DISPARITIES IN BREAST CANCER SUBTYPE, STAGING, AND ACCESS TO MAMMOGRAPHY SERVICES IN THE LOWER MISSISSIPPI DELTA REGION

BY

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DISSERTATION

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ABSTRACT

The Delta Regional Authority (Delta Region) is a federal-state partnership aiming to improve socioeconomic conditions in 252 counties and parishes in the eight state Lower Mississippi Delta Region (LMDR). The Delta Region has a higher proportion of black residents, is poorer, and is more rural than the country as a whole. It also has far higher breast cancer mortality rates than the nation. Black women in the Region have higher breast cancer mortality rates than white women in the Delta Region and have higher breast cancer mortality rates than black women in other parts of the country. More aggressive breast cancer subtypes, more advanced stage at diagnosis, and less access to screening mammography may play a role in these high mortality rates. Studies have shown that black women have higher rates of the most aggressive breast cancer subtype-- triple-negative--than white women and are often diagnosed at a more advanced stage. Additionally, while poor and rural women tend to have lower incidence rates of breast cancer, they often have a higher odds of late-stage cancer and less access to screening services.

This dissertation sought to elucidate the Delta Region's breast cancer mortality disparity by determining differences between the Delta and non-Delta Regions of the LMDR and by exploring racial differences within the Delta Region among the following areas: breast cancer subtype, breast cancer staging, and spatial access to mammography services. Population-based cancer surveillance data from the North American Association of Central Cancer Registries were analyzed to determine age-adjusted, subtype-specific incidence rates and rate ratios in the Delta and non-Delta Regions of the LMDR. Multilevel negative binomial regression models were constructed to evaluate if identified disparities were attenuated after accounting for race/ethnicity, age, and contextual factors. These analyses were performed for all cases by

subtype and separately for early stage and late stage cancers by subtype. Higher rates of triple-negative breast cancer were identified in the Delta Region compared to the non-Delta Region, but this was attenuated in multivariable models. However, triple-negative breast cancer rates were higher in the urban Delta compared to the urban non-Delta, even after accounting for race/ethnicity, age, and contextual factors. Black residents in the Delta Region had higher rates of hormone receptor-negative breast cancers and higher rates of breast cancer overall compared to white women in the Region. Further, there were no particularly notable differences in late-stage breast cancers between the Delta and non-Delta Regions. However, black women in the Delta Region had lower rates of early-stage breast cancer, but higher rates of late-stage breast cancers compared to white, Delta Region women, even after accounting for age and contextual factors.

To evaluate spatial access to mammography services, this study applied the enhanced two-step floating catchment area method to Food and Drug Administration data and census tract level American Community Survey data. The Food and Drug Administration data provided addresses of all approved mammography facilities in the LMDR and adjacent states while American Community Survey data were used to estimate populations of women of recommended screening age at the census tract level. For the most part, women in the Delta Region had similar spatial access to mammography services as non-Delta Region women. However, clusters of low spatial access within the Delta Region were identified in parts of Arkansas, Tennessee, and Mississippi.

The identified higher incidence of breast cancer in black women in the Delta compared to white women was driven by higher rates of hormone receptor-positive cancers, but further research is needed to determine what individual or contextual factors may be driving the higher

incidence rates. Additionally, this dissertation underscores the importance of community-based, culturally tailored interventions to improve mammography utilization rates and subsequently improve early detection of hormone receptor-positive breast cancers. Furthermore, this dissertation signaled a need for improved state-level policy and geographically targeted regional resource allocation to improve screening access and utilization. Additionally, these findings provide the foundation for further research to explore regional breast cancer disparities at other points along the cancer control continuum (e.g. treatment), to examine regional disparities for other cancers, and to promote collaborative academic partnerships across the Delta Region.

Dedicated to Dereama and Jo.

This dissertation is in honor of my great grandma, Elsie Long, who died of breast cancer when my mom was only seven. May advances in primary prevention, detection, and treatment provide the opportunity for all children to grow up knowing their grandparents.

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My prayer is that, whatever new opportunities that this doctorate brings in my life, God will be glorified.

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CHAPTER 1: INTRODUCTION AND BACKGROUND

The Delta Regional Authority (Delta Region) is a federally designated region of approximately 10 million people in 252 counties and parishes in eight states along the Mississippi River (the Lower Mississippi Delta Region-LMDR). It is a mostly rural region with a high proportion of black residents and high rates of poverty. Because of its sociodemographic composition and limited access to care, it experiences numerous and startling health disparities, including both cancer and access to care inequities. Compared to the nation as a whole, residents in the Delta Region have higher rates of all-cause, cancer, and breast cancer mortality (1-3). Further, breast cancer mortality rates are not only higher among black women in the Delta Region compared to white women, they are also higher among black women in the Delta Region compared to black women in other parts of the country (1). Residents of the Delta Region have limited access to primary care physicians and federally qualified health centers (4,5). Historically, a lower proportion of women in the Delta Region regularly utilize mammography services (4,6). All of these factors may be indicative of less access to mammography services and may lead to an increased risk of late-stage breast cancer. However, there is limited research on what specific cancer factors—subtype, staging, and access to mammography services—may exist in this region that contribute to these higher breast cancer mortality rates. Risk factors for the triple-negative breast cancer subtype and for more advanced cancer staging are more prevalent in this region, including a higher proportion of black residents, geographic location in the South/Midwest, rurality, and higher rates of poverty (7-9). Understanding subtype, staging, and access to mammography differences might help explain the mortality disparities and guide development of preventive interventions and regional policies. These potential solutions are

especially relevant because this study assessed a federally designated region that receives annual appropriations to address specific healthcare infrastructure needs.

Using data from the North American Association of Central Cancer Registries, the Food and Drug Administration, the American Community Survey, the United States Department of Agriculture, and the National Cancer Institute, this dissertation explored the breast cancer subtype, breast cancer staging, and access to mammography differences that exist between the Delta and non-Delta Regions within the LMDR states. Multilevel regression modeling methods were used to examine differences in breast cancer subtype and staging, and geographic information system methods were used to evaluate differences in spatial access to mammography within the LMDR states. This chapter will provide a comprehensive description of the Delta Region and its disparities and a brief summary of breast cancer incidence and mortality in the United States. Finally, this chapter will delineate the specific aims of this dissertation, provide corresponding conceptual frameworks, and review the relevant breast cancer epidemiology literature for each respective specific aim.

The Delta Region

Definition

The Delta Region, as currently defined by the Delta Regional Authority (DRA), includes 252 counties and parishes in eight states along the Mississippi River and the Alabama Black Belt (Figure 1.1). These states include Alabama, Arkansas, Illinois, Kentucky, Louisiana, Mississippi, Missouri, and Tennessee.

History

The first discussion of a Delta Region designation occurred at a meeting of the Southern Regional Growth Policy Board in 1971 which, of particular note, led to an agreement among

nine Southern and Midwestern governors to develop strategies to improve the region's economic situation (10). This state-level collaboration paved the way for future federal action, and in 1988, Congress established the Lower Mississippi Delta Development Commission through the Rural Development, Agriculture, and Related Agencies Appropriations Act. This Commission was the vision of Senator Dale Bumpers of Arkansas and Representative Mike Espy of Mississippi. It sought to evaluate the needs, goals, and objectives of the residents of the Delta Region, which at that time, included 187 counties and parishes in Arkansas, Illinois, Kentucky, Louisiana, Mississippi, Missouri, and Tennessee. Senator Bumpers stated that the counties and parishes of the Delta Region, "share common economic, social and cultural ties, and….suffer from any combination of high unemployment, low net family income, agriculture and oil industry decline, a decrease in small business activity, or poor or inadequate transportation infrastructure, health care, housing, or educational opportunities" (11). This Commission studied the region and created a ten-year plan for economic development. In the subsequent decade, numerous federal agencies and entities also studied the Region's infrastructure and economy to determine how to best to address the region's challenges (12). Then, in 2000, Congress codified the Delta Region as one of the nation's four chartered regional commissions—the Delta Regional Authority-- and extended its geographic reach into the Black Belt of Alabama (13). The regional designation was later expanded to its current extent of 252 counties and parishes across eight states.

Current Delta Regional Authority Efforts

The DRA's current mission is to "work to improve regional economic opportunity by helping to create jobs, build communities, and improve the lives of the 10 million people who reside in the 252 counties and parishes of the eight-state Delta region" (14). In addition to broad socioeconomic efforts, the DRA aims to improve health outcomes, specifically, as a means to

maintaining a healthy workforce. In 2010, the DRA developed an action plan to improve health in the Region. This plan included developing regional personnel infrastructure (e.g. hiring a Director of Health Programs), convening stakeholders throughout the region, developing tools and amassing relevant health data, and initiating grant programs to fund local health initiatives (15).

Additional DRA efforts include Innovative Readiness Training and the Delta Doctors program. Innovative Readiness Training is a partnership between the DRA and the Department of Defense to conduct annual medical missions and provide no-cost medical, optical, and dental services throughout the Region (15). The Delta Doctors Program provides J-1 visa waivers to foreign physicians who agree to practice within medically underserved areas in the Delta Region for at least three years (5). The program has located 346 physicians in practice within the Region, including 80 physicians in 2014 alone. Additionally, DRA investments coupled with both public and private monies have resulted in $101.6 million in healthcare investments between 2002 and 2013 (16). Recent efforts supported by other federal entities include health services grant funding from the United States Department of Agriculture's Rural Development program which provided $5.7 million of funding in 2016 and technical assistance and Affordable Care Act enrollment assistance provided by the Health Resource and Services Administration.

Demographic and Socioeconomic Contextual Characteristics of the Delta Region

The Delta Region's population as of the 2010 census was 9,920,395 people (9). Demographically, the Delta Region has a higher proportion of individuals who are black compared to the nation as a whole (Table 1.1). Socioeconomically, the Delta Region has a higher proportion of residents who live in poverty and a lower proportion of adults who have a high school degree compared to the United States as a whole. Additionally, the Delta Region has a far

higher proportion of counties with persistent poverty (43.3%) than the nation as a whole (11.2%). Persistent poverty counties are defined as areas where 20% or more of the population has been in poverty for the past four census surveys. The Delta Region has a smaller population density than the nation as a whole, indicative of greater rurality in the Region.

Collective Social Factors in the Delta Region

The rural context of the Delta Region coupled with the high proportion of black residents indicates that this region may be particularly susceptible to health disparities (17). Additionally, the social and historical context of the Delta Region (e.g. racism, persistent poverty) have unfortunately facilitated the Region's health disparities (18). Furthermore, a commentary by Hyland suggests that the pervasive, regional cultural beliefs of fatalism (i.e. focus on religious beliefs that leads to ultimate salvation), personalism (i.e. a trust in authority to provide for them), and factionalism (i.e. isolation and distrust of "others") may be additional factors that play a role in the Region's persistent poverty and poor health (10).

Health-Related Disparities in the Delta Region

Studies have found that Delta Region residents indeed experience a myriad of health disparities—ranging from poor health behaviors, high rates of chronic disease, and elevated mortality rates. Multiple studies suggest that Delta Region residents have higher obesity rates and tobacco use compared to people nationwide (2,4). One study found that diabetes and hypertension were more prevalent in Delta Region residents in Arkansas, Mississippi, and Louisiana than they were nationally (19). After controlling for factors like age, income, and gender, blacks in the Region were found to be at particular risk for these chronic diseases. Several studies have indicated that residents of the Delta Region experience mortality rates—for all causes and for cancer specifically—that are persistently in excess of national rates (2-4).

Murray's study of the "eight Americas" (unique demographic groups in the U.S.), although not explicitly evaluating the designated Delta Region, characterized two of these "eight Americas" as reasonably, demographically representative of the Delta Region: 1) low-income whites in Appalachia and the Mississippi Valley and 2) Southern low-income blacks (20). Murray explored the disparities in these "eight Americas" and found that the life expectancy of white women of Appalachia and the Mississippi Valley actually declined during the study period (1982-2001). Similarly, there was a notable 12.8-year life expectancy gap between women in the Southern/Mississippi low-income black group and the group with the longest life expectancy.

Furthermore, Delta Region residents also experience access to care disparities. More Delta Region residents are uninsured (19.2%) compared to both residents in non-Delta Region counties in the eight Delta Region states (17.4%) and residents in the United States a whole (18.0%) (4). Residents also have less access to primary care providers. There are 42.14 primary care providers for every 100,000 residents in the Delta Region compared to 55.24 providers per 100,000 residents nationwide (4). Additionally, 230 counties and parishes (91%) in the Delta Region are considered Health Professional Shortage Areas, and 95 counties and parishes (38%) do not have a Federally Qualified Health Center (5).

More germane to the current study, a limited number of studies suggest that women in the Delta Region experience breast cancer disparities. Trends in breast cancer mortality have varied over the past 30+ years in the Delta Region, but recent rates indicate significant disparities. A 2004 study examined breast cancer mortality rates in the Delta Region compared to the rest of the country between 1979 and 1998 (21). At the beginning of the study period, breast cancer mortality rates in the Delta Region were lower than the rest of the country, but by the end of the study period, the rate of breast cancer mortality in the Delta Region was no different than the rest

of the country. In economically distressed counties, there was no difference in death rates compared to the rest of the country. In non-distressed counties, black women in the Delta had a modestly higher breast cancer mortality rate than black women elsewhere (32.8 vs. 31.0 per 100,000, respectively). A more recent study assessing cancer mortality in the Delta Region between 2008 and 2012 found that breast cancer mortality rates in the Delta were statistically significantly higher than the rest of the country (RR=1.10; 95% CI=1.07-1.13) (1). When stratified by race, there was no difference in breast cancer mortality between Delta Region and non-Delta Region white women. However, breast cancer mortality was higher in black women in the Delta (34.9 per 100,000) compared to their white Delta Region counterparts (21.3 per 100,000) and compared to black women in the rest of the country (29.8 per 100,000). Additionally, the recent study found that breast cancer mortality rates overall in the Delta Region were 24.9 per 100,000 between 2008 and 2012, essentially the same rate reported in the 2004 Hall study for 1994-1998 (24.5 per 100,000), which likely indicates sustained poor breast cancer mortality rates in the region over the last twenty years (1,21). A study by Mokdad and colleagues assessed cancer mortality rates throughout the country using small area estimation methods and found that the Delta Region contains nine of ten counties with the highest breast cancer mortality rates in the United States (22).

Additionally, studies suggest that women in the Delta Region may engage in behaviors that may put them at greater risk for breast cancer, broadly speaking, and at greater risk for late-stage breast cancer, specifically. A study among women of reproductive age in the Mississippi Delta of Mississippi specifically as well as Louisiana, Arkansas, and Tennessee found that women in this area had poorer preconception health behaviors and conditions (i.e. less fruit and vegetable consumption and higher obesity rates) compared to women elsewhere (23). Another

study among women in the rural Delta Region of Mississippi found that breastfeeding rates were low—especially among blacks—as only 24% of study participants had initiated breastfeeding (24). Studies have shown that a smaller proportion of Delta Region women are up-to-date with mammography screening compared to women outside the region (4,6). While more recent data are not available on all women of recommended screening age, a 2004 study found that the age-adjusted percentage of women in the Delta Region over the age of 40 who had a mammogram within the past two years was 69.3%--6.7 percentage points lower than other U.S. women (6). A more recent 2016 study found that, among Medicare women aged 67-69, only 56.9% had a mammogram in the past two years compared to 60.8% nationwide (4).

