)	1202 (22.2)	<.001
>40	89 (3.2)	858 (2.7)	1289 (2.5)	3125 (10.9)	621 (11.5)	
Unknown	1944 (69.9)	9935 (31.0)	13 624 (26.2)	9423 (32.7)	1582 (29.2)	
ER status						
Positive	729 (26.2)	10 852 (33.8)	24 356 (46.8)	9905 (34.4)	2806 (51.8)	
Negative	127 (4.6)	1604 (5.0)	4601 (8.8)	3172 (11.0)	645 (11.9)	<.001
Unknown	1926 (69.2)	19 620 (61.2)	23 069 (44.3)	15 702 (54.6)	1966 (36.3)	
PR status						
Positive	602 (21.6)	9065 (28.3)	20 296 (39.0)	7959 (27.7)	2297 (42.4)	
Negative	191 (6.9)	2549 (8.0)	7076 (13.6)	4332 (15.1)	957 (17.7)	<.001
Unknown	1989 (71.5)	20 462 (63.8)	24 654 (47.4)	16 488 (57.3)	2163 (39.9)	
Living						
Rural	21 (0.8)	255 (0.8)	481 (0.8)	323 (1.1)	51 (0.9)	
Urban small	910 (32.7)	9999 (31.2)	17 722 (34.1)	10 006 (34.8)	1783 (32.9)	<.001
Urban large	1840 (66.1)	21 764 (67.9)	33 781 (64.9)	18 387 (63.9)	3578 (66.1)	
Unknown	11 (0.4)	58 (0.2)	42 (0.1)	63 (0.2)	5 (0.1)	
Less than high school grade, %, quartiles						
I (<14.72)	544 (19.6)	6882 (21.5)	13 727 (26.4)	6718 (23.3)	1519 (28.0)	
II (14.72–17.63)	700 (25.2)	8101 (25.3)	15 163 (29.2)	7236 (25.1)	1561 (28.8)	
III (17.64–24.41)	661 (23.8)	7355 (22.9)	11 295 (21.7)	7196 (25.0)	1077 (19.9)	<.001
IV (≥24.42)	871 (31.3)	9732 (30.3)	11 838 (22.8)	7628 (26.5)	1259 (23.2)	
Unknown	6 (0.2)	6 (0.0)	3 (0.0)	1 (0.0)	1 (0.0)	
Median household income, $, quartiles						
I (<38.8)	645 (23.2)	8217 (25.6)	11 679 (22.5)	9264 (32.2)	894 (16.5)	
II (38.8–44.93)	817 (29.4)	8704 (27.1)	12 756 (24.5)	7065 (24.6)	1293 (23.9)	
III (44.94–53.16)	623 (22.4)	7164 (22.3)	13 909 (26.7)	6446 (22.4)	1491 (27.5)	<.001
IV (≥53.16)	691 (24.8)	7985 (24.9)	13 679 (26.3)	6003 (20.9)	1738 (32.1)	
Unknown	6 (0.2)	6 (0.0)	3 (0.0)	1 (0.0)	1 (0.0)	
Year‡						
1991–1995	181 (1.6)	3435 (30.9)	3240 (29.1)	4261 (38.3)	0	
1996–2000	519 (2.4)	6487 (30.2)	8256 (38.5)	5841 (27.2)	359 (1.7)	<.001
2001–2005	892 (2.2)	11 198 (27.1)	18 161 (44.0)	9328 (22.6)	1674 (4.1)	
2006–2010	1190 (2.5)	10 956 (23.2)	22 369 (47.3)	9349 (19.8)	3384 (7.2)	
Status						
Alive	2252 (81.0)	27 499 (85.7)	48 732 (93.7)	25 357 (88.1)	5308 (98.0)	
Dead breast	106 (3.8)	351 (1.1)	353 (0.7)	324 (1.1)	18 (0.3)	<.001
Dead other	424 (15.2)	4226 (13.2)	2941 (5.7)	3098 (10.8)	91 (1.7)	

* DCIS = ductal carcinoma in situ; ER = estrogen receptor; PR = progesterone receptor.
† P values based on Pearson's Chi-square test for categorical (counts, percentage) and analysis of variance for continuous (mean+/-standard deviation) variables.
‡ Numbers and row percentages.

bilateral mastectomy were in the youngest age group and more likely to be white, married, and in the highest income categories. Among those who underwent surgery, women treated with lumpectomy alone were oldest, least likely to be married, and most likely to have low-grade DCIS.

Between 1991 and 2010, we observed a statistically significant change in treatment patterns. The proportion of patients undergoing lumpectomy with XRT increased (24.2%-46.8%), as did those treated with bilateral mastectomy (0%-8.5%) and no treatment (1.2%-3.2%). In contrast, there was a statistically significant reduction in the rate of unilateral mastectomy (44.9%-19.3%) and lumpectomy alone (29.8%-22.3%, $P_{trend} < .001$ for all groups) (Figure 1A).

