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EFFECT OF RURALITY ON STAGE AT DIAGNOSIS, TUMOR SIZE AT DIAGNOSIS, AND RECEIPT OF CANCER-DIRECTED SURGERY IN PATIENTS WITH BREAST CANCER: A SURVEILLANCE, EPIDEMIOLOGY, AND END RESULTS (SEER) ANALYSIS

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by

Jorge Benavides-Vasquez

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The thesis of Jorge Benavides-Vasquez was reviewed and approved by the following:

Li Wang
Associate Professor, Department of Public Health Sciences
Thesis Advisor

Alicia McDonald
Assistant Professor, Department of Public Health Sciences
Thesis Committee Member

Chan Shen
Associate Professor, Department of Public Health Sciences
Thesis Committee Member

Li Wang
Associate Professor, Department of Public Health Sciences
Head of the Department of Public Health Sciences

ABSTRACT

Background

Few studies have analyzed the influence of rural/urban disparities on the risks of advanced stage and large tumor size of breast cancer at diagnosis in the United States using a large population sample from national cancer registry data. The aim of the present study was to assess the influence of rural/urban residence as a risk factor for advanced-stage at diagnosis, tumor size larger than 2 cm at diagnosis, and receipt of cancer-directed surgery in females with primary breast cancer in the United States.

Methods

A selected sample of female patients with a primary diagnosis of breast cancer between 2010-2015 was obtained from the National Cancer Institute (NCI)'s Surveillance, Epidemiology, and End Results (SEER) database. Outcome variables were: Probability of advanced stage (AJCC stages II-IV) at diagnosis, probability of tumor size >2 cm at diagnosis, and receipt of cancer-directed surgery (surgery aimed at treating the main tumor). The primary independent variable was county-level rural/urban residence. Logistic regression was used to measure the association between the main independent and the main outcome variables, adjusted for age, grade, immunohistochemical subtype, marital status, county percentage of families below poverty level, and county percentage of individuals with at least bachelor's degree. Statistical analysis was stratified by race/ethnicity.

Results

The final sample included 272,448 female breast cancer cases, of which 42.53% were older than 75 years, 68.26% were non-Hispanic Whites, and 90.36% lived in metropolitan counties. Cases in non-metropolitan counties were diagnosed at more advanced stages (III and IV), had more tumors larger than 2 cm at diagnosis, and had more aggressive immunohistochemical breast cancer subtypes (HR-/HER2+, TNBC) at diagnosis. A lower percentage of women living in metropolitan

counties (95.9%) received cancer-directed surgery than those living in rural/adjacent counties (97.32%). Adjusted multivariate logistic regression analysis showed that non-Hispanic White patients living in urban/not adjacent counties were significantly more likely to be diagnosed with advanced breast cancer than those in metro counties (OR=1.055; 95%CI, 1.005-1.107), and those living in urban/not adjacent (OR=1.065; 95%CI, 1.014-1.117) or urban/adjacent counties (OR=1.172; 95%CI, 1.045-1.314) were more likely to have a breast tumor larger than 2 cm at diagnosis than those living in metro counties. These differences were not significant for other urban/rural residence and race/ethnicity categories.

Conclusion

Urban/rural residence was found to be significantly associated with advanced stage and a tumor larger than 2 cm at diagnosis in non-Hispanic White female breast cancer cases in the United States. However, statistically significant associations were not observed among non-Hispanic Black, non-Hispanic Asian/Pacific Islander, and Hispanic patients. Future research efforts will need to further investigate the complex association between rurality and cancer outcomes across different race/ethnicity categories.

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Chapter 1

Introduction

Introduction to Breast Cancer

Worldwide, female breast cancer has surpassed lung cancer as the most commonly diagnosed cancer, with an estimated 2.3 million new cases (11.7%), and is still the leading cause of cancer-related death (15.5%) [1]. Incidence rates of breast cancer are higher in North America, Australia/New Zealand, and Northern and Western Europe, and lower in most African and Asian countries [2]. In the United States, breast cancer is the most common cancer in females -accounting for 30% of all female cancers- and the second cancer-related cause of death in females after lung cancer, accounting for 15% of deaths [3].

Established risk factors for worse outcomes from breast cancer include: (a) Clinical-pathological (such as stage at diagnosis,[4] tumor size at diagnosis,[5] and immunohistochemical [IHC] subtype[6]); (b) demographic (such as gender[7] and race/ethnicity[8]); (c) socioeconomic (such as lower education level,[9] and lower income level [10]); diet, lifestyle, and behavioral factors (such as obesity,[11] alcohol consumption,[12] use of hormonal replacement therapy,[13] and physical inactivity[14]); no early screening;[15] and not receiving timely and appropriate treatment.[16]

Early breast cancer -that is, cancer that is confined in the breast or that has only disseminated to axillary lymph nodes- is considered curable: in both stage 0 and stage I, breast cancer is a cause of death for only a minority of patients.[17] Consequently, thanks to advances in treatment approaches and efforts in effective screening, survival for female breast cancer is one of the highest among all cancers, about 90%.[18]

Racial and Socio-Economic Disparities in Breast Cancer

The study of cancer disparities has largely focused on the influence of race/ethnicity on cancer outcomes. A clear example is the differential effect of race in cancer outcomes in the United States where White women have the highest overall cancer incidence (9% higher than Black women who rank second), but Black women have the highest cancer mortality rates (12% higher than White women).[18]

The role of race/ethnicity in breast cancer outcomes has been extensively characterized. In the United States, non-Hispanic Black females are more likely to be diagnosed at advanced stages (II-IV).[19] to have a larger tumor size at diagnosis,[20] and to die of breast cancer than non-Hispanic White patients.[8, 21] However, it is important to note that racial/ethnical disparities are mostly driven by differential inequalities in wealth that lead to differences in risk factor exposures and barriers to high-quality cancer prevention, early detection, and treatment.[22] A larger percentage of African American women with breast cancer in the US are uninsured or on Medicaid and are in the lowest quartiles of socioeconomic status (SES) compared to Whites.[20] On the other hand, socioeconomic (SE) determinants do not explain the total of racial/ethnic disparities observed in cancer outcomes, and inherent biological characteristics may play a role. African American women are more likely to have breast cancer subtypes associated with a more aggressive behavior, such as the hormone receptor (HR) (-)/human epidermal growth factor receptor-2 (HER2) (-) subtype, also known as triple negative breast cancer (TNBC).[23, 24] In conclusion, it is difficult to elucidate the particular contributions of biological factors and SE determinants to the effects of race/ethnicity on breast cancer outcomes, and some studies have indeed reported statistically significant interactions between race/ethnicity and SES for breast cancer and other types of cancer.[25]

The role of SE deprivation and other SE determinants in breast cancer outcomes has also been described for years and several studies have addressed the role of different measures of SE deprivation as risk factors for worse outcomes in all types of cancer [26]. For example, using a composite score of socioeconomic deprivation, Singh *et al*. found that breast cancer patients in the most deprived group had a 19% higher mortality rate than those in the least-deprived group for all cancers [27]. Some of the SE determinants that have been associated with worse cancer outcomes are lower family income level,[10, 28] insurance status (Medicaid or uninsured),[29] lower educational attainment,[30] and blue-collar occupational category.[31]

In the United States, health insurance has been shown to affect the survival in patients with breast cancer: In patients younger than 65 years (age at which all US citizens are eligible for Medicare coverage), those insured under Medicaid and those who are uninsured are more likely to have distant disease at diagnosis[32, 33] and die of breast cancer[34] than patients with other types of insurance. Household income and poverty level are other SE factors that have been shown to influence breast cancer outcomes. Patients in the highest quartiles of median household income have more favorable survival rates than those in the lowest quartiles.[34]

Rural/Urban Disparities in Cancer

The concept of rurality, that is, the quality of residing in a rural geographic area compared to an urban one, has also been studied as a factor for cancer outcomes. Although studies in different countries around the world have shown mixed results, the majority of them report worse outcomes for cancer patients living in rural and remote areas relative to those living in urban regions.[35, 36]

Urban/rural residence influences cancer outcomes in several ways: (a) Remoteness from hospitals or cancer centers, in terms of either distance of travel time, appears to have a negative effect on stage of cancer at diagnosis and receipt of optimal treatment;[37] (b) rural populations tend to have less access to health care resources and to receive less adequate cancer screening coverage than those in urban areas;[38, 39] (c) poor geographical access to primary care providers (PCPs) increases the likelihood of late-stage diagnosis of some cancers;[40] (d) there is a correlation between rurality and SE deprivation;[27] (e) certain diet and lifestyle factors affect urban and rural populations differently, e.g., obesity and tobacco use are more prevalent in rural communities;[41-43] and (f) patients living in rural locations are less likely to receive adequate information about participation in clinical trials than their urban counterparts.[44]

Cancer disparities between urban and rural locations differ among countries, and even among regions within the same country.[45] Differences in geographic, economic, or social factors particular to each country complicate the analysis of the effect of rurality on cancer outcomes. For example, the rural/urban disparity in developing countries can be very different than in developed countries but even within developed countries, disparities between urban and rural communities may be nuanced by differences in healthcare systems or access to healthcare resources.