Breast Cancer Incidence and Mortality Disparities

Age

Women aged 60-69 (26% of cases) comprise the highest proportion of the breast cancer cases, while the greatest proportion of deaths occur in women 80+ years old (25). Eighty percent of invasive breast cancer cases are diagnosed in women 50 years old or older, and 88% of breast cancer death occur among women 50+. The median age of diagnosis and death varies by race. The median age at diagnosis is 58 and 62 years of age for blacks and whites, respectively. The median age of death is also younger for black women (62 years old) than white women (69 years old) (26).

Race/Ethnicity

Historically, white women have higher breast cancer incidence rates while black women have higher mortality rates. However, recent studies have suggested that breast cancer incidence rates are converging among white and black women while mortality rates remain higher in blacks (27,28). The age-adjusted breast cancer incidence rate was 123.6 and 121.5 per 100,000

among whites and blacks, respectively, between 2009 and 2013 (27). However, breast cancer mortality rates differed more markedly by race. The breast cancer mortality rate in black women was 29.2 per 100,000 compared to 20.6 per 100,000 is white women from 2009 to 2014(27). While breast cancer mortality rates have decreased in both black and white women, the disparity in mortality has widened (28).

Socioeconomic Status

Breast cancer incidence rates are generally positively associated with socioeconomic status (SES), regardless of race/ethnicity (i.e. more affluent women have higher rates of breast cancer incidence) (29). A study of California breast cancer cases found a monotonic relationship between a composite measure of neighborhood SES and breast cancer incidence. Compared to the lowest SES group, the medium-low, medium-high, and high SES groups had rate ratios of 1.21, 1.35, and 1.59, respectively (30). A study by Robert and colleagues found that, even after controlling for individual risk factors, women who lived in the highest SES communities had a greater odds of breast cancer incidence (31). SES and breast cancer mortality tend to show a different relationship, as poorer women have higher mortality rates. Analysis of data from the California Breast Cancer Survivorship Consortium found that, except for Asian Americans, women of any race/ethnic group who lived in a low SES neighborhood had higher breast cancer mortality rates regardless of their individual educational attainment (32).

Geographic Location

Breast cancer incidence and mortality vary by rural-urban status and other geographic factors as well. A systematic review and meta-analysis of thirty-one international studies (23 of which were performed in the United States) evaluated the association of residential environment, including rural-urban status, and breast cancer incidence (33). This meta-analysis found that, in

the eight studies that included rural-urban status, breast cancer incidence was modestly higher in urban areas than in rural areas (pooled relative risk=1.09, 95% CI=1.01-1.19). Two recent analyses of population-based cancer registry data representing >90% of the United States population found also indicated that breast cancer incidence rates are higher in urban populations compared to rural (34,35). Both rural and urban populations have experienced a similar decrease in breast cancer incidence, with annual percentage changes of -0.52% and -0.51%, respectively between 1995 and 2013 (35). For the most part, breast cancer mortality rates are similar in rural and urban areas, although the most isolated rural counties had higher rates than those in smaller urban counties (34).

In addition to rural-urban differences in breast cancer incidence and mortality, there are state-to-state differences. Of particular note is that in seven states --Alabama, Kentucky, Louisiana, Mississippi, Missouri, Oklahoma and Tennessee-- breast cancer incidence rates are now higher in black women than in white women (25). Among white women, age-adjusted breast cancer incidence rates range from 107.7 per 100,000 in Arkansas to 164.4 in the District of Columbia (white U.S. rate=128.1 per 100,000) (25). Among black women, age-adjusted breast cancer incidence rates range from 94.0 per 100,000 in Minnesota to 141.7 in Alaska (black US rate=124.3 per 100,000) (25). Age-adjusted breast cancer mortality rates varied from 18.7 per 100,000 in Vermont to 25.4 in Nevada among whites (white US rate=21.9 per 100,000) (25). Among blacks, the breast cancer mortality rate varied from 21.7 per 100,000 in Minnesota to 35.4 in Oklahoma (black US rate=31.0 per 100,000).

Specific Aim #1

Specific Aim #1: To determine differences in breast cancer risk and breast cancer risk by subtype between those living in Delta region and women living in non-Delta region counties in

the Lower Mississippi Delta Region states and between black and white women in the Delta region.

- *Hypothesis 1.1. Delta Region women will have a higher risk of HR- (including triple-negative) breast cancers.*
- *Hypothesis 1.2. Delta Region women will have a lower risk of HR+ breast cancers than non-Delta Region women.*
- *Hypothesis 1.3. Delta Region black women will have a higher risk of HR- breast cancers (especially triple-negative breast cancer) than white Delta Region women.*
- *Hypothesis 1.4. When relevant factors are controlled for, these elevated risks (Hypothesis 1.1-1.3) will be at least partially attenuated.*

In order to achieve the aim of determining whether or not there are differences in breast cancer incidence overall and by subtype between the Delta Region and non-Delta Region of the LMDR states, three types of analyses were performed utilizing population-based cancer surveillance data from the North American Association of Central Cancer Registries. First, incidence rates were calculated to describe the breast cancer burden for all invasive breast cancers and for each breast cancer subtype individually in the Delta Region and non-Delta Regions and by race/ethnicity, rural-urban status, and SES. Second, rate ratios were calculated to assess the magnitude of the difference between the Delta Region and non-Delta Region and by stratifications noted above for all invasive breast cancers and for breast cancer subtypes individually. Third, multilevel models were constructed to calculate rate ratios of all invasive breast cancers and of each breast cancer subtype, separately, while adjusting for age, race/ethnicity, and contextual factors. Thus, it was determined whether or not any differences between the Delta Region and non-Delta Region were attenuated when relevant, confounding

factors are considered. These three types of analyses were also performed as part of a sub-analysis that considers only cases diagnosed within the Delta Region with a particular focus on describing and determining the racial differences in breast cancer burden by subtype within the Region.

Specific Aim 1 Conceptual Framework

The conceptual framework for this aim is largely based on Warnecke's Model for Analysis of Population Health and Health Disparities and Wingo's Framework for Cancer Surveillance (Figure 1.2) (36,37). Warnecke's model is a framework that specifically focuses on the multilevel determinants of health (e.g. cancer) disparities (38). Wingo's framework considers the continuum of cancer progression, including tumor characteristics, such as subtype, that is identified as part of the diagnostic process. The multilevel nature of this model is ideal for the multilevel modeling analytical approach that was employed in the dissertation (Chapter 2) to test Hypothesis 1.4, as hypothesis 1.1-1.3 were tested by calculation of breast cancer incidence rates and rate ratios. The multilevel nature of Warnecke's model indicates that distal, intermediate, and proximal factors play a role in health disparities. Distal factors include social conditions and policies, which may include policy-relevant contexts like the Delta Region designation. Intermediate factors include measures of social and physical context which may include sociodemographic factors like county-level poverty or racial composition, measures of rural-urban status, and utilization of mammography (i.e. a measure of realized accessibility). Additionally, this model includes proximal factors that describe the individual, like age and race. Such intermediate and proximal may explain differences in breast cancer subtype between the Delta and non-Delta Regions (i.e. a distal context) of the LMDR states. The conceptual model

displays the covariates that were determined *a priori* for consideration for inclusion in the model building process. Covariates in the final model are delineated in Chapter 2.

Relevant Literature Review- Sociodemographic Disparities in Breast Cancer Subtypes

Subtype Definition and Descriptive Epidemiology. Clinical assessment of breast cancer routinely includes identification of tumor marker expression that can determine the molecular signature of this cancer, categorizing it into one of four "intrinsic subtypes" (39). These subtypes are defined using three different tumor characteristics—the presence of two hormone tumor receptors (estrogen and progesterone receptors, ER and PR, respectively) and the expression of the protein human epidermal growth factor two (HER2). The four main subtypes of breast cancer are:1) ER+ or PR+ or both, HER2- (also known as HR+/ HER2-); 2) ER+ or PR+ or both, HER2+ (also known as HR+/HER2+); 3) ER- or PR- or both, HER2+ (also known as HR-/ HER2+); or 4) ER- or PR- or both, HER2- (also known as HR-/ HER2- or Triple Negative). For the remainder of this chapter, these subtypes will be referred to by the following designations: HR+/HER2+, HR+/HER2-, HR-/ HER2+, and triple-negative. The inclusion of ER and PR statuses have been required by central cancer registries since 1990, but HER2 status has only been required since 2010 (39).

The hormone receptors and the HER2 protein are often targets for drug therapies that are initiated in combination with chemotherapy following surgical treatment (40). For example, drugs like selective ER modulators (e.g. Tamoxifen) and aromatase inhibitors (e.g. Arimidex) are used to target HR+ cancers in all HR+ cancers and HR+ cancers in postmenopausal women, respectively. For cancers that overexpress HER2 (i.e. HR+/HER2+ and HR-/HER2+), Herceptin is often prescribed. However, for triple-negative cancers, there are no targets for such drugs, which limits treatment options and negatively affects prognosis.

Two of these types are hormone receptor-positive breast cancers: HR+/ HER2- and HR+/ HER2+. HR+/HER2- is the most common subtype (74% of all cases) and has the best prognosis (41). The distribution of this subtype varies by race ranging from 62% of breast cancers in blacks and 76% of cases in whites. All race/ethnicity HR+/HER2- incidence rate in the United States is 86.5 per 100,000, while rates for whites and blacks are 92.7 and 74.4 per 100,000, respectively (41). HR+/ HER2+ is far less frequent comprising only 10% of all cases. The all-race/ethnicity rate of 12.4 per 100,000 and the rate for whites and blacks 12.8 and 12.9 per 100,000, respectively (41). HR+ cancers have better survival rates than HR- subtypes (42). A study found that five-year disease-specific survival for HR+ cancers ranged from 85.8% to 91.6% compared to 76.2% to 82.4% for HR- cancers (42).

There are two types of hormone receptor-negative breast cancers: HR-/ HER2+ and triple-negative. HR-/ HER2+ breast cancer is the least common cancer type (only 4% of breast cancer cases); the all-race/ethnicities incidence rate is 5.5 per 100,000, with rates of 5.4 and 6.7 per 100,000 in white and black women, respectively (25,41). Triple-negative is the more common HR- breast cancer. Studies of large clinical databases and population-based registries estimate that triple-negative cases comprise 11.7-12.9% of breast cancer cases in the United States (7,41,43). The triple-negative breast cancer incidence rate is 15.5 per 100,000 among all women, and age-adjusted rates are 14.4 and 27.2 per 100,000 in white and black women, respectively. HR- breast cancers present at a higher grade and a more advanced stage than other breast cancers (43). Analysis of the Carolina Breast Study found that women with HR- cancers had poorer survival than those with HR+ cancers, while analysis of SEER data found a nearly twofold risk of cancer-specific death in women with HR- cancers compared to those with HR+ cancers (HR=1.91, 95% CI=1.88-1.94) (44,45).

Age. The odds of triple-negative breast cancer are higher in younger women. Studies have indicated HR- breast cancers are more likely to be diagnosed in women under 50 years old (46,47). A study of women with breast cancer in Atlanta showed that the odds of triple-negative cancer were higher among women aged 20 and 39 (OR=2.13, 95% CI=1.34-3.39) than aged 50-54 years when controlling for other factors (47). A study of California Cancer Registry breast cancer cases diagnosed from 1999 to 2003 found that triple-negative breast cancer cases were more likely to be diagnosed in women younger than 40 (OR=1.53, 95% CI=1.37-1.70) and aged 40-49 (OR=1.20, 95% CI=1.02-1.22) compared to the reference group (age 60-69), controlling for race, stage, socioeconomic status, and tumor grade (46). Similarly, a study of SEER 18 data found that triple-negative breast cancer is 10-30% less likely to be diagnosed in women over the age of 65 compared to HR+/HER2- cancers (43).

Race/Ethnicity. Genetic and hereditary factors play a role in the racial and ethnic disparities in incidence of breast cancer incidence rates by subtype (48,49). Although not population-based, some studies of breast cancer patients in west African countries like Ghana found that the proportion of triple-negative breast cancers was as high as 61% or 82% of breast cancers. Newman reviewed seven studies that included diverse samples of breast cancer cases in women of European and African descent (including women of West, Central, Southern, and east African descent) (49). A higher proportion of triple-negative breast cancers was found in women of African descent compared to cases in women of European descent. In studies that included women from different regions of Africa and the United States, the proportion of triple-negative breast cancer cases was highest among West Africans, followed by African Americans, East Africans, and white Americans, respectively (50).

Epidemiologic studies reflect this racial variation in risk of HR- cancers, broadly, and triple-negative cancers, specifically, in the United States. Multiple studies have indicated that the odds of triple-negative breast cancer are twice as high in black women as in white women, even after controlling for relevant factors like age, tumor grade, and stage (41,43,51). Some studies have also shown a higher odds in Hispanic women. An analysis of 2010 data from SEER registries representing approximately 28% of the United States population found that, controlling for age, stage, tumor grade, and registry, black women were twice as likely to have a triple-negative breast cancer diagnosis than white women (OR=2.0, 95 % CI=1.8-2.2) and were also more likely to have a HR-/HER2+ diagnosis (OR=1.4, 95% CI=1.2-1.6) (43). Similarly, Hispanic women had a higher odds of triple negative (OR=1.3, 95% CI=1.2-1.5) and HR-/HER2+ (OR=1.4, 95% CI=1.2-1.6) than non-Hispanic white women. An analysis of National Cancer Database data, which includes ~73% of breast cancer cases diagnosed in the United States, found that non-Hispanic blacks (OR=1.91, 95% CI=1.80-2.03) and Hispanic women (1.36, 95% CI=1.20-1.55) had a higher odds of triple-negative breast cancer than white women after controlling for demographic, socioeconomic, and clinical characteristics(7). A study of 629 breast cancer cases in New Jersey found a borderline association between race and triple negative subtype (OR=1.9, 95% CI=1.0-3.4) when controlling for demographic and clinical factors (51).

Socioeconomic Status (SES). In addition to individual-level factors like age and race/ethnicity, social factors, such as SES, may play a role in the development of different breast cancer subtypes. Studies have shown that more affluent women have higher rates of both breast cancer overall and HR+ breast cancers (29-31,41). However, the relationship between SES and incidence of HR- breast cancers, broadly, and triple-negative breast cancers, specifically, is

unclear. Some suggest that socioeconomic factors may play a role in the etiology of HR- cancers. In a comprehensive review, Williams and colleagues suggest that stressors across the life-course (i.e. allostatic load) may impact breast cancer incidence (52). Although black race has been identified as an independent predictor of triple-negative breast cancer, Dietze and colleagues suggest that the intersection of socioeconomic disparities and African ancestry may play a role in more aggressive tumor biology (53). Similarly, Vona-Davis posits that poverty may be a factor, independent of race/ethnicity, which facilitates angiogenesis and increases leptin subsequently stimulating the growth of breast cancer cells in triple-negative cancers (54).

A study utilizing a population-based cancer registry in Scotland indicated a higher proportion of estrogen receptor-negative cancers in those who lived in areas with less affluence (55). Similarly, an association of borderline significance was seen between social deprivation and estrogen receptor negative cancers in England (56). A study by Gordon of breast cancer clinical trial participants found that women who lived in impoverished (OR=1.77, 95% CI=1.28-2.44) or less educated (OR=1.98, 95% CI=1.43-2.73) areas had a higher odds of estrogen receptor-negative cancers (57). However, a recent study of high quality, population-based registries in the United States found no clear association between census tract level poverty and estrogen receptor negative subtypes' incidence rates—at least at an ecological level (41).