Axillary management differed statistically significantly between patients undergoing mastectomy and those undergoing lumpectomy. For patients undergoing mastectomy, SLNB

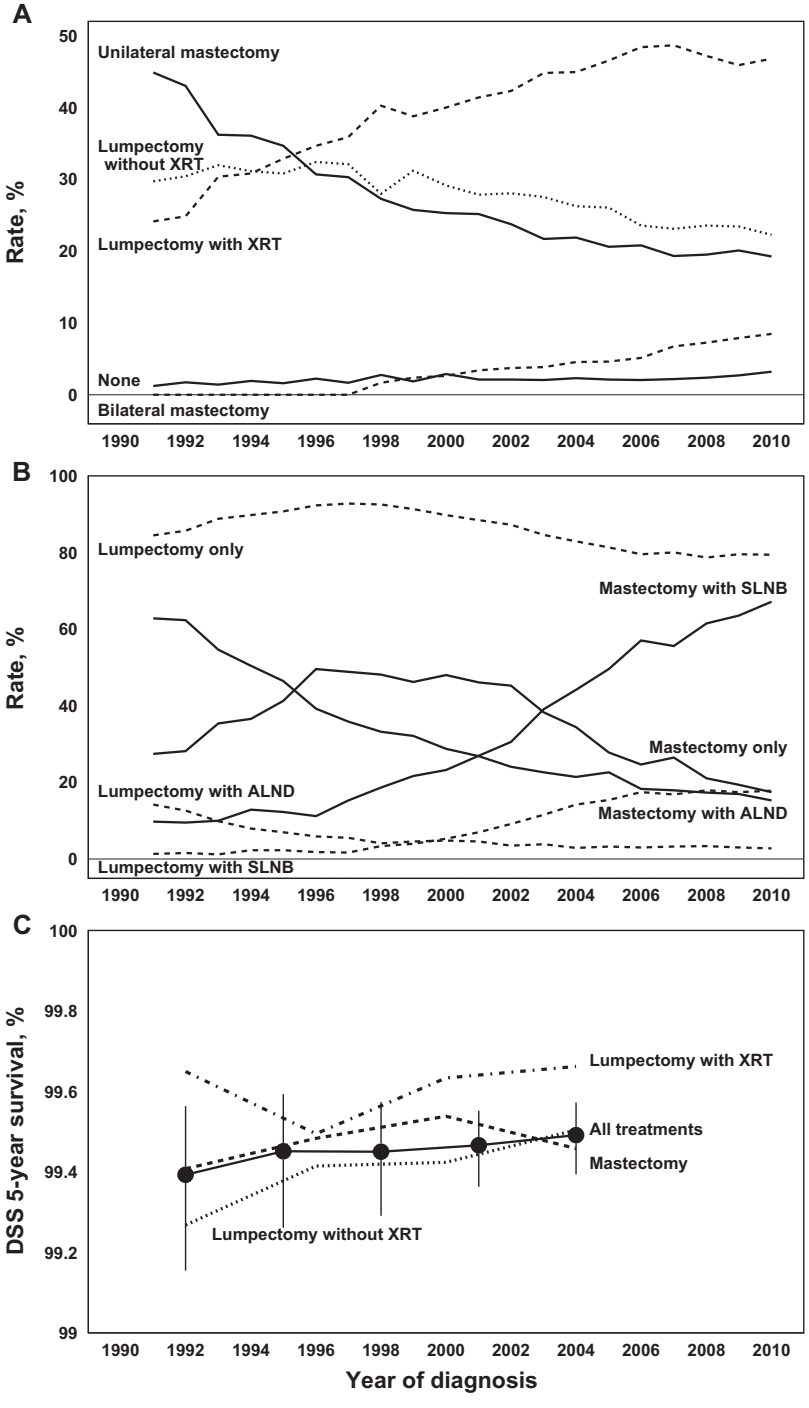

Figure 1. Time trends of treatment and survival among ductal carcinoma in situ (DCIS) patients diagnosed from 1991 to 2010. **A)** Trends of breast locoregional treatment. **B)** Trends of axillary surgery procedures grouped by mastectomy and lumpectomy. **C)** Trend of five-year disease-specific survival overall and for patients undergoing mastectomy, lumpectomy with/without radiation therapy. 95% confidence interval provided for "All Treatments" only. ALND = axillary lymph node dissection (4+ LNs), if no nodes were indicated, case coded as having had no lymph node surgery; DSS = disease-specific survival; LN = lymph node; SLNB = sentinel lymph node biopsy (1–4 LN); XRT = radiation therapy.

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increased from 9.7% to 67.1% and axillary dissections dropped from 62.9% to 15.3% (P_{trend} < .001 for both comparisons). For patients undergoing lumpectomy, the rate of SLNB increased from 1.4% to 17.8% and the rate of axillary dissections decreased from 14.2% to 2.8% (P_{trend} < .001 for both comparisons) (Figure 1B).

The increased use of adjuvant radiation after lumpectomy was observed among all patient groups (Table 2). Overall, the rate increased from 48.5% in 1991 to 1995 to 67.1% in 2006 to 2010 (P < .001). Major differences in the rate of radiation use after lumpectomy were found among SEER registries. For the first time period (1991–1996), rates varied from 37.5% in Alaska to 65.7% in Hawaii (Figure 2). Major differences persisted during the last time period (2006–2010), with rates varying from 50.3% in Utah to 84.6% in Iowa.

