Impacts of Neighborhood Characteristics on Treatment and Outcomes in Women with Ductal Carcinoma *In Situ* of the Breast

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Abstract

Background: This study examines associations of neighborhood characteristics with treatment and outcomes of ductal carcinoma *in situ* (DCIS) of the breast.

Methods: From the Missouri Cancer Registry, we identified 9,195 women with DCIS diagnosed between 1996 and 2011. A composite index using U.S. Census data and American Community Survey data was developed to assess census tract–level socioeconomic deprivation, and rural–urban commuting area codes were used to define rural census tracts. ORs and 95% confidence intervals (CIs) of the treatment were estimated using logistic regression. Hazard ratios (HRs) of DCIS outcomes were estimated using Cox proportional hazards regression.

Results: Women in the most socioeconomically deprived census tracts were more likely than those in the least deprived to have mastectomy (OR = 1.44; 95% CI, 1.25–1.66; $P_{trend} < 0.0001$), no surgery (OR = 1.54; 95% CI, 1.02–2.30; $P_{trend} = 0.04$), no radiotherapy post-breast conserving surgery (OR = 1.90; 95% CI, 1.56–2.31; $P_{trend}<0.0001$), delayed radiotherapy (OR = 1.26; 95% CI, 1.01–1.57; $P_{trend} = 0.02$), and ipsilateral breast tumors (HR = 1.59; 95% CI, 1.07–2.38; $P_{trend} = 0.03$). There was no significant difference in risk of contralateral breast tumors. Compared with urban women, rural women had significantly higher odds of underutilization of radiotherapy (OR = 1.29; 95% CI, 1.08–1.53). Rural locations were not associated with risk of ipsilateral or contralateral breast tumors.

Conclusions: Neighborhood socioeconomic deprivation was associated with higher risks of suboptimal treatment and ipsilateral breast tumors. While DCIS treatment significantly varied by rural/urban locations, we did not observe any statistically significant rural–urban differences in risks of second breast tumors.

Impact: Neighborhood attributes may affect treatment and outcomes of patients with DCIS. *Cancer Epidemiol Biomarkers Prev; 27(11); 1298–306. ©2018 AACR.*

Introduction

Ductal carcinoma *in situ* (DCIS) is a heterogeneous group of preinvasive neoplastic lesions in the breast that has increased in clinical significance during recent years. The incidence of DCIS has grown drastically from 2% to 25%–30% in the past several decades, resulting largely from widespread adoption of mammographic screening. Although 10-year survival is greater than 98% (1), 11%–19% of women with DCIS experience recurrent breast tumors within 10 years of diagnosis (1, 2). Risk of recurrence is influenced by tumor characteristics as well as treatment modality, which includes mastectomy and breast conserving surgery (BCS) with or without radiotherapy (3, 4). Endocrine therapy is recommended with surgery for patients with estrogen receptor positive (ER^+) DCIS or who cannot receive radiotherapy (5). Although mastectomy has a nearly 100% cure rate in the ipsilateral breast, it is associated with significant physical and psychological morbidity. BCS is typically accompanied by radiotherapy, which reduces recurrence by half (4). However, radiotherapy requires much greater coordination between patients, specialists, and healthcare providers and may not provide local control benefits to DCIS patients at low risk of recurrence (6). There is no consensus on best management of DCIS.

Both individual- and area-level factors influence breast cancer outcomes. Low socioeconomic status (SES), as measured either at the individual or area level, has been associated with later stage of diagnosis, suboptimal treatment, and lower survival in women with invasive breast cancer (7–11). Less is known about socioeconomic disparities in DCIS treatment and their impact on outcomes.

There are also disparities in breast cancer treatment and outcomes between rural and urban areas. Women residing in rural areas are less likely than those residing in urban areas to receive radiotherapy following BCS and more likely to receive mastectomy for both DCIS and invasive breast cancer (12–14). It is unclear whether urban–rural differences in breast cancer treatment are attributable to SES as poverty rates vary between rural and urban areas (15). Singh and colleagues (16) found that rural–urban location and neighborhood SES interacted in their

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contributions to breast cancer mortality and that socioeconomic gradients in mortality were steeper in nonmetropolitan populations. Research on potential differences in DCIS outcomes between rural and urban areas is lacking. Here, we examined the associations of neighborhood socioeconomic deprivation and rural/urban residency with treatment utilization and risk of second breast tumors after DCIS using population-based cancer registry data in Missouri.

Materials and Methods

Data source

The Missouri Cancer Registry (MCR) has been involved in the National Program of Cancer Registries and complies with its data collecting and coding rules. It periodically audits to ensure case completeness and high-quality data. The MCR also uses the criteria for case reportability defined by the Surveillance, Epidemiology, and End Results (SEER) program of the National Cancer Institute. The MCR includes over 95% of incident cases of cancer diagnosed in Missouri and collects demographic and clinical information. The MCR also has information on residential census tract at the time of cancer diagnosis, start dates of surgical treatment, adjuvant therapies, and surgical margins, which is not available in the SEER database. Treatment dates were collected for over 90% of cases (17). This study was performed in accordance with the ethical guidelines including Belmont Report and U.S. Common Rule. Because of the use of deidentified data, this study was determined exempt by the institutional review boards of the Missouri Department of Health and Senior Services and Washington University in St. Louis, Missouri. Informed written consent from patients was not required.

Patient selection

This study included women who were diagnosed with primary DCIS between 1996 and 2011, had no cancer history, and were followed through December 31, 2011 (n = 10,589). Figure 1 shows the exclusion criteria and sample size. We excluded patients with missing geographic data at the time of diagnosis ($n = 158$); unknown follow-up periods, or periods less than 2 months ($n = 878$); and bilateral DCIS, or those who received bilateral mastectomies ($n = 358$). The analytic sample consisted of 9,195 women of whom 7,074 lived in urban areas and 2,121 lived in rural areas at the time of diagnosis.

