Cancer Causes & Control (2019) 30:409–415
https://doi.org/10.1007/s10552-019-01151-9

ORIGINAL PAPER

Demographic, clinical, and geographical factors associated with lack of receipt of physician recommended chemotherapy in women with breast cancer in Texas

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Received: 29 July 2018 / Accepted: 22 February 2019 / Published online: 13 March 2019

Abstract

Purpose Identifying demographic, clinical, and geographical factors that contribute to disparities in the receipt of physician recommended chemotherapy in breast cancer patients.

Methods The Texas Cancer Registry was used to identify women aged ≥ 18 years with invasive breast cancer diagnosed from 2007 to 2011 who received a recommendation for chemotherapy. Multivariable logistic regression was performed to determine associations between demographic and clinical factors and the receipt of chemotherapy. Cox proportional regression was used to estimate the hazard ratio (HR) for overall survival. Spatial analysis was conducted using Poisson models for breast cancer mortality and receipt of chemotherapy.

Results Age ≥ 65 years, residence in areas with > 20% poverty index, and early disease stage were associated with lack of receipt of chemotherapy (all $p<0.001$). Lack of receipt of chemotherapy was associated with decreased overall survival (HR 1.33, 95% CI 1.12–1.59, $p=0.001$). A 38-county cluster in West Texas had lower receipt of chemotherapy (relative risk 0.88, $p=0.02$) and increased breast cancer mortality ($p=0.03$) compared to the rest of Texas.

Conclusion Older age, increased poverty and rural geographical location are barriers to the receipt of chemotherapy. Interventions that target these barriers may reduce health disparities and improve breast cancer survival.

Keywords Breast cancer · Receipt of chemotherapy · Spatial analysis · Breast cancer mortality · Poverty

Introduction

Breast cancer is the most common cancer affecting women in the United States, as well as in Texas [1]. Approximately 18,260 Texan women will be diagnosed with breast cancer and approximately 2,880 will die of breast cancer in 2018 [1]. Although the overall breast cancer mortality rate in Texas is lower than the national average, differences have been noted by race/ethnicity and geographic location [2, 3]. In particular, black women in Texas have a higher age-adjusted rate of breast cancer mortality (30.1 per 100,000) compared to the White women (20.4 per 100,000) [3]. However, in a spatial analysis of breast cancer mortality in Texas, Bambhroliya et al. identified multiple clusters of counties with higher than expected breast cancer mortality that was not due to race/ethnic disparities, suggesting that a complex set of factors likely contribute to disparities in breast cancer mortality [2].

In addition to demographic factors e.g., poverty, race/ethnicity, and socioeconomic status, disparities in the receipt of adjuvant chemotherapy have also been identified as contributing to breast cancer mortality [4–7]. Griggs et al. evaluated disparities in receipt of adjuvant chemotherapy using survey data from 1,403 patients who were reported to the Surveillance, Epidemiology, and end Results (SEER) registry in Los Angeles County, California, and Detroit, Michigan

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[8]. They found no association between race/ethnicity and decreased receipt of chemotherapy. However a limitation of this and other studies evaluating barriers to the receipt of breast cancer treatment is the lack of information on whether the chemotherapy was recommended or not by the physician. Since a patient's co-morbidities and life expectancy could influence whether chemotherapy is recommended, identifying the demographic and clinical factors associated with the lack of receipt of physician recommended chemotherapy may lead to the development of effective interventions to improve the receipt of chemotherapy among patients most likely to benefit from treatment.

The Texas Cancer Registry is a state-wide, population-based registry of cancer cases in Texas that collects data on whether chemotherapy was recommended by the treating physician and received or not by the patient. This unique feature of this registry enabled us to analyze breast cancer cases throughout Texas to assess demographic, clinical, and geographical factors associated with lack of receipt of physician recommended chemotherapy and its association with overall survival. A spatial analysis of geographical variations at the county level was also conducted to assess locations with lower receipt of receiving chemotherapy and higher breast cancer mortality.