The relationship of socioeconomic status on triple-negative breast cancer risk, specifically, is unclear. Bauer and colleagues used California Cancer Registry data and found that breast cancer cases in the lowest two quintiles of socioeconomic status are 12-22% more likely to be diagnosed with triple-negative breast cancer than the most affluent quintile, even after controlling for race, age, stage, and tumor grade (46). Similarly, in a study using National Cancer Database data, Sineshaw and colleagues found that those in the lowest socioeconomic

group were 14% more likely to be diagnosed with triple-negative breast cancer than more affluent women (7). However, a recent population-based study of SEER 18 registry data found no association between lower socioeconomic status and greater odds of triple negative breast cancer (58). No associations between socioeconomic status and odds of triple negative breast cancer were found when stratified by race in that same study.

Studies have suggested a positive relationship between HR+ breast cancer and socioeconomic status. The 2015 Annual Report to the Nation on Cancer found that HR+/HER2- incidence rates decreased with increasing census tract poverty levels (i.e. hormone receptor-positive rates are higher among the most affluent) (41). Similarly, a study by Krieger and colleagues utilizing SEER 13 data found that breast cancer cases in counties with large income inequities had higher rates of estrogen receptor-positive breast cancers (59). A study by Akinyenmiju found that, in whites, there was a higher incidence rate of HR+/HER2- cancers in the higher income compared to lower income areas (IRR=1.32, 95%CI=1.27-1.39) (58). A similar association was seen with HR+/HER2+ cases as well (IRR=1.45, 95% CI=1.27-1.68) (58). The relationship between affluence and elevated incidence of HR+/HER2- cancers was also seen for Hispanics, but not for blacks.

Another social factor, residential segregation, includes neighborhood conditions that facilitate poor health outcomes in blacks. These conditions include lower income and education levels, less home ownership, residential instability, and less access to parks and sources of healthy foods. Williams and colleagues suggest that such conditions may facilitate breast cancer risk (52). As such, residential segregation is a common contextual factor that has been considered in breast cancer disparity studies (60-62). Studies evaluating the relationship between residential segregation and breast cancer subtype, specifically, are limited and have

shown mixed results. Although Krieger and colleagues found an association between income inequality and ER+ breast cancer, they found no association between and higher residential segregation levels of ER+ breast cancer (59). A study by Linnenbringer found that, among black women, living in a neighborhood with higher concentrations of black residents actually reduced the odds of HR- breast cancers (63).

Geographic Location. There are few studies that have explored geographic differences in breast cancer by subtype in the United States, and none of these have explored rural-urban differences. A descriptive study showed that the highest quartile of triple-negative breast cancer rates is concentrated in southern states with a few Midwestern states (Illinois, Missouri, and Indiana) also ranking in this top quartile (41). State level proportion of the black population was strongly positively correlated with triple-negative breast cancer incidence ($r=0.80$, $p<0.001$) (41). Another study utilizing National Cancer Database data indicated that compared to the Northeast, the odds of triple-negative breast cancer were statistically significantly higher in the Midwest (OR=1.13, 95%=1.08-1.17) and the South (OR=1.18, 95% CI=1.14-1.23), even after controlling for factors like age, race/ethnicity, and socioeconomic factors (7). An analysis of SEER 18 registries showed that the percentage of breast cancer cases that had a triple negative status ranged from 9.3% in the Seattle/Puget Sound registry to 15.7% in the Louisiana and Detroit metropolitan registries (43). Kohler and colleagues found that the highest quartile of HR+/HER2- cancers were clustered in the Northeast (41). One study evaluated differences in breast cancer subtypes between two states—Ohio and South Carolina—and found an elevated incidence of estrogen receptor-positive cancers in black women in Ohio compared to their South Carolinians (64). This suggests that geographic factors and/or related socioeconomic, behavioral, or other factors may play a role in subtype differences, even among black women.

Specific Aim #2

To evaluate differences in breast cancer staging by subtype between women in the Delta region and women in non-Delta Region counties within the LMDR states and between black and white women in the Delta region.

- *Hypothesis 2.1. Delta Region women will have a higher risk of advanced stage breast cancers across all subtypes.*
- *Hypothesis 2.2.Delta Region black women will have a higher risk of advanced stage cancer than white Delta Region women.*
- *Hypothesis 2.3. When relevant factors are controlled for, these risks will be at least partially attenuated.*

In order to determine whether or not there are differences in breast cancer staging between the Delta Region and non-Delta region of the LMDR states, three types of analyses were performed using population-based cancer surveillance data from the North American Association of Central Cancer Registries. First, incidence rates were calculated to describe the breast cancer burden by stage (early and late) for all invasive breast cancers and for all breast cancer subtypes individually in the Delta Region and non-Delta Region and by race/ethnicity, rural-urban status, and other relevant stratifications. Second, rate ratios were calculated to assess the stage by subtype differences between the Delta Region and non-Delta Region and by stratifications noted above. Third, multilevel models were constructed to assess the odds of early-stage and late-stage diagnoses, respectively, for all invasive breast cancers and for each breast cancer subtype, separately, while adjusting for the effect of individual level and neighborhood level factors. Thus, any stage differences between the Delta Region and non-Delta Region were determined after accounting for individual and contextual factors. These three types of analyses were also

performed by considering only cases diagnosed within the Delta Region with a particular focus on describing and determining the racial differences in breast cancer staging by subtype within the region.

Specific Aim #2 Conceptual Framework

The conceptual framework applied to specific aim #1 was also applied to specific aim #2 with the outcome of interest being breast cancer stage by subtype. To test Hypotheses 2.1-2.2, incidence rates and rate ratios were calculated, while multilevel regression models were employed to test Hypothesis 2.3 (Chapter 3). As described for Specific Aim #1, the conceptual framework in Figure 2 displays all covariates (individual characteristics and measures of social and physical context) that were *a priori* considered for inclusion in the model building process. The final model is described and depicted in Chapter 3.

Relevant Literature Review-Sociodemographic Disparities in Breast Cancer Staging

Breast cancer staging characterizes how far cancer has spread from its origin (i.e. spread to nearby lymph nodes and/or metastasized to other parts of the body). Staging helps healthcare providers and patients understand the progression and prognosis of the disease and guides what treatment options may be most appropriate. There are multiple ways to characterize staging. The TNM staging system considers the tumor size (T), number of regional lymph nodes involved (N), and whether or not cancer has metastasized (M) (65). The American Joint Commission on Cancer also has a staging scheme that uses the TNM designations to generate a stage designation of 0, I, II, III, or IV with 0 indicating abnormal cells that have not spread and IV indicating the most progressive spread of disease (66). There are two main types of staging: 1) clinical, which is based upon physical examination, imaging, and biopsy; and 2) pathological, which uses information from the clinical staging plus information from surgery to make a determination.

The Surveillance Epidemiology and End Results (SEER) staging system categorizes cancers using both clinical and pathological documentation of disease spread for characterization in cancer registries (67). This staging system often categorizes cancers as in situ, localized, regional, or distant, indicating more advanced spread of the disease. In situ indicates that abnormal cells have not penetrated the membrane of the tissues. Localized staging means that the cancerous cells are confined only to the organ of origin. Regional staging indicates cancer has spread beyond the organ of origin, such as to nearby lymph nodes. Distant staging is defined as cancer that has spread beyond the organ of origin, has traveled to other parts of the body, and has started to grow in a new location. Additionally, staging can be characterized as "unknown/unstaged" if there is not sufficient information to stage, if a patient refuses diagnostic procedures or treatment, if there is a contraindication for diagnostic procedures or treatment, or if a patient dies before stage can be determined.

In the United States between 2007 and 2013, 62% of breast cancer cases were localized, 31% were regional, 6% were distant stage, and 2% were of unknown stage (68). More advanced staging has been associated with reduced 5-year relative survival. Breast cancer cases diagnosed at a localized stage have very good 5-year disease-specific survival (98.9%) (68). With more advanced staging, 5-year survival decreases, as regional and distant stage cancers have 85.2% and 26.9% 5-year survival rates, respectively.

Race/Ethnicity. The distribution and rates of staging, and subsequently survival, vary by race and ethnicity. Descriptively, 64% of white female breast cancer cases are diagnosed at a localized stage, compared to 53% in blacks, 56% in Hispanics, 63% in Asian and Pacific Islanders, and 57% in American Indian/Alaska Natives (25). A third of white cases are diagnosed at a regional or distant stage, while 43% of blacks, 40% of Hispanics, 35% of Asians and Pacific

Islanders, and 38% of American Indian/Alaska Natives are diagnosed at these more advanced stages. Five-year disease-specific survival rates for localized cancers are similar for all race/ethnic groups, ranging from 93-98% (25). However, greater survival disparities occur for more advanced stages. This is most starkly seen in distant stage survival where 5-year survival is 34% for whites and 24% for blacks, with other race/ethnic groups ranging from 38-39%.

Additional studies have shown associations between race/ethnicity and staging independent of confounding factors. A study by Lantz and colleagues found that blacks and Hispanics have a lower odds of being diagnosed at an earlier stage, even after controlling for age and SES (69). Similarly, both Hispanic and non-Hispanic black women were at a greater odds of being diagnosed with Stage II-IV compared to whites and Stage IV cancers in two SEER-based studies, respectively (70,71).

Rural Status and Socioeconomic Status. In addition to race and ethnicity, there are other socioeconomic and demographic factors, such as rurality, poverty, and insurance status that are associated with more advanced staging at diagnosis. A meta-analysis of 21 studies indicated that rural women had a higher odds of being diagnosed at a more advanced stage than their urban counterparts (OR=1.19, 95% CI =1.12-1.27) (8). However, a recent population-based descriptive analysis in the United States found that the most rural counties had a lower incidence of late-stage breast cancer compared to the most urban counties (34). Late stage breast cancers decreased at similar rates in both rural and urban populations between 2004 and 2013 (34).

Additionally, regardless of race or ethnicity, lower SES was associated with more advanced staging in multiple studies (72-74). A population-based study of cancers diagnosed in 16 states in the United States and in Los Angeles found a higher risk of advanced stage breast cancer in women who live in census tracts with greater than 20% of the population living poverty

compared to census tracts with less than 5% living in poverty (72). Another study utilizing Texas Cancer Registry data found a higher odds of distant stage breast cancer in low SES census tracts compared to more affluent census tracts (OR=1.35, 95% CI=1.31-1.39) (73). Similarly, women without private insurance (i.e. uninsured, Medicaid, or Medicare) had a greater odds of being diagnosed at a more advanced stage of breast cancer (75,76). As previously noted, residential segregation is a commonly considered covariate in breast cancer disparity studies (59,61,62). Studies evaluating the association between racial segregation and breast cancer stage at diagnosis have yielded mixed results. Dai found that women living in areas of higher racial segregation in Detroit had a higher risk for late-stage breast cancer (77). However, studies using data from the California Cancer Registry and from SEER found no association between segregation and late-stage breast cancer diagnosis (61,78).

Breast Cancer Stage and Subtype. Breast cancer stage varies by subtype, with HR- subtypes generally being diagnosed at a later stage. A study utilizing National Cancer Database data found that compared to HR+/HER2-, all other subtypes had an increased odds of Stage II or later, with triple-negative cancers showing the greater magnitude of an increased odds (7). An analysis of breast cancer cases in the 2010 SEER 18 registries indicated that HR- cases were more likely to be diagnosed at a late stage (OR=1.29, 95% CI=1.27-1.31), even after controlling for other factors (45). However, another study of very similar data (SEER 17-the Alaskan registry was excluded) found that HR+/HER2- and triple-negative breast cancers had similar stage distributions, but HR+/HER2+ and HR-/HER2+ had a higher odds of being diagnosed at Stage III or IV (43).

Age-adjusted breast cancer subtype incidence rates vary by stage and race/ethnicity. HR+/HER2- localized incidence is highest among white women (63.51 per 100,000) compared

to blacks (44.43 per 100,000), Asian/Pacific Islanders (43.16 per 100,000), and Hispanics (40.94 per 100,000) (41). Distant stage HR+/HER2- incidence rates were higher in black women than white women (5.79 vs. 4.32 per 100,000, respectively). For triple-negative breast cancer, black women had the highest rates across all stages.

Several analyses of SEER data suggest that black women are diagnosed at more advanced stages of breast cancer either stratified by subtype or controlling for subtype. A study from Chen and colleagues found that, compared to white breast cancer cases, black women with breast cancer had a higher odds of being diagnosed at a later stage of cancer across all four subtypes (79). Similarly, three studies found that black women have a greater odds of late-stage breast cancer or a lower odds of early-stage breast cancer compared to white women, respectively, even after controlling for estrogen receptor/hormone receptor status and other factors (45,80,81).

Specific Aim #3

To compare spatial accessibility to mammography services for women living in the Delta region compared to those living in the non-Delta region of the LMDR states and between black and white women in the Delta region.

- *Hypothesis 3.1.Delta Region women will have less spatial access to mammography services than non-Delta women.*
- *Hypothesis 3.2. Black women will have less spatial access to mammography services than white women.*
- *Hypothesis 3.3. Rural women will have less spatial access to mammography services than their urban counterparts.*

In order to achieve this aim, the enhanced two-step floating catchment area method was used to calculate a spatial accessibility score for each census tract in the LMDR states. Data from the Food and Drug Administration on mammography facility locations and population estimates from the American Community Survey were utilized. To determine whether or not there were differences between the Delta and non-Delta Regions and between rural and urban populations (Hypotheses 3.1 and 3.3), summary statistics were calculated and compared. To assess differences in access by race within the Delta Region (Hypothesis 3.2), bivariate statistical and spatial analyses were performed. Spatial statistics were also calculated to identify clusters of low spatial access in the Delta Region.

Specific Aim #3 Conceptual Framework

This aim utilized a conceptual framework based on Khan's Typology of Access to Health Care (82) (Figure 1.3). In particular, this aim characterized the potential accessibility to mammography services in the Lower Mississippi Delta Region as a measure of spatial access. Potential accessibility is defined as the availability of services (i.e. mammography) relative to the population in need. Spatial access was considered in relation to aspatial access measures like racial composition and rurality, a construct that transcends both spatial and aspatial measures.

Relevant Literature Review-Disparities in Spatial Access to Mammography Services

Mammography Screening Recommendations. Regular mammograms are recommended to detect breast cancer at an earlier stage, thus improving survival and reducing mortality. Different entities, such as the United States Preventive Services Task Force (USPSTF), the American Cancer Society (ACS), and the National Comprehensive Cancer Network (NCCN), have different recommendations for age for initiation of screening and frequency of screening. The USPSTF's most recent guideline releases (2009 and 2016) recommend biennial screening for

women aged 50-74 (83,84). Screening for average-risk women between the ages 40 and 49 is recommended on an individual basis only in accordance with patient preference and provider recommendation, while women 75 and older are not explicitly recommended to get screened. The 2003 ACS recommendation indicated that average-risk women should receive an annual mammogram beginning at age 40. However, the most recent (2015) ACS guidelines recommend that women with average risk aged 45-54 receive annual screening, and women aged 55 and older should receive biennial screening as long as they are of good health with a life expectancy of 10 years or more (85). Additionally, the ACS recommends magnetic resonance imaging (MRI) screening for women whose lifetime risk of breast cancer exceeds 20% (86). The NCCN recommends that women of average risk be screened annual starting at the age of 40 (87).