Treatment

We used information on surgical and adjuvant treatment for the first diagnosis of DCIS, excluding treatment related to tumor progression or recurrence. The most invasive surgical procedure was recorded for the cases with more than one surgery on a primary site. Delayed radiotherapy was defined as an interval of at least 8 weeks between BCS and initiation of radiotherapy, as it was associated with an increased risk of recurrence in women with invasive breast cancer (18). Although aromatase inhibitors have not been approved by the FDA for DCIS, they have been prescribed for a small group of women and demonstrated to have comparable efficacy (19). Thus, endocrine therapy included both tamoxifen and aromatase inhibitors.

Outcomes

Second breast tumor was defined as either an ipsilateral breast tumor or contralateral breast tumor identified two or more months after the first diagnosis of DCIS (17). Ipsilateral breast tumors included any histologic type of carcinoma *in situ* or invasive tumors in the ipsilateral breast and contralateral breast tumors were defined analogously in the contralateral breast. Person-times were estimated from two months after the index DCIS through either the date of diagnosis of a second breast tumor, last follow-up, death, or December 31, 2011, whichever was earliest.

Neighborhood socioeconomic deprivation index

There are 1,320 census tracts in Missouri. The socioeconomic deprivation indices for 2000 and 2010 were assessed separately

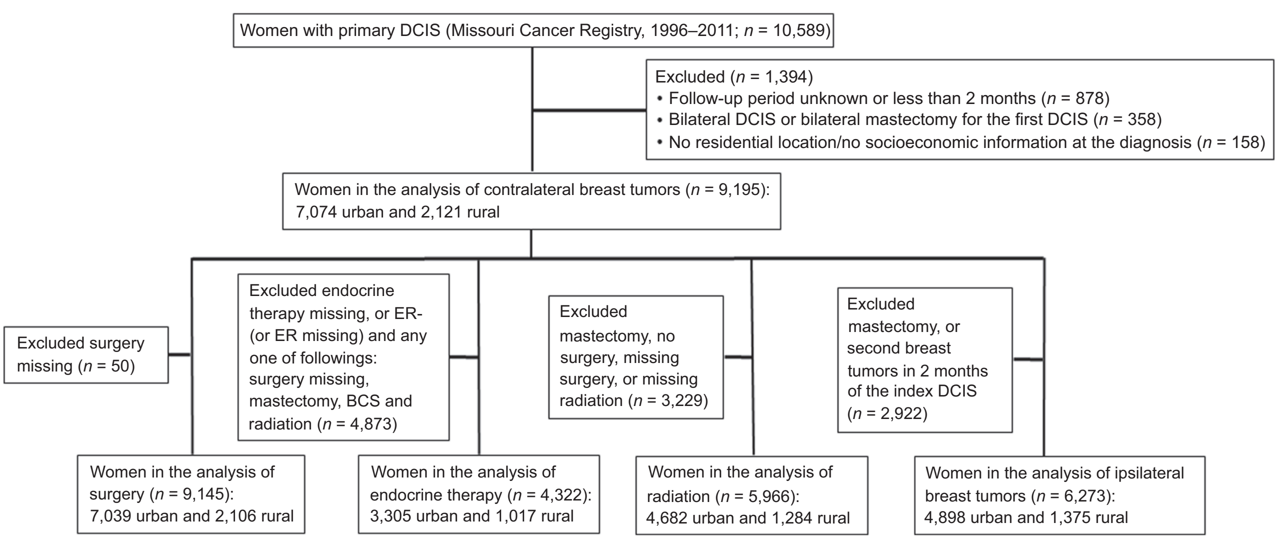

Figure 1.
Flow chart of cohort inclusion and exclusion criteria and the number of women with DCIS in the Missouri Cancer Registry.

using a composite index based on 21 variables from the 2000 U.S. Census data and the 2005–2009 American Community Survey data, as described elsewhere (9, 20–22). The 2000 socioeconomic deprivation index was linked to the cases diagnosed between 1996 and 2004, and the 2010 socioeconomic deprivation index to the cases diagnosed after 2004. The selected variables reflected six aspects of socioeconomic deprivation, including education, occupation, housing environment, income/poverty, race/ethnicity, and residential stability, and were incorporated into a multivariate common factor analysis with the varimax rotation. Seven variables, accounting for 43.4% of overall variance, were identified in the first common factor with high loading coefficients and internal consistency (Cronbach alpha = 0.92). They included percentage of persons with an education level lower than high school, percentage of working class, percentage of vacant housing units, percentage of households in poverty, percentage of households with family income under $30,000 per year, income disparity, and percentage of population below federal poverty line. These variables were standardized and weighed by their loading coefficients. A socioeconomic deprivation index for a given census tract was obtained by summing the weighted variables. Socioeconomic deprivation index scores were divided into tertiles, with a higher tertile suggesting greater socioeconomic deprivation.

Rurality

Rural census tracts were determined using the rural–urban commuting area (RUCA) codes developed by the U.S. Department of Agriculture. The RUCA codes are based on a combination of population density, proximity on an urban area as defined by the U.S. Census Bureau, and daily commuting patterns. The 2000 RUCA codes were used for the cases diagnosed between 1996 and 2009, and the 2010 RUCA codes for the cases diagnosed after 2009. Rural areas were defined as census tracts coded as 4, 4.2, 5, 5.2, 6, 6.1, 7, 7.2, 7.3, 7.4, 8, 8.2, 8.3, 8.4, 9, 9.1, 9.2, 10, 10.2, 10.3, 10.4, 10.5, or 10.6, and urban areas as 1, 1.1, 2, 2.1, 3, 4.1, 5.1, 7.1, 8.1, or 10.1.