Methods

Data sources

Data were extracted from the Texas Cancer Registry, a public-use, state-wide population-based registry. Women age 18 years and older diagnosed with local or regional invasive breast cancer from 1 January 2007, to 31 December 2011, were included in the study. Women with a second breast cancer diagnosis within 6 months were counted as 1 case, and the highest stage of the cancer was included. We identified 63,067 breast cancer cases. Demographic and clinical variables, including age at diagnosis, year of diagnosis, race/ethnicity, poverty index, tumor subtypes (approximated by estrogen receptor [ER], progesterone receptor [PR] and HER2 status), grade, stage, tumor size, and lymph node status were extracted from the registry. The poverty index is based on the patient's residence, determined at the census tract (neighborhood) level, and is defined as the percentage of the population in that census tract who are below the federal poverty level (less than 5%, 5–9.9%, 10–19.9%, and 20% or greater). Therefore, an individual with a poverty index level of $<5\%$ is from an area where $<5\%$ of the population is below the federal poverty level. Geographic coordinate data (the centroid of each county) for Texas were collected from the 2000 U.S. Census.

We included in the study analysis, cases who were recommended chemotherapy by their physician. Cases were coded as having been recommended and received chemotherapy (either single agent or multiple agents) or having been recommended chemotherapy but did not receive chemotherapy (because of patient refusal, death prior to therapy, or unknown reason). Cases for whom it was unknown whether the patient was recommended chemotherapy or whether the patient received chemotherapy were excluded from the analysis.

Statistical analysis

The chi-squared test was used to evaluate differences in the distribution of patients receiving chemotherapy versus not receiving chemotherapy by demographic and clinical characteristics. The multivariable logistic regression model for the association between demographic and clinical characteristics and the receipt of chemotherapy included variables with a Chi square $p<0.01$. Cox proportional hazards analyses were conducted in a similar manner, first by separate univariate analyses, using survival as the independent variable and receipt of chemotherapy or one of the demographic or clinical characteristics as the dependent variable. Multivariate Cox proportional hazards analysis was then conducted using all dependent variables identified with $p<0.05$ in the univariate analysis. Overall survival time was calculated from the date of diagnosis to the date of death and patients without a reported death were censored at the date of last contact. Two-sided p-values <0.05 were considered statistically significant.

Spatial analysis was conducted using SaTScan's implementation of spatial scan statistics [9]. The discrete Poisson model was used to detect clusters of counties that differed in the receipt of recommended chemotherapy, adjusted for age, race/ethnicity, poverty index, stage, grade, tumor size, and lymph node status. This model assumes the number of "cases" by county is Poisson-distributed, with an expected value estimated from the county-level "population" characteristics. Cases were defined as patients who received chemotherapy and the population was defined as all patients recommended chemotherapy. The discrete Poisson model was also used to detect clusters of counties that differed in breast cancer mortality, adjusted for race/ethnicity and poverty index. For the mortality analysis, cases were defined as the number of breast cancer deaths within the study period. Population information on the county level was obtained from the American Community Survey, as this resource includes race/ethnicity categories consistent with the Texas Cancer Registry [10]. For both analyses, expected county-level counts under the null hypothesis were calculated in SaTScan using indirect standardization, which uses the overall state-wide rates by subgroup and the county-level subgroup populations to determine the expected county-level counts. Two-sided p-values were assigned to the most likely clusters using Monte Carlo simulations, with 0.05 as the level of statistical significance [11]. The scanning window was allowed to vary in size, up to 50% of the population of Texas. Secondary clusters with p-values below 0.05 were also reported that did not overlap with primary clusters. Statistically significant clusters were plotted in R, using the rgdal, rgeos, and maptools libraries [12].

Statistical analyses were performed in R Version 3.4.0 [13]. This research was reviewed by the institutional review board of The University of Texas MD Anderson Cancer Center and was considered exempt under the code of federal regulations.

