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Area Deprivation Index in Patients with Invasive Lobular Carcinoma of the Breast: Associations with Tumor Characteristics and Outcomes

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ABSTRACT

Background: Although investigators have shown associations between socioeconomic status (SES) and outcomes in breast cancer, there is a paucity of such data for invasive lobular carcinoma (ILC), the second most common type of breast cancer. Herein we evaluated the relationship between SES with tumor features and outcomes in stage I to III patients with ILC.

Methods: We analyzed a prospectively maintained institutional ILC database and utilized the area deprivation index (ADI) to determine neighborhood adversity, an indicator of SES. We used Cox proportional hazards models in Stata 17.0 to evaluate relationships between ADI quintile (Q), race, body mass index (BMI), clinicopathologic features, treatment type, and event-free survival (EFS).

Results: Of 804 patients with ILC, 21.4% lived in neighborhoods classified as ADI Q1 (least resource-deprived) and 19.7% in Q5

(most resource-deprived). Higher deprivation was significantly associated with larger tumor size (3.6 cm in Q5 vs. 3.1 cm in Q1), increased presence of lymphovascular invasion (8.9% in Q5 vs. 6.7% in Q1), and decreased use of adjuvant endocrine therapy (67.1% in Q5 vs. 73.6% in Q1). On multivariable analysis, tumor size, receptor subtypes, and omission of adjuvant endocrine therapy were associated with reduced EFS.

Conclusions: These data show that patients with ILC and higher ADI experience more aggressive tumors and differences in treatment. More data evaluating the complex relationships between these factors is needed to optimize outcomes for patients with ILC, regardless of SES.

Impact: ADI is associated with differences in patients with ILC.

Introduction

Approximately 1 in 8 women will develop breast cancer in their lifetime (1, 2). Invasive lobular carcinoma (ILC) is the second most common subtype of breast cancer, accounting for approximately 10% to 15% of cases (1, 2). ILC is differentiated from the more common subtype, invasive ductal carcinoma (IDC), by its loss of the adhesion molecule E-cadherin which contributes to its distinct pattern of growth (1, 2). The majority of ILC tumors are hormone receptor (HR) positive and lack overexpression of HER2 (3). ILC remains an understudied subtype of breast cancer, with recent literature showing significant differences in presentation, response to therapy, and outcomes between ILC and IDC (2, 4). One particular dearth of research is in the relationship between social determinants of health and ILC.

The impact of social determinants of health on breast cancer pathology and outcomes is a growing area of research (5). Patients with lower socioeconomic status (SES) are known to present with a higher stage of disease, develop more aggressive tumors, and face increased mortality (6, 7). Interestingly, patients with higher SES experience a higher incidence of breast cancer but lower case fatal-

ity (8). Recent literature has made use of the area deprivation index (ADI), a robust tool for categorizing neighborhood disadvantage relative to state and national levels in the United States, to link SES with health outcomes (9–12). Higher area deprivation has been linked to lower rates of breast cancer screening, and worse overall and breast cancer-specific survival (13, 14). Other factors associated with worse breast cancer outcomes, such as self-identified Black race and increased body mass index, have also been linked to elevated ADI (15–19).

Despite associations between ADI and breast cancer outcomes in general, there are no data evaluating the impact of area deprivation in patients with ILC specifically. We, therefore, sought to investigate relationships between SES as measured by the ADI and race and ethnicity, patient characteristics, tumor biology, and event-free survival (EFS) in a large institutional cohort of patients with stage I to III ILC of the breast.

Materials and Methods

We retrospectively evaluated a prospectively maintained institutional database of ILC patients who received surgical treatment at the University of California, San Francisco between January 1996 and September 2019. The study was conducted according to the Declaration of Helsinki and approved by the UCSF Institutional Review Board (IRB; study no. 17–23655). Because no patients were contacted for this data analysis, the UCSF IRB waived the requirement for written informed consent.

Race and ethnicity data were self-reported, abstracted from medical records, and categorized as Black, Asian American and Pacific Islander (AAPI), White, or other; ethnicity was recorded as Hispanic/Latino or non-Hispanic/Latino. Tumor receptor subtype was classified by estrogen receptor (ER), progesterone receptor (PR), and HER2 status. We included body mass index (BMI) as a predictor, grouped by WHO

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definitions (underweight: <18.5 kg/m^2, normal: 18.5–24.9 kg/m^2, overweight: 25–29.9 kg/m^2, obese: ≥30 kg/m^2). Menopausal status was abstracted from patient medical records as documented in medical oncology notes; this status was determined by either absence of menses or laboratory evaluation as clinically indicated. The presence of co-morbid medical diagnoses (diabetes mellitus, hypertension, hyper-cholesterolemia, and hypertriglyceridemia) was determined by review of medical records.