Covariates

Potential covariates included age (<50, 50–59, 60–69, or ≥70), race (non-Hispanic white, non-Hispanic black, or others), year of diagnosis (1996–1999, 2000–2004, 2005–2009, or 2010–2011), health insurance (private, Medicare, Medicaid/uninsured, or other/unknown), tumor grade (well differentiated, moderately differentiated, poorly differentiated, or unknown), tumor size (<2 cm, ≥2 cm, or unknown), histology (comedo, papillary, cribriform, solid, or NOS), and ER status (positive, negative, or unknown).

Statistical analysis

We used the χ^2 test to compare categorical variables and the *t*-test and the ANOVA to compare continuous variables. Logistic regression analyses were performed to estimate the ORs for treatment with surgery (mastectomy and no surgical treatment vs. BCS), radiation (delayed initiation and no radiation vs. timely initiation), and endocrine therapy. The models were adjusted for the aforementioned covariates. The analysis of radiation utilization was restricted to women with BCS and also adjusted for surgical margins (clear, positive, or unknown). The analysis of endocrine therapy utilization was restricted to women with ER^+ DCIS and those who did not receive radiation after BCS. The ORs for endocrine therapy were additionally adjusted for surgical treatment (no surgery, BCS, mastectomy, or unknown) and radiation (yes, no, or unknown). We also assessed the interaction between neighborhood socioeconomic deprivation and rural locations in DCIS treatment by including a cross-product term in the multivariable-adjusted logistic regression models.

Because women undergoing mastectomy experience extremely low risk of ipsilateral recurrence, women who received mastectomy for DCIS were excluded from the analysis of ipsilateral breast tumors ($n = 2{,}929$). The analysis of contralateral breast tumors included all patients, regardless of their surgical categories. We used Kaplan–Meier estimates with the log-rank test to compare 10-year cumulative probabilities of ipsilateral and contralateral breast tumors. The risks of second breast tumors were compared between the tertiles of neighborhood socioeconomic deprivation and between rural and urban residencies using HRs derived from Cox proportional hazards regression analyses. We tested the proportional hazards assumption by assessing the significance of an interaction term between socioeconomic deprivation and follow-up time and an interaction term between urban/rural location and follow-up time. The HRs were adjusted for age, race, and year of diagnosis as outlined above. Further covariates were added in succession and included insurance, tumor characteristics (grade, size, histology, ER status), and treatment modality (surgery, surgical margin, radiation, endocrine therapy). Trend across socioeconomic deprivation tertiles was tested using Wald statistic in multivariable models with the median scores of deprivation groups as continuous variables. All analyses were performed using SAS (version 9.4, SAS Institute). Statistical significance was suggested by two-sided $P < 0.05$.

Results

Eligible DCIS patients came from 1,245 census tracts of Missouri. Table 1 summarizes demographic and tumor characteristics of DCIS cases by neighborhood socioeconomic deprivation and rural/urban residency. Compared with women in the lowest tertile of socioeconomic deprivation, women in the highest tertile were older (mean age 62.3 vs. 59.5, $P < 0.0001$), comprised of a greater proportion of non-Hispanic African Americans (25.2% vs. 4.5%, $P < 0.0001$), had a shorter follow-up (71 vs. 77 months, $P = 0.0006$), and were more likely to lack health insurance or have Medicaid (12.0% vs. 2.4%, $P < 0.0001$). There was a significant difference in histologic subtypes across socioeconomic deprivation tertiles ($P = 0.01$); more women in the most socioeconomically deprived tertile had the comedo (13.7% vs. 11.6) and papillary subtypes (8.7% vs. 6.8%). No difference was found in tumor grade, size, ER status, or year of first DCIS diagnosis across the neighborhood socioeconomic deprivation groups.

Compared with urban women, rural women with DCIS were older (61.7 vs. 60.1, $P < 0.0001$), had a smaller proportion of racial minorities (1.8% vs. 12.4%, $P < 0.0001$), and were less likely to have private health insurance (47.9% vs. 61.4%, $P < 0.0001$). There were no significant urban-rural differences in tumor grade or size, although rural women were more likely to have the comedo subtype (14.9% vs. 11.7%, $P < 0.0001$) and less likely to have ER^+ tumors (79.7% vs. 83.1%, $P = 0.02$). Median length of follow-up was 74 months in the urban group compared with 78 months in the rural group ($P = 0.001$). More urban women were diagnosed recently with DCIS than their rural counterparts (13.5% vs. 7.2%, $P < 0.0001$).

Table 1. Characteristics of women with DCIS by socioeconomic deprivation and urban/rural locations at the time of diagnosis in the Missouri Cancer Registry, 1996–2011