The association between rurality and cancer outcomes is even more complicated by the relationship between geographical location and SES. In most countries, like the United States or Australia, rurality is associated with remoteness and lower overall SES indexes, but that is not true for every country. For example, in England, where all communities and cities are relatively close to each other and where all citizens are covered by a single-payer health care system, SE deprivation is not associated with rurality, but to urbanicity.[46]

Several studies have examined the role of urban/rural residence in cancer outcomes in different countries around the world, and the magnitude and direction of the associations vary widely by type of cancer and country.[35] For example, in Scotland, 1-year mortality rates for lung, colorectal, breast, stomach, and prostate cancers were significantly higher in locations with smaller settlement sizes, but interestingly, they were lower for towns that were located further away from cancer centers for lung and prostate cancers.[47] In South Korea, mortality rates were significantly higher for residents of rural vs. urban areas for lung and liver cancers, but lower for breast, uterine, and colon cancers, and differences were non-significant for prostate and pancreatic cancers.[48] In the United States, people living in rural and nonmetropolitan counties have been shown to have at least 8% higher cancer mortality rates than those in more urban counties.[27] Rural populations have higher incidence rates of lung and bronchus, colorectal, oral and pharynx, larynx, and cervical cancers than urban populations, while people living in urban areas have higher incidence rates of female breast, prostate, and thyroid cancers.[49]

Rural/Urban Disparities in Breast Cancer

Rural/urban disparities also play an important role in female breast cancer outcomes. Whereas the incidence of most cancers is higher in patients living in rural areas when compared to those in urban locations, breast and prostate cancer incidence rates are higher in urban areas than in rural areas [50]. Factors that mediate the association between urban residence and breast cancer incidence include: (a) Breast cancer incidence is positively dependent on the screening rate in a population and mammography rates are higher in urban than rural areas [51]; and (b)

Factors that increase mammography rates are also associated to residence in urban areas: higher SES, higher health literacy rates, higher proportions of patients with non-Medicaid health insurance,[52] and higher densities of primary care providers (PCP) or obstetricians/gynecologists.[53]

The role of rurality as a risk factor for advanced stage at diagnosis of breast cancer has been examined in various studies. A study in Queensland, Australia in 2011 found that rates of advanced breast cancer were higher for females living in remote or very remote localities and for those living in socio-economically disadvantaged areas, when compared to women living in the most socio-economically advantaged areas.[54] In the United States, there is an inadequate knowledge on the intricacies of rural/urban disparities in breast cancer. For example, breast cancer incidence rates have been reportedly to be higher in urban than in rural or suburban counties, particularly in non-Hispanic white women,[49, 55, 56] and this association seems to be mediated by higher SES levels and higher densities of primary care physicians (PCPs) found in more urban counties.[50] Additionally, what defines a "rural" county is not uniform across the US: in a study that compared female patients with breast cancer in 4 US geographic regions (Northeast, Midwest, South, and West), the South region had a higher percentage of cases of advanced stage at diagnosis, but also higher percentages of non-White patients and rural/non-urban counties than the Northeast region [57].

Various studies in the US have analyzed the association between rurality and breast cancer outcomes only within a single state. In a study by Amey *et al*. in Florida, patients living in rural communities not adjacent to metropolitan areas were less likely to be diagnosed at a late stage in an unadjusted analysis, but after controlling for county-level SE characteristics such as percentage of population below the federal poverty level (FPL), this relationship was reversed.[58] Williams et al. examined the association of rurality and race with stage at diagnosis in the state of Missouri: even when only 9.8% of the study population was Black, African Americans had much larger rates of late-stage breast cancer in rural vs. urban counties than White patients.[59] None of these studies linked the association between rurality and breast cancer outcomes to other county-level SE characteristics that could be acting as confounders, such as poverty level or insurance status.

Objectives

The aim of the present study is to assess the association of rural vs. urban residence as a risk factor for advanced-stage breast cancer at diagnosis, tumor size larger than 2 cm at diagnosis, and receipt of cancer-directed surgery (that is, surgery aimed at treating the primary tumor) in females in the United States, stratifying the analysis by race/ethnicity, using the SEER database, one of the most comprehensive cancer databases in the US. To the best of our knowledge, very few studies in recent years have used the SEER database to study rural-urban disparities in these specific breast cancer outcomes.

Chapter 2

Methods

Data Sources

Breast cancer cases were identified through the National Cancer Institute (NCI)'s Surveillance, Epidemiology, and End Results (SEER) Public Use Data Set released in 2018.[60] The SEER program is a widely used database of cancer incidence, staging, treatment, and survival information. The database pools data from 18 cancer registries, including a large and representative sample of 8,131,919 cancer cases covering approximately 27.8% of the US population. The geographic areas covered in this submission of SEER include California (San Francisco-Oakland, San Jose-Monterey, Los Angeles, rest of California), Connecticut, Michigan (metropolitan Detroit), Hawaii, Iowa, New Mexico, Washington (Seattle-Puget Sound), Utah, Georgia (metropolitan Atlanta, rural Georgia, greater Georgia), Kentucky, Louisiana, New Jersey, and Alaska (native).[61] The SEER program routinely collects individual-level data on patient demographics, primary tumor site, tumor morphology and stage at diagnosis, first course of treatment, and follow-up for vital status, and the SEER database is linked to the US Census Bureau to provide county-level information about socioeconomic determinants and mortality data.[62] This study employed the specific database named "SEER 18 Regs Research Data + Hurricane Katrina Impacted Louisiana Cases, Nov 2018 Sub (1975-2016 varying)".[63]

This research project received approval from SEER after signing the SEER Research Data Agreement. The study was considered exempt for Institutional Review Board (IRB) review because it did not involve any direct contact with participants and contained only review of de-identified SEER Public Use Data.

Inclusion and Exclusion Criteria

All females with a new diagnosis of primary breast cancer, diagnosed between 2010 and 2016 were identified in the public-use SEER database using the built-in SEER*Stat software (Surveillance Research Program, National Cancer Institute SEER*Stat Software version 8.3.8.). This time period was chosen because SEER started including information about IHC subtype in 2010 and the dataset chosen includes patient data up to 2016, A total of 292,737 patients were eligible. Entries were excluded from analysis for subjects of Alaskan/Native American or otherwise classified as unknown race (3,596), and all patients with unknown information for status of surgery to the primary tumor (13), rural/urban residence (56), and marital status (15,624).

Key Variables

The main outcome variables in this study were stage at diagnosis, tumor size at diagnosis, and receipt of cancer-directed surgery. Stage at diagnosis was defined using the American Joint Commission on Cancer (AJCC) staging system for breast cancer, classified as early stage (stages 0-I) or late stage (stages II-IV) [64]. Tumor size was defined as size of the primary breast tumor at diagnosis and classified as small (≤2 cm) or large (>2 cm), the 2 cm cutoff being the maximum size to define a stage T1 in the TNM staging system. Receipt of cancer-directed surgery was defined as documented surgical treatment of the primary tumor (classified as “yes” or “no).