ADI was calculated for each subject and ascertained from the University of Wisconsin's publicly available atlas, which uses seven-teen measures from the U.S. Census to compare an individual neigh-borhood's resource deprivation relative to other neighborhoods across the United States (9, 10). Ranks are assigned using percentiles, with 1 signifying the least disadvantaged neighborhoods in the country and 100 signifying the most disadvantaged. Patients' residential addresses from the time of diagnosis were geocoded and assigned ADI percen-tiles based on their U.S. Census block groups. We log transformed ADI data to reduce left-skewing, and then evaluated the log transformed ADI in quintiles, with quintile 1 signifying the least resource-deprived neighborhoods and quintile 5 signifying the most resource-deprived neighborhoods. For event free survival analyses, ADI groups were also consolidated into low ADI (quintile 1) and high ADI (quintiles 2–5) categories.

Patients with de novo stage IV disease, and those missing self-reported race data and ADI data were excluded from the analysis.

Statistical analysis

Data were analyzed in Stata 17.0 (RRID:SCR_012763) using chi-squared tests for categorical variables, t tests, and the Kruskal–Wallis test for normally and nonnormally distributed continuous variables respectively, and the Cochran–Armitage test for trend to evaluate associations between ADI and clinicopatho-logic variables. We used logistic regression to evaluate associations between ADI and treatment received, adjusting for BMI, age at diagnosis, tumor size, number of positive lymph nodes, and self-identified race. For EFS, local recurrence, distant recurrence, and death from any cause were considered events. The presence of local and/or distant recurrence events was ascertained from review of the electronic medical record, with patients having routine annual clinical follow up for a minimum of 5 years at our institution; similarly, survival status was determined by documented vital status in the electronic medical record. Those without 5 years of follow up or those without an EFS event were censored at the date of last documented follow up. Because not all patients had the same follow up time, we used the log rank test, Kaplan–Meier method, and Cox proportional hazards models when evaluating EFS.

We performed univariable analyses to evaluate the relationships between ADI category, BMI category (grouped as overweight/obese vs. not overweight/obese), comorbid conditions, treatment received (type of surgery, use of chemotherapy, and adjuvant endocrine therapy) and EFS. In a multivariable Cox proportional hazards model, we evaluated the relationship between ADI quintile and EFS adjusting for age at diagnosis, self-identified race, tumor receptor subtype, tumor size, number of positive lymph nodes, BMI category, presence of lympho-vascular invasion (LVI), and treatment. The two-sided P value sig-nificance threshold was <0.05. EFS analyses included only those with at least 6 months of follow up time.

Data availability

The data generated in this study are not publicly available to protect patient privacy but are available upon reasonable request from the corresponding author with appropriate institutional review board approval.

Results

Study cohort

Of 837 cases in the institutional ILC database, 14 with *de novo* metastatic disease, 15 missing self-reported race data, and 4 missing ADI were excluded, leaving 804 cases in the final study cohort (**Table 1**; Supplementary Table S1). Average age at time of diagnosis was 59.7 years, ranging from 21 to 97, with 68.0% of patients being postmenopausal. Of the 729 cases with BMI data available, BMI was in the underweight range for 3.0%, normal for 49.9%, overweight for 27.9%, and obese for 19.2%. Average tumor size was 3.13 ± 2.92 cm and most patients had ER positive/PR positive/HER2 negative tumor subtype (73.1%). Tumors were most commonly grade 2 (66.0%), and rarely grade 3 (5.5%), and LVI was present in 7.0% of cases with available data.

Out of the 804 patients in the study cohort, 28 (3.5%) identified as Black, 83 (10.3%) identified as AAPI, 634 (78.9%) as White, and 59 (7.3%) as other. Of the 780 subjects for which ethnicity data were reported, 6.1% identified as Hispanic or Latino. On a continuous scale, ADI ranged from 1 to 98, with a median percentile of 4. When grouped into log-transformed quintiles, 172 patients (21.4%) were in quintile 1 (least deprived), 208 (25.9%) in quintile 2, 110 (13.7%) in quintile 3, 156 (19.4%) in quintile 4, and 158 (19.7%) in quintile 5 (most deprived).