	Socioeconomic deprivation			Urban/rural location		
	Lowest tertile, *N* (%)	**Highest tertile, *N* (%)**	***P***	**Urban, *N* (%)**	**Rural, *N* (%)**	***P***
Number of cases	4,306	1,997		7,074	2,121	
Age at diagnosis, y						
Mean (SD)	59.5 (12.5)	62.3 (12.9)	<0.0001	60.1 (12.6)	61.7 (12.4)	<0.0001
<50	1,021 (23.7)	360 (18.0)		1,595 (22.6)	372 (17.5)	
50–59	1,234 (28.7)	481 (24.1)		1,918 (27.1)	563 (26.5)	
60–69	1,070 (24.9)	541 (27.1)		1,809 (25.6)	570 (26.9)	
≥70	981 (22.8)	615 (30.8)	<0.0001	1,752 (24.8)	616 (29.0)	<0.0001
Race and ethnicity						
Non-Hispanic white	3,989 (92.6)	1,458 (73.0)		6,013 (85.0)	2,052 (96.8)	
Non-Hispanic black	194 (4.5)	503 (25.2)		877 (12.4)	38 (1.8)	
Others	123 (2.9)	36 (1.8)	<0.0001	184 (2.6)	31 (1.5)	<0.0001
Length of follow-up, months						
Median (range)	77 (2–191)	71 (2–191)	0.0006	74 (2–191)	78 (2–191)	0.001
6–11	294 (6.8)	123 (6.2)		536 (7.6)	88 (4.2)	
12–59	1,362 (31.6)	721 (36.1)		2,340 (33.1)	709 (33.4)	
60–119	1,473 (34.2)	688 (34.5)		2,415 (34.1)	768 (36.2)	
≥120	1,177 (27.3)	465 (23.3)	0.001	1,783 (25.2)	556 (26.2)	<0.0001
Year of the first DCIS diagnosis						
1996–1999	932 (21.6)	392 (19.6)		1,481 (20.9)	418 (19.7)	
2000–2004	1,411 (32.8)	656 (32.9)		2,232 (31.6)	755 (35.6)	
2005–2009	1,446 (33.6)	722 (36.2)		2,409 (34.1)	796 (37.5)	
2010–2011	517 (12.0)	227 (11.4)	0.15	952 (13.5)	152 (7.2)	<0.0001
Health insurance						
Private	966 (66.9)	299 (44.3)		1,532 (61.4)	301 (47.9)	
Medicare	445 (30.8)	295 (43.7)		842 (33.7)	285 (45.3)	
Medicaid or uninsured	34 (2.4)	81 (12.0)	<0.0001	122 (4.9)	43 (6.8)	<0.0001
Other or missing	2,861	1,322		4,578	1,492	
Histologic subtype						
Not otherwise specified	3,101 (72.0)	1,397 (70.0)		5,062 (71.6)	1,484 (70.0)	
Comedo	499 (11.6)	274 (13.7)		824 (11.7)	315 (14.9)	
Papillary	291 (6.8)	174 (8.7)		518 (7.3)	167 (7.9)	
Cribriform	243 (5.6)	82 (4.1)		394 (5.6)	87 (4.1)	
Solid	172 (4.0)	70 (3.5)	0.01	276 (3.9)	68 (3.2)	<0.0001
Grade						
Well differentiated	628 (20.8)	291 (22.6)		1,063 (21.4)	273 (21.5)	
Moderately differentiated	1,078 (35.7)	452 (35.1)		1,800 (36.3)	472 (37.1)	
Poorly differentiated	1,314 (43.5)	546 (42.4)	0.05	2,094 (42.2)	526 (41.4)	0.83
Missing	1,286	708		2,117	850	
Tumor size, cm						
<2.0	927 (72.9)	467 (70.3)		1,604 (71.6)	487 (70.8)	
≥2.0	345 (27.1)	197 (29.7)	0.32	635 (28.4)	201 (29.2)	0.66
Missing	3,034	1,333		4,835	1,433	
Estrogen receptor						
Negative	304 (16.1)	160 (18.9)		538 (16.9)	175 (20.3)	
Positive	1,590 (84.0)	686 (81.1)	0.05	2,648 (83.1)	687 (79.7)	0.02
Missing	2,412	1,151		3,888	1,259	
Surgery for first DCIS						
None	89 (2.1)	64 (3.2)		166 (2.4)	55 (2.6)	
BCS	2,965 (69.1)	1,191 (60.0)		4,717 (67.0)	1,307 (62.1)	
Mastectomy	1,237 (28.8)	729 (36.7)	<0.0001	2,156 (30.6)	744 (35.3)	0.0001
Missing	15	13		35	15	
Surgical margin[a]						
Clear	3,874 (96.0)	1,730 (95.8)		6,337 (96.0)	1,794 (95.6)	
Positive	162 (4.0)	75 (4.2)	0.97	261 (4.0)	82 (4.4)	0.42
Missing	166	115		275	175	
Radiotherapy for first DCIS						
No	1,980 (46.2)	1,207 (61.3)		3,489 (49.6)	1,274 (61.3)	
Yes	2,303 (53.8)	763 (38.7)	<0.0001	3,545 (50.4)	803 (38.7)	<0.0001
Missing	23	27		40	44	
Surgery and radiotherapy for first DCIS						
No surgical treatment	89 (2.1)	64 (3.2)		166 (2.4)	55 (2.6)	
BCS alone	683 (16.0)	442 (22.4)		1,220 (17.4)	508 (24.4)	
BCS and radiation	2,271 (53.1)	738 (37.4)		3,479 (49.6)	776 (37.3)	
Mastectomy	1,237 (28.9)	729 (37.0)	<0.0001	2,156 (30.7)	744 (35.7)	<0.0001
Missing	26	24		53	38	
Weeks from surgery to radiation, mean (SD)[b]	6.2 (3.8)	7.2 (4.7)	<0.0001	6.5 (4.2)	6.4 (3.8)	0.53

(Continued on the following page)

Table 1. Characteristics of women with DCIS by socioeconomic deprivation and urban/rural locations at the time of diagnosis in the Missouri Cancer Registry, 1996–2011 (Cont'd)

	Socioeconomic deprivation			Urban/rural location		
	Lowest tertile, *N* (%)	Highest tertile, *N* (%)	*P*	Urban, *N* (%)	Rural, *N* (%)	*P*
Guideline concordant use of endocrine therapy[c]						
No	1,171 (59.6)	655 (67.1)		2,018 (61.1)	689 (67.8)	
Yes	794 (40.4)	321 (32.9)	0.0002	1,287 (38.9)	328 (32.3)	0.0001
Missing	113	48		214	37	

[a]The comparison was made in the patients with surgical treatment.
[b]The analysis was limited to the patients who received radiotherapy following definitive BCS.
[c]The analysis included the patients with estrogen receptor–positive DCIS and the patients with BCS alone.