Screening Options. The most common screening option is a film mammography, which is a scan of the breast to detect breast cancer in women with no signs or symptoms (88). Other, less common options are digital mammography and 3D mammography. Digital mammography allows for easier, electronic transfer between healthcare providers and clearer distinction between normal and abnormal tissue. 3D mammography is similar to a film mammography, but it records multiple images rather than solely one to create a three-dimensional image of the breast. Other radiographic methods are being tested for sensitivity and specificity including MRI, positron emission tomography (PET), and diffuse optical tomography. MRI is generally only recommended for women at high risk for breast cancer, such as the recommendation of the ACS.

Screening and breast cancer subtype. While adherence to mammography screening is recommended to help ensure that breast cancer is detected at an early stage, X-ray mammography may not always be sufficient to detect HR- breast cancers. Triple-negative breast cancer lacks the shape, margin, and calcification characteristics of other breast cancer subtypes

that are detectable on X-Ray mammography (89). Thus, other screening modalities, such as ultrasound or MRI may be preferable in women with high risk for triple-negative breast cancer. A study has also shown that, while digital and film mammography were comparable overall, digital mammography is more accurate than X-Ray mammography to detect breast cancer among women under 50 who are premenopausal or perimenopausal, factors often associated with triple-negative cancers (90). Similarly, another study showed that digital mammography was more sensitive to detect HR- cancers compared to film mammography, and digital mammography had borderline better sensitivity than film mammography in women between the age of 40 and 49, were premenopausal/perimenopausal, and who had dense breasts (91).

Screening's effect on cancer staging and mortality. Implementation of regular mammography screening has had a strong effect on trends in stage at diagnosis, but only a modest effect on reduction of breast cancer mortality rates. A study of more than thirty years of SEER data found that the proportion of breast cancers diagnosed at an early stage doubled between 1976 and 2008, while advanced stage cancers decreased by just 8% (92). A pooled analysis of numerous domestic and international studies suggests that mammography screening was associated with an approximate 20% reduction in breast cancer mortality, but the benefits for screening women under the age of 50 was unclear (93). Another study showed that 15% of the reduction in breast cancer mortality between 1975 and 2000 was due to mammography—a modest absolute reduction of 0.29% (94). A study by Bleyer, Baines, and Miller suggested that mammography utilization and penetrance (i.e. expansion of mammography services) was not associated with breast cancer mortality reduction (95). Instead, much of the reduction in mortality is due to improved chemotherapy and radiation treatment (96). Indeed, there is a growing body of

evidence suggesting that women are more likely to be "overdiagnosed" with breast cancer than they were to be detected early with a tumor that would later become large (96-97).

Screening adherence by demographic groups. Results from studies assessing mammography guidelines adherence across different demographic groups—race/ethnicity, insurance status, and rural-urban-status—have yielded mixed results. Findings from the Health Information and National Trends Survey found that black women were more likely than white women to have had a mammogram in the past three years (Adjusted prevalence ratio=1.48, 95% CI=1.06-2.07) even after adjusting for age, insurance status, income, education, and other factors (98). A 2016 study found that black women on Medicaid had a lower odds of mammography use than white women (OR=0.87, 95% CI=0.87-0.88) while Hispanic women had a higher odds (OR=1.06, 95% CI=1.05-1.07) (99). A systematic review and meta-analysis of 28 international studies (16 of which were from the United States) found that rural women were less likely than urban women to have ever had a mammogram (OR=0.74, 95% CI=0.62-0.89) (100). However, a study utilizing data from the Utah Behavioral Risk Factor Surveillance System found that geographic factors (i.e. rurality) were not associated with nonadherence to mammography guidelines, but not having a regular physician, not having health insurance, low income, and other factors were associated with nonadherence (101).

Geographic variability in mammography access in the United States. Access to health care is often defined across five dimensions: availability, accessibility, accommodation, affordability, and acceptability (102). Two of these dimensions are constructs of spatial access--availability and accessibility. Availability of care defines service supply related to need for services. Availability is often assessed using area measures, which are generally defined as the ratios of health care providers or service locations to the population in need within a specific geographic

context, such as an administratively defined area (e.g. number of physicians per 100,000 population in a county). Accessibility characterizes the geographic relationship between health services and a population or individual (e.g. distance or travel time to services). Access to mammography facilities, specifically, can be quantitatively characterized by availability and accessibility. Availability can be considered as geographic capacity and mammography facility density (i.e. the number of facilities per population) (103). Accessibility to mammography may be characterized by distance or travel time to a mammography facility or by utilizing methodologies that take both distance and travel time into account (103).

There is geographic and socioeconomic variability in mammographic availability in the United States. A study by Elkin and colleagues found that mammography capacity per 10,000 women 40 years of age and older dropped 20% during between 2000 and 2010, but capacity increased in rural areas (104). Additionally, they found that counties with high population density and poorer socioeconomic status had lower mammography capacity, and one in five counties had no mammographic capacity. A study by Peipins and colleagues assessed characteristics of counties with no mammographic capacity and found that low population density was associated with no mammographic capacity, even after controlling for other factors (OR=11.0, 95% CI=7.7-15.9) (105). Another study looked at mammography supply and demand in 14 southern states between 2002 and 2008 (106). The authors found that during the study period, the proportion of women who lived in an area with low mammography capacity increased 10%. Capacity decreased in ten states: Arkansas, Louisiana, Mississippi, Alabama Oklahoma, Kentucky, Georgia, Florida, South Carolina, and Texas, with Mississippi showing the largest decrease in capacity.

Geographic access to mammography services and cancer outcomes. Studies that have explored the relationship between geographic access to mammography facilities and cancer outcomes have yielded conflicting results. Several studies utilizing city, state, and multi-state data found associations between limited access to mammography and later stage of cancer at diagnosis (77,107-110). A study in Detroit, Michigan found that poorer mammography access was associated with later stage at diagnosis (77). One study utilizing data from 8 SEER registries found that low density of mammography facilities was associated with later stage of breast cancer at diagnosis (107). A study of a Wisconsin healthcare system suggested increased travel time to the nearest mammography facility was associated with later stage at diagnosis (108). A study of Kentucky cancer registry cases showed that cases residing more than 15 minutes from a mammography facility had greater odds of being diagnosed at more advanced stage than those who lived closer (111). Similarly, a study of women in Los Angeles showed that further distance from mammography facilities was associated with later stage of breast cancer diagnosis (110). However, two population-level studies of cancer registry data from 10 states showed that, after controlling for other factors, travel time to mammography facilities was not associated with later stage at diagnosis (76,101). The first study evaluated the association between travel time to mammography and stage at diagnosis and found no association when controlling for race, age, poverty level and other factors (101). The second study looked at the association between spatial access to mammography and breast cancer stage at diagnosis and found no relationship when controlling for census tract level poverty (76).

Tables and Figures

Table 1.1: Sociodemographic Characteristics of the Delta Region and the United States

	Delta Region	United States
% African American	32.5%	13.2%
% of Adults 25+ Years of Age with a High School Degree	82.7%	86.3%
% of Population Living below Poverty Level	21.3%	15.6%
% of Counties in Persistent Poverty	43.3%	11.2%
Median Household Income	$40,833	$53,482
Unemployment Rate	7.2%	6.2%
Population per square mile	65.0	90.3

Source: Delta Regional Authority. Today's Delta A Research Tool for the Region 3rd Edition. Available at http://dra.gov/images/uploads/content_files/DRA_Todays_Delta_2016.pdf

Figure 1.1: Map of Counties within the Delta Regional Authority Designation

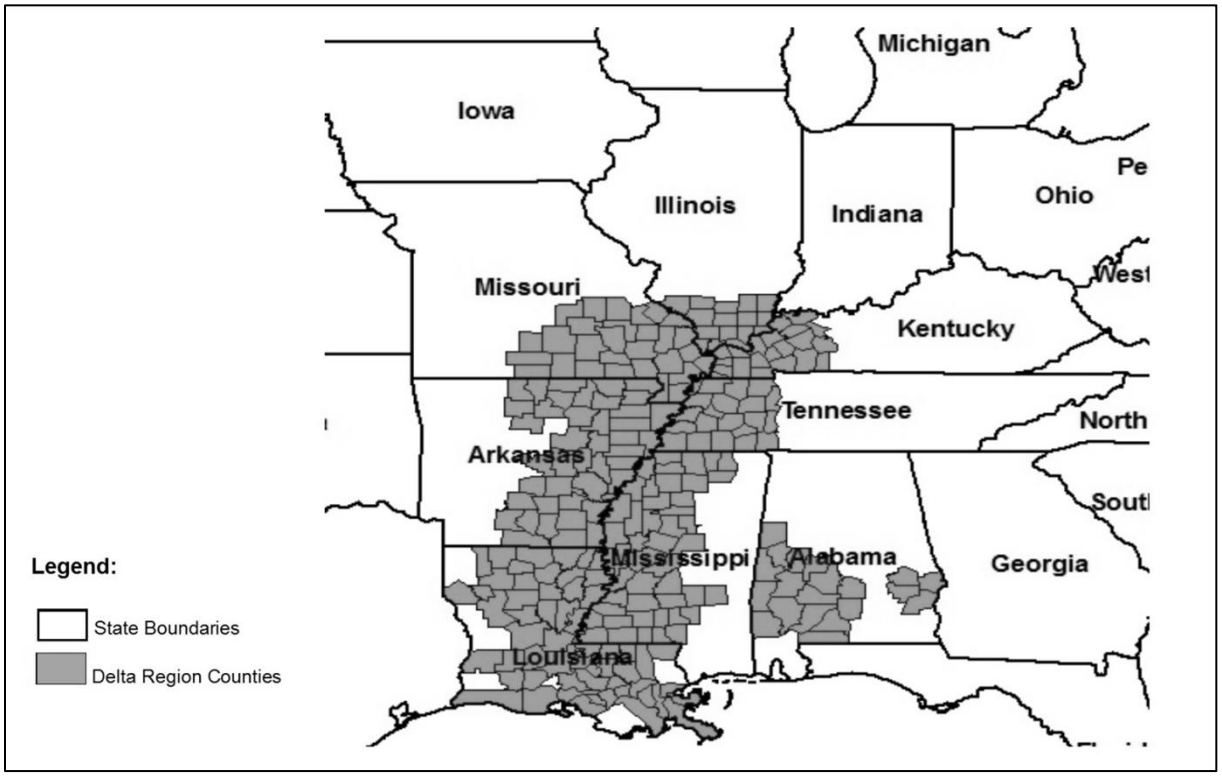


Figure 1.2: Conceptual Model for Elucidating Breast Cancer Disparities in the Delta Region

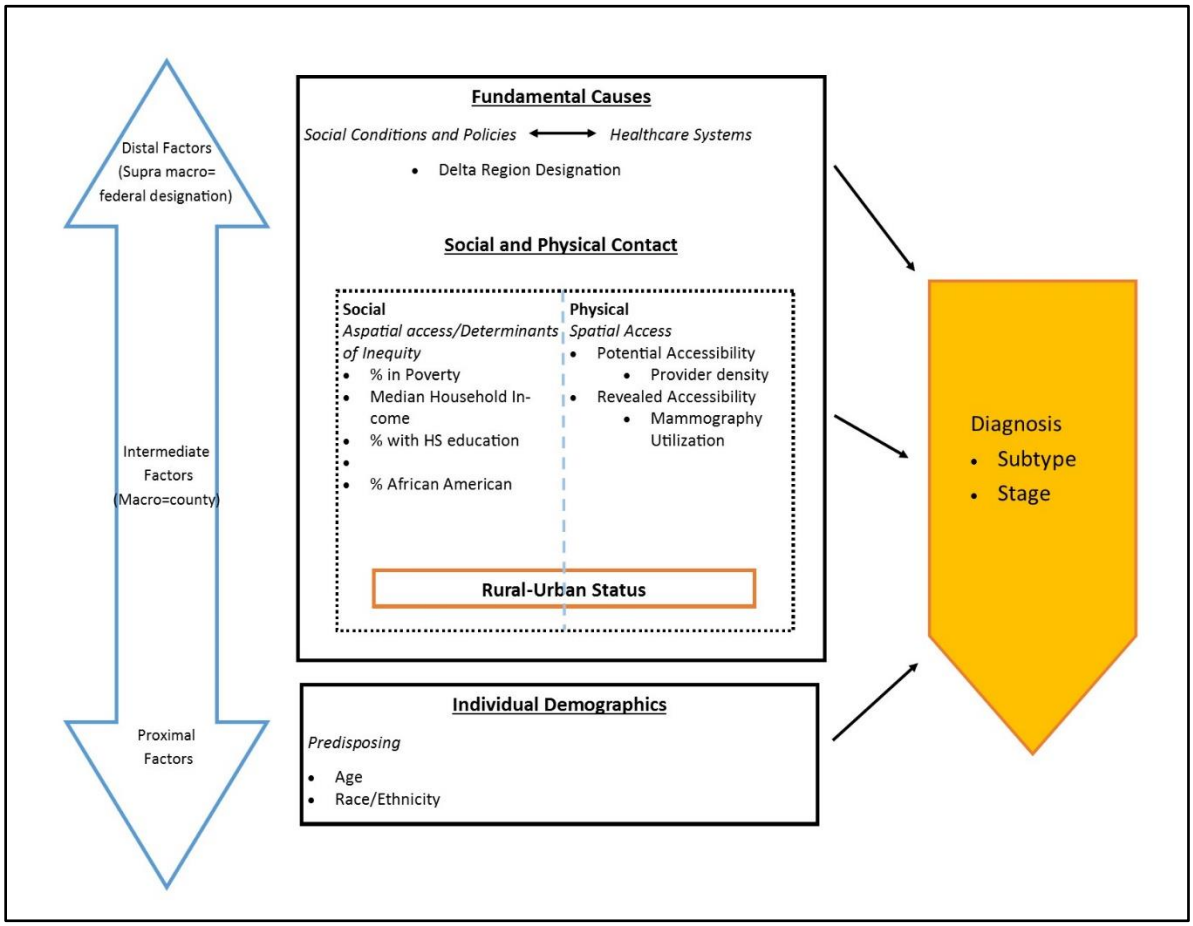
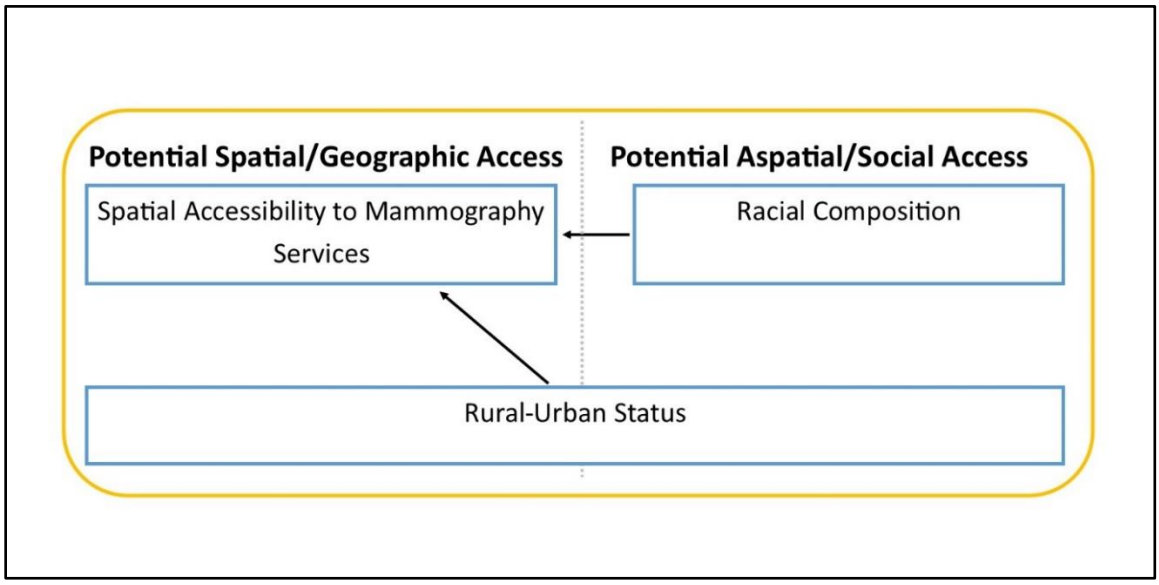