Associations between patient and tumor characteristics

We found that patients in higher ADI quintile groups were more likely to have overweight or obese category BMI (59.9% in quintile 5 vs. 32.7% in quintile 1, **Table 1**). The age-adjusted odds of overweight/ obese category BMI for ADI quintile 5 versus all other ADI quintiles was 2.0 ($P < 0.001$). The trend of increasing overweight and obese category BMI with increasing ADI was significant for both premen-opausal and postmenopausal patients ($P = 0.0005$ for each group). In addition, the presence of hypertension differed by ADI category, with 27.7% of those in quintile 1 being diagnosed with hypertension versus 36.0% of those in quintile 5. The distribution of self-identified race varied by ADI. Fewer Black-identifying patients were identified in ADI quintile 1 and fewer AAPI-identifying were identified in quintile 5 (0% and 5.1%, respectively). There were no differences in self-identification of Hispanic ethnicity by ADI quintile. Age at diagnosis, postmeno-pausal status, incidence of diabetes mellitus, presence of hyperchol-esterolemia or hypertriglyceridemia, and the number of positive lymph nodes were not significantly different across the ADI quintiles.

Tumor size was larger by increasing ADI quintile (mean 2.8 ± 2.7 cm in quintile 1 vs. mean 3.6 ± 3.1 cm in quintile 5). This association between larger tumor size and increasing ADI was statis-tically significant in premenopausal patients ($P = 0.0425$), but not among postmenopausal patients. Patients from lower ADI quintiles were more likely to have grade 1 tumors (31.3% vs. 22.5% for patients from ADI quintile 5). Overall, the most common tumor receptor subtype was ER+/PR+/HER2 negative, present in 73.1% of cases. However, more patients from ADI quintile 5 had ER+/PR+/HER2− tumors (81.6% compared with 69.0% in ADI quintile 1), whereas those with ADI 1 had more ER+/PR−/HER2− tumors (20.7% vs. 13.6% in ADI quintile 5). Patients from lower ADI quintiles had lower rates of LVI in their tumors (4.3% in ADI quintile 1 vs. 9.2% in ADI quintile 5).

Of note, patients who self-identified as Black were more likely to have overweight and obese category BMI, and patients who

Table 1. ILC patient and tumor characteristics overall and by ADI quintile.