The main independent variable was county-level rural/urban residence, which was defined according to the Rural-Urban Continuum Code (RUCC) system built in the SEER database. The RUCC is a system launched by the US Department of Agriculture (USDA)’s Economic Research Service (ERS) to classify metropolitan counties by the population size of their metro area, and non-metropolitan counties by degree of urbanization and contiguity to metropolitan areas [65]. The 2013 submission uses 9 categories to classify counties in the US: 1-3 (metropolitan counties), 4-7 (urban counties), and 8-9 (rural counties). For the present study, the 9 RUCC categories were grouped in 5 categories: metropolitan counties (codes 1-3), urban counties adjacent to a metro area (codes 4 and 6), urban counties not adjacent to a metro area (codes 5 and 7), rural counties adjacent to a metro area (code 8), and rural counties not adjacent to a metro area (code 9).

The analysis was stratified by race/ethnicity, which was defined as non-Hispanic Whites (NHWs), non-Hispanic Blacks (NHBs), Asian/Pacific Islanders (API), and Hispanics. The main covariables used in the analysis were: age at diagnosis, tumor grade, immunohistochemical (IHC) subtype, marital status, and county-level SE indicators (percentage of families below poverty level, percentage of individuals with at least bachelor's degree). Tumor grade refers to the microscopic appearance and degree of differentiation of the tumor cells as described by a pathologist, which in most types of cancer is directly related to the prognosis. A four-grade system is common in cancer: I (well-differentiated), II (moderately differentiated), III (poorly differentiated), and IV (undifferentiated/anaplastic) [66]. Immunohistochemical subtype is a pathological classification system that considers the presence or absence of estrogen or progesterone receptors, grouped by SEER as hormone receptors (HR), and human epidermal growth factor 2 (HER2) in expression microarray patterns, first described by Perou *et al* [67]. IHC subtype is associated with clinical prognosis, especially the HR(-)/HER2(+) and the HR(-)/HER2(-) (also known as triple negative breast cancer, TNBC), which have been linked to worse survival rates.[6] The SEER program does not routinely collect individual-level information on SE determinants except for marital status and insurance status, but it offers information on various county-level SE factors obtained through linkage to data from the US Decennial Census and the American Community Survey (ACS).

Statistical Analysis

Pearson's χ^2 statistic was used to assess significance of differences among proportions in assessments of univariate associations. Multivariate logistic regression models were used to determine the associations between rural/urban residence and each of the main outcome variables in this study: stage at diagnosis, tumor size, and receipt of cancer-directed surgery. Regression analysis was performed using 3 different models: (a) Model 1, unadjusted; (b) model 2, adjusted for clinical-pathological characteristics (age, tumor grade, and IHC subtype), (c) model 3, adjusted for SE characteristics (marital status, county percentage of families below poverty level, and county percentage of individuals with at least bachelor's degree) in addition to the previous three clinical-pathological variables. All analyses were stratified by race/ethnicity. A *p*-value ≤ 0.05 was used to determine statistical significance, and all statistical analyses were performed using SAS software (SAS ver. 9.4, Cary, NC. USA).

Chapter 3

Results

A total of 272,448 breast cancer cases were included in the final analysis. *Table 1* shows selected demographic, clinical, pathological, and socioeconomic characteristics of women 20-84 years of age with a diagnosis of breast cancer between 2010-2016. A disproportionately larger percentage of the study population lived in metropolitan counties (90.36%). Univariate analysis showed that rural counties in the United States had higher proportions of cases who were older than 60 years, non-Hispanic White, married, and in the lower quartiles of county-level percentages of individuals with at least bachelor's degree and individuals below poverty level (see *Table 1*). Regarding clinical and pathological characteristics, a greater percentage of women with breast cancer in the study population were diagnosed at advanced stages compared to early stages (51.21% vs. 48.78%), but also with tumors ≤2 cm compared to tumors >2 cm in size (52.39% vs. 47.61%). Cases living in rural/adjacent (54.6%) and rural/not adjacent counties (52.74%) were diagnosed at more advanced stages (III and IV) than those in metro counties (51.15%). Similarly, cases living in rural/adjacent (50.92%) and rural/not adjacent (49.16%) counties had a higher proportion of tumors larger than 2 cm at diagnosis than cases in metropolitan counties (47.55%). Cases in rural/adjacent counties (12.45%) had a higher proportion of the TNBC subtype than those living in metropolitan counties (10.54%). Cases living in metropolitan counties received statistically less cancer-directed surgery (95.95%) than those living in rural/adjacent (97.32%) and rural/not adjacent counties (97.05%).

In *Table 2,* when compared by race/ethnicity, NHB women had the highest percentage of advanced stage at diagnosis (61.35%) and NHWs had the lowest (48.12%). In all racial groups, cases living in non-metropolitan counties presented with a more advanced stage of disease when compared to cases residing in metropolitan counties. Non-Hispanic White patients living in rural/not adjacent (53.07%) and rural/adjacent (52.25%) counties had significantly higher proportions of advanced stage at diagnosis than those in metropolitan counties (47.83%) (p<.0001). Among non-Hispanic Asian/Pacific Islander (NHAPI) cases, there was a statistically significant trend towards gradually higher proportions of advanced-stage cancer at diagnosis with higher degrees of rurality, but these differences were confounded by the extremely low numbers of NHAPIs living in rural counties (a total of 8 cases in rural/adjacent and 5 in rural/not adjacent counties). And although there was a similar trend towards gradually higher proportions of advanced stage of breast cancer at diagnosis with higher degrees of rurality, there were no statistically significant differences observed for NHB or Hispanic patients.

Table 3 shows the distribution of cases by tumor size at diagnosis. Non-Hispanic Black patients had the highest percentage of tumor sizes >2 cm at diagnosis (56.72%) and NHWs had the lowest (44.59%). A similar trend than the one seen with advance stage could be observed with the proportions of tumors >2 cm at diagnosis, where NHW women living in rural/not adjacent and rural/adjacent counties had a significantly higher proportion of tumors >2 cm at diagnosis (48.77% and 49.96%, respectively) than those in metropolitan areas (44.29%, p<.0001). No significant differences regarding the proportions of tumors >2 cm were seen in NHBs, NHAPIs, or Hispanics.

Table 4 shows the distribution of receipt of cancer-directed surgery by rural/urban residence and race/ethnicity. A lower proportion of NHW cases living in metropolitan areas received surgical treatment for their primary breast tumor (96.57%) than those in rural/adjacent counties (97.42%) and other urban-rural residence categories (p<.0001). Also, NHB cases in metropolitan counties also were significantly less likely to receive cancer-directed surgery (93.97%) than those in urban/adjacent (95.57%), urban/not adjacent (95.35%), or rural/adjacent counties (95.16%; p=.0179); a much smaller proportion of NHB cases did not receive surgery in rural/not adjacent counties (87.27%). Non-Hispanic Asian/Pacific Islander women in metro areas also were less likely to receive cancer-directed surgery (95.69%) than those living in urban/ adjacent (96.26%) and urban/not adjacent counties (99.39%; *p*=.0022). There were no significant differences observed in Hispanic women.

Table 5 shows the adjusted logistic regression analysis for advanced stage at diagnosis using three models: (1) unadjusted, (2) after adjustment for clinical-pathological factors (age, grade, IHC subtype), and (3) after adjustment for clinical-pathological and socioeconomic (median household income level, percentage of individuals with at least bachelor's degree, marital status), stratified by race/ethnicity. Metropolitan residence was used as a reference category for all regression analyses. In Model 1, cases in urban/not adjacent (OR=1.056; 95%CI, 1.013-1.101) and rural/adjacent counties (OR=1.148; 95%CI, 1.033-1.275) were more likely than cases in metropolitan counties to be diagnosed with advanced-stage breast cancer. After stratification by race/ethnicity, non-Hispanic White patients living in rural/not adjacent (OR=1.193; 95%CI, 1.081-1.318), rural/adjacent (OR=1.233; 95%CI, 1.103-1.378), urban/not adjacent (OR=1.141; 95%CI, 1.09-1.194), and urban/adjacent (OR=1.051; 95%CI, 1.012-1.091) counties were all significantly more likely to be diagnosed at advanced stages than those living in metropolitan counties. Non-Hispanic Asian/Pacific Islander patients living in urban/adjacent counties were 46% more likely to be diagnosed at advanced stages than those in metro counties (OR=1.461; 95%CI, 1.01-2.112), but differences were not significant for women in other rural/urban categories. And Hispanic women only in urban/adjacent counties were 28% more likely to be diagnosed with advanced-stage breast cancer (OR=1.282; 95%CI, 1.049-1.567) than patients in metro counties. No significant differences were observed for non-Hispanic Black patients. In Model 2, after adjusting for age, grade, and IHC subtype, unstratified odds ratios were significant and increased for urban/not adjacent (OR=1.098; 95%CI, 1.052-1.145), rural/adjacent (OR=1.188; 95%CI, 1.068-1.236), and rural/not adjacent