Overall and Disease-Specific Survival

Survival analyses were performed on patients undergoing mastectomy (unilateral or bilateral), lumpectomy with XRT, and lumpectomy alone (n = 118 298 patients). Median follow-up for patients with DCIS was 71 months (interquartile range [IQR] = 33–115). Ninety-seven point eight percent of patients age 49 years or younger at diagnosis were alive at their last follow-up, while 72.0% of patients older than 70 years were alive (Table 3).

Crude five- and 10-year OS for the cohort undergoing surgery for DCIS were 95.0% and 85.9%, respectively. Overall survival was highest for patients undergoing lumpectomy with XRT (96.8% and 89.6%), followed by mastectomy (95.1% and 86.1%) and lumpectomy alone (92.3% and 80.6%, P < .001). Both unadjusted and multivariable-adjusted analyses showed that compared with patients undergoing mastectomy those undergoing lumpectomy with XRT had higher OS (Supplementary Table 2, available online). These findings were confirmed even after IPW-adjustment (hazard ratio [HR] = 0.79, 95% confidence interval [CI] = 0.76 to 0.83, P < .001) (Supplementary Table 2, available online). Patients with lumpectomy alone had the highest risk of all-cause mortality (HR = 1.17, 95% CI = 1.13 to 1.23). In IPW-adjusted analysis, older patients, blacks, nonmarried patients, and those with larger tumors and lower median household income showed worse OS compared with their counterparts.

Given that breast cancer mortality comprised a relatively small proportion of overall mortality, we analyzed competing causes of death in women stratified by age group and treatment (Table 3). In the overall cohort, breast cancer was identified as the cause of death in 9.2% of women. However, the predominant cause of mortality was attributed to cardiovascular disease,

Table 2. Trends of patient characteristics undergoing lumpectomy with radiation therapy compared with lumpectomy alone*

Characteristic	Number of patients who underwent lumpectomy with XRT (% of all lumpectomy patients)				
Year of diagnosis	1991–1995	1996–2000	2001–2005	2006–2010	P_{trend}
Number of patients	3240 (48.5)	8256 (56.0)	18.161 (61.9)	22 369 (67.1)	<.001
Age group, y					
18–49	1039 (56.5)	2319 (62.0)	4553 (65.2)	5419 (71.7)	<.001
50–58	795 (56.1)	2243 (61.5)	5133 (65.9)	6325 (71.1)	<.001
59–69	881 (51.1)	2124 (57.1)	5012 (65.3)	6750 (70.6)	<.001
70–90	525 (31.0)	1570 (43.3)	3463 (50.2)	3875 (53.0)	<.001
Race					
White	2699 (48.9)	6696 (55.8)	14 799 (62.0)	17 596 (67.3)	<.001
Black	243 (44.6)	656 (52.6)	1679 (61.0)	2382 (67.9)	<.001
Other/unknown	298 (48.5)	904 (60.2)	1683 (61.7)	2391 (65.2)	<.001
Hispanic					
Yes	171 (45.6)	502 (52.4)	1386 (60.3)	2012 (63.5)	<.001
No	3069 (48.7)	7754 (56.3)	16 775 (62.0)	20 357 (67.5)	<.001
Married					
Yes	2112 (53.3)	5255 (59.4)	11 661 (65.0)	14 165 (70.5)	<.001
No	1050 (43.3)	2678 (51.4)	6086 (58.0)	7407 (63.1)	<.001
Unknown	78 (26.7)	323 (46.7)	414 (44.4)	797 (53.8)	<.001
Median household income, $, quartiles					
I (<39.11)	2238 (47.5)	3288 (55.1)	3127 (64.9)	3738 (68.7)	<.001
II (39.39–45.09)	639 (55.7)	1821 (54.7)	4519 (57.4)	5408 (62.0)	<.001
III (45.20–54.10)	356 (44.6)	1872 (60.2)	5404 (66.1)	6483 (71.0)	<.001
IV (≥54.27)	7 (53.9)	1275 (54.4)	5111 (60.2)	6737 (67.3)	<.001
Unknown	0	0	0	3 (33.3)	
Less than high school grade, %, quartiles					
I (<14.72)	692 (51.1)	1985 (58.7)	4791 (65.7)	6259 (73.0)	<.001
II (14.72–17.62)	498 (51.0)	1923 (61.4)	5059 (65.2)	6015 (68.8)	<.001
III (17.64–24.36)	1278 (49.7)	2482 (57.0)	4073 (60.5)	5130 (67.0)	<.001
IV (≥24.42)	772 (43.6)	1866 (48.2)	4238 (55.9)	4962 (59.4)	<.001
Unknown	0	0	0	3 (33.3)	
Living					
Rural	16 (48.5)	79 (66.4)	162 (60.7)	224 (70.7)	0.003
Urban small	995 (54.5)	2720 (61.2)	6226 (62.5)	7781 (67.7)	<.001
Urban large	2223 (46.3)	5451 (53.7)	11 759 (61.5)	14 348 (66.8)	<.001
Unknown	6 (54.6)	6 (24.0)	14 (46.7)	16 (47.1)	0.77

* XRT = radiation therapy.

