Treatment differences between urban and rural women with hormone receptor-positive early-stage breast cancer based on 21-gene assay recurrence score results

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Background Women who live in rural and urban settings have different outcomes for breast cancer. A 21-gene assay predicts 10-year distant recurrence risk and potential benefit of chemotherapy for women with hormone receptor-positive (HR+) breast cancer.
Objective To assess differences in scores and cancer therapies received by rural versus urban residence.
Methods We conducted a multi-institutional retrospective chart review of breast cancer patients diagnosed 2005-2010 with score results. Comparisons by rural versus urban residence (determined by rural-urban commuting area (RUCA) codes derived from zip codes) were made using the Fisher exact test for discrete data such as recurrence score results (<18 vs >18; score range, 0-100, with lower results correlated with less risk of distant recurrence), stage, and receptor status. The Wilcoxon rank sum test was used for continuous data (score results 0-100 and age.) All tests were at a 2-sided significance level of .05.
Results 504 patients had RUCA codes (92% white, 62% postmenopausal). For rural (n = 135) compared with urban (n = 369) patients, the median scores were 16 and 18, respectively, $P = .18$. Most of the patients received endocrine therapy, 123 of 135 (91%) rural, compared with 339 of 369 (92%) urban ($P = .19$). For scores 18-30, 20 of 56 (36%) rural patients, compared with 82 of 159 (52%) urban patients received chemotherapy ($P = .03$).
Limitations Limitations include lack of randomization to receipt of the assay.
Conclusions Recurrence score results did not significantly differ between women based on residence, although women living in a rural area received significantly less chemotherapy for scores >18. This suggests that for HR-positive breast cancer, discrepancies between rural and urban residence are driven by treatment factors rather than differences in biology.
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Breast cancer is the most common invasive cancer in women in the United States, and the second leading cause of cancer death.[1] Differences in breast cancer mortality have been linked to socioeconomic and population differences, but the etiologic relationship among these factors remains unclear.[2] Although some studies have found that rural populations have an increased overall breast cancer-associated mortality,[2] others have suggested decreased mortality[3] or no difference after adjusting for age, sex, or race.[4,5] Proposed factors that possibly contribute to increased mortality in rural patients include presentation with later stage disease,[4,6,7] less access to mammographic screening,[8,9] lower socioeconomic status,[10] and less access of because of geographic location to newer more effective therapies and technologies.[11,12] Individual risk factors[13,14] such as body mass index (BMI),[15,16] par-

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ity,[13] or differences in exogenous hormone use[17] may also contribute. Finally, regardless of predisposing risk factors, women from different population settings may choose or receive different treatment modalities for similarly staged cancers.[11,13]

It remains unclear whether tumor biology or treatment factor differences drive these population mortality differences. Comparing breast cancer prognostic characteristics might be hypothesis-generating with regard to whether differences in inherent tumor biology drive these population mortality differences. The 21-gene assay (Oncotype DX) predicts the 10-year risk of distant breast cancer recurrence in patients with estrogen receptor-positive (ER-positive), human epidermal growth factor receptor 2 (HER2) negative early-stage breast cancer (EBC) based on testing of tumor tissue.[18] The assay has been commercially available since 2004 in hormone receptor-positive (HR-positive) breast cancer and is used in clinical practice.[19] Recurrence scores on the assay range from 0-100, with lower results correlated with less risk of distant recurrence.[18] Patients can be divided into 3 groups based on the assay scores: low, intermediate, or high risk. The high-risk group (score results, >31) is likely to benefit from chemotherapy, whereas the low-risk group (<18) does not benefit.[20-22] Current recommendations for the intermediate-risk group (18-30) include offering chemotherapy,[23,24] although the risk reduction from chemotherapy in this group remains uncertain. An ongoing study (TAILORx/PACCT-01) is specifically designed to answer whether chemotherapy benefits women with node-negative HR-positive EBC with an intermediate score result. TAILORx is expected to report results in 2017.[25]

Differences between rural and urban populations on the basis of recurrence scores have not been reported. Score results may offer insight into prognostic differences between rural and urban women who present with breast cancers of similar stage and receptor-status. Therefore, we retrospectively assessed rural and urban differences by recurrence scores to understand possible causes for rural-urban differences in breast cancer outcomes such as overall breast cancer-associated mortality. Secondary objectives included assessing rural and urban differences in other risk factors as well as therapies received based on recurrence score.