Figure 1.3: Conceptual Model for Assessing Spatial Access to Mammography in the Delta Region



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CHAPTER 2: DISPARITIES IN BREAST CANCER SUBTYPES AMONG WOMEN IN THE LOWER MISSISSIPPI DELTA REGION STATES

Introduction

The Delta Regional Authority (Delta Region) is a federally designated region that includes 252 counties and parishes in the eight Lower Mississippi Delta Region (LMDR) of Alabama, Arkansas, Illinois, Kentucky, Louisiana, Mississippi, Missouri, and Tennessee. More than a third of residents in the Delta Region are black, and more than 20% of the population live in poverty(1). Additionally, this region is largely rural and has limited access to healthcare services (2,3). All of these factors make the Region vulnerable to a myriad of health disparities, including breast cancer disparities. Women in the Delta Region have higher rates of breast cancer mortality than women in the rest of the country, including the similarly impoverished Appalachian Region (4). Further, black women in the Delta Region have a higher breast cancer mortality rate than white women in the Region as well as a higher rate than black women in other parts of the country (4). Nine of the ten counties with the nation's highest breast cancer mortality rates are in the Delta Region (5). Recent state-level studies have yielded some breast cancer incidence findings that require additional exploration. One study found that in six LMDR states, black women had higher breast cancer incidence rates than white women (6). Another study found that the LMDR states of Illinois, Kentucky, Louisiana, Mississippi, Missouri, and Tennessee (Alabama and Arkansas did not have sufficient data for analysis) are in the top quartile in the nation for triple-negative breast cancer incidence, the breast cancer subtype with the worst prognosis (7). There is limited research on what factors contribute to these mortality disparities and how breast cancer incidence is distributed within the Delta and non-Delta Regions of the LMDR states and by race within the Delta Region.

Breast cancer can be classified into four molecular subtypes based upon the presence or absence of two broad tumor characteristics—hormone (i.e. estrogen and progesterone) receptor (HR) and human epidermal growth factor 2 (HER2) status: 1)HR+/HER2-; 2) HR+/HER2+;3) HR-/HER+; 4) HR-/HER2- ("triple-negative") (8). The subtype of a breast cancer tumor plays a role in its aggressiveness and informs the use of targeted drug treatments. HR+ cancers tend to have a better prognosis and more comprehensive treatment options than HR- cancers (9-11). Triple-negative breast cancer is the most aggressive and has limited treatment options (11). While central cancer registries have been required to collect information on HR status since 1990, they have only been required to collect information on HER2 status since 2010 (8). Therefore, population-based assessment of the distribution of breast cancer by subtype is burgeoning but still limited.

Risk of breast cancer by subtype varies by race/ethnicity, age, socioeconomic status, and geography. Multiple studies indicate that black women have greater than twice the rate or risk of triple-negative breast cancers compared to white women, even after controlling for other factors (12,13). Similarly, black women have a higher odds of both HR- breast cancer subtypes (12). Meanwhile, white women have higher rates of the HR+/HER2- cancers than other racial/ethnic groups (7). Women under the age of 50 are at greater risk for HR- breast cancers (14,15). Although the relationship between HR- cancers and socioeconomic status is unclear in current studies (16,17), some have suggested that the poverty may be an upstream social factor facilitating angiogenesis and other biological processes related to cancer growth, especially amongst black women (18-20). Other studies have shown that incidence of each breast cancer subtype varies by geographic region with HR+/HER2- cancers clustered in the Northeast and triple-negative cancers clustered in the South and Midwest (7,16).

The sociodemographic composition of the Delta Region suggests the Region may have higher incidence rates of triple-negative cancers that may contribute to its high breast cancer mortality rate. The objective of this present study was to three-fold. First, it aimed to describe the subtype-specific incidence rates of breast cancer in the Delta Region compared to those in the non-Delta Region of the LMDR states. Second, it aimed to determine how subtype specific incidence rates differ between white and black women within the Delta Region. Thirdly, it sought to determine how the differences in these subtype rates may be explained by contributing individual level and contextual factors, like age and county-level poverty rates, respectively.

Methods

Conceptual Model

A conceptual model, drawing from Warnecke's Model for Analysis of Population Health and Health Disparities, was developed to identify individual and area-level factors that may be associated with breast cancer incidence by subtype within the Delta Region (21) (Figure 2.1). The Delta Region is a conceptualized as a supramacro, policy-relevant context that may affect the distribution of the incidence of breast cancer by subtype. Specifically included are individual-level factors—age and race/ethnicity-- that have been shown in previous studies to affect one's risk for any breast cancer or one's risk for developing specific subtypes of breast cancer (7,12). Also included are measures of social and physical context that have been identified to affect breast cancer incidence rates overall or by specific subtype, including socioeconomic factors, racial composition, rural-urban status, mammography utilization, and provider density (16,17,22-24).

Data

Data from the North American Association of Central Cancer Registries (NAACCR) Cancer in North America (CINA) Deluxe File were used (25). This file provided individual-level data on all breast cancer cases diagnosed between 2012 and 2014 in the LMDR States. To be included in this dataset, data from central cancer registries must have 90+% case ascertainment, passing edits of 97% or better, and other quality indicators. These data are based on the NAACCR December 2016 data submission. Support for cancer registries is provided by the state, province or territory in which the registry is located. In the U.S., registries also participate in the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) Program or the Centers for Disease Control and Prevention's National Program of Cancer Registries (NPCR) or both. In Canada, all registries submit data to the Canadian Cancer Registry maintained by Statistics Canada. Seven of the eight LMDR states provided active consent for their data to be included in this analysis (Alabama, Arkansas, Illinois, Kentucky, Louisiana, Mississippi, and Tennessee). Missouri's data were not included in this study as this registry did not provide the necessary consent for their data to be used.

Inclusion/exclusion criteria were based on Kohler's study and were employed to optimize the accuracy of rate calculations and data quality for breast cancer subtype analyses (7). Cases included all invasive female breast cancers (International Classification of Disease for Oncology 3rd Edition (ICD-O-3) of C500-C509). Cases with histology codes of 9050-9055 (mesothelioma), 9140 (Kaposi's sarcoma), 9590-9992 (leukemia and lymphoma) were excluded as were cases who were diagnosed who were missing on race/ethnicity and county of residence and cases who were 85 years of age or older. Cases that were reported to their respective central

cancer registry by way of a death certificate, autopsy report, or by nursing home or hospice were also excluded.

Relevant to this study, the NAACCR CiNA Deluxe data file included individual-level data on age (19 groups), race/ethnicity, county of residence at diagnosis, and collaborative staging site-specific factors, 1,2, and 15, which corresponded to estrogen receptor (ER), progesterone receptor (PR), and HER2 statuses, respectively. County of residence at diagnosis was used to determine if a patient lived in the Delta or non-Delta Regions of these states. ER and PR statuses were considered jointly and described as hormone receptor (HR) status. HR+ cases included those that were ER+ or PR+ or borderline. HR- included those cases that were both ER- and PR-. Cases with unknown HR status were considered unknown. For HER2 status, HER2+ and HER2- were categorized accordingly, while cases with borderline or unknown status were considered to be of unknown status. Based upon these site-specific factors, molecular subtypes of breast cancer cases were approximated: 1) HR+/HER2-; 2) HR+/HER2+; 3)HR-/HER2+; 4) HR-/HER2- (triple-negative); 5) unknown (12).

Because data in cancer registries are not missing at random, especially with HR and HER2 statuses, subtype-specific analyses are subject to bias. Previous studies have shown that racial minorities and those from impoverished areas have a greater risk for missing/unknown status data in cancer registries (26). Failing to account for missing/unknown data may produce inaccurate estimates of disparities (27). While missing subtype information may be addressed through imputation (28,29), it is also important to understand and elucidate what individual level and area level factors are associated with unknown subtype status, especially as HER2 status information has only been required to be collected since 2010. There is an opportunity to intervene to improve clinical ascertainment to better inform targeted treatment and ensure quality

care (30) and to enhance the quality of cancer surveillance to improve cancer control efforts and better estimate biases (31). Thus, this analysis also aimed to evaluate differences in unknown status by Delta Region designation.

Age-adjusted Incidence Rates and Rate Ratio Calculations

Age-adjusted incidence rates (IR) and rate ratios (RR) with 95% confidence intervals for all invasive breast cancer combined and individually by molecular subtype and unknown subtype status by Delta and non-Delta Region status. These IRs and RRs were also calculated stratified by race/ethnicity, rural-urban status, and percent of a county living in poverty. Additional IR and RR calculations were performed to evaluate racial, rural-urban, and poverty level differences within the Delta Region specifically. Rates were expressed per 100,000 population and were age-adjusted using the 2000 US standard population. Tiwari modifications were used in all analyses which were performed using SEER*Stat 8.4.3.

Multilevel Regression Models

Proc GLIMMIX in SAS 9.4 was used to construct multilevel regression models to calculate RRs for all breast cancers, each subtype individually, and breast cancers of unknown subtype as a means of comparing the Delta Region to the non-Delta Region overall and stratified by race/ethnicity, rural-urban status, and poverty level. Similar analyses were performed examining solely Delta Region cases to assess race/ethnic, rural-urban, and poverty level differences within the Region.

Because counts were overdispersed for all cancers combined, each individual subtype, and for cancers of unknown subtype, multilevel negative binomial regression models were constructed. For these models, analyses cells were constructed containing the number of cases in each county within each analysis cell, which were divided by age (<50 years of age and 50+

years of age) and race/ethnicity (Non-Hispanic White, Non-Hispanic Black, Hispanic/Non-Hispanic Other). Analysis groups were divided at age 50 as it is the age at which estrogen receptor negative cancer rates peak, making 50 a good demarcation for risk, and because 50 years of age is the recommended starting age for mammography for women of average risk (32,33) (Figure 2.2). A three-level model in which analysis cells were nested within counties and counties were nested by the state was initially tested, but models did not converge for analyses of the less common breast cancer subtypes. Therefore, for consistency, a two-level model in which analysis cells were nested by county was used for all analyses. County was included in the model as both a random and a fixed effect and analysis cells were considered in the model as fixed effects. Age and race/ethnicity-specific rates were calculated for the entire geographic area of our study to estimate the expected counts for each analysis cell. The natural log of these expected counts was included in each model as an offset variable.

Contextual factors that may affect breast cancer incidence and had been explored in previous research, as shown in Figure 2.1, were considered in the regression model building process. These factors may explain any differences in incidence between the Delta and non-Delta Regions within the seven LMDR states. Contextual factors were county-level variables extracted from the American Community Survey (ACS), National Cancer Institute, United States Department of Agriculture (USDA), and the Area Health Resource File to describe the physical and social context of the county of residence of each cancer case (34-36). The ACS is an ongoing national survey performed by the U.S. Census Bureau that collects information on a variety of factors, including county-level sociodemographic characteristics (34). 2010-2014 ACS county-level factors on % living in poverty, median household income, % with at least a high school education, and % of the population that identify as black were extracted. Counties were

considered rural or urban based upon the USDA's Rural-Urban Continuum Codes, which consider a county's population size and adjacency to a metropolitan area (36). A code of 1-3 was considered urban; a code of 4-9 was considered rural. The National Cancer Institute's State Cancer Profile includes county-level modeled estimates of the percentage of women aged 40+ who had a mammogram in the past two years (35). Data on the number of primary care physician per county was extracted from the Area Health Resource File for the years 2011 to 2014 to determine the average number of primary care physicians per 100,000 (i.e. provider density) for each county(37). Because sociodemographic variables may cause multicollinearity, correlations among these variables were assessed and were indeed found to be highly correlated. Therefore, only one sociodemographic variable was considered in the model—poverty level—as that variable has been considered the most robust socioeconomic variable for measuring inequalities in cancer incidence (38). All other variables were considered in the analysis: rural-urban status, provider density, and mammography utilization. Provider density proved to non-significantly contribute to all models and caused poorer goodness of fit as measured by the Akaike Information Criterion, and therefore was excluded from inclusion in final models. Because of the important, but understudied, consideration of the interaction between race and rural context, particularly in the South (39), the interaction between rural-urban status and race were considered in all models and was retained if the interaction was statistically significant. Exponentials of coefficients estimated RRs. 95% confidence intervals were used to determine whether there were statistically significant differences in cancer incidence between the Delta Region and non-Delta Region after accounting for the aforementioned potential confounders.

Results

A total of 82,223 invasive breast cancer cases were diagnosed in these seven LMDR states between 2012 and 2014. Among these cases, 19,334 (23.5%) occurred in the Delta Region, and 62,889 (76.5%) occurred in the non-Delta Region. Table 2.1 summarizes the distribution of subtypes by sociodemographic characteristics.

Age-adjusted IRs and RRs by Delta Region designation are displayed overall and stratified by age, race/ethnicity, rural-urban status, and poverty level for all breast cancer cases and HR+ cases are displayed in Table 2.2. For all breast cancer cases, the age-adjusted incidence rate was higher in the non-Delta Region (120.8 per 100,000) than the Delta Region (116.2), with a corresponding rate ratio of 0.96 (95% CI=0.95-0.98; non-Delta Region as the reference group). The rates of all breast cancers combined and stratified by age (<50 or 50+ years of age) were higher in the non-Delta Region for both stratifications. When rates were stratified by race/ethnicity, non-Hispanic white women in the Delta Region (IR=114.5 per 100,000) had a lower rate of breast cancer than women in the non-Delta Region (IR=123.9). There was no statistically significant difference in the overall breast cancer rate among and Delta Region (IR=122.9) and non-Delta Region (IR=123.9) for non-Hispanic black women or Hispanic women (IR=89.1 and 84.8 in the Delta and non-Delta Regions, respectively). Urban women in the Delta Region had a slightly lower overall rate of breast cancer than their non-Delta counterparts (RR=0.97, 95% CI=0.95-0.99), but there was no statistically significant rural difference between the regions.

For the most part, the Delta/non-Delta Regions differences for HR+ cancers were similar to the differences seen in overall breast cancers with a few exceptions. For the overall breast cancer rates, the Delta Region had lower rates of both HR+/HER2+ (RR=0.93; 95% CI=0.88-

0.98) and HR+/HER2- (RR=0.88; 95% CI=0.86-0.90) cancers. Non-Hispanic black Delta women (RR=0.93; 95% CI=0.88-0.97) had lower rates of HR+/HER2- cancers than those in the non-Delta Region, as did non-Hispanic white women (RR=0.88; 95% CI=0.86-0.90). Both rural and urban women in the Delta had lower rates of HR+/HER2- cancers than non-Delta women.