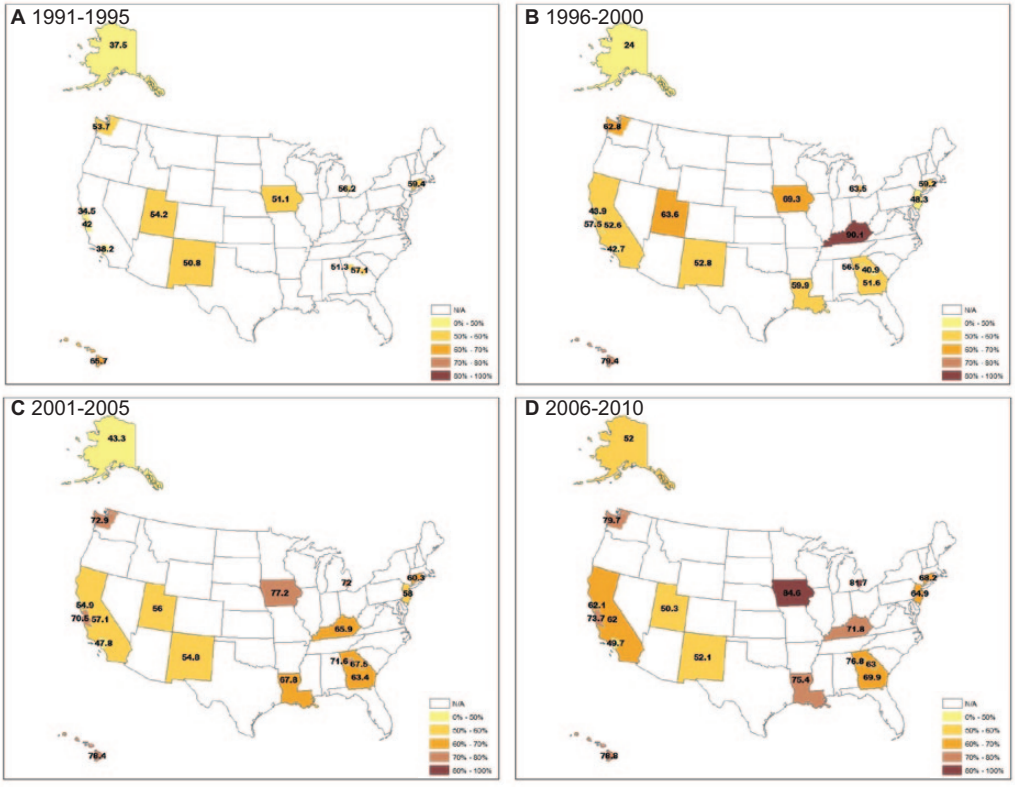

Figure 2. Adjuvant radiation rates per Surveillance, Epidemiology, and End Results (SEER) registry among patients undergoing lumpectomy: **A)** 1991–1995 (SEER 9 and 13); **B)** 1996–2000 (SEER 13 and 18); **C)** 2001–2005 (SEER 18); **D)** 2006–2010 (SEER 18). Registries: SEER 9: Atlanta, Connecticut, Detroit, Hawaii, Iowa, New Mexico, San Francisco, Seattle, Utah. SEER 13: SEER 9 plus Alaska Natives, Los Angeles, Rural Georgia, San Jose-Monterey. SEER 18: SEER 13 plus California, Greater Georgia, Kentucky, Louisiana, New Jersey. XRT = Radiation Therapy.

Table 3. Causes of mortality stratified by 3 age groups and 3 treatment groups*

	Age group, y			Treatment group		
Causes of death	18–49 No. (%)	50–69 No. (%)	≥70 No. (%)	Mx No. (%)	Lx - XRT No. (%)	Lx + XRT No. (%)
Number of patients	31 036 (26.2)	63 229 (53.5)	24 033 (20.3)	34 196 (28.9)	32 076 (27.1)	52 026 (44.0)
Alive at last follow-up	30 344 (97.8)	59 254 (93.7)	17 298 (72.0)	30 665 (89.7)	27 499 (85.7)	48 732 (93.7)
Cause of death, %						
- Breast cancer	236 (34.1)	443 (11.1)	367 (5.4)	342 (9.7)	351 (7.7)	353 (10.7)
- Other malignant disease	180 (26.0)	1201 (30.2)	1152 (17.1)	731 (20.7)	916 (20.0)	886 (26.9)
- Cardiovascular disease	73 (10.5)	986 (24.8)	2708 (40.2)	1157 (32.8)	1681 (36.7)	929 (28.2)
- Pulmonary disease	5 (0.7)	232 (5.8)	351 (5.2)	182 (5.2)	267 (5.8)	139 (4.2)
- Infectious disease	18 (2.6)	127 (3.2)	249 (3.7)	120 (3.4)	162 (3.5)	112 (3.4)
- Diabetes mellitus	12 (1.7)	112 (2.8)	169 (2.5)	112 (3.2)	104 (2.3)	77 (2.3)
- Other/unknown	168 (24.3)	874 (22.0)	1739 (25.8)	887 (25.1)	1096 (23.9)	798 (24.2)

* Lx = lumpectomy; Mx = mastectomy; XRT = radiation therapy.

accounting for 33.0% of all deaths, followed by other malignancies (22.2% of all deaths). In women 70 years or older at diagnosis, 40.2% of all deaths were from cardiovascular disease, compared with 5.4% from breast cancer.