Methods

Study population

Three Wisconsin medical institutions participated in this retrospective study. The institutions provide cancer care across much of Wisconsin, with catchment areas including northern Illinois, eastern Iowa, eastern Minnesota, and the Upper Peninsula of Michigan. This study was approved by the University of Wisconsin Institutional Review Board and the Wisconsin Institutional Review Board Consortium. Women who had been diagnosed with breast cancer during January 1, 2005-December 31, 2010 were identified using the ICD-9 code for female breast cancer (174.9). Pathology or lab records were used to identify those for whom a 21-gene assay had been performed. Genomic Health Inc, the maker of the assay, provided a list containing patient initials, date of birth, and recurrence score to each center. This list was used to cross-check and confirm completeness and accuracy of the institutional lists. Individuals identified at each center were excluded if they were not on both lists.

Data abstraction

Abstraction was completed by manual review of medical records. Abstracted data included patien zip code, age, height, weight, exogenous hormone use, gravidity and parity at diagnosis, tumor size, number of positive lymph nodes, stage, tumor grade, ER status, progesterone receptor (PR) status, HER2 status, recurrence score result, and treatment modalities pursued (including surgery type, chemotherapy, endocrine therapy, and radiotherapy).

Definitions of rural and urban

Zip codes were used to generate rural-urban commuting area (RUCA) codes. The codes categorize regions based on data from the 2000 US Census, using an algorithm to account for population density, urbanization, and work commuter flow to the nearest urban area. We used a 2-category classification (type D) that collapses subcategories of rural regions into one, allowing for more generalized rural versus urban comparison. Under category D, urban is defined by places that have 30% or more of their workers commuting to a Census Bureau-defined urbanized area.[26]

Statistical analysis

Descriptive statistics were produced to summarize demographic and clinical information. Categorical variables such as recurrence score result (<18, 18-30, >31) were summarized as frequency and percent, and a Fisher exact test was used to compare rural and urban patients. Continuous variables such as score results (0-100) and age were summarized as median and range, and the Wilcoxon rank sum test was used to compare rural and urban patients. All tests were at a 2-sided significance level of 0.05.

Results

Demographics and risk factors

In all, 538 patients from the 3 institutions were identified with the 21-gene assay and breast cancer diagnosed by tissue biopsy between January 1, 2005 and December 31, 2010 (Figure 1). Of those, 31 patients were excluded because they did not have recurrence score results from both the institutional medical record and the maker of the assay. Therefore, data abstraction was performed on 507 patient

charts. Three patients were not included in this analysis because they did not have zip codes available. Patient demographics and tumor characteristics for the rural (n = 135) and urban (n = 369) cohorts are shown in Table 1. Most of the participants resided in Wisconsin; however a few had out-of-state zip codes, including patients from Illinois and Iowa who commuted to Wisconsin for their medical care. The rural cohort was slightly older at time of breast cancer diagnosis; parous rural women were slightly younger at the age of their first-term birth. The 2 cohorts were otherwise similar in terms of demographic characteristics. Tumor characteristics were also similar between the cohorts except notably, in tissue histology. Rural women were significantly less likely to be diagnosed with ductal carcinoma and had a greater incidence of less common histologies ("other" category), which included mammary, tubular, or the presence of more than one histology ($P < .001$).