Results

Patient population

From 2007 to 2011, 58,908 breast cancer cases were identified and 22,124 (37.6%) were recommended to receive chemotherapy, 31,162 (52.9%) were not recommended to receive chemotherapy, and 5,622 (9.5%) had missing information. Of the cases recommended for chemotherapy, 18,345 (82.9%) received chemotherapy, 1,141 (5.2%) did not, and 2,638 (11.9%) had missing information. We only included the 19,486 cases in the study analysis who were recommended chemotherapy by their physician with a documented status of the receipt of chemotherapy along with their demographic and clinical characteristics (Table 1). The majority of the cases were 50–64 years old, and 22.1% of the cases were 65 years of age or older. 58% of cases had tumors 2 cm or larger and 55% of cases had regional nodal disease. The majority of cases (48.1%) had poorly differentiated grade tumors. The number of cases by year of diagnosis was evenly distributed amongst all years.

Patient characteristics and multivariable analysis of receipt of recommended chemotherapy

Patients were more likely to have received chemotherapy if they were younger in age ($p < 0.001$); 98% of patients younger than age 50 years received chemotherapy, compared with 85.6% of patients 65 years and older. Patients with regional nodal disease and tumors larger than 2 cm were more likely to have received chemotherapy than those without nodal disease or tumors < 2 cm (Table 2). Among subtypes of breast cancer, HER2 positive and triple negative (i.e., ER, PR and Her2 negative) had a higher proportion of patients who received chemotherapy. Poverty index was found to be significantly associated with receipt of chemotherapy; patients who lived in areas with greater than 20% of the population in poverty were less likely to have received chemotherapy (OR 0.56, CI 0.43–0.72). Race/ethnicity was found to be a significant factor for receipt of chemotherapy in univariable analysis ($p < 0.0001$) but was also highly correlated with poverty level ($p < 0.001$). Thus, in the multivariable analysis, race was no longer found to be significantly associated with the receipt of chemotherapy (Table 2). Non-Hispanic black (48%) and Hispanic (52%) women were more likely to live in areas with greater than 20% poverty compared to non-Hispanic white women (17%).

Survival data were available for 19,452 patients and survival time was calculated for 2,230 patients who had died; all others were censored at date of last contact. All clinical and demographic factors were identified as statistically significant by univariate Cox proportional hazards analysis, so they were all included in the multivariable analysis. In the adjusted multivariable analysis, lack of receipt of physician recommended chemotherapy was associated with decreased overall survival (hazard ratio 1.33, 95% CI 1.12–1.59, $p = 0.001$) (Fig. 1).

Spatial analysis at the county level for receipt of recommended chemotherapy

Spatial analysis at the county level was completed for all cases for whom chemotherapy was recommended and compared to the number of cases expected to receive chemotherapy based on census data. Figure 2 shows a spatial analysis of a cluster of counties that had a significantly lower than expected receipt of receiving chemotherapy in 2007–2011 when adjusted for age, race/ethnicity, and poverty index. The cluster consists of 38 counties in West Texas with women who had a 12% lower likelihood of receiving chemotherapy when compared to the rest of Texas ($p = 0.02$). Higher breast cancer mortality was noted in clusters of counties along the southern border ($p < 0.001$) as well as in the area of West Texas that had lower receipt of chemotherapy adjusted for race/ethnicity ($p = 0.03$) (Fig. 3).

Discussion

The majority of women with breast cancer in Texas who were recommended chemotherapy by their physician went on to receive therapy. Older age, early stage disease, and living in areas with increased poverty were associated with lack of receipt of chemotherapy. Decreased overall survival was also found to be strongly associated with lack of receipt of chemotherapy. Spatial analysis identified a cluster of counties in West Texas with lower rates of receipt of recommended chemotherapy, as well as increased breast cancer mortality compared to the rest of Texas.