IPW-adjusted five- and 10-year DSS for all patients were 99.5% and 98.5%, respectively. Similar to our findings for OS, IPW-adjusted DSS was highest in the group that underwent lumpectomy with XRT (99.6% and 98.9%), followed by mastectomy (99.5% and 98.5%) and lumpectomy alone (99.4% and 98.4%, $P = .0089$) (Figure 3). IPW-adjusted competing risk analysis for DSS revealed that patients undergoing lumpectomy with XRT had similar survival compared with mastectomy (HR = 0.89, 95% CI = 0.76 to 1.03), while patients undergoing lumpectomy alone showed increased breast cancer mortality compared with mastectomy (HR = 1.18, 95% CI = 1.02 to 1.36) (Supplementary Table 3, available online). Based on these data, 200 patients would need to be treated with radiation after lumpectomy for each breast cancer death averted at 10 years. Multivariable-adjusted five-year DSS statistically significantly improved over time overall (HR per one year increment = 0.972, 95% CI = 0.952 to 0.993) and for lumpectomy without radiation therapy (HR = 0.962, 95% CI = 0.928 to 0.0.996), while no such increase was found for mastectomy (HR = 0.977, 95% CI = 0.943 to 1.012) or lumpectomy with radiation therapy (HR = 0.986, 95% CI = 0.951 to 1.023) (Figure 1C).

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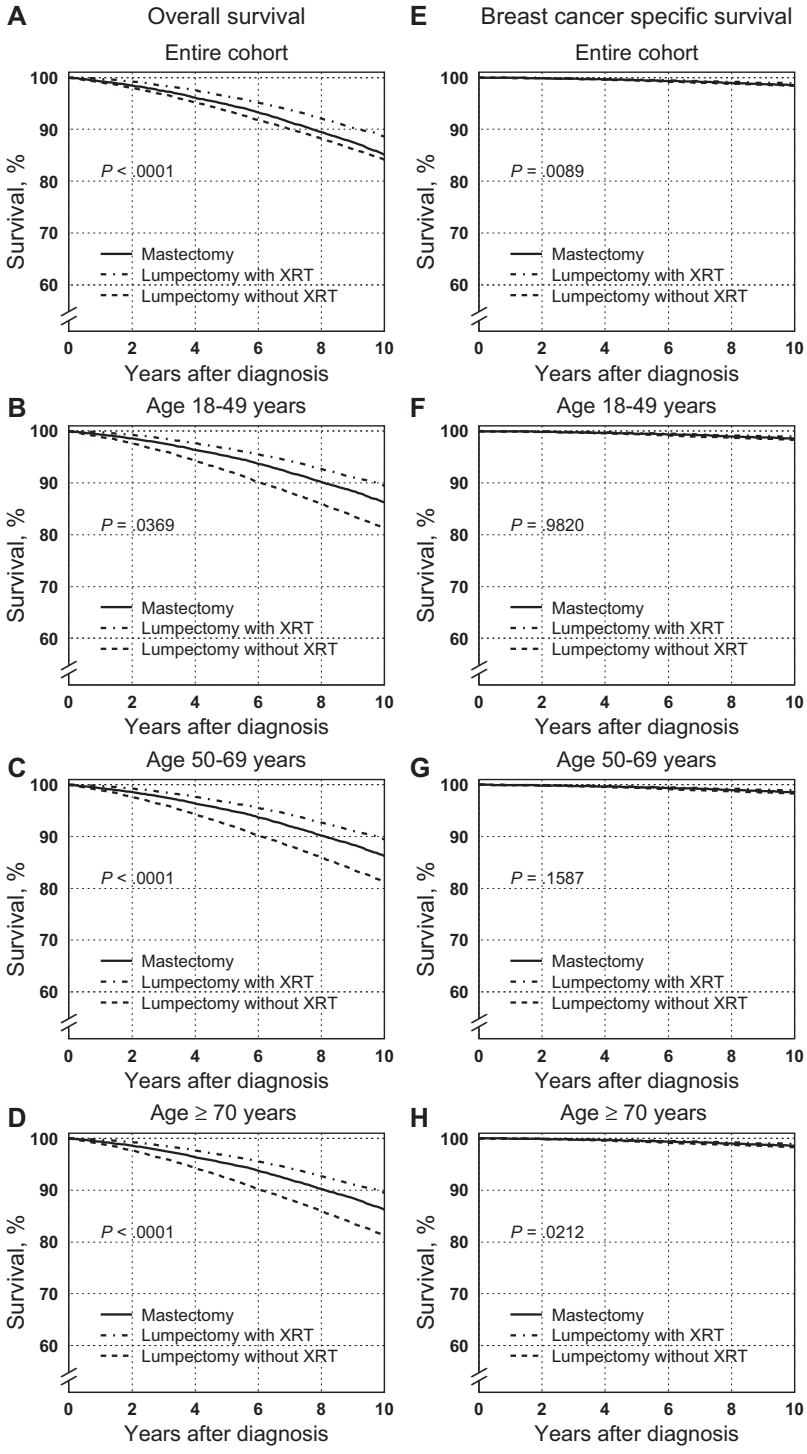