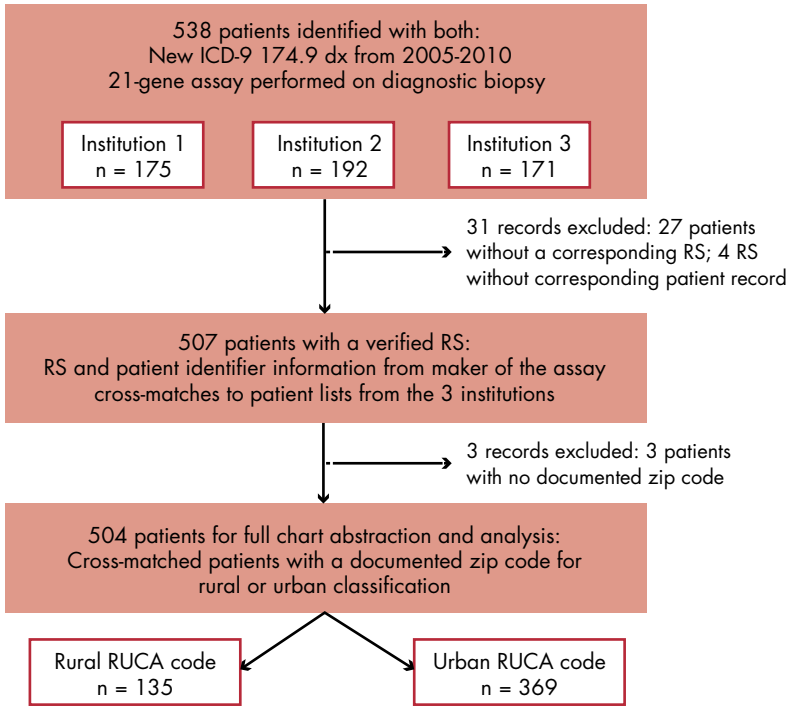

FIGURE 1 Identifying the study population

RS, recurrence score; RUCA, rural-urban commuting area

Rural and urban differences by recurrence scores

The differences in recurrence between the 2 populations based on the assay score is shown in Table 2. No significant difference was seen based on recurrence rcore results or risk groups. Data was analyzed using both the standard cut-offs for low-, intermediate-, and high-risk groups as well as those being used in the TAILORx trial (low, 0-10; intermediate, 11-25; high, >26).

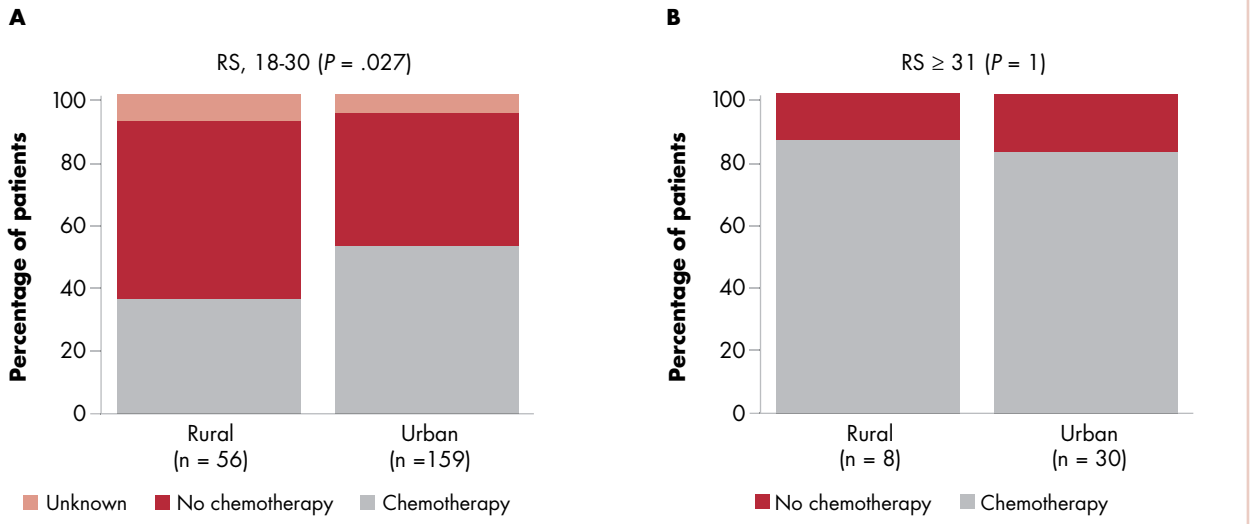

FIGURE 2 Receipt of chemotherapy for rural versus urban women with recurrence score (RS) results of 18-30 (A) and 31 or higher (B). Score range is 0-100, with lower results correlated with less risk of distant recurrence. RS of 18-30 indicates intermediate risk. Total number of rural women = 135; total number of urban women = 369.