Characteristic	Overall (N = 804)	Quintile 1 (n = 172)	Quintile 2 (n = 208)	Quintile 3 (n = 110)	Quintile 4 (n = 156)	Quintile 5 (n = 158)
Mean Age, years[a]	59.7	59.9	60.0	61.4	58.9	58.9
Post-Menopausal[b]	463 (68.0%)	92 (62.6%)	132 (72.9%)	62 (67.4%)	89 (68.5%)	88 (67.2%)
Race[a]						
AAPI	83 (10.3%)	18 (10.5%)	33 (15.7%)	10 (9.1%)	14 (9.0%)	8 (5.1%)
Black	28 (3.5%)	0 (0.0%)	3 (1.44%)	5 (4.6%)	12 (7.7%)	8 (5.1%)
White	634 (78.9%)	143 (83.1%)	156 (75.0%)	90 (81.8%)	113 (72.4%)	132 (83.5%)
Other	59 (7.3%)	11 (6.4%)	16 (7.7%)	5 (4.6%)	17 (10.9%)	10 (6.3%)
Hispanic/Latino Ethnicity[c]	49 (6.3%)	9 (5.4%)	12 (5.9%)	7 (6.7%)	11 (7.4%)	10 (6.4%)
BMI[d]						
<18.5 kg/m^2	21 (3.0%)	5 (3.2%)	3 (1.6%)	2 (2.2%)	6 (4.4%)	5 (3.5%)
18.5–24.9 kg/m^2	356 (49.9%)	100 (64.1%)	101 (54.3%)	49 (53.3%)	54 (39.4%)	52 (36.6%)
25–29.9 kg/m^2	199 (27.9%)	34 (21.8%)	54 (29.0%)	21 (22.8%)	47 (34.3%)	43 (30.3%)
≥30 kg/m^2	137 (19.2%)	17 (10.9%)	28 (15.1%)	20 (21.7%)	30 (21.9%)	42 (29.6%)
Overweight/obese[d]	336 (47.1%)	51 (32.7%)	82 (44.1%)	41 (44.6%)	77 (56.2%)	85 (59.9%)
Hypertension[e]	251 (35.6%)	43 (27.7%)	69 (37.3%)	44 (47.8%)	45 (33.3%)	50 (36.0%)
Diabetes Mellitus[f]	69 (9.9%)	12 (7.8%)	18 (9.9%)	11 (12.2%)	10 (7.4%)	18 (13.3%)
Hypercholesterolemia[g]	153 (22.6%)	28 (18.8%)	46 (26.4%)	28 (30.4%)	23 (17.4%)	28 (21.7%)
Hypertriglyceridemia[h]	68 (10.1%)	13 (8.7%)	24 (13.9%)	8 (8.8%)	10 (7.6%)	13 (10.1%)
Tumor Size, cm (standard deviation)[i]	3.1 (± 2.9)	2.8 (± 2.7)	2.7 (± 2.6)	3.1 (± 2.9)	3.6 (± 3.2)	3.6 (± 3.1)
Positive Lymph Nodes, n[j]	1.5 (± 4.4)	1.1 (± 3.2)	1.6 (± 5.0)	1.1 (± 2.8)	1.8 (± 4.8)	2.0 (± 5.4)
Tumor Receptor Subtype[k]						
ER+/PR+/HER2-	539 (73.1%)	107 (69.0%)	129 (67.2%)	79 (79.0%)	104 (72.7%)	120 (81.6%)
ER+/PR-/HER2-	129 (17.5%)	32 (20.7%)	33 (17.2%)	14 (14.0%)	30 (21.0%)	20 (13.6%)
ER-/PR-/HER2-	17 (2.3%)	4 (2.6%)	5 (2.6%)	1 (1.0%)	5 (3.5%)	2 (1.4%)
HER2+	52 (7.1%)	12 (7.7%)	25 (13.0%)	6 (6.0%)	4 (2.8%)	5 (3.4%)
Tumor Grade[l]						
1	221 (28.5%)	52 (31.3%)	50 (24.6%)	40 (38.1%)	45 (29.8%)	34 (22.5%)
2	512 (66.0%)	109 (65.7%)	135 (66.5%)	61 (58.1%)	99 (65.6%)	108 (71.5%)
3	43 (5.5%)	5 (3.0%)	18 (8.9%)	4 (3.8%)	7 (4.6%)	9 (6.0%)
Lymphovascular invasion[m]	54 (7.0%)	7 (4.3%)	10 (5.0%)	4 (3.9%)	19 (12.8%)	14 (9.2%)

Note: Overweight/obese BMI ≥25 kg/m^2. The P-value significance threshold was <0.05.
[a]Data available in n = 804.
[b]Data available in n = 681.
[c]Data available in n = 780.
[d]Data available in n = 713.
[e]Data available in n = 706.
[f]Data available in n = 695.
[g]Data available in n = 676.
[h]Data available in n = 675.
[i]Data available in n = 786.
[j]Data available in n = 789.
[k]Data available in n = 737.
[l]Data available in n = 776.
[m]Data available in n = 767.

self-identified as AAPI were less likely to have overweight and obese category BMI (79.2% and 32.5%, respectively). Patients with overweight and obese category BMI were significantly more likely to have larger tumors (mean 3.5 ± 3.0 cm compared with 2.9 ± 2.9 cm tumor size for normal or underweight BMI), but this trend was only statistically significant in postmenopausal patients (mean 3.4 ± 2.9 cm vs. 2.7 ± 2.6 cm, P = 0.0059). There were no differences in tumor grade, receptor subtype, presence of LVI, or the number of positive nodes by BMI.

Treatment characteristics

There were no differences in use of chemotherapy by ADI (**Table 2**). However, patients from higher ADI quintiles were more likely to receive mastectomy, whereas patients from lower ADI quintiles were more likely to receive breast-conserving surgery (39.9% mastectomy in quintile 5 vs. 33.7% in quintile 1, 17.4% lumpectomy in quintile 1 vs.

11.4% in quintile 5). Patients from lower ADI quintiles were also significantly more likely to receive adjuvant endocrine therapy (77.9% and 82.7% in quintiles 1 and 2 vs. 68.2%, 67.3%, and 67.1% in quintiles 3, 4, and 5, respectively). In a multivariable logistic regression model, patients from ADI quintiles 1 and 2 were noted to haver higher odds of receiving adjuvant endocrine therapy compared with patients from ADI quintile 5 [quintile 1 OR, 1.82 (95% CI, 1.01–3.29); quintile 2 OR, 2.76 (95% CI, 1.51–5.03); **Table 3**].