Figure 3. Overall and breast cancer–specific survival by locoregional treatment, overall group, and stratified by three age groups based on inverse probability weight (IPW)–adjusted survival data. All *P* values based on IPW-adjusted, two-sided log-rank test. **Left column,** overall survival: **A)** entire cohort, **B)** 18–49 years, **C)** 50–69 years, **D)** ≥70 years. **Right column,** breast cancer–specific mortality: **E)** entire cohort, **F)** 18–49 years, **G)** 50–69 years, **H)** ≥70 years. XRT = Radiation Therapy.

For patients diagnosed younger than 50 years, breast cancer was identified as the cause of mortality for 236 deaths (34.1%) at a median of 84 months after diagnosis, while it accounted for 443 deaths (11.1%) among patients age 50 to 69 years (median time to breast cancer death = 82 months) and 367 deaths (5.4%) among patients age 70 years and older (median time to breast cancer death = 71 months) (Table 3). Age-stratified analyses were performed for both OS and DSS. IPW-adjusted analyses for patients age 18 to 49 years showed similar OS and DSS for lumpectomy with XRT, while it was worse for lumpectomy alone compared with mastectomy (Table 4). For patients age 50 to 69 and older than 70 years, IPW-adjusted analysis showed better OS for lumpectomy with XRT and worse for lumpectomy alone. There was no difference in DSS in these age groups.

Table 4. Subgroup analysis of overall and breast cancer–specific survival, stratified by 3 age-groups (18–49 years, 50–69 years, ≥70 years)*

Age and treatment	Unadjusted		Multivariable-adjusted		IPWS-adjusted		IPW-adjusted survival rates	
	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P	5-year	10-year
Overall survival								
Age 18–49 y								
Mx	Ref.		Ref.		Ref.		0.989 (0.988 to 0.991)	0.969 (0.966 to 0.971)
Lx + XRT	0.85 (0.71 to 1.01)	.06	0.91 (0.76 to 1.10)	.33	0.89 (0.74 to 1.07)	.21	0.993 (0.991 to 0.994)	0.975 (0.973 to 0.978)
Lx - XRT	1.13 (0.94 to 1.37)	.19	1.21 (0.99 to 1.47)	.06	1.26 (1.06 to 1.50)	.008	0.985 (0.983 to 0.986)	0.961 (0.958 to 0.964)
Age 50–69 y								
Mx	Ref.		Ref.		Ref.		0.970 (0.968 to 0.971)	0.911 (0.907 to 0.914)
Lx + XRT	0.83 (0.77 to 0.90)	<.001	0.88 (0.81 to 0.96)	.002	0.87 (0.80 to 0.94)	<.001	0.976 (0.974 to 0.977)	0.925 (0.921 to 0.928)
Lx - XRT	1.07 (0.99 to 1.16)	.11	1.09 (1.00 to 1.19)	.05	1.09 (1.01 to 1.17)	.03	0.965 (0.963 to 0.966)	0.907 (0.904 to 0.910)
Age ≥70 y								
Mx	Ref.		Ref.		Ref.		0.860 (0.855 to 0.865)	0.617 (0.608 to 0.625)
Lx + XRT	0.70 (0.66 to 0.75)	<.001	0.74 (0.70 to 0.79)	<.001	0.75 (0.70 to 0.79)	<.001	0.904 (0.900 to 0.908)	0.695 (0.687 to 0.703)
Lx - XRT	1.18 (1.12 to 1.25)	<.001	1.21 (1.14 to 1.28)	<.001	1.22 (1.16 to 1.29)	<.001	0.815 (0.810 to 0.820)	0.561 (0.552 to 0.569)
Breast cancer–specific survival								
Age 18–49 y								
Mx	Ref.		Ref.		Ref.		0.997 (0.996 to 0.998)	0.989 (0.987 to 0.990)
Lx + XRT	0.83 (0.61 to 1.12)	.60	1.04 (0.76 to 1.42)	.82	1.02 (0.74 to 1.41)	.92	0.998 (0.997 to 0.998)	0.992 (0.990 to 0.993)
Lx - XRT	1.09 (0.79 to 1.50)	.23	1.37 (0.98 to 1.92)	.06	1.55 (1.16 to 2.09)	.004	0.995 (0.994 to 0.996)	0.984 (0.982 to 0.986)
Age 50–69 y								
Mx	Ref.		Ref.		Ref.		0.996 (0.996 to 0.997)	0.988 (0.987 to 0.989)
Lx + XRT	0.85 (0.67 to 1.06)	.15	0.94 (0.75 to 1.19)	.60	0.90 (0.71 to 1.13)	.37	0.997 (0.996 to 0.997)	0.991 (0.990 to 0.992)
Lx - XRT	0.93 (0.72 to 1.18)	.53	1.02 (0.79 to 1.31)	.91	1.00 (0.79 to 1.26)	.99	0.997 (0.996 to 0.997)	0.989 (0.988 to 0.990)
Age ≥70 y								
Mx	Ref.		Ref.		Ref.		0.990 (0.988 to 0.991)	0.975 (0.972 to 0.978)
Lx + XRT	0.81 (0.62 to 1.05)	.11	0.92 (0.70 to 1.20)	.52	0.84 (0.66 to 1.08)	.18	0.992 (0.990 to 0.993)	0.978 (0.975 to 0.980)
Lx - XRT	1.14 (0.90 to 1.44)	.29	1.21 (0.95 to 1.55)	.13	1.17 (0.92 to 1.48)	.20	0.988 (0.987 to 0.990)	0.971 (0.967 to 0.974)