Therapies received

The differences in the types of therapy patients received

TABLE 1 Patient demographic and tumor characteristics by residence

Demographic/tumor characteristic	Total[a] (N = 504)	Rural (n = 135)	Urban (n = 369)	*P* value
Median age at diagnosis, y (range)	56 (27-86)	58 (27-82)	56 (30-86)	.049
BMI, median (range)	29 (17-62)	29 (17-56)	28 (17-62)	.904
Exogenous hormone use at diagnosis, n (%)				
Yes, all types	80 (15.9)	17 (12.6)	63 (17.1)	.218
No, none	405 (80.4)	114 (84.4)	291 (78.9)	
Use unknown	19 (3.8)	4 (3)	15 (4.1)	
Menopausal status, n (%)				
Pre	176 (34.9)	39 (28.9)	137 (37.1)	.164
Post	311 (61.7)	87 (64.4)	224 (60.7)	
Unknown	17 (3.4)	9 (6.7)	8 (2.2)	
Median age of menarche, y (range)	13 (8-17)	13 (10-17)	13 (8-17)	.157
Median age of menopause, y (range)	50 (29-60)	50 (31-60)	50 (29-60)	.169
Median age at 1st full-term birth, y (range)	25 (16-43)	23 (16-35)	25 (16-43)	.002
Stage, n (%)				
I	353 (70)	93 (68.9)	260 (70.5)	.908
II	133 (26.4)	36 (26.7)	97 (26.3)	
Unknown	18 (3.6)	6 (4.4)	12 (3.3)	
Grade, n (%)				
1	155 (30.8)	36 (26.7)	119 (32.2)	.149
2	273 (54.2)	72 (53.3)	201 (54.5)	
3	67 (13.3)	24 (17.8)	43 (11.7)	
Unknown	9 (1.8)	3 (2.2)	6 (1.6)	
Nodal status, n (%)				
Positive	47 (9.3)	16 (11.9)	31 (8.4)	.299
Negative	446 (88.5)	117 (86.7)	329 (89.2)	
Unknown	11 (2.2)	2 (1.5)	9 (2.4)	
Tissue histology, n (%)				
Ductal	377 (74.8)	89 (65.9)	288 (78)	<.001
Lobular	75 (14.9)	22 (16.3)	53 (14.4)	
Other	46 (9.1)	24 (17.8)	22 (6)	
Unknown	6 (1.2)	0 (0)	6 (1.6)	
ER status, n (%)				
Positive	490 (97.2)	130 (96.3)	360 (97.6)	.291
Negative	4 (0.8)	2 (1.5)	2 (0.5)	
Unknown	10 (2)	3 (2.2)	7 (1.9)	
PR status, n (%)				
Positive	435 (86.3)	120 (88.9)	315 (85.4)	.343
Negative	58 (11.5)	12 (8.9)	46 (12.5)	
Unknown	11 (2.2)	3 (2.2)	8 (2.2)	
HER2 status, n (%)				
Positive	5 (1)	2 (1.5)	3 (0.8)	.617
Negative	468 (92.9)	127 (94.1)	341 (92.4)	
Unknown	31 (6.2)	6 (4.4)	25 (6.8)	

BMI, body-mass index; ER, estrogen receptor; PR, progesterone receptor; HER2, human epidermal growth factor receptor 2
[a]Missing values (Unknown) were excluded when calculating *P* values. Wilcoxon rank sum test is used to compare numerical variables. Fisher's exact test is used to compare categorical variables.