Table 1 Patient demographic and clinical characteristics and the receipt of chemotherapy from the Texas Cancer Registry, 2007–2011

Characteristic	Total (%)	Recommended chemotherapy was received, *n* (%)		P^a
		Yes	No	
Overall	19,486	18,345 (94.1)	1,141 (5.9)	
Age, years				< 0.001
18–49	6,719 (34.5)	6,583 (98)	136 (2)	
50–64	8,457 (43.4)	8,073 (95.5)	384 (4.5)	
≥ 65	4,310 (22.1)	3,689 (85.6)	621 (14.4)	
Race/ethnicity				< 0.001
Non-Hispanic white	11,782 (60.5)	11,026 (93.6)	756 (6.4)	
Non-Hispanic black	2,725 (14)	2,595 (95.2)	130 (4.8)	
Hispanic	4,315 (22.1)	4,082 (94.6)	233 (5.4)	
Non-Hispanic other	636 (3.3)	615 (96.7)	21 (3.3)	
Missing	28 (0.1)	27 (96.4)	1 (3.6)	
Census tract poverty index				< 0.001
< 5%	3,680 (18.9)	3,535 (96.1)	145 (3.9)	
5–9.9%	4,183 (21.5)	3,943 (94.3)	240 (5.7)	
10–19.9%	6,011 (30.8)	5,644 (93.9)	367 (6.1)	
≥ 20%	5,589 (28.7)	5,200 (93)	389 (7)	
Missing	23 (0.1)	23 (100)	0 (0)	
Grade				< 0.001
Well/moderately differentiated	7,620 (39.1)	6,956 (91.3)	664 (8.7)	
Poorly/undifferentiated	9,382 (48.1)	8,993 (95.9)	389 (4.1)	
Missing	2,484 (12.7)	2,396 (96.5)	88 (3.5)	
Stage				< 0.001
Localized	8,754 (44.9)	7,985 (91.2)	769 (8.8)	
Regional	10,732 (55.1)	10,360 (96.5)	372 (3.5)	
Tumor subtype				< 0.001
ER/PR + HER2−	2,109 (10.8)	1,939 (91.9)	170 (8.1)	
ER/PR + HER2+	683 (3.5)	651 (95.3)	32 (4.7)	
ER/PR − HER2+	300 (1.5)	291 (97)	9 (3)	
Triple negative	873 (4.5)	840 (96.2)	33 (3.8)	
ER/PR + HER2 unknown	6,398 (32.8)	5,854 (91.5)	544 (8.5)	
ER/PR-HER2 unknown	1,017 (5.2)	965 (94.9)	52 (5.1)	
Other[b]	2,174 (11.2)	2,087 (96)	87 (4)	
All biomarkers unknown	5,932 (30.4)	5,718 (96.4)	214 (3.6)	
Tumor size				< 0.001
< 2 cm	6,677 (34.3)	6,070 (90.9)	607 (9.1)	
2–5 cm	8,882 (45.6)	8,482 (95.5)	400 (4.5)	
≥ 5 cm	2,502 (12.8)	2,413 (96.4)	89 (3.6)	
Missing	1,425 (7.3)	1,380 (96.8)	45 (3.2)	
Lymph node status				
No	10,360 (53.2)	9,505 (91.7)	855 (8.3)	
Yes	8,807 (45.2)	8,562 (97.2)	245 (2.8)	
Missing	319 (1.6)	278 (87.1)	41 (12.9)	
Year of diagnosis				< 0.001
2007	4,174 (21.4)	3,938 (94.3)	236 (5.7)	
2008	3,782 (19.4)	3,597 (95.1)	185 (4.9)	
2009	3,906 (20)	3,692 (94.5)	214 (5.5)	
2010	3,669 (18.8)	3,382 (92.2)	287 (7.8)	
2011	3,955 (20.3)	3,736 (94.5)	219 (5.5)	