Event-free survival

Overall, there were 129 recurrence events (16.0%) and 82 deaths (10.2%) with a mean follow up time of 7.2 years for the entire cohort. Of the 82 patients who died, 59 of them also had a recurrence event (72.0%). Compared with patients with the lowest ADI (quintile 1), those with higher ADI (quintiles 2–5) had significantly worse EFS (P =

Table 2. ILC treatment overall and by ADI quintile.

Treatment type	Overall, N (%)	Quintile 1, n (%)	Quintile 2, n (%)	Quintile 3, n (%)	Quintile 4, n (%)	Quintile 5, n (%)
Chemotherapy use						
Yes	280 (34.8)	53 (30.8)	74 (35.6)	34 (30.9)	53 (34.0)	66 (41.8)
No	524 (65.2)	119 (69.2)	134 (64.4)	76 (69.1)	103 (66.0)	92 (58.2)
Surgical therapy						
Lumpectomy	137 (17.0)	30 (17.4)	35 (16.8)	21 (19.1)	33 (21.2)	18 (11.4)
Lumpectomy/radiation	250 (31.1)	59 (34.3)	75 (36.1)	26 (23.6)	44 (28.2)	46 (29.1)
Mastectomy	284 (35.3)	58 (33.7)	60 (28.9)	48 (43.6)	55 (35.3)	63 (39.9)
Mastectomy/radiation	120 (14.9)	21 (12.2)	35 (16.8)	15 (13.6)	24 (15.4)	25 (15.8)
Missing	13 (1.6)	4 (2.3)	3 (1.4)	0 (0.0)	0 (0.0)	6 (3.8)
Adjuvant endocrine therapy						
Yes	592 (73.6)	134 (77.9)	172 (82.7)	75 (68.2)	105 (67.3)	106 (67.1)
No	190 (23.6)	35 (20.4)	32 (15.4)	31 (28.2)	48 (30.8)	44 (27.9)
Missing	22 (2.7)	3 (1.7)	4 (1.9)	4 (3.6)	3 (1.9)	8 (5.1)

Note: The P value significance threshold was <0.05. Data available in $n = 804$.

0.0403, log rank) on unadjusted analysis. Patients who did not receive adjuvant endocrine therapy were noted to have reduced EFS when compared with patients who did receive adjuvant endocrine therapy ($P = 0.0001$, log rank). Similarly, patients with overweight/obese category BMI also had reduced EFS when compared with patients with lower category BMI ($P = 0.0066$, log rank). We performed a test of interaction between overweight/obesity and all five ADI quintiles and found that the impact of overweight/obesity on EFS appeared significant only in ADI quintiles 2 to 5 (**Table 4**).

In a multivariable model containing ADI quintiles, race, average age at diagnosis, BMI category, ILC tumor size, LVI, receptor subtype, and receipt of adjuvant endocrine therapy, the factors significantly associated with worse EFS were larger tumor size, and tumor receptor subtype (ER+/PR−/HER2− or triple-negative subtype). The use of adjuvant endocrine therapy was associated with significantly improved EFS (HR, 0.39; 95% CI, 0.2–0.6). These findings were similar when variables with missing data were included as a separate category; as such, results from complete case analysis are shown (**Table 5**).

Discussion

We found significant associations between high area deprivation and increased tumor aggressiveness, including larger ILC tumors, higher grade, and higher rates of LVI in those with higher ADI.

Although ADI has been linked to increased tumor aggressiveness in breast cancer in general (20, 21), to our knowledge this is the first report showing this association specifically in those with ILC. This is notable because ILC has historically been viewed as a non-aggressive, homogenous, hormonally driven tumor type.

Those with the lowest ADI were noted to have improved EFS compared with the other ADI groups combined. The underlying reason for this outcome disparity appears to be multifactorial. Those with the highest ADI had more hormone-receptor (HR) positive disease and elevated BMI, which together have been linked to worse outcomes in prior studies (16, 17, 19, 22, 23). In a multivariable model, the association between elevated ADI and worse EFS was no longer significant when adjusting for other factors, including the presence of overweight/obese BMI. Interestingly, in nearly all ADI quintiles having obese/overweight BMI was associated with worse EFS except for ADI quintile 1 in a test of interaction. Although the mechanisms through which obesity mediates ILC proliferation remain incompletely understood, ILC is known to express estrogen receptor and obesity is linked with states of increased estrogen due to peripheral production in adipose tissue (16, 24, 25). These suggest that high estrogen states, including the use of hormone replacement therapy, drive the growth of ILC beyond that of other histological subtypes, such as the more common IDC (26).