TABLE 2 Differences in recurrence results by residence

	Total[a] (N = 504)	Rural (n = 135)	Urban (n = 369)	*P* value
Median RS (range)	18 (0-68)	16 (0-58)	18 (1-68)	.184
Risk group, n (%)				
Low, RS <18	251 (49.8)	71 (52.6)	180 (48.8)	
Intermediate, RS 18-30	215 (42.7)	56 (41.5)	159 (43.1)	.642
High, RS ≥31	38 (7.5)	8 (5.9)	30 (8.1)	
TAILORx trial				
Participants, n (%)	80 (15.9)	28 (20.7)	52 (14.1)	.173
RS groups, n (%)				
RS <11	72 (14.3)	19 (14.1)	53 (14.4)	
RS 11-25	350 (69.4)	97 (71.9)	253 (68.6)	.739
RS ≥26	82 (16.3)	19 (14.1)	63 (17.1)	

RS, recurrence score
Missing values (Unknown) were excluded when calculating *P* values. Wilcoxon rank sum test is used to compare numerical variables. Fisher's exact test is used to compare categorical variables.

TABLE 3 Treatment modalities in rural and urban women

Type of therapy	Total[a] (N = 504)	Rural (n = 135)	Urban (n = 369)	*P* value
Chemotherapy				
RS <18, n (%)				
Yes	34 (13.5)	11 (15.5)	23 (12.8)	
No	204 (81.3)	58 (81.7)	146 (81.1)	.684
Unknown	13 (5.2)	2 (2.8)	11 (6.1)	
RS ≥18, n (%)				
Yes	134 (53)	27 (42.2)	107 (56.6)	.037
No	107 (42.3)	35 (54.7)	72 (38.1)	.084*
Unknown	12 (4.7)	2 (3.1)	10 (5.3)	
RS 18-30, n (%)				
Yes	102 (47.4)	20 (35.7	82 (51.6	.027
No	101 (47)	34 (60.7)	67 (42.1)	.076*
Unknown	12 (5.6)	2 (3.6)	10 (6.3)	
RS ≥31, n (%)				
Yes	32 (84.2)	7 (87.5)	25 (83.3)	1.000
No	6 (15.8)	1 (12.5)	5 (16.7)	
Endocrine, n (%)				
Yes	462 (91.7)	123 (91.1)	339 (91.9)	.185
No	19 (3.8)	8 (5.9)	11 (3)	.17*
Unknown	23 (4.6)	4 (3)	19 (5.1)	
Surgery, n (%)				
Lumpectomy	339 (67.3)	86 (63.7)	253 (68.6)	.821
Mastectomy	146 (29)	39 (28.9)	107 (29)	.98*
Unknown	19 (3.8)	10 (7.4)	9 (2.4)	
Radiation, n (%)				
Yes	328 (65.1)	87 (64.4)	241 (65.3)	.741
No	153 (30.4)	43 (31.9)	110 (29.8)	.57*
Unknown	23 (4.6)	5 (3.7)	18 (4.9)	

RS, recurrence score
[a]Missing values (Unknown) were excluded when calculating *P* values. Wilcoxon rank sum test is used to compare numerical variables. Fisher's exact test is used to compare categorical variables.
**P* value calculated using logistic regression to control for institution.

based on rural and urban residence is shown in Table 3. As expected, given the generally early-stage (and thus better prognosis) breast cancers eligible for a 21-gene assay, only 168 of 504 women (33.3%) received chemotherapy. Of the 504 women with HR-positive breast cancer, 19 (4%) did not receive endocrine therapy, and 6 of those 19 received chemotherapy. In addition, urban women with score results >18 were more likely to get chemotherapy, specifically women with an intermediate score result (Figure 2A). A similar proportion of rural and urban women received chemotherapy for score results >31 (high-risk; Figure 2B). Fifty-two percent of urban women with an intermediate result received chemotherapy, compared with 36% of rural women (P = .03). That difference in therapeutic modality was also statistically significant when analyzed with the TAILORx cutoffs for rural and urban women. After controlling for institution, because most of the rural patients drew from 1 location, the significance of these results was lost (P = .08).