Age-adjusted IRs and RRs by Delta Region designation are displayed overall and stratified by age, race/ethnicity, rural-urban status, and poverty level for HR- cases and cases of unknown subtype are displayed in Table 2.3. Women in the Delta Region (IR=17.0) had higher rates of triple-negative breast cancer than non-Delta Region women (IR=14.4) (RR=1.18; 95% CI=1.13-1.24). In stratified analysis, Delta Region women had higher rates of triple-negative breast cancer than women in the non-Delta Region for the following sociodemographic stratifications: under 50 years old, 50+ years old, non-Hispanic black, urban, <20% living in poverty, and 20+% living in poverty. The greatest rate difference was among Delta women under 50 years of age (IR=8.4) who had higher rates of triple-negative breast cancer than their non-Delta counterparts (IR=6.6) (RR=1.29; 95% CI=1.18-1.40). Also of note, non-Hispanic black women in the Delta Region (IR=26.8) had higher rates of triple-negative breast cancer than their non-Delta counterparts (IR=24.6) (RR=1.09; 95 CI=1.01-1.17). Urban women in the Delta Region had higher triple-negative breast cancer than urban women in the non-Delta Region (RR=1.26; 95% CI=1.19-1.33). Among women in counties with 20% or greater of the population living in poverty, Delta Region women had notably higher rates of triple-negative breast cancer (RR=1.21; 95 CI=1.12-1.31). Rates of unknown breast cancer subtype were higher in the Delta Region among all stratifications, except among Hispanics and those living in counties with 20%+ of the population living in poverty. Rates of unknown subtype were higher in the Delta Region than the non-Delta Region (RR=1.30; 95% CI=1.23-1.37). The magnitude of Delta/non-

Delta Region differences in unknown subtype rates had the highest magnitude among rural populations (RR=1.37; 95% CI=1.29-1.49) and among those living in counties with less than 20% living below the poverty level (RR=1.39; 95% CI=1.29-1.49).

The age-adjusted IRs and RRs for racial/ethnic, rural-urban, and poverty level stratifications for all invasive breast cancers and HR+ breast cancers within the Delta Region alone are displayed in Table 2.4. For all breast cancer cases, non-Hispanic black women had higher rates than non-Hispanic white women (RR=1.07; 95% CI=1.04-1.11). For HR+/HER2- breast cancers, non-Hispanic black (IR=63.3) and Hispanic women (IR=59.4) had lower rates than white Delta Region women (IR=72.9). Both overall rates of breast cancer and HR+/HER2- breast cancers were lower in the rural and more impoverished Delta Region compared to the urban and less impoverished areas of the Delta Region.

Age-adjusted IRs and RRs for HR- breast cancers and for cancers of unknown subtype stratified by race/ethnicity, rural-urban status, and poverty for Delta Region cases only are displayed in Table 2.5. Rates of HR-/HER2+ are higher in non-Hispanic blacks than whites (IR=6.9 and 4.6, respectively). Triple-negative breast cancer rates are more than twice as high among Delta Region non-Hispanic blacks (IR=26.8) compared to non-Hispanic whites (IR=12.8) (RR=2.10; 95% CI=1.94-2.27). Rates of both HR- subtypes are lower in rural populations in the Delta Region. Rates of triple-negative breast cancers are higher among more impoverished counties than counties with less than 20% of the population in poverty (RR=1.10; 95% CI=1.01-1.19). Rates of cancers of unknown subtype are higher in non-Hispanic black women compared to non-Hispanic white women (RR=1.15; 95% CI=1.35-1.61) as well as rural compared to urban women in the Delta Region (RR=1.48; 95% CI=1.35-1.41).

Table 2.6 displays the results of multivariable, multilevel negative binomial regression modeling for all breast cancer cases, individual subtypes, and cases of unknown subtype for all cases and stratification by age, race/ethnicity, rural-urban status, and poverty level which assesses the difference in rates in the Delta and non-Delta Regions. For non-stratified analyses, the Delta Region had higher rates of unknown subtype (RR=1.19; 95% CI=1.05-1.35) compared to the non-Delta Region after accounting for age and race/ethnicity groupings and contextual factors. There were no significant Delta/non-Delta differences in rates of any kind after controlling for relevant factors for either age stratification, except for unknown subtype in women aged 50+ in the Delta Region (RR=1.17; 95% CI=1.03-1.34). For all race/ethnic stratifications, there were no Delta/non-Delta Region differences, except for an elevated rate of unknown subtype in non-Hispanic whites in the Delta Region. Among rural populations, the Delta Region had lower rates of HR-/HER2+ (RR=0.80; 95% CI=0.69-0.93) and higher rates of unknown status (RR=1.26; 95% CI=1.08-1.47) compared to the non-Delta Region after accounting for confounders. Among urban populations, the Delta Region had higher rates of triple-negative breast cancer (RR=1.10; 95% CI=1.01-1.20) after controlling for relevant factors. Among populations who live in counties with less than 20% of the population living in poverty, the Delta Region had a lower rate of HR+/HER2+ breast cancer (RR=0.91; 95% CI=0.86-0.96) and a higher rate of breast cancers of unknown status (RR=1.29; 95% CI=1.07-1.55) after accounting for confounders. There were no Delta/non-Delta Region differences across subtypes for the cases in counties with greater than 20% of the population in poverty.

Table 2.7 displays the findings of the multivariable, multilevel negative binomial regression modeling of Delta Region breast cancer cases for all cases combined, individual subtypes, and cancers of unknown subtype. Rates were higher among non-Hispanic blacks for all

breast cancers (RR=1.06; 95% CI=1.02-1.10). Hispanics had lower rates of HR+/HER2- cancers (RR=0.82; 95% CI=0.69-0.97) compared to non-Hispanic whites after accounting for age and contextual variables. Compared to urban populations, rural populations had higher rates of breast cancers of unknown subtypes (RR=1.42; 95% CI=1.14-1.76) after controlling for confounders.

Discussion

Population-level cancer registry data were analyzed to examine breast cancer incidence rate differences between the Delta and non-Delta regions of seven LMDR states for breast cancer overall and stratified by subtype. Overall breast cancer incidence rates were higher in the non-Delta Region. However, women in the Delta Region had higher incidence rates of triple-negative breast cancer compared to non-Delta Region women, which was also true among black women specifically, but not white women. Regardless of stratifications, Delta women had higher rates of unknown subtype. After accounting for confounding characteristics, the elevated rate of triple-negative breast cancer in the Delta Region was attenuated to non-statistical significance. However, the elevated rate of triple-negative breast cancer in urban women in the Delta Region remained in the multivariable analysis. The elevated rate of unknown subtype in the Delta also remained after adjustment. Analyses of data from the Delta Region only indicated that black women in the region had higher rates of breast cancer overall than white women, but rates of HR+/HER2- were higher in the white women. Black women in the Delta Region had higher rates of both HR- subtypes, most prominently triple-negative breast cancer. The elevated overall breast cancer incidence rate in black Delta women remained after adjustment.

Descriptively, this current study found that women in the Delta Region had lower incidence rates of invasive breast cancer overall and of the HR+/HER2- subtype than women in the Delta Region across most stratifications, although this was explained by factors like

mammography utilization, rural-urban status, and other variables included in multivariable analysis. Previous studies have shown that—generally speaking at a state level-- mammography utilization is associated with higher rates of breast cancer overall and HR+/HER2- specifically (7). Similarly, a pooled analysis by Akinyemiju and colleagues found higher rates of breast cancer in urban populations (22). Indeed, over the last twenty years, the Delta Region has consistently had lower rates of mammography utilization compared to the non-Delta part of the LMDR and the rest of the country (3,40). Further, the Delta Region is more rural the rest of the LMDR (3,41). The lower overall rates of breast cancer and HR+/HER2- cancers in the Delta Region corroborate previous studies and are explained by utilization of mammography and rurality of the Delta Region.

Triple-negative breast cancer incidence rates were higher in the Delta Region compared to the non-Delta Region overall and among non-Hispanic blacks and urban populations, specifically. The higher rates of triple-negative breast cancer in the Delta Region overall was explained by age, race, and contextual factors. However, it may help explain the higher breast cancer mortality rate that is seen in the Region (4), as triple-negative breast cancers have worse survival than other subtypes. Also, as multiple studies have shown higher rates of triple-negative breast cancer in the South and Midwest than other parts of the country(7,16), the findings of the present study indicate that elevated rates may be particularly high within specific areas (i.e. the Delta Region) within the Midwest and the South.

Urban women in the Delta Region had higher rates of triple-negative breast cancer, even after accounting for important risk factors like age and race. There are other risk factors like greater parity and lack of breastfeeding/short duration of breastfeeding among parous women, that were unable to be accounted for in the present study, that can increase one’s risk for triple-

negative breast cancer (42). Of metropolitan areas with greater than half a million residents, the Memphis metropolitan area—the largest city in the Delta Region-- has the highest birth rates in the country (43). Caution must be exercised not to fall prey to ecological fallacy, but the higher birth rate among urban women in the Delta Region may play a role in the higher rate of triple-negative breast cancer compared to non-Delta urban areas. Additionally, breastfeeding has been shown to reduce a women's risk for triple-negative breast cancer. Multiple studies have shown that parous women who do not breastfeed or who had short breastfeeding duration are at greater risk for triple-negative breast cancer (42,44). Additionally, a meta-analysis of 27 studies found reduced odds of triple-negative breast cancer among parous women who breastfeed (45). Breastfeeding is one of the few modifiable risk factors for triple-negative breast cancer. Interventions aimed at improving breastfeeding initiation and duration in urban areas of the Delta Region may help reduce the incidence of triple-negative breast cancer. While rates of breastfeeding initiation and duration are lower in southern states than in the rest of the country, there is a reason to be optimistic about the urban Delta Region (46). For example, in recent years, attitudes towards breastfeeding have improved in urban areas of the Delta Region like Memphis (47). Additionally, in the most recent CDC Breastfeeding Report Cards, all Lower Mississippi Delta Region states have experienced increased breastfeeding initiation rates and/or improved Maternal Practice in Infant Nutrition and Care scores, which is an indicator of breastfeeding-promoting policies in maternal care facilities (48,49). Interventions to continue to improve attitudes, practices, and policies around breastfeeding has the potential to reduce future triple-negative breast cancer incidence rates in the Region.

In the Delta Region, higher incidence rates of breast cancer were observed in non-Hispanic black women compared to non-Hispanic white women in both descriptive and

multivariable analyses. This finding corroborates a study by DeSantis and colleagues which found that breast cancer incidence rates in the Delta Region states of Alabama, Kentucky, Louisiana, Mississippi, and Tennessee were higher in black women than in white women (6). Previous studies have suggested that the convergence of breast cancer incidence rates in black and white populations is driven by increased mammography utilization and increased rates of HR+/HER2- or ER+ breast cancers among black women (6,50). In the Delta Region, however, the elevated rates of breast cancer among black women are driven by HR- cancers, as both HR-/HER2+ and triple-negative breast cancer rates are higher among black women. The elevated incidence of breast cancer in black women, even after accounting for age and contextual factors, suggests that there may be other contextual factors or individual factors specific to black women in the region that may contribute to higher rates. Studies have found that perceived experiences of racial discrimination are associated with increased risk of breast cancer, especially among young black women, among whom HR- cancers are more common (51). Similarly, Geronimus and colleagues posit a "weathering hypothesis" that black women disproportionately experience a myriad of life stressors compared to white women that contribute to biological indicators of stress (i.e. shorter telomere length and increased allostatic load) subsequently putting them at greater risk for chronic diseases, potentially including HR- breast cancers (52-54). A study by Krieger found that black women born in or living in states that once had discriminatory Jim Crow laws (which includes six of the seven states in the present study) had higher rates of estrogen receptor-negative cancers than those born in states that did not have Jim Crow laws (55). While the relationship between racial discrimination and increased cumulative stressors and their impacts on breast cancer is still a burgeoning field of study, the history and lasting effects of slavery, segregation, and marginalization in the Delta Region may indeed play a role in the

elevated risk of breast cancer among black women in the Region (56). There is a great opportunity for social epidemiologists and other researchers to further explicate the relationship between the historical and current social context of the Delta Region and its effect on breast cancer.

Although not central to the study, higher rates of unknown subtype in the Delta Region were found in both descriptive and multivariable analyses across many stratifications. The study inclusion/exclusion criteria aimed to maximize completeness of subtype data by excluding cases in women over the age of 85 or cases that were reported in death certificates, autopsy, nursing home, or hospice care. However, missing information on cancer cases is more common among blacks and in areas of low socioeconomic status (26,27,31). Race and county level poverty were included in multivariable analysis and rates of unknown subtype, yet higher rates of unknown status remained, especially in rural areas of the Delta Region. In addition to socioeconomic factors, the location of case ascertainment may play a role in data completeness (7,26). Breast cancer cases diagnosed among rural Delta Regions women may be more likely to be diagnosed in smaller hospitals in impoverished areas where data reporting may be incomplete. Further, there is a nationwide cancer registrar shortage, of which, like any healthcare profession, could be at an even greater shortage in the Delta Region (57). This may affect the abstraction of cancer information in the Region's rural hospitals in particular. Additionally, the rate of unknown subtype subsequently has an effect on the other rates. For example, HER2+ is the more common HER2 status, but in order for a case to be defined by that status, a definitive HER2 status of positive must be reported. Thus, HER2+ cancers, in particular, may be underrepresented. While HR status has been required to be reported for many years, HER2 status has only been required

since 2010. As healthcare professionals become more accustomed to reporting that information, data completeness should improve in the Delta Region and throughout the country.

The current study was not without limitations. First, Missouri did not provide active consent for their data to be included in this study. While Missouri includes less than seven percent of the Delta Region population and is the Delta Region state with the largest percentage of white population, its exclusion may affect the study findings (1). For example, Delta Region disparities were identified for triple-negative breast cancers in urban populations especially. The absence of data from non-Delta urban areas with a high proportion of black residents like St. Louis and Kansas City may attenuate the identified disparity if data were included. Additionally, the non-Delta Region also included areas of Kentucky, Tennessee, Mississippi and Alabama that are part of the impoverished, federally designated Appalachian Regional Commission. This may make Delta Region disparities more difficult to identify than if national comparisons were able to be made, as the comparison group experience notable economic disparities as well. Also, data on individual-level factors that affect the risk of different breast cancer subtype are not available, including breastfeeding, oral contraceptive use, parity, age a first live birth, age at first pregnancy, obesity, and physical activity. Additionally, a three-level model proved to be too complex for the less common subtypes of breast cancer, and thus state-to-state variability was unable to be accounted for. Further, county of residence at diagnosis was used to characterize the contextual effects the cancer patient experienced. However, it is unknown where a cancer patient lived throughout her life and how the social and physical context of her residence throughout her life course may have affected her risk for breast cancer.

The present study had several strengths as well. First, this study was one of the first to explore cancer incidence across the multi-state Delta Region, as well as one of the first to

explore differences in breast cancer subtype at a sub-state level. Previous studies have explored cancer mortality and screening disparities in the Delta Region (3,4), but the present study is likely the first to explore cancer incidence disparities within this federally designated, underserved region. Second, it utilizes population-based data inclusive of all cancer cases diagnosed in the LMDR states. Third, it employed multilevel modeling to explore place-based effects on cancer, which is underutilized in rural cancer research in particular (58). Because multilevel models assume the nonindependence of group membership, they produce less biased standard errors, reducing the risk of Type I errors.