Table 3. Multivariable logistic regression model showing odds ratio for receipt of adjuvant endocrine therapy for ILC.

Variables	Unadjusted odds ratio (95% CI)	Adjusted odds ratio (95% CI)
ADI Quintile 5 (reference)		
ADI Quintile 1	1.65 (0.97–2.81)	1.82 (1.01–3.29)
ADI Quintile 2	2.68 (1.54–4.66)	2.76 (1.51–5.03)
ADI Quintile 3	0.98 (0.56–1.71)	1.12 (0.60–2.07)
ADI Quintile 4	1.00 (0.60–1.68)	0.95 (0.54–1.66)

Note: Unadjusted and adjusted odds ratios shown. Adjusted model included BMI, age at diagnosis, tumor size, number of positive lymph nodes, and self-identified race. ADI quintile 1 = least deprived; ADI quintile 5 = most deprived. Data available in $n = 721$ hormone receptor positive cases.

Table 4. Test of interaction for overweight/obesity by ADI quintile predicting event-free survival in patients with ILC.

Variables	HR (95% CI)
ADI Quintile 1 without overweight/obesity (reference)	
ADI Quintile 2 without overweight/obesity	1.51 (0.63–3.60)
ADI Quintile 3 without overweight/obesity	3.48 (00.98–6.29)
ADI Quintile 4 without overweight/obesity	2.06 (0.81–5.22)
ADI Quintile 5 without overweight/obesity	1.54 (0.53–4.44)
ADI Quintile 1 with overweight/obesity	2.50 (0.96–6.47)
ADI Quintile 2 with overweight/obesity	2.47 (1.05–5.83)
ADI Quintile 3 with overweight/obesity	2.71 (1.04–7.03)
ADI Quintile 4 with overweight/obesity	2.97 (1.28–6.88)
ADI Quintile 5 with overweight/obesity	2.66 (1.11–6.38)

Note: Overweight/obese BMI ≥25 kg/m². The P value significance threshold was <0.05. Data available in $n = 707$.

Table 5. Multivariable cox proportional hazards model for event-free survival with ADI, average age at diagnosis, BMI, tumor size, lymphovascular invasion, receptor subtype, and receipt of adjuvant endocrine therapy in patients with ILC.

Variables	HR (95% CI)
ADI Quintile 1 (reference)	
ADI Quintile 2	1.21 (0.61–2.41)
ADI Quintile 3	1.64 (0.78–3.45)
ADI Quintile 4	0.98 (0.47–2.02)
ADI Quintile 5	0.83 (0.37–1.90)
White-identifying (reference)	
AAPI-identifying	0.63 (0.25–1.60)
Black-identifying	2.28 (0.94–5.54)
Other-identifying	1.82 (0.82–4.07)
Age at diagnosis (per 1 year)	1.01 (0.99–1.03)
BMI < 25 kg/m^2 (reference)	
Overweight or obese BMI	1.38 (0.88–2.16)
Tumor size (per 1 cm)	1.09 (1.01–1.16)
No lymphovascular invasion (reference)	
Lymphovascular invasion	1.39 (0.67–2.90)
ER+/PR+/HER2− (reference)	
ER+/PR-/HER2−	2.21 (1.33–3.68)
Triple negative	2.84 (1.21–6.68)
HER2+	1.63 (0.57–4.65)
Receipt of adjuvant endocrine therapy	0.39 (0.24–0.63)

Note: Model adjusted for all included variables. Data available in $n = 635$. ADI quintile 1 = least resource-deprived; ADI quintiles 2–5 = most resource-deprived; overweight BMI 25–29.9 kg/m^2; obese BMI ≥30 kg/m^2; Normal BMI 18.5–24.9 kg/m^2; +, receptor status positive; −, receptor status negative.