[a]Analysis conducted in each category using the chi-squared test

[b]Other was defined as 2 biomarkers with missing data

Table 2 Multivariable model of association between demographic and clinical characteristics and the receipt of chemotherapy

Characteristic	OR (95% CI)	P
Age, years		
18–49	Reference	
50–64	0.46 (0.37–0.58)	< 0.001
≥ 65	0.15 (0.12–0.18)	< 0.001
Race/ethnicity		
Non-Hispanic white	Reference	
Non-Hispanic black	1.08 (0.85–1.39)	0.52
Hispanic	0.91 (0.75–1.12)	0.38
Non-Hispanic other	1.07 (0.66–1.75)	0.78
Census tract poverty index		
< 5%	Reference	
5–9.9%	0.69 (0.54–0.89)	0.005
10–19.9%	0.66 (0.52–0.85)	< 0.001
≥ 20%	0.56 (0.43–0.72)	< 0.001
Grade		
Well/moderately differentiated	Reference	
Poorly/undifferentiated	1.86 (1.57–2.19)	< 0.001
Stage		
Localized	Reference	
Regional	1.80 (1.40–2.32)	< 0.001
Tumor subtype		
ER/PR + HER2−	Reference	
ER/PR + HER2+	2.04 (1.33–3.12)	0.001
ER/PR − HER2+	2.58 (1.22–5.44)	0.01
Triple negative	2.35 (1.54–3.57)	< 0.001
ER/PR + HER2 unknown	1.33 (0.98–1.82)	0.07
ER/PR − HER2 unknown	2.19 (1.43–3.34)	< 0.001
Other[a]	2.39 (1.59–3.58)	< 0.001
Tumor size		
< 2 cm	Reference	
2–5 cm	1.71 (1.45–2.00)	< 0.001
≥ 5 cm	1.78 (1.32–2.40)	< 0.001
Lymph node status		
No	Reference	
Yes	1.97 (1.49–2.60)	< 0.001
Year of diagnosis		
2007	Reference	
2008	1.29 (0.99–1.69)	0.06
2009	1.20 (0.94–1.54)	0.15
2010	0.94 (0.73–1.20)	0.62
2011	1.58 (1.10–2.29)	0.01

[a]Other was defined as 2 biomarkers with missing data

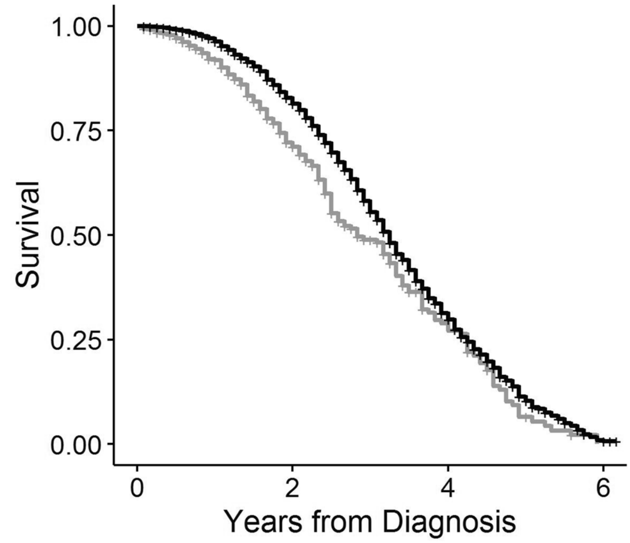

Fig. 1 Kaplan–Meier plot for overall survival of patients who received (black) and did not receive (gray) recommended chemotherapy