Conclusions

The higher rate of triple-negative breast cancer in the Delta Region identified in the present study may help explain the breast cancer mortality disparity that exists in the Region. Both the elevated rates of triple-negative breast cancer in the urban Delta region and the overall elevated rate of breast cancer among black women in the Delta may be explained by individual-level factors like parity and breastfeeding initiation or duration. Additionally, these elevated rates may be explained by more upstream, contextual factors like discrimination that affect the biology of cancer etiology in black, urban women. Future research should explore the effect of unmeasured individual and contextual factors that may contribute to the disparities experienced by women in the Delta Region.

Figures and Tables

Figure 2.1: Conceptual Model for Elucidating Breast Cancer Disparities in the Delta Region

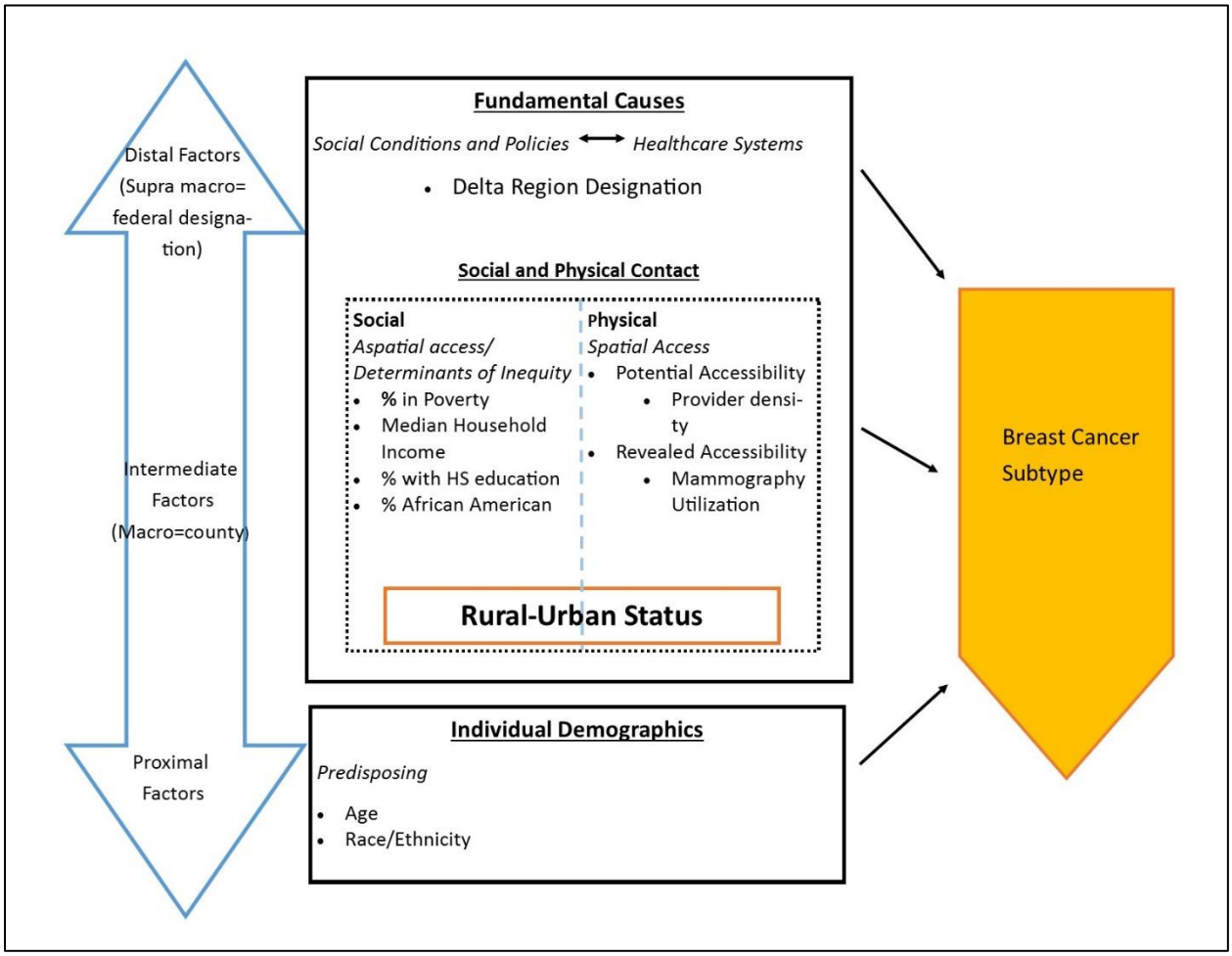

Figure 2.2: Diagram of Multilevel Regression Models

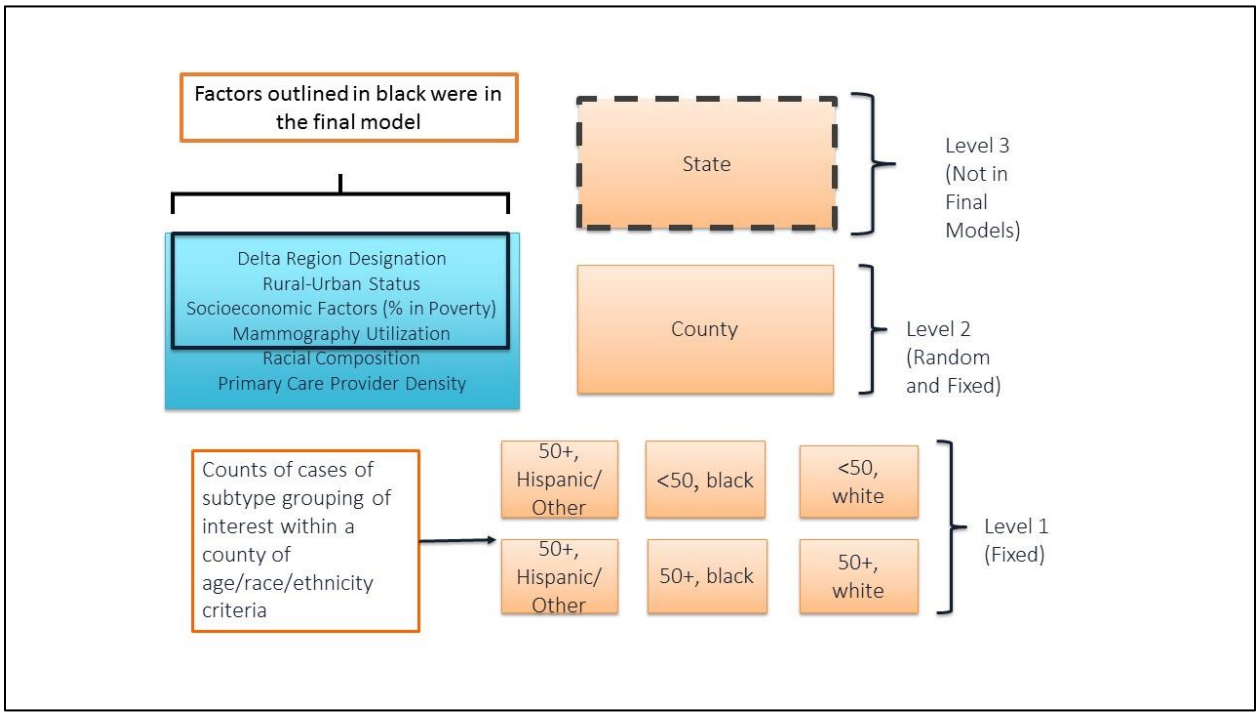

Table 2.1: Distribution of Breast Cancer Cases in the Lower Mississippi Delta States by Region and Subtype

	Delta (N=19, 334)					**Non-Delta (N=62,889)**				
	HR+/ HER2+ N (%)	**HR+/ HER2- N (%)**	**HR- /HER2+ N (%)**	**Triple Negative N (%)**	**Unknown N (%)**	**HR+/ HER2+ N (%)**	**HR+/ HER2- N (%)**	**HR-/ HER2+ N (%)**	**Triple Negative N (%)**	**Unknown N (%)**
All	1,991 (9.9%)	11,684 (60.2%)	872 (4.5%)	2,735 (14.1%)	2,132 (11.0%)	6,419 (10.2%)	41,311 (65.6%)	2,677 (4.2%)	7,344 (11.7%)	5,150 (8.2%)
Age										
<50	469 (12.8%)	1,918 (52.4%)	190 (5.2%)	735 (20.1%)	352 (9.6%)	1,728 (14.2%)	7,126 (58.4%)	2,044 (16.8%)	1,858 (15.2%)	855 (7.0%)
50+	1,442 (9.2%)	9,766 (62.3%)	682 (4.4%)	2,000 (12.8%)	1,780 (11.4%)	5,052 (10.0%)	34,281 (67.6%)	2,011 (4.0%)	5,476 (10.8%)	4,295 (8.5%)
Race/ Ethnicity										
NH White	1,273 (9.9%)	8,285 (64.8%)	502 (3.9%)	1,341 (10.5%)	1,394 (10.9%)	5,052 (10.0%)	34,281 (67.8%)	2,011 (4.0%)	5,176 (10.2%)	4,066 (8.0%)
NH Black	591 (9.7%)	3,118 (51.2%)	348 (5.7%)	1,340 (22.0%)	692 (11.4%)	911 (10.4%)	4,772 (54.7%)	461 (5.3%)	1,760 (20.2%)	824 (9.4%)
Hispanic	31 (11.0%)	184 (65.2%)	***	31 (11.0%)	28 (9.9%)	289 (13.1%)	1,383 (62.5%)	114 (5.2%)	269 (12.2%)	158 (7.1%)
Rural-Urban Status										
Rural	711 (10.0%)	4,155 (58.4%)	287 (4.0%)	932 (13.1%)	1,027 (14.4%)	1,337 (10.2%)	8,129 (62.2%)	606 (4.6%)	1,629 (12.5%)	1,371 (10.5%)
Urban	1,200 (9.8%)	7,529 (61.6%)	585 (4.9%)	1,803 (14.8%)	1,105 (9.0%)	5,082 (9.7%)	33,182 (63.5%)	2,069 (4.2%)	5,705 (11.5%)	3,779 (7.6%)

Table 2.1 (cont.)

	Delta (N=19, 334)					Non-Delta (N=62,889)				
	HR+/ HER2+ N (%)	**HR+/ HER2- N (%)**	**HR- /HER2+ N (%)**	**Triple Negative N (%)**	**Unknown N (%)**	**HR+/ HER2+ N (%)**	**HR+/ HER2- N (%)**	**HR-/ HER2+ N (%)**	**Triple Negative N (%)**	**Unknown N (%)**
Poverty Level										
<20%	891 (10.1%)	5,425 (61.5%)	389 (4.4%)	1,151 (13.0%)	968 (11.0%)	5,288 (10.1%)	34,816 (66.6%)	2,175 (4.2%)	5,983 (11.4%)	4,003 (7.7%)
20+%	1,020 (9.6%)	6,259 (58.9%)	483 (4.5%)	1,584 (14.9%)	1,164 (11.0%)	1,131 (10.6%)	6,495 (61.1%)	500 (4.7%)	1,351 (12.7%)	1,147 (10.7%)

NH=Non-Hispanic; *** indicates suppressed data due to fewer than 16 cases

Table 2.2: Age-adjusted Incidence Rates of Invasive Breast Cancer and Hormone Receptor Positive Breast Cancers by Delta Region Status and Stratified by Age, Race/Ethnicity, Rural-Urban Status, and Poverty Level

	All Cases			HR+/HER2+			HR+/HER2-		
	Cases	**IR†**	**RR (95%CI)**	**Cases**	**IR†**	**RR (95%CI)**	**Cases**	**IR†**	**RR (95%CI)**
All									
Delta	19,334	116.2	0.96 (0.95-0.98)	1,911	11.8	0.93 (0.88-0.98)	11,684	69.4	0.88 (0.86-0.90)
Non-Delta	62,889	120.8	Ref	6,419	12.7	Ref	41,311	78.7	Ref
<50 Years Old									
Delta	3,664	42.1	0.98 (0.94-1.02)	469	5.4	0.88 (0.79-0.98)	1,918	22.0	0.88 (0.84-0.93)
Non-Delta	12,198	43.0	Ref	1,728	6.1	Ref	7,126	25.0	Ref
50+ Years Old									
Delta	15,670	321.9	0.96 (0.94-0.97)	1,442	29.4	0.95 (0.90-1.01)	9,766	200.7	0.88 (0.86-0.90)
Non-Delta	50,691	336.6	Ref	4,691	30.8	Ref	34,185	227.6	Ref
Non-Hispanic Whites									
Delta	12,795	114.5	0.92 (0.91-0.94)	1,273	11.9	0.92 (0.86-0.98)	8,285	72.9	0.88 (0.86-0.90)
Non-Delta	50,586	123.9	Ref	5,052	13.0	Ref	34,281	82.9	Ref
Non-Hispanic Blacks									
Delta	6,089	122.9	0.99 (0.96-1.03)	591	11.9	0.94 (0.84-1.04)	3,118	63.3	0.93 (0.88-0.97)
Non-Delta	8,728	123.8	Ref	911	12.7	Ref	4,772	68.4	Ref
Hispanics									
Delta	282	89.1	1.05 (0.92-1.19)	31	8.8	0.84 (0.55-1.23)	184	59.4	1.09 (0.92-1.27)
Non-Delta	2,213	84.8	Ref	289	10.4	Ref	1,383	54.8	Ref
Urban									
Delta	12,222	119.7	0.97 (0.95-0.99)	1,200	11.9	0.93 (0.87-0.99)	7,529	73.2	0.90 (0.87-0.92)
Non-Delta	49,817	123.2	Ref	5,082	12.8	Ref	33,182	81.6	Ref
Rural									
Delta	7,112	110.8	0.98 (0.96-1.01)	711	11.4	0.95 (0.87-1.05)	4,155	63.4	0.92 (0.88-0.96)
Non-Delta	13,072	112.6	Ref	1,337	12.0	Ref	8,129	69.0	Ref
< 20% Below Poverty									
Delta	8,824	119.0	0.97 (0.95-0.99)	891	12.2	0.96 (0.89-1.03)	5,425	72.3	0.89 (0.86-0.92)
Non-Delta	52,265	122.9	Ref	5,288	12.7	Ref	34,816	81.3	Ref

Table 2.2 (cont.)