Treatment

Table 1 summarizes treatment characteristics in our sample. There were different patterns of surgical treatment and radiotherapy across the tertiles of socioeconomic deprivation ($P < 0.0001$). Compared with women from the least deprived tertile, more women from the most deprived tertile did not receive surgical treatment (3.2% vs. 2.1%) or underwent mastectomy (37.0% vs. 28.9%), and fewer women received radiotherapy following BCS (37.4% vs. 53.1%). When they received radiotherapy, they waited on average 7.2 weeks after BCS versus 6.2 weeks in the least deprived tertile ($P < 0.0001$). There was no significant difference in surgical margins across neighborhood socioeconomic deprivation tertiles. Endocrine therapy use was lower in the most versus least deprived census tracts. (32.9% vs. 40.4%, $P = 0.0002$). Table 2 shows the odds of receiving treatment for DCIS. After adjustment for age, race, year of diagnosis, health insurance, and tumor characteristics, women from the most deprived tertile had greater odds of receiving mastectomies [OR 1.44; 95% confidence interval (CI), 1.25–1.66; $P_{trend} < 0.0001$] and lack of surgery (OR 1.54; 95% CI, 1.02–2.30; $P_{trend} = 0.04$). After further adjusting for surgical factors, women in the most socioeconomically deprived census tracts had higher odds of radiation underutilization (OR 1.90; 95% CI, 1.56–2.31; $P_{trend} < 0.0001$) and delayed radiotherapy after BCS (OR 1.26; 95% CI, 1.01–1.57; $P_{trend} = 0.02$). There was no significant difference in the odds of receiving endocrine therapy (OR 0.96; 95% CI, 0.77–1.20; $P_{trend} = 0.75$).

As shown in Table 1, there were different patterns of surgery and radiotherapy between rural women and urban women ($P < 0.0001$). More rural patients received mastectomy than urban ones (35.7% vs 30.7%) and fewer rural patients undertook radiotherapy after BCS (37.3% vs 49.6%), although rates of no surgery were similar (2.6% vs. 2.4%). There was no significant difference in radiation delay or surgical margins between urban and rural groups. Fewer rural women underwent endocrine therapy in concordance with guidelines (32.3% vs. 38.9%, $P = 0.0001$). After adjusting for the aforementioned covariates, rural patients were less likely than urban patients to receive radiotherapy following BCS (OR 1.29; 95% CI, 1.08–1.53; Table 2). There were no significant urban–rural differences in the odds of receiving mastectomy (OR 1.09; 95% CI, 0.96–1.24), no surgery (OR 1.02; 95% CI, 0.70–1.49), delayed radiation (OR 0.95; 95% CI, 0.77–1.18), or endocrine therapy (OR 1.17; 95% CI, 0.96–1.44). We did not observe any significant interactions between socioeconomic deprivation and rural locations in treatment for DCIS ($P_{interaction} = 0.07$ for mastectomy, $P_{interaction} = 1.00$ for no surgical treatment, $P_{interaction} = 0.39$ for delays in radiotherapy, $P_{interaction} = 0.42$ for no radiotherapy, $P_{interaction} = 0.36$ for endocrine therapy)

Outcomes

During an average 72-month follow-up period, the rate of ipsilateral breast tumors was 3.5% (218 cases in 6,273 women with BCS or no surgical treatment). The rate of contralateral breast

Table 2. Adjusted ORs and their 95% CIs of treatment associated with neighborhood socioeconomic deprivation and urban/rural locations among women with DCIS of the breast

	Surgical treatment[a]				Radiation therapy[b]				Endocrine therapy[c]	
	Mastectomy		No surgery		Delayed		No radiation			
	N	OR (95% CI)	*N*	OR (95% CI)	*N*	OR (95% CI)	*N*	OR (95% CI)	*N*	OR (95% CI)
Socioeconomic deprivation										
Tertile 1 (lowest)	1,237	1.00 (reference)	89	1.00 (reference)	516	1.00 (reference)	668	1.00 (reference)	794	1.00 (reference)
Tertile 2	934	1.16 (1.07–1.35)	68	1.18 (0.83–1.67)	322	1.16 (0.98–1.39)	600	1.57 (1.35–1.84)	500	1.03 (0.86–1.23)
Tertile 3 (highest)	729	1.44 (1.25–1.66)	64	1.54 (1.02–2.30)	227	1.26 (1.01–1.57)	437	1.90 (1.56–2.31)	321	0.96 (0.77–1.20)
		$P_{trend} < 0.0001$		$P_{trend} = 0.04$		$P_{trend} = 0.02$		$P_{trend} < 0.0001$		$P_{trend} = 0.75$
Urban/rural location										
Urban	2,156	1.00 (reference)	166	1.00 (reference)	871	1.00 (reference)	1,199	1.00 (reference)	1,287	1.00 (reference)
Rural	744	1.09 (0.96–1.24)	55	1.02 (0.70–1.49)	194	0.95 (0.77–1.18)	506	1.29 (1.08–1.53)	328	1.17 (0.96–1.44)