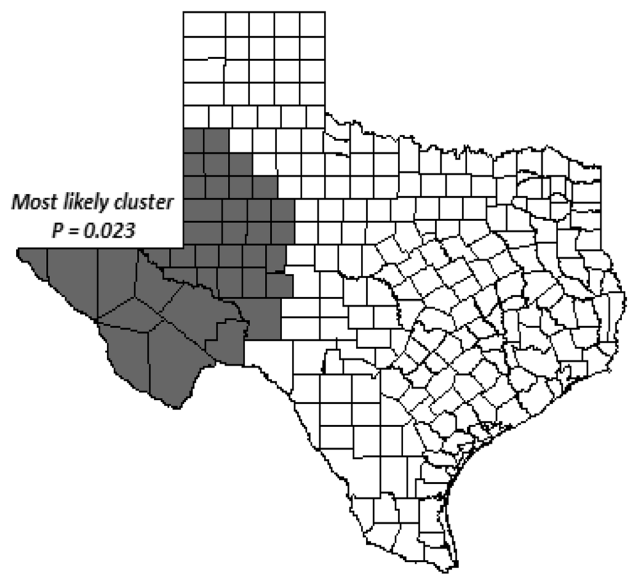

Fig. 2 Cluster of Texas counties with lower receipt of recommended chemotherapy, 2007–2011

Our finding that younger women, poorly differentiated grade, tumors > 2 cm, lymph node involvement and those with HER2 positive or triple negative breast cancer were more likely to receive chemotherapy are similar to the results of Kurian et al. which examined utilization of chemotherapy in the Kaiser Permanante health care system [14]. Similar to Griggs et al. [6], we showed no association between race/ethnicity and decreased receipt of chemotherapy, however, race/ethnicity was highly correlated with poverty and increased poverty was strongly associated with lack of receipt of chemotherapy. Our results are also consistent with the study by Dreyer et al. that showed a positive association between socioeconomic status and receipt of adjuvant chemotherapy for breast cancer [15]. Bhargava and Du showed

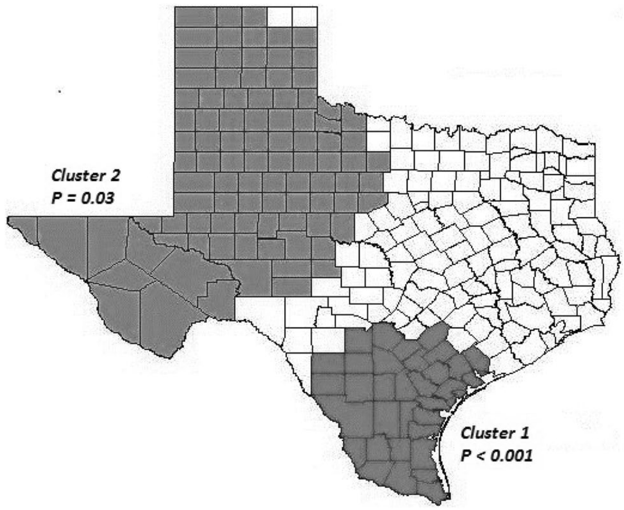

Fig. 3 Cluster of Texas counties with higher breast cancer mortality, 2007–2011

a significant interaction between poverty and race in older women with operable lymph node positive breast cancer and the decreased receipt of chemotherapy in black women was mediated by poverty level [16]. The consistency of the findings between these studies and ours suggest that both race/ethnicity and poverty are significant contributing factors to the receipt of physician recommended chemotherapy.

This is the first study to identify a cluster of counties with breast cancer cases with lower receipt of chemotherapy compared to expected rates based on census data in Texas. Bambhroliya et al's finding of increased breast cancer mortality in West Texas led to the conclusion that other etiological factors, not related to race and ethnicity, may contribute to geographical differences in breast cancer mortality in Texas [2]. Indeed, our spatial analysis identified an overlapping cluster of counties in West Texas that had lower than expected rate of receiving chemotherapy as well as higher breast cancer mortality after adjustment for age, race/ethnicity, and poverty index.