* Cox proportional hazard regression analysis for overall survival and competing risk survival models for breast cancer–specific survival were used (two-sided). Covariates for multivariable/IPW adjustment: age, race, Hispanic origin, marital status, place of residence, laterality, tumor grade, tumor size, estrogen receptor status, progesterone receptor status, high school education, household income level, and year of diagnosis. CI = confidence interval; HR = hazard ratio; Lx = lumpectomy; Mx = mastectomy; IPW = inverse probability weight; Ref. = referent; XRT = radiation therapy.

Discussion

The increased incidence of DCIS following widespread adoption of mammographic screening has been well described (2,14). National efforts to promote screening and early detection have dramatically increased the rate of diagnosis of this disease, although the public health implications of DCIS treatment remain poorly understood. Based on our study, only 2.3% of patients did not undergo surgery for DCIS; the majority of patients had treatment involving lumpectomy with or without radiation therapy, or mastectomy, with each treatment likely impacting long-term quality of life (15,16). Natural history studies support that only 20% to 30% of DCIS lesions managed with biopsy alone will eventually progress to invasive breast cancer; for other women with low risk of recurrence or progression, treatment may provide little benefit in DSS with clear risk of harm from treatment. Apart from the morbidity of surgery, serious albeit rare long-term complications may result from radiation therapy. These include development of angiosarcomas, increased morbidity associated with heart and lung disease, rib fracture, lymphedema, and tissue necrosis and fibrosis (17–19). Identification of DCIS subtypes that are at high risk of invasive progression would aid in weighing the risks of treatment against the benefits of therapy. Molecular risk stratification tools have been developed but are not yet in widespread use (20,21). Additional advances are urgently needed in order to provide both patients and providers actionable risk assessment based on potential for invasion (22).

In this study, we found a substantial shift in locoregional treatment patterns for DCIS. The use of lumpectomy with radiation increased by almost 100%, whereas use of unilateral mastectomy dropped by 60%. The bilateral mastectomy rate for DCIS increased from 0% to 8.5%, a trend likely driven by prophylactic contralateral mastectomy rather than by bilateral DCIS (23,24). Our analysis supports other studies, which have shown that compared with patients treated with lumpectomy and radiation those electing bilateral mastectomy were younger and more likely to be white and married with a higher median household income. In addition, when using mortality from causes other than breast cancer, the group undergoing bilateral mastectomy was least likely to die of non-breast cancer–related causes compared with any other surgical treatment group (data not shown). Our results also show that in patients undergoing lumpectomy, the use of adjuvant radiation therapy increased among all patient subgroups. Smaller differences were identified on a patient level. However, more striking differences in radiation use were found on a SEER registry level. While this variation in treatment pattern by region may in part be because of differences in ascertainment between regions, it confirms a recent finding based on Kaiser Permanent data where use of radiation therapy after breast-conserving therapy differed statistically significantly by location (25). Reasons for such geographical variation remain unclear and are of concern, as these data suggest that treatment decisions are much more strongly driven by the geography where the diagnosis was made, rather than by DCIS disease characteristics.

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DCIS is a noninvasive diagnosis and, as such, has little propensity for lymphatic spread (26,27). However, axillary surgery continued to be employed in both lumpectomy and mastectomy groups. We observed that in 2010, 60% of patients did not undergo surgical assessment of the axilla. The use of sentinel node biopsy for DCIS has increased markedly, reflecting a similar trend for invasive breast cancers (28). Concomitantly, there has been an encouraging reduction in the use of axillary node dissection. We observed that in 2010 71.6% of mastectomy procedures included sentinel lymph node biopsy. This is appropriate, given an up to 20% upstaging rate following surgical excision of DCIS and the technical difficulty of accurately identifying the sentinel node after mastectomy (29,30). However, sentinel lymph node biopsy was observed in almost 20% of patients undergoing lumpectomy. The low prevalence of node involvement in the setting of DCIS and minimal impact of lumpectomy on feasibility of subsequent axillary surgery supports a more restrained use of sentinel node biopsy with lumpectomy for DCIS. Moreover, 15.3% of women undergoing mastectomy and 2.8% undergoing lumpectomy underwent axillary node dissection in 2010. Thus, the current rate of axillary surgery overall, and of axillary dissection specifically, remains higher than indicated based upon the recent American Society of Clinical Oncology clinical practice guidelines and represents both a source of concern as well as a target for further education (31). Despite the reduction in extent of surgery performing more lumpectomy over mastectomy and decline in axillary surgery rates, disease-specific survival statistically improved throughout the study period. However, the clinical relevance of this improvement is likely not clinically meaningful.