Given this strong association with estrogen, endocrine therapy is generally indicated for patients with ILC. The Breast International Group's 1–98 trial showed that the use of an aromatase inhibitor, a form of endocrine therapy that reduces estrogen production from adipose tissue, conferred a relatively larger disease-free survival benefit to those with ILC than those with IDC, suggesting that endocrine therapy is particularly important for improving the prognosis of patients with ILC (27). In our evaluation of ADI, race, BMI, tumor size, LVI, tumor receptor subtype, and receipt of adjuvant endocrine therapy, we found that tumor size, ER+/PR−/HER2− and triple-negative receptor subtypes, and, notably, omission of adjuvant endocrine therapy were associated with significantly reduced EFS. We also found that the omission of adjuvant endocrine therapy was strongly associated with higher ADI, consistent with a recent analysis showing that Medicaid-insured patients with breast cancer experienced longer times to initiation of adjuvant endocrine therapy and had lower odds of adherence to therapy (28). In addition, patients with lower ADI were more likely to receive lumpectomy, whereas patients with higher ADI were more likely to receive mastectomy, similar to a prior finding suggesting patients from higher SES are more likely to receive breast-conserving surgery (29). Reasons for these findings are multifarious, but may be partially attributed to the systemic barriers patients from more resource-deprived backgrounds might encounter in accessing and receiving high-quality medical care (30, 31).

Although the proportion of Black-identifying patients in our cohort is low, there is an association between this group and high ADI, as well as with overweight or obese category BMI. We found that patients with elevated BMIs had reduced EFS, suggesting that outcomes for Black-identifying patients with high ADI might in-part be related to the known impact of obesity on ILC outcomes (16, 17, 32). Two prior analyses showed that Black-identifying patients with ILC had worse survival than White-identifying patients (15, 33). Although data on race and outcomes in ILC specifically are very limited, this finding is consistent with recent data showing that outcomes disparities in breast cancer are most pronounced among those with HR+/HER2− tumors, despite the known association between Black race and increased rates of more aggressive HR− tumors (34, 35).

A recent large analysis found that among those with HR+HER2− breast cancer, individual socioeconomic disadvantage and tumor biology mediated the impact of racial disparity in breast cancer survival, but analysis by histologic subtype (lobular vs. ductal) was not reported (36). Of note, in that study Black race was associated with increased incidence of PR− tumors, which is a poor prognostic indicator among HR+ breast cancer. In our study focused specifically on ILC, we were limited by a small number of Black-identifying patients, but our findings suggest the opposite. We found more Black-identifying patients to have higher ADI quintile, and higher ADI quintile to be associated with more PR+ tumors.

We found evidence of more aggressive tumor biology among those with higher ADI, evidenced by fewer grade 1 tumors and increased rates of LVI. LVI, or the presence of tumor cells within lymphatic channels in the breast, is associated with higher grade tumors and worse breast cancer survival (37). Studies suggest that LVI is less common in ILC than invasive ductal carcinoma, and have not shown an association with race (37, 38). There are no data evaluating LVI by ADI, so the finding of significantly more LVI in patients with ILC and higher ADI is novel and intriguing. This suggests that within this distinct subtype of breast cancer, social determinants of health impact tumor biology.

There are several limitations of our study, including lack of diversity in self-reported race. With much of our population composed of White-identifying patients, we were unable to perform additional analyses for more discrete racial groups; ethnicity data was missing for most of the study population. In addition, given the location of our institution and the proximity of many of our patients (median ADI = 4), factors like access to transportation, insurance coverage, access to screening mammography, and distance traveled might compound the outcomes for patients who are not local or who might otherwise come from higher ADI neighborhoods. In addition, the retrospective nature of this study results in multiple confounders regarding treatment and outcomes.

Overall, our findings reflect the prior literature regarding increased tumor aggressiveness, increased grade, less adjuvant endocrine therapy, and worse disease outcomes in patients with breast cancer who have increased ADI. These findings are unique, however, in that they represent a cohort of patients with ILC, the second most common histologic type of breast cancer. Although factors such as elevated BMI and adherence to adjuvant endocrine therapy may not account fully for worse outcomes in patients with ILC, these may be actionable areas towards which to focus potential interventions. In addition, the relationship between ADI, race, and ILC is complex, with some studies suggesting a lower prevalence of ILC in Black-identifying patients, but others showing opposite results (39–43). Our findings suggest that studies focusing on sociodemographic factors like race in ILC should take into account social determinants of health that are reflected by ADI. These data highlight the need for additional data in ILC, particularly because factors such as obesity and adherence to endocrine therapy are especially important in this largely hormonally driven tumor type.

Authors' Disclosures

Authors' Contributions

Acknowledgments

Note

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