There are several reasons for the geographical disparity in the receipt of chemotherapy in Texas. 70% of counties are designated as rural areas [17] and of these rural counties, 14% do not have primary care physicians, and 36% do not have a hospital. In the cluster of counties identified in West Texas with decreased receipt of chemotherapy, 90% of the counties are rural and have no practicing oncologists (Table 3). Although the population of the cluster of counties is mainly concentrated in 4 urban counties, there are 2 oncologists per 100,000 residents in this area whereas other urban areas in the US have approximately 5 oncologists per 100,000 residents [18].

The average distance to access a hospital in rural counties in Texas is 35 miles, with some Texans having to travel

Table 3 Characteristics of Counties in West Texas Area cluster identified in Fig. 2 [17, 19]

County type and number (*n*)	Population	Total oncologists	Hospitals/medical centers
Rural (34)	295,813	0	25
Urban (4)	1,467,651	33	11

greater than 100 miles to reach the nearest hospital [17, 19]. Geographic access to care and its association with receipt of chemotherapy was evaluated by Lin et al. in stage III colon cancer patients for the period 2007–2010 utilizing the National Cancer Data Base [20]. They found that patients having to travel greater than 50 miles to their treatment center had a lower likelihood of receipt of adjuvant chemotherapy. A study of breast cancer patients in North Carolina found that patients living in urban areas were less likely to receive recommended adjuvant radiation therapy if they had longer travel distances to a treatment center compared to those in rural areas with similar travel distances [21]. These findings suggested that access to reliable public transportation in addition to travel distance can affect patients receiving recommended evidence based treatment. Our findings highlight the challenges of accessing and coordinating breast cancer chemotherapy treatment in rural areas and its impact on breast cancer mortality.

In the 2017 State of Cancer Care in America report by the American Society of Clinical Oncology (ASCO), geographic access to care was highlighted as an issue due to the uneven distribution of oncologists across the country leading to patients having to travel long distances for treatment [18]. Telehealth interventions are being evaluated in the oncology setting to expand access to cancer care, especially in rural areas. Remote chemotherapy supervision models are being explored and evaluated in Queensland, Australia by videoconferencing of oncologists in local cancer centers with general practitioners and nurses competent in chemotherapy administration in rural towns. High levels of patient satisfaction have been reported but training is necessary for primary care providers and nurses in these rural areas [22, 23]. Further evaluation and implementation of these types of services should be considered especially in counties without oncology specialists.

The use of patient navigators has also been evaluated to determine whether they improve receipt of breast cancer care for individuals who face various barriers such as low socioeconomic status that lead to decreased screening rates and more advanced disease at presentation as well as delays in the initiation and completion of treatment. The National Patient Navigation Research Program evaluated the use of navigators among women with triple negative breast cancer for the initiation of physician recommended chemotherapy and found no significant difference between navigated women and control participants in the receipt of chemotherapy [24]. However, the study was limited to patients with triple negative breast cancer and from metropolitan areas. Future studies should be conducted to evaluate whether patient navigators can help address barriers faced by patients residing in rural counties that have low rates of receipt of chemotherapy.

There were some limitations to our study that should be considered in interpreting the findings. Although the Texas Cancer Registry provided unique data on physician recommendation of chemotherapy, we were unable to evaluate the role of additional factors that may have affected the receipt of chemotherapy, such as patient choice, availability of transportation and childcare, and family support. A possible limitation to our spatial analyses was the use of a circular scanning window to identify clusters of interest. This is a common practice in spatial scanning, but it potentially neglects effects due to features that are not simply due to distance (e.g., high rates of a disease that may occur along a river). Other methods can explore flexibly shaped areas, but at a cost of increasing multiplicity therefore we deemed a circular search area to be appropriate for the analyses [25].

Our study highlights that although the majority of women with breast cancer in Texas receive chemotherapy following a physician recommendation, older age, increased poverty, and geographical location are barriers to the receipt of chemotherapy. Interventions such as patient navigation and teleoncology services that target these barriers may reduce health disparities and improve breast cancer mortality rates.

Acknowledgments MD Anderson's Department of Scientific Publications provided editorial assistance.

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