This is the largest population-based study to date assessing the association between locoregional treatment and survival outcomes in women with DCIS. SEER has long employed a consistent algorithm to ascertain cause of death and to ensure that disease-specific survival is adjudicated as accurately as possible (11). Moreover, we applied advanced statistical methodology for retrospective data to account for known biases between treatment groups. We found that overall survival was highly associated with choice of treatment, even after IPW adjustment. In contrast, we observed that 10-year DSS differed by only 0.5% between the groups undergoing lumpectomy (98.4%) compared with lumpectomy with XRT (98.9%), with mastectomy resulting in essentially the same DSS as lumpectomy alone (98.5%), differences among treatment groups of an amount that might have very limited clinical impact but supporting that ultimately clinical value should drive treatment decisions. Because of the very low disease-specific mortality, the statistically significant differences in OS between treatment groups were largely attributed to selection bias, likely based on comorbidities at presentation. In fact, when we used age at diagnosis as a proxy for comorbidity, breast cancer accounted for about one third of deaths in patients younger than age 50 years but only for 5.4% in patients age 70 or older. It has been shown that comorbidities in older women are responsible for many if not most of the deaths in breast cancer patients, a particularly important consideration for women diagnosed with DCIS given the even lower attendant mortality of this diagnosis (32). In contrast, given that one third of deaths in the youngest age group occurred because of breast cancer highlights the importance of aggressive treatment for those patients. Further characterization of patients who did not undergo surgical treatment of DCIS as well as detailed assessment of which patients may most likely benefit from active surveillance are critical areas to pursue in future research as attention moves towards minimizing overtreatment for this disease.

While randomized trials clearly show the benefit of adjuvant radiation on local recurrence, we were unable to demonstrate an effect of radiation on DSS (33). The excellent overall disease-specific outcome regardless of treatment raises the possibility that patients may derive little clinically meaningful benefit of treatment for DCIS in the presence of comorbidities, particularly if life expectancy does not exceed 10 years. This is highly relevant for DCIS treatment because as in many other cancers the incidence rate increases, with age peaking around 74 years (2). Although our analysis does not provide information on survival related to watchful waiting or nonsurgical strategies, it does suggest a limited benefit from standard multimodality treatment of DCIS among patients with important competing causes of mortality. Thus, we contend that less aggressive treatment for DCIS should be considered in select subsets of patients. The role of watchful waiting for DCIS must be further assessed but might follow the treatment strategies of contemporary prostate cancer treatment, where overall health and expected survival of patients play a crucial role, weighed against morbidity of treatment (34). Observational or registry studies designed to address this issue would be of tremendous benefit.

As with all retrospective studies, outcomes such as overall and disease-specific survival must be interpreted with caution, particularly for a disease that rarely results in death. The present analysis suggests an important selection bias in favor of more fit patients undergoing the most invasive treatments, supported by our observation that the five-year OS differed statistically between treatment groups by as much as 4.5%, whereas the DSS only differed by 0.2%. This limits the ability to derive meaningful associations between treatment, or indeed absence of treatment, and disease-specific outcomes, although it does afford the opportunity to contextualize the contribution of DCIS treatment to overall health outcomes among different age groups. Despite availability of information on cause of death including breast cancer, it remains unclear whether the responsible tumor was de novo or a consequence of DCIS progression to invasive breast cancer. In addition, the relatively small number of patients for whom accurate systemic treatment data are available in SEER precludes the evaluation of adjuvant endocrine therapy on outcomes, which will be important in future analyses as such data become available. Another key limitation in this, as in all other analyses using the SEER registry, is the absence of data with which to study the direct effects of baseline comorbidities, individual treatment decision-making, surgical resection margin, or performance status on primary outcomes. It is also known that radiation therapy is often underreported in administrative datasets like SEER (35). This said, disease-specific survival differences could potentially be bigger than reported in this manuscript, although very unlikely to change the results to a more clinically important degree. Finally, although the present analysis evaluated the association of treatment on survival endpoints only, it is important to acknowledge that recurrence endpoints and impact on quality of life are also meaningful to patients and thus must be considered in future studies.

In summary, surgical treatment patterns for DCIS have evolved substantially between 1991 and 2010 in the United States, paralleling treatment trends in the management of invasive breast cancer. The choice of locoregional treatment had a strikingly small impact on breast cancer–specific survival, calling for a more thoughtful and restrained treatment approach for this disease. Consideration of an individual's health and life expectancy as well as implementation of less invasive treatment options, including active surveillance in thoughtfully selected patients, could yield the greatest benefit and minimize

treatment-related harms for future patients diagnosed with DCIS.

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