[a]Mastectomy and no surgical treatment were compared with BCS. The ORs were adjusted for age (<50, 50–59, 60–69, ≥70), race (white, black, other), year of diagnosis (1996–1999, 2000–2004, 2005–2009, 2010–2011), health insurance (private, Medicare, Medicaid/uninsured, others/unknown), tumor grade (well differentiated, moderately differentiated, poorly differentiated, unknown), tumor size (<2 cm, ≥2 cm, unknown), histology (comedo, papillary, cribriform, solid, NOS), and estrogen receptor status (positive, negative, and unknown).
[b]The analysis was restricted to women with BCS and complete data on timing of surgery and first radiotherapy. Radiation delay was defined as an interval of 8 weeks or longer between BCS and the start of radiotherapy. Delayed initiation of radiotherapy and no radiotherapy were compared with timely initiation of radiotherapy. The ORs were adjusted for age, race, surgery, surgical margins, year of diagnosis, health insurance, tumor grade, tumor size, histology, and estrogen receptor status.
[c]The analysis included patients with estrogen receptor–positive DCIS and patients with BCS only. The OR was adjusted for age, race, year of diagnosis, insurance, tumor grade, tumor size, histology, estrogen receptor status, surgery, surgical margin, and radiotherapy.

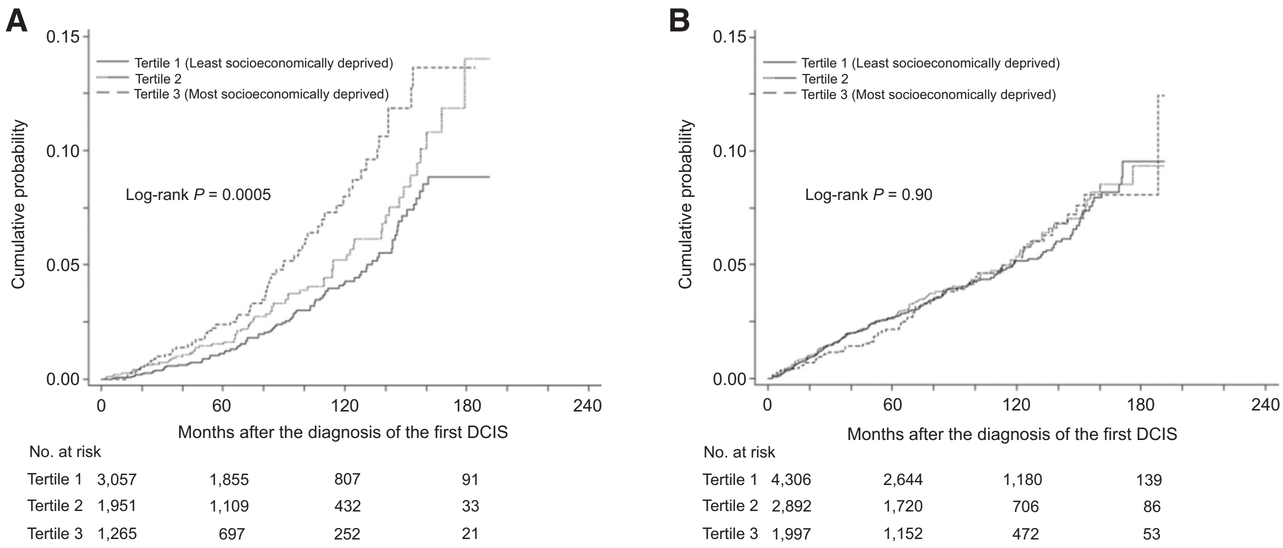

Figure 2.
Cumulative incidences of ipsilateral breast tumors (**A**) and contralateral breast tumors (**B**) in women with DCIS by neighborhood socioeconomic deprivation.

tumors was 3.8% over an average 76-month follow-up period (354 cases in our entire cohort of 9,195 women). Figure 2 shows the cumulative incidences of second breast tumors by neighborhood socioeconomic deprivation. Women in the most deprived tertile had a 10-year ipsilateral breast tumor incidence of 8.0% compared with 5.2% and 4.3% in women in the middle and least deprived tertiles, respectively ($P = 0.0005$; Fig. 2A). Ten-year incidences of contralateral breast tumors were comparable across neighborhood socioeconomic deprivation tertiles, with a rate of 5.2% in the least deprived tertile, 5.4% in the middle tertile, and 5.2% in the most deprived tertile ($P = 0.90$; Fig. 2B).

Table 3 shows adjusted HRs for second breast tumors by neighborhood socioeconomic deprivation and rural/urban location. After adjusting for age, race, and year of diagnosis, women in the most deprived tertile had a significantly higher risk of developing second breast tumors in the same breast than those in the least deprived tertile (HR 1.65; 95% CI, 1.11–2.46; $P_{trend} = 0.02$). After further adjustment for health insurance, tumor characteristics, and treatment modality, the risk of ipsilateral breast tumors was still statistically significant (HR 1.59; 95% CI, 1.07–2.38; $P_{trend} = 0.03$). The HR of contralateral breast tumors in women from the most deprived tertile was 0.87 (95% CI, 0.62–1.21; $P_{trend} = 0.43$). Additional adjustment for insurance, tumor characteristics, and treatment did not affect the risk (HR 0.86; 95% CI, 0.61–1.20; $P_{trend} = 0.40$).

There were no significant urban–rural differences in the incidences of second breast tumors. The 10-year incidence of ipsilateral breast tumors was 5.3% in rural women and 5.2% in urban women ($P = 0.83$; Fig. 3A). The 10-year incidence of contralateral breast tumors was 5.2% in rural women and 5.2% in urban women ($P = 0.95$; Fig. 3B). After adjustment for age, race, and year of diagnosis, the HR of ipsilateral breast tumors in rural women was 0.88 (95% CI, 0.60–1.29; Table 3). This remained similar after further adjustment for insurance, tumor characteristics, and treatment (HR 0.85; 95% CI, 0.58–1.25). The HR of contralateral breast tumors in rural women was 1.08 (95% CI, 0.80–1.45). This was unaffected by further adjustment as mentioned above (HR 1.08; 95% CI, 0.81–1.46).