(OR=1.121; 95%CI, 1.013-1.236). Non-Hispanic White cases living in rural/not adjacent (OR=1.219; 95%CI, 1.102-1.348), rural/adjacent (OR=1.244; 95%CI, 1.112-1.393), urban/not adjacent (OR=1.16; 95%CI, 1.108-1.215), and urban/adjacent (OR=1.064; 95%CI, 1.024-1.105) counties still were significantly more likely to be diagnosed at advanced stages than those living in metropolitan counties. After adjustment, NHAPI patients in urban/adjacent counties maintained their increased likelihood of advanced-stage breast cancer at diagnosis (OR=1.466; 95%CI, 1.008-2.133) in comparison to those from metropolitan counties, and those in other urban/rural categories also did not show significant differences. Hispanic women living in urban/not adjacent counties still were 27% more likely to be diagnosed at advanced stages (OR=1.271; 95%CI, 1.034-1.561) than those in metropolitan counties, but no significant differences were observed for other rural/urban categories. No significant differences were seen for any rural/urban residence categories in NHB patients. Finally, in Model 3 after adjusting for clinical-pathological and SE factors (percentage of individuals with at least bachelor's degree, percentage of families below poverty level, and marital status), unstratified analysis showed that cases in urban/adjacent counties about 5% less likely than those in metro counties to present advanced breast cancer at diagnosis (OR=0.954; 95%CI, 0.919-0.989). In stratified analysis, the inclusion of SE factors in the model attenuated the differences seen in Model 2 and only NHW cases living in urban/not adjacent counties had significantly but only slightly larger odds of advanced-stage breast cancer at diagnosis than those in metro counties (OR=1.055; 95%CI, 1.005-1.107), while the rest of the comparisons were not significant. In all categories, the highest odds ratios were observed in women living in rural/adjacent counties.

Table 6 shows the adjusted odds ratios of advanced stage at diagnosis using the same regression models. In the crude analysis, unstratified odds ratios were significant for cases in urban/not adjacent (OR=1.049; 95%CI, 1.006-1.093) and rural/adjacent (OR=1.145; 95%CI, 1.271) counties compared to those in metro counties. In stratified analysis, NHW cases in rural/adjacent (OR=1.256; 95%CI, 1.124-1.403), rural/not adjacent (OR=1.197; 956%CI, 1.084-1.322), urban/adjacent (OR=1.056; 95%CI, 1.017-1.096), and urban/not adjacent (OR=1.135; 95%CI, 1.085-1.188) were all more likely to have a breast cancer tumor larger than 2 cm at diagnosis than those in metropolitan counties. Only NHBs (OR=1.203; 95%CI, 1.002-1.443) and Hispanics (OR=1.22; 95%CI, 1.003-1.483) in urban/not adjacent counties were more likely than their peers living in metro counties to be diagnosed with breast tumors >2 cm at diagnosis, while the differences in the rest of rural/urban categories for NHBs, NHAPIs, and Hispanics were not significant. After adjustment for age, tumor grade at diagnosis, and IHC subtype, unstratified odds ratios were significant for NHWs in urban/not adjacent (OR=1.098; 95%CI, 1.052-1.145), rural/adjacent (OR=1.188; 95%CI, 1.068-1.322), and rural/not adjacent counties (OR=1.121; 95%CI, 1.016-1.236) compared to metro counties. In stratified analysis, the inclusion of age, grade, and IHC subtype in the model increased the odds ratios for all the urban and rural categories for NHWs, but the differences became not significant for NHBs and Hispanics living in urban/not adjacent counties. After adjustment for SE factors, all odds ratios were reduced and significant differences were only observed in NHW patients in urban/not adjacent (OR=1.065; 95%CI, 1.014-1.117) and rural/adjacent (OR=1.172; 95%CI, 1.045-1.314) counties.

Table 7 shows the adjusted odds ratios of receipt of cancer-directed surgery using the same models. This analysis only included a subsample of 253,823 patients with stages 0-III, because patients with stage-IV breast cancer (metastatic) are not candidates for surgery in current guidelines.[68] In the crude and unstratified regression analysis, cases in urban/adjacent (OR=1.403; 95%CI, 1.264-1.557), urban/not adjacent (OR=1.389; 95%CI, 1.224-1.576), rural/adjacent (OR=1.535; 95%CI, 1.096-2.149), and rural/not adjacent (OR=1.39; 95%CI, 1.036-1.865) counties were all more likely to receive cancer-directed surgery than cases in metropolitan counties. In stratified analysis, only NHW cases in urban/adjacent (OR=1.266; 95%CI, 1.125-1.424) or urban/not adjacent counties (OR=1.163; 95%CI; 1.013-1.335), as well as NHB cases in urban/adjacent counties (OR=1.383; 95%CI, 1.06-1.804), and Hispanic patients in urban/adjacent counties (OR=1.885; 95%CI, 1.105-3.216) were all significantly more likely to have received cancer-directed surgery than those living in metropolitan counties. An inverse relationship was seen for NHBs in rural/not adjacent counties, where cases were only 43% as likely to receive cancer-directed surgery than those living in metro counties. In Model 2, unstratified odds ratios were significantly higher for urban/adjacent (OR=1.472; 95%CI, 1.325-1.635), urban/not adjacent (OR=1.45; 95%CI, 1.276-1.647), rural/adjacent (OR=1.535; 95%CI, 1.096-2.149), and rural/not adjacent (OR=1.39; 95%CI, 1.036-1.865) than in Model 1. In stratified analysis, the inclusion of clinical-pathological covariates to the regression model increased the odds in urban/adjacent (OR=1.31; 95%CI, 1.163-1.475), urban/not adjacent (OR=1.201; 95%CI, 1.045-1.38), and rural/not adjacent counties (OR=1.417; 95%CI, 1.022-1.963) for NHWs. Finally, in Model 3 after adjustment for SE factors, unstratified odds ratios significant only for cases in urban/adjacent (OR=1.313; 95%CI, 1.177-1.464), urban/not adjacent (OR=1.355; 95%CI, 1.188-1.545), and rural/not adjacent (OR=1.515; 95%CI, 1.122-2.045). In stratified analysis, however, the odds ratios for almost all rural/urban and racial/ethnic categories were greatly reduced when compared to the results from Model 2 and became non-significant.

Table 1: Demographic, Clinical, and Socioeconomic Characteristics of Study Population.