Discussion

In this retrospective analysis of rural versus urban women with HR-positive, HER2-negative EBC, there was no significant difference in recurrence score distribution or several prognostic risk factors potentially linked to higher mortality including age, BMI, exogenous hormone use, tumor stage and grade. In addition, there were no significant differences for surgery, radiation, or endocrine therapy treatment modalities between the rural and urban groups. However, rural women received significantly less chemotherapy for an intermediate recurrence score result.

This study is the first to assess differences between rural and urban women with EBC who have had the 21-gene assay performed on their breast cancer. Although many rural-urban comparison studies highlight differences in mammography screening[8,9] and disease stage at diagnosis[4,6,7] or difference in prediagnostic risk factors such as BMI[16] to explain increased mortality in rural patients, our study compared rural and urban women who presented with similar cancers in terms of stage, grade, and receptor status. Furthermore, our results show that there was no significant difference in the distribution of recurrence score results between rural and urban women. This suggests similar tumor biology in terms of prognosis and treatment impact. However, we found a significant difference in treatment modalities among women with intermediate recurrence score results, with a higher proportion of urban women receiving chemotherapy.

For HR-positive, HER2-negative EBC, the addition of adjuvant chemotherapy to endocrine therapy affects long-term outcomes for only a small portion of the many women treated. In the absence of TAILORx results, it is difficult to know whether less chemotherapy for rural women with an intermediate score result would have a positive or negative impact on outcomes such as disease-free and overall survival. But in a broader sense, our results suggest that treatment differences for similarly staged cancers may play a larger role in rural-urban cancer mortality differences than suggested by previous studies, as we found no statistically significant difference in the recurrence scores, which are prognostic for the 10-year distant recurrence risk. In other words, for women with HR-positive, HER2-negative EBC, discrepancies between rural and urban patient outcomes *might* be more likely due to differences in treatment factors than in tumor biology. However, that is an extrapolation based off the recurrence scores. Although we looked at recurrence and survival, the numbers were too low to be meaningful.

Limitations of this study include the retrospective nature of the analysis and the fact that this is not a random sample of all HR-positive, HER2-negative EBC patients seen at the 3 institutions. Various unmeasureable factors may have influenced whether urban or rural women chose to have the assay performed, introducing a selection bias in the cohorts. Moreover, we could not determine the duration of residence for the women in our study – only their residence at time of diagnosis. Finally, we are not able to determine what factors may have influenced these women and their oncologists to choose or not choose chemotherapy. Most of the rural women were drawn from 1 institution; after controlling for institution, our results were no longer statistically significant (P = .08; Table 3). However, it is not clear whether this loss of significance is because of sample size or whether there was a rural versus urban institutional difference in chemotherapy use for patients with an intermediate recurrence score result. All other therapies that were rendered, including type of surgery, use of endocrine and radiation therapies, and use of chemotherapy for low- or high-risk score results, did not differ significantly between the populations. Our study population included patients enrolled in the TAILORx trial, which would preclude either patient or clinician from opting for or against chemotherapy. However, TAILORx trial enrollment rates were similar between the 2 groups, so this is unlikely to have significantly influenced the findings.

Particular strengths of this analysis include our data abstraction methods, including cross-matching medical record and Genomic Health data. Another asset to our study is its catchment: we drew data from 3 large medical centers in Wisconsin. Based on the most recent cancer registry numbers available (2006), 29% of breast cancers diagnosed in Wisconsin were from 1 of the 3 medical centers in the study. Finally, we have used a novel method (gene assay) for assessing differences in rural and urban women – a method that gives additional information about the tumor biology and ultimate breast cancer prognosis.

Conclusion

The results of this study demonstrated no significant difference in recurrence score between women based on rural or urban residence. However, women living in a rural area received significantly less chemotherapy for recurrence scores of 18 or less. This suggests that for HR-positive EBC, rural versus urban discrepancies in breast cancer outcomes may be driven more by treatment factors than by differences in tumor biology. It is not clear why urban women received significantly more chemotherapy than rural women. Socioeconomic factors and patient preferences likely play some role, but local health care resources and individual provider preferences may also contribute. A prospective comparison or confirmation in another population would elucidate some of these details.

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