Discussion

Using population-based cancer registry data, we observed significant differences in the treatment received by women with DCIS from different socioeconomic and rural–urban census tracts in Missouri. Both neighborhood socioeconomic deprivation and rural residency were independently associated with underutilization of radiotherapy. Women in the most socioeconomically deprived areas were also more likely than those in the least deprived areas to receive mastectomy if treated with surgery, lack surgical treatment, and have delays if receiving radiotherapy. Neighborhood socioeconomic deprivation was associated with a higher risk of ipsilateral breast tumors, but not with the risk of contralateral breast tumors, after DCIS. However, there was no significant difference in the risk of second breast tumors between rural and urban residencies.

Neighborhood-level socioeconomic differences in surgical treatment and radiotherapy have been reported for invasive breast cancer. Neighborhoods with lower socioeconomic levels was associated with higher odds of receiving mastectomy and lower odds of receiving radiation after BCS, although rural–urban residency was not taken in to account (8, 23, 24). Other studies have yielded similar results in women with disabilities and women on Medicaid (25, 26). Underutilization of radiotherapy after BCS in low SES populations may reflect financial barriers, including limited access to transportation (27), daycare (28), time off work (28), and the ability to afford copayments (29). Although lack of adequate health insurance has been associated with poorer treatment (30), the variations we observed persisted despite adjustment for this factor. Patients' health literacy and cultural preferences may also influence surgical treatment choices (31). Low SES women and women living in the socioeconomic deprived areas may prefer mastectomy to BCS probably due to the longer surveillance and higher degree of financial and logistical

Table 3. Adjusted HRs and their 95% CIs of ipsilateral and contralateral breast tumors for neighborhood socioeconomic deprivation and urban/rural locations among women with primary DCIS of the breast in the Missouri Cancer Registry, 1996–2011

	Neighborhood socioeconomic deprivation			Urban/rural location	
	Tertile 1 (lowest)	Tertile 2	Tertile 3 (highest)	Urban	Rural
Ipsilateral breast tumors					
Person-years	21,060	12,463	7,927	32,340	9,110
No. of events	90	68	60	170	48
Model 1[a]					
HR	1.00	1.33	1.65	1.00	0.88
95% CI	Reference	0.95–1.86	1.11–2.46	Reference	0.60–1.29
			$P_{trend} = 0.02$		
Model 1+health insurance					
HR	1.00	1.33	1.64	1.00	0.88
95% CI	Reference	0.95–1.86	1.10–2.44	Reference	0.60–1.28
			$P_{trend} = 0.02$		
Model 1+health insurance+tumor characteristics[b]					
HR	1.00	1.34	1.67	1.00	0.87
95% CI	Reference	0.95–1.87	1.12–2.49	Reference	0.60–1.28
			$P_{trend} = 0.01$		
Model 1+health insurance+tumor characteristics+treatment[c]					
HR	1.00	1.29	1.59	1.00	0.85
95% CI	Reference	0.92–1.81	1.07–2.38	Reference	0.58–1.25
			$P_{trend} = 0.03$		
Contralateral breast tumors					
Person-years	30,091	19,361	13,224	47,692	14,984
No. of events	169	113	72	269	85
Model 1[a]					
HR	1.00	0.99	0.87	1.00	1.08
95% CI	Reference	0.76–1.28	0.62–1.21	Reference	0.80–1.45
			$P_{trend} = 0.43$		
Model 1+health insurance					
HR	1.00	0.99	0.87	1.00	1.08
95% CI	Reference	0.76–1.28	0.62–1.21	Reference	0.81–1.45
			$P_{trend} = 0.44$		
Model 1+health insurance and tumor characteristics[b]					
HR	1.00	0.99	0.86	1.00	1.09
95% CI	Reference	0.76–1.28	0.62–1.21	Reference	0.81–1.46
			$P_{trend} = 0.43$		
Model 1+health insurance, tumor characteristics, and treatment[c]					
HR	1.00	0.99	0.86	1.00	1.08
95% CI	Reference	0.76–1.28	0.61–1.20	Reference	0.81–1.46
			$P_{trend} = 0.40$		

[a]The HRs were adjusted for age, race/ethnicity, and year of diagnosis of the index DCIS.
[b]Tumor characteristics included grade, size, histology, and estrogen receptor status.
[c]Treatment included surgery, surgical margin status (in the analysis of ipsilateral breast tumors), radiotherapy, and endocrine therapy.

commitment in the latter. Women in the most deprived areas also have higher rates of comorbidities (32), resulting in contraindications to surgery or radiotherapy. Differences in cancer treatment may also reflect either disparities in patients' access to providers or in the care provided by providers themselves (33, 34). We have demonstrated in the same cohort of DCIS patients that black women were more likely than white women to have mastectomy, underutilize radiotherapy after BCS, and delayed initiation of radiotherapy (17). Larger proportions of black women in more socioeconomically deprived areas did not explain the observed socioeconomic differences in DCIS treatment.