Characteristics	**RURAL/URBAN RESIDENCE**						
	Total	**Metropolitan Area**	**Urban/Adjacent to Metropolitan Area**	**Urban/Not Adjacent to Metropolitan Area**	**Rural/Adjacent to Metropolitan Area**	**Rural/Not Adjacent to Metropolitan Area**	***p***
TOTAL	**272,448**	*246,185 (90.36%)*	*13,914 (5.1%)*	*9,259 (3.4%)*	*1,414 (0.52%)*	*1,676 (0.62%)*	
	Age: Mean±SD = 60.4±13.43 years						
<49 years	*61,263 (22.48%)*	56,707 (23.03%)	2,430 (17.46%)	1,638 (17.69%)	249 (17.61%)	239 (14.26%)	**<.0001**
50-59 years	*68,878 (25.28%)*	62,726 (25.48%)	3,244 (23.31%)	2,174 (23.48%)	341 (24.12%)	393 (23.45%)	
60-74 years	*26,412 (9.69%)*	23,361 (9.49%)	1,599 (11.49%)	1,070 (11.56%)	150 (10.61%)	232 (13.84%)	
>75 years	*115,895 (42.53%)*	103,391 (42%)	6,641 (47.73%)	4,377 (47.27%)	674 (47.67%)	812 (48.45%)	
	Race/Ethnicity						
Non-Hispanic White	*185,994 (68.26%)*	163,505 (66.42%)	11,831 (85.03%)	7,824 (84.5%)	1,255 (88.76%)	1,579 (94.21%)	**<.0001**
Non-Hispanic Black	*30,148 (11.06%)*	27,994 (11.37%)	1,459 (10.49%)	495 (5.35%)	139 (9.83%)	61 (3.64%)	
Non-Hispanic API	*24,325 (8.92%)*	23,675 (9.62%)	120 (0.86%)	517 (5.58%)	8 (0.57%)	5 (0.3%)	
Hispanic	*31,981 (11.73%)*	31,011 (12.6%)	504 (3.62%)	423 (4.57%)	12 (0.85%)	31 (1.85%)	
	AJCC Stage						
0	*354 (0.13%)*	312 (0.13%)	22 (0.16%)	15 (0.16%)	2 (0.14%)	3 (0.18%)	**.0007**
I	*132,548 (48.65%)*	119,938 (49.69%)	6,799 (49.71%)	4,382 (48.15%)	640 (45.91%)	789 (47.99%)	
II	*89,796 (32.95%)*	81,137 (33.62%)	4,524 (33.08%)	3,105 (34.12%)	485 (34.79%)	545 (33.15%)	
III	*31,125 (11.42%)*	28,031 (11.61%)	1,587 (11.6%)	1,104 (12.13%)	180 (12.91%)	223 (13.56%)	
IV	*13,346 (4.89%)*	11,936 (4.95%)	744 (5.44%)	495 (5.44%)	87 (6.24%)	84 (5.11%)	
Unknown	*5,279 (1.93%)*	4,831 (1.96%)	238 (1.71%)	158 (1.71%)	20 (1.41%)	32 (1.91%)	
	Advanced Stage at Diagnosis						
Yes	*139,546 (51.21%)*	125,935 (51.15%)	7,093 (50.98%)	4,862 (52.51%)	772 (54.6%)	884 (52.74%)	**.0048**

No	*132,902 (48.78%)*	120,250 (48.85%)	6,821 (49.02%)	4,397 (47.49%)	642 (45.4%)	792 (47.26%)	
	Tumor Size >2 cm						
Yes	*129,713 (47.61%)*	117,062 (47.55%)	6,594 (47.39%)	4,513 (48.74%)	720 (50.92%)	824 (49.16%)	**.0103**
No	*142,735 (52.39%)*	129,123 (52.45%)	7,320 (52.61%)	4,746 (51.26%)	694 (49.08%)	852 (50.84%)	
	Immunohistochemical (IHC) Subtype						
HR+/HER-	*185,662 (68.14%)*	168,116 (68.29%)	9,280 (66.7%)	6,225 (67.23%)	941 (66.55%)	1,100 (65.63%)	**<.0001**
HR+/HER2+	*28,626 (10.5%)*	25,961 (10.55%)	1,404 (10.09%)	935 (10.1%)	149 (10.54%)	177 (10.56%)	
HR-/HER2+	*12,364 (4.53%)*	11,180 (4.54%)	606 (4.36%)	432 (4.67%)	64 (4.53%)	82 (4.89%)	
HR-/HER2-	*28,964 (10.63%)*	25,954 (10.54%)	1,632 (11.73%)	1,015 (10.96%)	176 (12.45%)	187 (11.16%)	
Unknown	*16,832 (6.17%)*	14,974 (6.08%)	992 (7.13%)	652 (7.04%)	84 (5.94%)	130 (7.76%)	
	Grade						
Well Differentiated (I)	*56,067 (20.57%)*	50,420 (20.48%)	3,031 (21.78%)	1,956 (21.13%)	300 (21.22%)	360 (21.48%)	**<.0001**
Moderately Differentiated (II)	*115,703 (42.46%)*	104,903 (42.61%)	5,725 (41.15%)	3,848 (41.56%)	542 (38.33%)	685 (40.87%)	
Poorly Differentiated (III)	*87,280 (32.03%)*	78,678 (31.96%)	4,480 (32.2%)	3,054 (32.98%)	516 (36.49%)	552 (32.94%)	
Undifferentiated (IV)	*866 (0.31%)*	786 (0.32%)	44 (0.32%)	24 (0.26%)	4 (0.28%)	8 (0.48%)	
Unknown	*12,532 (4.6%)*	11,398 (4.63%)	634 (4.56%)	377 (4.07%)	52 (3.68%)	71 (4.24%)	
	Receipt of Cancer-Directed Surgery						
Yes	243,813 (96.05%)	220,121 (95.95%)	12,554 (97.08%)	8,352 (97.05%)	1,272 (97.32%)	1,514 (97.05%)	**<.0001**
No	10,010 (3.94%)	9,297 (4.05%)	378 (2.92%)	254 (2.95%)	35 (2.68%)	46 (2.95%)	
	County % of Families Below Poverty Level (Quartiles)						
Q1 (1.74%-7.28%)	67,875 (24.91%)	62,997 (25.59%)	3,105 (22.32%)	1,360 (14.69%)	235 (16.62%)	178 (10.62%)	**<.0001**
Q2 (7.29%-10.16%)	65,107 (23.89%)	62,349 (25.33%)	1,333 (9.58%)	1,007 (10.88%)	118 (8.35%)	300 (17.9%)	
Q3 (10.17%-13.93%)	54,986 (20.18%)	50,209 (20.39%)	2,217 (15.93%)	1,960 (21.17%)	307 (21.71%)	293 (17.48%)	
Q4 (13.94%-41.45%)	84,480 (31%)	70,630 (28.69%)	7,259 (52.17%)	4,932 (53.27%)	754 (53.32%)	905 (54%)	

	County % of Individuals with at Least Bachelor's Degree (Quartiles)						
Q1 (4.94%-23.7%)	65,995 (24.22%)	45,853 (18.63%)	10,471 (75.26%)	6,749 (72.89%)	1,411 (99.79%)	1,511 (90.16%)	**<.0001**
Q2 (23.8%-31.28%)	69,361 (25.45%)	65,448 (26.58%)	1,395 (10.03%)	2,443 (26.39%)	3 (0.21%)	72 (4.3%)	
Q3 (31.29%-38.44%)	61,698 (22.64%)	59,906 (24.33%)	1,725 (12.4%)	67 (0.72%)	0 (0%)	0 (0%)	
Q4 (38.45%-64.59%)	75,394 (27.67%)	74,978 (30.46%)	323 (2.32%)	0 (0%)	0 (0%)	93 (5.55%)	
	Marital Status						
Married	158,061 (58.01%)	142,364 (57.83%)	8,327 (59.85%)	5,479 (59.17%)	864 (61.1%)	1,027 (61.28%)	**<.0001**
Not Married	114,387 (41.98%)	103,821 (42.17%)	5,587 (40.15%)	3,780 (40.83%)	550 (38.9%)	649 (38.72%)	

Abbreviations: NHWs, non-Hispanic Whites; NHBs, non-Hispanic Blacks; APIs, Asian/Pacific Islanders, HR, hormone receptor; HER2, human epidermal growth factor receptor 2. All results are number (%).

Table 2: Stage at Diagnosis and Rural/Urban Residence by Race/Ethnicity.

Characteristics	**RURAL/URBAN RESIDENCE**						
	Total	***Metropolitan Area***	***Urban/Adjacent to Metropolitan Area***	***Urban/Not Adjacent to Metropolitan Area***	***Rural/Adjacent to Metropolitan Area***	***Rural/Not Adjacent to Metropolitan Area***	***p***
Non-Hispanic Whites (NHWs)							
Early Stage (0-I)	*96,488 (51.87%)*	85,295 (52.17%)	6,026 (50.93%)	3,824 (48.88%)	589 (46.93%)	754 (47.75%)	**<.0001**
Advanced Stage (II-IV)	*89,506 (48.12%)*	78,210 (47.83%)	5,805 (49.07%)	4,000 (51.12%)	666 (53.07%)	825 (52.25%)	
Non-Hispanic Blacks (NHBs)							
Early Stage (0-I)	*11,651 (38.64%)*	10,871 (38.83%)	535 (36.67%)	173 (34.95%)	48 (34.53%)	24 (39.34%)	.154
Advanced Stage (II-IV)	*18,497 (61.35%)*	17,123 (61.17%)	924 (63.33%)	322 (65.05%)	91 (65.47%)	37 (60.66%)	
Non-Hispanic Asian/Pacific Islanders (NHAPIs)							
Early Stage (0-I)	*11,567 (47.55%)*	11,266 (47.59%)	46 (38.33%)	250 (48.36%)	1 (12.5%)	4 (80%)	.036
Advanced Stage (II-IV)	*12,758 (52.45%)*	12,409 (52.41%)	74 (61.67%)	267 (51.64%)	7 (87.5%)	1 (20%)	
Hispanics							
Early Stage (0-I)	*13,196 (41.26%)*	12,818 (41.33%)	214 (42.46%)	150 (35.46%)	4 (33.33%)	10 (32.26%)	.108
Advanced Stage (II-IV)	*18,785 (58.74%)*	18,193 (58.67%)	290 (57.54%)	273 (64.54%)	8 (66.67%)	21 (67.74%)	

Abbreviations: NHWs, non-Hispanic Whites; NHBs, non-Hispanic Blacks; APIs, Asian/Pacific Islanders. All results are number (%).

Table 3: Tumor Size at Diagnosis and Rural/Urban Residence by Race/Ethnicity.

Characteristics	RURAL/URBAN RESIDENCE						
	Total	***Metropolitan Area***	***Urban/Adjacent to Metropolitan Area***	***Urban/Not Adjacent to Metropolitan Area***	***Rural/Adjacent to Metropolitan Area***	***Rural/Not Adjacent to Metropolitan Area***	***p***
Non-Hispanic Whites (NHWs)							
Tumor ≤ 2 cm	103,072 (55.41%)	91,090 (55.71%)	6,432 (54.37%)	4,113 (52.57%)	628 (50.04%)	809 (51.23%)	**<.0001**
Tumor >2 cm	82,922 (44.59%)	72,415 (44.29%)	5,399 (45.63%)	3,711 (47.43%)	627 (49.96%)	770 (48.77%)	
Non-Hispanic Blacks (NHBs)							
Tumor ≤ 2 cm	13,049 (43.28%)	12,166 (43.46%)	605 (41.47%)	193 (38.99%)	58 (41.73%)	27 (44.26%)	.1852
Tumor >2 cm	17,099 (56.72%)	15,828 (56.54%)	854 (58.53%)	302 (61.01%)	81 (58.27%)	34 (55.74%)	
Non-Hispanic Asian/Pacific Islanders (NHAPIs)							
Tumor ≤ 2 cm	12,072 (49.62%)	11,748 (49.62%)	50 (41.67%)	268 (51.84%)	2 (25%)	4 (80%)	.0977
Tumor >2 cm	12,253 (50.38%)	11,927 (50.38%)	70 (58.33%)	249 (48.16%)	6 (75%)	1 (20%)	
Hispanics							
Tumor ≤ 2 cm	14,542 (45.47%)	14,119 (45.53%)	233 (46.23%)	172 (40.66%)	6 (50%)	12 (38.71%)	.3111
Tumor >2 cm	17,439 (54.53%)	16,892 (54.47%)	271 (53.77%)	251 (59.34%)	6 (50%)	19 (61.29%)	

Abbreviations: NHWs, non-Hispanic Whites; NHBs, non-Hispanic Blacks; NHAPIs, non-Hispanic Asian/Pacific Islanders. All results are number (%).

Table 4: Receipt of Cancer-Directed Surgery and Rural/Urban Residence by Race/Ethnicity.

Characteristics	**Rural-Urban Residence**						
	Total	***Metropolitan Area***	***Urban/Adjacent to Metropolitan Area***	***Urban/Not Adjacent to Metropolitan Area***	***Rural/Adjacent to Metropolitan Area***	***Rural/Not Adjacent to Metropolitan Area***	***p***
Non-Hispanic Whites (NHWs)							
Yes	168,317 (96.64%)	147,967 (96.57%)	10,718 (97.27%)	7,062 (97.03%)	1,135 (97.51%)	1,435 (97.42%)	**<.0001**
No	5,846 (3.36%)	5,262 (3.43%)	301 (2.73%)	216 (2.97%)	29 (2.49%)	38 (2.58%)	
Non-Hispanic Blacks (NHBs)							
Yes	25,598 (94.06%)	23,729 (93.97%)	1,272 (95.57%)	431 (95.35%)	118 (95.16%)	48 (87.27%)	**.0179**
No	1,615 (5.94%)	1,522 (6.03%)	59 (4.43%)	21 (4.65%)	6 (4.84%)	7 (12.73%)	
Asian/Pacific Islanders (APIs)							
Yes	21,882 (95.77%)	21,281 (95.69%)	103 (96.26%)	486 (99.39%)	7 (100%)	5 (100%)	**.0022**
No	1,583 (4.23%)	959 (4.31%)	4 (3.74%)	3 (0.61%)	0 (0%)	0 (0%)	
Hispanics							
Yes	28,016 (94.65%)	27,144 (94.58%)	461 (97.05%)	373 (96.38%)	12 (100%)	26 (96.3%)	.067
No	1,583 (5.35%)	1,554 (5.42%)	14 (2.95%)	14 (3.62%)	0 (0%)	1 (3.7%)	

Abbreviations: NHWs, non-Hispanic Whites; NHBs, non-Hispanic Blacks; APIs, Asian/Pacific Islanders. All results are number (%).

Table 5: Association of Rural/Urban Residence and Advanced Stage at Diagnosis Stratified by Race/Ethnicity.

Rural/Urban Residence	*Not Stratified*	Stratified by Race/Ethnicity			
		NHWs	*NHBs*	*NHAPIs*	*Hispanics*
MODEL 1					
Metropolitan	*Reference*				
Urban/Adjacent to Metropolitan Area	0.993 (0.96 - 1.027)	**1.051 (1.012 - 1.091)**	1.096 (0.983 - 1.223)	**1.461 (1.01 - 2.112)**	0.955 (0.799 -1.141)
Urban/Not Adjacent to Metropolitan Area	**1.056 (1.013 - 1.101)**	**1.141 (1.09 - 1.194)**	1.182 (0.981 - 1.424)	0.97 (0.814 - 1.154)	**1.282 (1.049 - 1.567)**
Rural/Adjacent to Metropolitan Area	**1.148 (1.033 - 1.275)**	**1.233 (1.103 - 1.378)**	1.204 (0.848 - 1.709)	6.347 (0.782 - 51.541)	1.409 (0.424 - 4.68)
Rural/Not Adjacent to Metropolitan Area	1.066 (0.968 - 1.173)	**1.193 (1.081 - 1.318)**	0.979 (0.585 - 1.637)	0.227 (0.025 - 2.031)	1.479 (0.697 - 3.143)
MODEL 2					
Metropolitan	*Reference*				
Urban/Adjacent to Metropolitan Area	1.028 (0.993 - 1.065)	**1.064 (1.024 - 1.105)**	1.108 (0.991 - 1.238)	**1.466 (1.008 - 2.133)**	1.021 (0.85 - 1.225)
Urban/Not Adjacent to Metropolitan Area	**1.098 (1.052 - 1.145)**	**1.16 (1.108 - 1.215)**	1.187 (0.982 - 1.435)	1.034 (0.866 - 1.235)	**1.271 (1.034 - 1.561)**
Rural/Adjacent to Metropolitan Area	**1.188 (1.068 - 1.322)**	**1.244 (1.112 - 1.393)**	1.228 (0.86 - 1.755)	7.17 (0.876 - 58.662)	1.648 (0.486 - 5.587)
Rural/Not Adjacent to Metropolitan Area	**1.121 (1.016 - 1.236)**	**1.219 (1.102 - 1.348)**	0.88 (0.519 - 1.494)	0.249 (0.028 - 2.235)	1.646 (0.765 - 3.543)
MODEL 3					
Metropolitan	*Reference*				
Urban/Adjacent to Metropolitan Area	**0.954 (0.919 - 0.989)**	0.991 (0.952 - 1.031)	1.051 (0.934 - 1.184)	1.310 (0.897 - 1.913)	0.987 (0.819 - 1.188)
Urban/Not Adjacent to Metropolitan Area	0.99 (0.948 - 1.035)	**1.055 (1.005 - 1.107)**	1.117 (0.919 - 1.357)	0.953 (0.796 - 1.14)	1.224 (0.994 - 1.507)
Rural/Adjacent to Metropolitan Area	1.075 (0.965 - 1.197)	1.120 (0.999 - 1.256)	1.155 (0.805 - 1.655)	6.172 (0.748 - 50.939)	1.650 (0.487 - 5.59)
Rural/Not Adjacent to Metropolitan Area	0.956 (0.866 - 1.056)	1.076 (0.971 - 1.192)	0.827 (0.486 - 1.408)	0.218 (0.024 - 1.967)	1.597 (0.739 - 3.451)