Rural areas generally have a lower level of geographic accessibility to cancer care (35, 36), which might explain in part the observed disparities in radiotherapy following BCS for DCIS in rural women. Underutilization of radiotherapy has been related to increased travel distances to radiotherapy facilities (37). Proximity to large National Comprehensive Cancer Network (NCCN) centers equipped with radiotherapy capabilities increased utilization of radiotherapy (38). In addition, urban–rural differences in radiotherapy use may represent less awareness of NCCN guidelines in rural areas. More than half of primary care physicians in rural North and South Carolina thought that BCS alone was sufficient for breast cancer treatment (39). Cultural differences, such as concern about radiation or preference for a shorter treatment course, may also influence rural women to decline radiotherapy after BCS (40).

While we identified large geographic variations in DCIS treatment, we did not observe significant associations between rural–urban residence and risks of second breast tumors after adjusting for demographic and clinical factors. In contrast, neighborhood socioeconomic deprivation was associated with a higher risk of ipsilateral breast tumors in women with DCIS. It corroborated with findings by Singh and colleagues (16) that rurality was not associated with breast cancer mortality after adjustment for SES. In that study, a higher level of neighborhood socioeconomic deprivation was associated with a higher risk of breast cancer mortality, which was stronger in nonmetropolitan areas. Compared with SES, differences in adherence to treatment, comorbid health conditions, or high-risk behaviors such as alcohol consumption might be smaller in the rural–urban continuum. Because of a relatively small number of DCIS cases with second breast tumors, we were unable to examine the potential

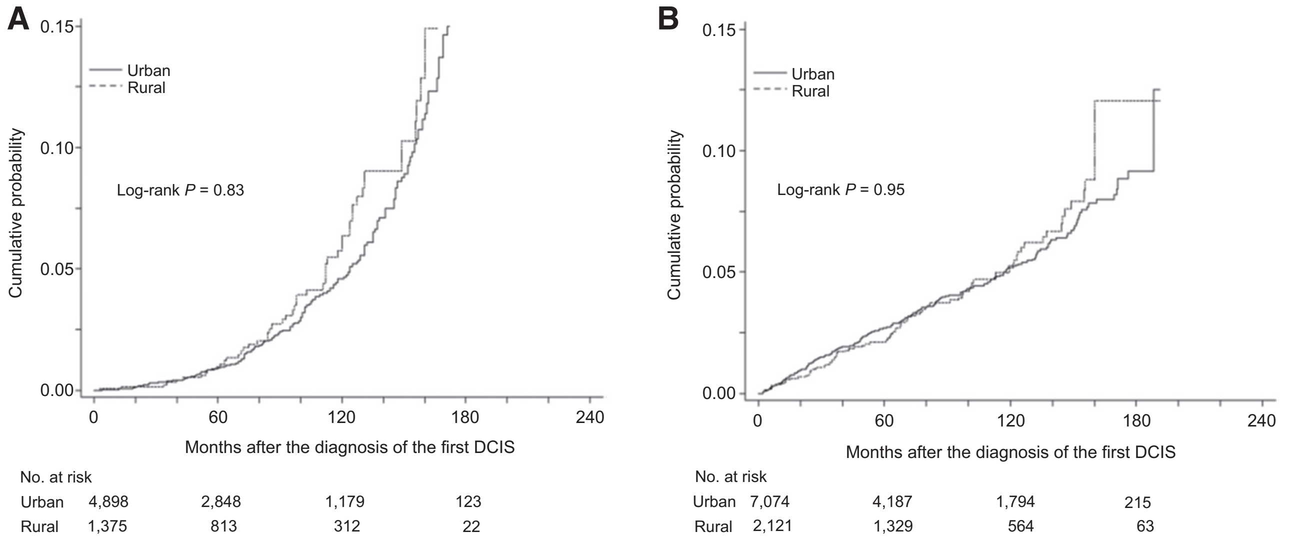

Figure 3.
Cumulative incidences of ipsilateral breast tumors (**A**) and contralateral breast tumors (**B**) in women with DCIS by rural–urban residency.

interaction between neighborhood socioeconomic deprivation and rural location in DCIS outcomes.

This study had several limitations. We utilized a rural–urban dichotomy which might have obscured variations in the rural–urban continuum. The MCR did not collect the information regarding comorbidities and risk behaviors (e.g., smoking and alcohol consumption), which might confound both treatment and outcomes. Data on completion of endocrine and radiotherapy were unavailable, and thus we could not further clarify the relationship between disparities in treatment and outcomes.

In conclusion, this study is the first to specifically examine both neighborhood-level socioeconomic factors and urban/rural residency in relation to DCIS outcomes. Neighborhood socioeconomic deprivation was associated with higher odds of underutilization of surgical treatment and radiotherapy after BCS and receiving mastectomy. However, sociodemographic and clinical factors could not explain the higher risk of ipsilateral breast tumors in women with DCIS living in socioeconomically disadvantaged areas. While rural women were less likely than urban women to receive radiotherapy after BCS, there were no significant urban–rural differences in the risks of second breast tumors. The results suggested that women in socioeconomically deprived areas and rural areas likely face barriers to care for DCIS, although the specific factors involved and their clinical significance may vary. Population-based studies with a larger sample size and a more nuanced conceptualization of rurality are needed to refine our understanding of the contributions of neighborhood characteristics to DCIS outcomes.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Authors' Contributions

Conception and design: Y. Liu, S. Yun, M. Lian, G.A. Colditz
Development of methodology: Y. Liu, M. Lian, G.A. Colditz
Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): Y. Liu, S. Yun, M. Lian, G.A. Colditz
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): S. Zhang, Y. Liu, M. Lian, G.A. Colditz
Writing, review, and/or revision of the manuscript: S. Zhang, Y. Liu, S. Yun, M. Lian, G. Komaie, G.A. Colditz
Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): Y. Liu, S. Yun, M. Lian, G. Komaie
Study supervision: Y. Liu, G.A. Colditz

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