Abbreviations: NHWs, non-Hispanic Whites; NHBs, non-Hispanic Blacks; NHAPIs, non-Hispanic Asian/Pacific Islanders. All results are odds ratios (OR) with 95% confidence intervals. All results that are significant for an α level of <.0001 are shown in boldface. The models used for logistic regression analysis were: (1) Unadjusted; (2) adjusted for clinical-pathologic factors (age, tumor grade, and immunohistochemical subtype); and (3) adjusted for socio-economic factors (median family income, percentage of individuals with at least bachelor’s degree, and marital status) in addition to the clinical-pathological factors used in Model 2.

Table 6: Association of Rural/Urban Residence and Tumor Size >2 cm at Diagnosis Stratified by Race/Ethnicity.

Rural/Urban Residence	*Not Stratified*	Stratified by Race/Ethnicity			
		NHWs	*NHBs*	*NHAPIs*	*Hispanics*
MODEL 1					
Metropolitan	*Reference*				
Urban/Adjacent to Metropolitan Area	0.994 (0.96 - 1.028)	**1.056 (1.017 - 1.096)**	1.085 (0.975 - 1.207)	1.379 (0.958 - 1.984)	0.972 (0.815 - 1.16)
Urban/Not Adjacent to Metropolitan Area	**1.049 (1.006 - 1.093)**	**1.135 (1.085 - 1.188)**	**1.203 (1.002 - 1.443)**	0.915 (0.769 - 1.09)	**1.22 (1.003 - 1.483)**
Rural/Adjacent to Metropolitan Area	**1.145 (1.031 - 1.271)**	**1.256 (1.124 - 1.403)**	1.073 (0.766 - 1.505)	2.948 (0.595 - 14.597)	0.836 (0.270 - 2.592)
Rural/Not Adjacent to Metropolitan Area	1.067 (0.969 - 1.174)	**1.197 (1.084 - 1.322)**	0.968 (0.584 - 1.605)	0.249 (0.028 - 2.211)	1.323 (0.642 - 2.727)
MODEL 2					
Metropolitan	*Reference*				
Urban/Adjacent to Metropolitan Area	1.028 (0.993 - 1.065)	**1.063 (1.023 - 1.104)**	1.086 (0.974 - 1.212)	1.379 (0.95 - 2.002)	1.027 (0.856 - 1.232)
Urban/Not Adjacent to Metropolitan Area	**1.098 (1.052 - 1.145)**	**1.149 (1.097 - 1.204)**	1.189 (0.987 - 1.432)	0.968 (0.809 - 1.158)	1.189 (0.972 - 1.454)
Rural/Adjacent to Metropolitan Area	**1.188 (1.068 - 1.322)**	**1.265 (1.130 - 1.416)**	1.093 (0.773 - 1.544)	3.409 (0.676 - 17.186)	0.937 (0.296 - 2.967)
Rural/Not Adjacent to Metropolitan Area	**1.121 (1.016 - 1.236)**	**1.213 (1.097 - 1.342)**	0.851 (0.504 - 1.438)	0.275 (0.031 - 2.46)	1.453 (0.692 - 3.048)
MODEL 3					
Metropolitan	*Reference*				
Urban/Adjacent to Metropolitan Area	**0.954 (0.919 - 0.989)**	1.008 (0.968 - 1.05)	1.040 (0.925 - 1.168)	1.242 (0.853 - 1.808)	1.009 (0.838 - 1.213)
Urban/Not Adjacent to Metropolitan Area	0.99 (0.948 - 1.035)	**1.065 (1.014 - 1.117)**	1.129 (0.932 - 1.367)	0.897 (0.749 - 1.076)	1.162 (0.948 - 1.425)
Rural/Adjacent to Metropolitan Area	1.075 (0.965 - 1.197)	**1.172 (1.045 - 1.314)**	1.038 (0.732 - 1.472)	2.969 (0.581 - 15.178)	0.958 (0.302 - 3.036)
Rural/Not Adjacent to Metropolitan Area	0.956 (0.866 - 1.056)	1.091 (0.984 - 1.209)	0.808 (0.477 - 1.369)	0.243 (0.027 - 2.188)	1.438 (0.683 - 3.029)

Abbreviations: NHWs, non-Hispanic Whites; NHBs, non-Hispanic Blacks; NHAPIs, non-Hispanic Asian/Pacific Islanders. All results are odds ratios (OR) with 95% confidence intervals. All results that are significant for an α level of <.0001 are shown in boldface. The models used for logistic regression analysis were: (1) Unadjusted; (2) adjusted for clinical-pathologic factors (age, tumor grade, and immunohistochemical subtype); and (3) adjusted for socio-economic factors (median family income, percentage of individuals with at least bachelor's degree, and marital status) in addition to the clinical-pathological factors used in Model 2.

Table 7: Association of Rural/Urban Residence on Receipt of Cancer-Directed Surgery Stratified by Race/Ethnicity.

Rural/Urban Residence	*Not Stratified*	Stratified by Race/Ethnicity			
		NHWs	*NHBs*	*NHAPIs*	*Hispanics*
MODEL 1					
Metropolitan	*Reference*				
Urban/Adjacent to Metropolitan Area	**1.403 (1.264 - 1.557)**	**1.266 (1.125 - 1.424)**	**1.383 (1.06 - 1.804)**	1.160 (0.426 - 3.157)	**1.885 (1.105 - 3.216)**
Urban/Not Adjacent to Metropolitan Area	**1.389 (1.224 - 1.576)**	**1.163 (1.013 - 1.335)**	1.316 (0.847 - 2.046)	**7.300 (2.342 - 22.756)**	1.525 (0.892 - 2.607)
Rural/Adjacent to Metropolitan Area	**1.535 (1.096 - 2.149)**	1.391 (0.961 - 2.012)	1.261 (0.555 - 2.869)	--	--
Rural/Not Adjacent to Metropolitan Area	**1.39 (1.036 - 1.865)**	1.342 (0.972 - 1.854)	**0.439 (0.199 - 0.973)**	--	1.489 (0.202 - 10.976)
MODEL 2					
Metropolitan	*Reference*				
Urban/Adjacent to Metropolitan Area	**1.472 (1.325 - 1.635)**	**1.31 (1.163 - 1.475)**	**1.453 (1.111 - 1.9)**	1.127 (0.412 - 3.083)	**7.408 (2.374 - 23.12)**
Urban/Not Adjacent to Metropolitan Area	**1.45 (1.276 - 1.647)**	**1.201 (1.045 - 1.38)**	1.438 (0.921 - 2.245)	**7.408 (2.374 - 23.12)**	1.568 (0.915 - 2.686)
Rural/Adjacent to Metropolitan Area	**1.585 (1.13 - 2.223)**	1.402 (0.966 - 2.035)	1.338 (0.585 - 3.061)	--	--
Rural/Not Adjacent to Metropolitan Area	**1.489 (1.108 - 2.002)**	**1.417 (1.022 - 1.963)**	0.548 (0.243 - 1.239)	--	1.587 (0.212 - 11.857)
MODEL 3					
Metropolitan	*Reference*				
Urban/Adjacent to Metropolitan Area	**1.313 (1.177 - 1.464)**	1.118 (0.987 - 1.266)	1.255 (0.945 - 1.667)	1.262 (0.457 - 3.484)	1.714 (0.997 - 2.945)
Urban/Not Adjacent to Metropolitan Area	**1.355 (1.188 - 1.545)**	1.034 (0.894 - 1.196)	1.243 (0.787 - 1.964)	**7.869 (2.516 - 24.611)**	1.480 (0.859 - 2.551)
Rural/Adjacent to Metropolitan Area	1.322 (0.94 - 1.859)	1.113 (0.764 - 1.622)	1.093 (0.474 - 2.519)	--	--
Rural/Not Adjacent to Metropolitan Area	**1.515 (1.122 - 2.045)**	1.232 (0.885 - 1.714)	0.451 (0.198 - 1.028)	--	1.325 (0.176 - 9.992)

Abbreviations: NHWs, non-Hispanic Whites; NHBs, non-Hispanic Blacks; NHAPIs, non-Hispanic Asian/Pacific Islanders. All results are odds ratios (OR) with 95% confidence intervals. All results that are significant for an α level of <.0001 are shown in boldface. The models used for logistic regression analysis were: (1) Unadjusted; (2) adjusted for clinical-pathologic factors (age, tumor grade, and immunohistochemical subtype); and (3) adjusted for socio-economic factors (median family income, percentage of individuals with at least bachelor's degree, and marital status) in addition to the clinical-pathological factors used in Model 2.

Chapter 4

Discussion

In this nationally representative study of women with new diagnosis of primary breast cancer, we sought to analyze the associations between rural/urban residence and three important breast cancer outcomes: the likelihood of being diagnosed at advanced stages, the likelihood of being diagnosed with a tumor larger than 2 cm, and the likelihood of receiving surgery for the primary tumor. We found that patients living in rural counties had higher odds of being diagnosed with advanced-stage breast cancer and/or with a breast tumor larger than 2 cm than those living in more urban areas, but these differences were significant mostly for NHW cases after adjusting for clinical-pathological and SE factors. A significant association was also observed in NHAPI cases in urban/adjacent counties and Hispanic cases in urban/not adjacent counties for advanced stage at diagnosis compared to NHAPIs in metro counties; in NHB cases in urban/not adjacent compared to metro counties for advanced stage at diagnosis; and Hispanics in urban/not adjacent compared to metro counties for tumor size >2 cm at diagnosis. The addition of clinical-pathological covariates (age, grade, IHC subtype) to the crude regression model did not affect much of these odds of advanced stage and tumor size >2 cm at diagnosis, but the inclusion of SE factors (percentage of families below poverty, percentage of individuals with at least bachelor's degree, marital status) greatly reduced these odds and attenuated the effect of rural/urban residence on both outcome variables, making most of them non-significant. This is an indication that the effect of rurality on the early detection of breast cancer in NHWs may be better explained by differences in SE determinants than by differences in clinical-pathological factors.

Some previous studies in the United States showed a positive association between rurality and higher probabilities of advanced-stage breast cancer at diagnosis. In 1990, Liff *et al*. showed that White female patients living in rural counties in the state of Georgia were more likely to be diagnosed with non-localized breast cancer when compared to patients in metropolitan Atlanta, but this difference was not significant (OR=1.25; 95%CI, 0.9-1.75), while Black rural patients were even more likely to have a non-localized breast tumor at diagnosis after adjustment for age and year of diagnosis, but this difference was also not significant (OR=1.37; 95%CI, 0.88-2.14).[39] In 1997, Amey *et al*. examined a sample of 79,946 females with diagnosis of breast cancer in Florida between 1981 and 1989 and reported that residents of rural/not adjacent counties in the state had greater odds (OR=1.11) of being diagnosed with advanced-stage breast cancer after adjusting for age, race, smoking status, and several county-level SE variables such as percentage of population below poverty level, but this difference was not significant. After stratifying by race, Black females in rural/not adjacent counties had even greater odds of advanced stage at diagnosis (OR=1.463) than Black females in metro counties, while there were no significant differences in White women (OR=1.076).[58]

However, other studies have shown an inverse association between rurality and risk of advanced stage of breast cancer at diagnosis. McLafferty & Wang (2009) studied cancer patients in the state of Illinois and showed that breast cancer patients living in rural areas and the Chicago metro area were more likely to have a late stage at diagnosis than those in smaller metro areas and large towns.[69] In addition, other studies have not found significant associations between urban/rural residence and stage at diagnosis of breast cancer. For example, Celaya et al. analyzed data from 5,966 females patients with breast cancer in the state of New Hampshire between 1998 and 2004 and found no significant associations between breast cancer stage at diagnosis and urban/rural residence or driving time to the nearest mammography facility.[70] Similarly, Henry *et al*. studied a very large sample of 161,619 female breast cancer patients from 10 state cancer registries and found no significant associations between stage at diagnosis and urban/rural residence or travel time to nearest mammography facility, adjusted for age, race, and poverty level.[71]

The present study also showed that women living in urban or rural counties had a higher likelihood of receiving cancer-directed surgery than those living in metropolitan counties. The addition of SE factors in the regression model reduced the odds for all categories and rendered them non-significant, and this may be an indicator that the effect of rurality on receipt of surgery is largely mediated by SE status. Obeng-Gyasi *et al*. reported in an analysis using the National Cancer Database that residence in a large metro area was associated with a higher probability of receiving breast-conservative surgery compared with rural areas (OR=1.25; 95%CI, 1.19-1.3), but the probability of receiving mastectomy was marginally higher in rural areas compared with metro areas (OR=1.04; 95%CI, 1.01-1.07).[72]

This study had several strengths and limitations. The strengths include the use of the SEER database, one of the most comprehensive and representative cancer registry databases in the United States, the large number of patients included in the analyses, and the use of various clinical-pathological and SE variables to better understand the associations between rurality and breast cancer outcomes.

In terms of limitations, the measure used for definition of rurality in the present study, the Rural-Urban Continuum Code (RUCC), defines rural and urban counties only in terms of their population size and their proximity to metropolitan areas. Other systems such as the Rural-Urban Commuting Area coding system (RUCA), also by the US Department of Agriculture's ERS, defines urban and rural in terms of population density, urbanization, and daily commuting.[73] The definition of rurality using the RUCC system only partially explains the disparities between urban and rural counties in cancer outcomes. Even when the RUCC allows for a very granular analysis with 9 categories that discern not only rurality by population size but also by proximity to metropolitan areas, it does not consider other factors associated with rurality that influence disparities in access to health care resources, such as remoteness to medical facilities or density of PCPs.

One of the limitations of the present study is that even though the SEER database is a comprehensive database covering about 28% of the total cancer patients in the United States, it does not contain much information to explore possible factors contributing to the rural/urban disparity. For example, there are no data about geographical disparities in terms of distance to cancer centers or mammography screening facilities, and the socioeconomic variables offered by SEER are not applicable to individuals but only to larger geographic units such as counties or ZIP codes, which makes analysis complicated by the fact that affluence and other SE determinants may be highly variable among the population within the same county.[74] This analysis did not include some factors that may mediate the complex relationship between rurality and cancer outcomes, such as diet and lifestyle, psychosocial and behavioral factors, and comorbidities that have been shown to influence cancer outcomes but are not included in the SEER database.[75]

Another limitation was the extremely low numbers of NHAPI cases in rural/adjacent (n=8) and rural/not adjacent counties (n=5) counties, as well as of Hispanic cases in rural/adjacent (n=12) and rural/not adjacent (n=31) counties. This fact made it difficult to draw solid statistical conclusions in our analysis and was the reason for the disproportionately high odds ratios seen for NHAPIs and Hispanics in rural counties.

Chapter 5

Conclusions

The present study showed a significant positive association between rurality and the likelihood to be diagnosed with advanced stage or a tumor larger than 2 cm in NHW female patients with primary breast cancer in the United States. However, significant associations between rurality and advanced stage at diagnosis or tumor size >2 cm were not observed among NHB, NHAPI, and Hispanic cases.

There are several definitions for rurality in the literature and this reflects the multidimensionality of the concept of what makes a community urban or rural.[36] Future research efforts will need to disaggregate the seemingly entangled effect of rurality on breast cancer outcomes and the mediation of biologic, lifestyle, socioeconomic, psychosocial, and ecological factors in this association with the goal in mind to collaborate with efforts to improve the access to adequate healthcare and the outcomes of patients with cancer, with special emphasis on disadvantaged and minority populations.

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