	All Cases			HR+/HER2+			HR+/HER2-		
	Cases	**IR†**	**RR (95%CI)**	**Cases**	**IR†**	**RR (95%CI)**	**Cases**	**IR†**	**RR (95%CI)**
20+% Below Poverty									
Delta	10,510	114.0	1.02 (1.00-1.05)	1,020	11.4	0.93 (0.85-1.02)	6,259	67.0	1.00 (0.96-1.03)
Non-Delta	10,624	111.3	Ref	1,131	12.2	Ref	6,495	67.2	Ref

IR=Incidence Rate; RR=Rate Ratio; Ref=Reference Group; †Rates are expressed per 100,000 population

Table 2.3: Age-adjusted Incidence Rates of Hormone Receptor Negative Breast Cancers and Unknown Subtype by Delta Region Status by Age, Race/Ethnicity, Rural-Urban Status, and Poverty Level

	HR-/HER2+			Triple Negative			Unknown		
	Cases	**IR**	**RR (95%CI)**	**Cases**	**IR**	**RR (95%CI)**	**Cases**	**IR**	**RR (95%CI)**
All									
Delta	872	5.3	1.03 (0.95-1.11)	2,735	17.0	1.18 (1.13-1.24)	2,132	12.7	1.30 (1.23-1.37)
Non-Delta	2,677	5.2	Ref	7,334	14.4	Ref	5,150	9.8	Ref
<50 Years Old									
Delta	190	2.2	0.98 (0.83-1.15)	735	8.4	1.29 (1.18-1.40)	352	4.0	1.34 (1.18-1.52)
Non-Delta	631	2.2	Ref	1,858	6.6	Ref	855	3.0	Ref
50+ Years Old									
Delta	682	14.0	1.05 (0.96-1.14)	2,000	40.9	1.13 (1.08-1.19)	1,780	36.9	1.28 (1.21-1.36)
Non-Delta	2,044	13.4	Ref	5,476	36.1	Ref	4,295	28.7	Ref
Non-Hispanic Whites									
Delta	502	4.6	0.91 (0.82-1.01)	1,341	12.8	0.97 (0.91-1.03)	1,394	12.3	1.26 (1.18-1.34)
Non-Delta	2,011	5.1	Ref	5,176	13.2	Ref	4,066	9.8	Ref
Non-Hispanic Blacks									
Delta	348	6.9	1.09 (0.94-1.26)	1,340	26.8	1.09 (1.01-1.17)	692	14.1	1.20 (1.08-1.33)
Non-Delta	461	6.3	Ref	1,760	24.6	Ref	824	11.8	Ref
Hispanics									
Delta	***	***	***	31	10.1	1.03 (0.68-1.50)	28	8.5	1.41 (0.90-2.13)
Non-Delta	114	3.8	Ref	269	9.8	Ref	158	6.0	Ref
Urban									
Delta	585	5.8	1.13 (1.02-1.24)	1,803	18.0	1.26 (1.19-1.33)	1,105	10.7	1.16 (1.08-1.24)
Non-Delta	2,069	5.2	Ref	5,705	14.3	Ref	3,779	9.3	Ref
Rural									
Delta	287	4.5	0.84 (0.72-0.98)	932	15.6	1.06 (0.97-1.16)	1,027	15.9	1.37 (1.26-1.49)
Non-Delta	606	5.4	Ref	1,629	14.7	Ref	1,371	11.6	Ref

Table 2.3 (cont.)

	HR-/HER2+			Triple Negative			Unknown		
	Cases	**IR**	**RR (95%CI)**	**Cases**	**IR**	**RR (95%CI)**	**Cases**	**IR**	**RR (95%CI)**
<20% Below Poverty									
Delta	389	5.3	1.03 (0.92-1.15)	1,151	16.2	1.13 (1.06-1.20)	968	13.0	1.39 (1.29-1.49)
Non-Delta	2,175	5.1	Ref	5,983	14.3	Ref	4,003	9.4	Ref
20+% in Poverty									
Delta	483	5.3	1.00 (0.88-1.14)	1,584	17.8	1.21 (1.12-1.31)	1,164	12.5	1.06 (0.97-1.15)
Non-Delta	500	5.3	Ref	1,351	14.7	Ref	1,147	11.9	Ref

IR=Incidence Rate; RR=Rate Ratio; Ref=Reference Group; †Rates are expressed per 100,000 population

Table 2.4: Age-adjusted Incidence Rates of All Breast Cancer Cases and Hormone Receptor Positive Breast Cancers by Race/Ethnicity, Rural-Urban Status, and Poverty Level in the Delta Region

	All Cases			HR+/HER2+			HR+/HER2-		
	Cases	**IR**	**RR (95%CI)**	**Cases**	**IR**	**RR (95%CI)**	**Cases**	**IR**	**RR (95%CI)**
Race/Ethnicity									
Hispanic	282	89.1	0.78 (0.69-0.88)	31	8.8	0.74(0.49-1.06)	184	59.4	0.82(0.70-0.95)
Non- Hispanic Black	6,089	122.9	1.07 (1.04-1.11)	591	11.9	1.00(0.90-1.11)	3,118	63.3	0.87(0.83-0.91)
Non- Hispanic White	12,795	114.5	Ref	1,273	11.9	Ref	8,285	72.9	Ref
Rural-Urban Status									
Rural	7,112	110.8	0.93 (0.90-0.95)	711	11.4	0.96 (0.87-1.06)	4,155	63.4	0.87(0.83-0.90)
Urban	12,222	119.7	Ref	1,200	11.9	Ref	7,529	73.2	Ref
Poverty Level									
20+% poverty	10,510	114.0	0.96 (0.93-0.99)	1,020	11.4	0.93 (0.85-1.02)	6,259	67.0	0.93 (0.89-0.96)
<20% poverty	8,824	119.0	Ref	891	12.2	Ref	5,425	72.3	Ref

IR=Incidence Rate; RR=Rate Ratio; Ref=Reference Group; †Rates are expressed per 100,000 population

Table 2.5: Age-adjusted Incidence Rates of Hormone Receptor Negative Breast Cancers and Unknown Subtype in the Delta Region by Race/Ethnicity, Rural-Urban Status, and Poverty Level in the Delta Region

	HR-/HER2+			Triple Negative			Unknown		
	Cases	**IR**	**RR (95%CI)**	**Cases**	**IR**	**RR (95%CI)**	**Cases**	**IR**	**RR (95%CI)**
Race/Ethnicity									
Hispanic	***	***	***	31	10.1	0.79 (0.53-1.13)	28	8.5	0.69 (0.45-1.00)
Non- Hispanic Black	348	6.9	1.49 (1.28-1.71)	1,340	26.8	2.10 (1.94-2.27)	692	14.1	1.15 (1.04-1.26)
Non- Hispanic White	502	4.6	Ref	1,341	12.8	Ref	1,394	12.3	Ref
Rural-Urban Status									
Rural	287	4.5	0.79 (0.68-0.91)	932	15.6	0.86 (0.80-0.94)	1,027	15.9	1.48 (1.35-1.61)
Urban	585	5.8	Ref	1,803	18.0	Ref	1,105	10.7	Ref
Poverty Level									
20+% poverty	483	5.3	1.00 (0.87-1.15)	1,584	17.8	1.10 (1.01-1.19)	1,164	12.5	0.97 (0.88-1.05)
< 20% poverty	389	5.3	Ref	1,151	16.2	Ref	968	13.0	Ref

IR=Incidence Rate; RR=Rate Ratio; Ref=Reference Group; †Rates are expressed per 100,000 population; *** Rate ratio suppressed as it is based on fewer than 16 cases

Table 2.6: Multilevel Negative Binomial Regression Modeling of Invasive Breast Cancers by Delta Region Status and Stratified by Age, Race/Ethnicity, Rural-Urban Status, and Poverty Level

	All Breast Cancers RR (95%CI)	**HR+/HER2+ RR (95%CI)**	**HR+/HER2- RR (95%CI)**	**HR-/HER2+ RR (95% CI)**	**Triple Negative RR (95%CI)**	**Unknown RR (95% CI)**
All Cases [a]	1.00 (0.97-1.02)	0.95 (0.89-1.01)	0.98 (0.94-1.02)	0.96 (0.87-1.05)	1.01 (0.95-1.08)	1.19 (1.05-1.35)
Age [b]						
50+ Years Old	0.99 (0.97-1.02)	0.94 (0.87-1.02)	0.98 (0.94-1.02)	0.96 (0.87-1.07)	0.99 (0.93-1.06)	1.17 (1.03-1.34)
<50 Years Old	1.01 (0.96-1.06)	0.96 (0.85-1.08)	0.98 (0.91-1.05)	0.93 (0.77-1.11)	1.09 (0.98-1.22)	1.22 (0.98-1.51)
Race/Ethnicity [c]						
Non-Hispanic White	0.98 (0.95-1.01)	0.95 (0.89-1.03)	0.96 (0.92-1.00)	0.92 (0.82-1.02)	1.00 (0.93-1.07)	1.18 (1.04-1.35)
Non-Hispanic Black	1.04 (0.98-1.09)	0.80 (0.70-0.90)	1.01 (0.94-1.09)	0.86 (0.69-1.06)	1.07 (0.96-1.18)	1.14 (0.90-1.44)
Hispanic	1.02 (0.85-1.21)	0.92 (0.62-1.36)	1.08 (0.88-1.32)	***	1.02 (0.75-1.38)	1.02 (0.66-1.58)
Rural-Urban Status [d]						
Rural	1.00 (0.97-1.03)	0.94 (0.85-1.03)	0.99 (0.94-1.04)	0.80 (0.69-0.93)	0.93 (0.85-1.02)	1.26 (1.08-1.47)
Urban	0.99 (0.95-1.03)	0.95 (0.87-1.04)	0.95 (0.90-1.02)	1.07 (0.95-1.20)	1.10 (1.01-1.20)	1.06 (0.85-1.31)
Poverty Level [e]						
<20% Below Poverty	0.98 (0.94-1.01)	0.97 (0.89-1.06)	0.91 (0.86-0.96)	1.01 (0.89-1.15)	1.07 (0.98-1.17)	1.29 (1.07-1.55)
20+% Below Poverty	1.00 (0.97-1.04)	0.93 (0.85-1.01)	1.02 (0.97-1.08)	0.90 (0.78-1.04)	0.93 (0.84-1.01)	1.15 (0.97-1.37)

Non-Delta Region is Reference Group; RR=Rate Ratio; [a] Adjusting for age, race/ethnicity, rural-urban status, poverty level, area mammography utilization, and race/rural-urban status interaction (if statistically significant) ;[b] Adjusting for race/ethnicity, rural-urban status, area mammography utilization, and race/rural-urban status interaction; [c] Adjusting for age, area mammography utilization, and poverty level; [d] Adjusting for age, race/ethnicity, area mammography utilization, and poverty level; [e] Adjusting for age, race/ethnicity, area mammography utilization, rural-urban status, and race/rural-urban status interaction. *** Rate ratio suppressed as it is based on fewer than 16 cases.

Table 2.7: Multilevel Negative Binomial Regression Modeling of Invasive Breast Cancer by Subtype in the Delta Region

	All Breast Cancers RR (95%CI)	**HR+/HER2+ RR (95%CI)**	**HR+/HER2- RR (95%CI)**	**HR-/HER2+ RR (95% CI)**	**Triple Negative RR (95%CI)**	**Unknown RR (95% CI)**
Race/Ethnicity						
Non-Hispanic White	Ref	Ref	Ref	Ref	Ref	Ref
Non-Hispanic Black	1.06 (1.02-1.10)	1.02 (0.89-1.16)	0.98 (0.92-1.04)	1.10 (0.93-1.29)	1.05(0.96- 1.15)	0.99 (0.89-1.11)
Hispanic	0.93 (0.84-1.03)	0.96 (0.67-1.36)	0.82 (0.69-0.97)	***	0.97 (0.74-1.29)	1.10 (0.81-1.49)
Rural-Urban Status						
Urban	Ref	Ref	Ref	Ref	Ref	Ref
Rural	0.99 (0.95-1.04)	0.97 (0.86-1.09)	0.98 (0.92-1.04)	0.86 (0.73-1.01)	0.97 (0.88-1.06)	1.42 (1.14-1.76)
Poverty Level						
<20% Below Poverty	Ref	Ref	Ref	Ref	Ref	Ref
20+% Below Poverty	0.96 (0.92-1.00)	0.94 (0.85-1.05)	0.99 (0.93-1.06)	0.98 (0.84-1.15)	0.89 (0.81-0.99)	0.97 (0.78-1.20)

RR=Rate Ratio; All models also adjusted for age group, mammography utilization, and race-rural-urban status interaction (if significant); *** Rate ratio suppressed as it is based on fewer than 16 cases.

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CHAPTER 3: BREAST CANCER STAGING BY SUBTYPE IN THE LOWER MISSISSIPPI DELTA REGION STATES

Introduction

The federally designated Delta Regional Authority (Delta Region) includes nearly 10 million people living in 252 counties and parishes in eight states along the Mississippi River (Alabama, Arkansas, Illinois, Kentucky, Louisiana, Mississippi, Missouri, and Tennessee; Lower Mississippi Delta Region-LMDR- states). Roughly one in three residents in the Delta Region are black, and more than 20% of the population live in poverty (1). Additionally, this region has lower population density and poorer access to healthcare services compared to other areas in the LMDR states and the country as a whole (1,2). These factors make the Delta Region vulnerable to a myriad of health disparities, including breast cancer disparities. Women in the Delta Region have higher rates of breast cancer mortality than women elsewhere in the country (3). Further, black women in the Delta Region have higher breast cancer mortality rates than white women in the Region and black women in other parts of the country (3). Nine of the ten counties with the nation's highest breast cancer mortality rates are in the Delta Region (4). Additionally, studies have shown that the Delta Region has historically lower rates of adherence to mammography screening--even among women covered by Medicare-- than women in other parts of the country (2,5). Identifying the contributing factors to these breast cancer mortality disparities and the effects of lower mammography utilization are imperative to improve the health of the region.

Several studies have shown that race/ethnicity, rural-urban status, socioeconomic position, and access to health care services affect the stage at which breast cancer is diagnosed. Cancers diagnosed at a more advanced stage have fewer treatment options and poorer survival. Multiple studies have shown descriptively that a higher percentage of black women are

diagnosed with more advanced stages of breast cancer compared to white women (6,7). Odds of advanced stage breast cancer remain high in black women, even after considering potential confounders (8,9). Other studies have shown that rural women have higher odds of being diagnosed with a breast cancer at a more advanced stage (10). Additionally, regardless of race or ethnicity, lower socioeconomic status was associated with more advanced staging in multiple studies (11-13). Other social factors—such as residential segregation—have been explored for possible association with more advanced stage of breast cancer, with studies showing mixed results (14-16). Some studies have also shown that women who live further from healthcare services or where there is a dearth of physicians are diagnosed with breast cancer at a more advanced stage (17).

Like breast cancer stage, the molecular subtype of breast cancer guides treatment options and is associated with differences in prognosis, due in part to the variation in stage at diagnosis by subtype. Hormone-receptor-negative breast cancers present at a more advanced stage than other breast cancer subtypes, have fewer treatment options, and are associated with poorer survival than hormone receptor-positive breast cancers (18,19). Studies indicate that women diagnosed with triple-negative breast cancer, in particular, have greater odds of more advanced stage at diagnosis (20,21). Other factors affect this dynamic between subtype and stage. Black women have higher incidence rates of distant stage breast cancer across subtypes, with studies also showing that black women have greater odds of advanced stage diagnosis across subtypes, even after controlling for confounding factors (22,23).

The sociodemographic composition of the Delta Region suggests that women in the Region may be at high risk for more advanced staging of breast cancer across subtypes, which may be due to poor screening adherence and may contribute to higher breast cancer mortality

rate. The objective of this present study was threefold. First, it sought to determine the differences in the distribution breast cancer stage by subtype between the Delta and non-Delta Regions of the LMDR states. Second, it sought to determine the difference in the distribution of breast cancer stage by subtype among white and black women in the Delta Region. Third, it explored how the differences in breast cancer stage by subtype may be explained by contributing individual level and contextual factors, like age and county-level poverty rates, respectively.

Methods

Conceptual Model

A conceptual model, drawing from Warnecke's Model for Analysis of Population Health and Health Disparities, was developed to identify individual and area-level factors that may be associated with breast cancer stage by subtype within the Delta Region (Figure 3.1) (24). The Delta Region is a conceptualized as a supramacro, policy-relevant context that may affect the distribution of the incidence of breast cancer staging by subtype. Specifically included are individual-level factors (age and race/ethnicity) that have been shown in previous studies to affect one's risk for any breast cancer, one's risk for developing specific subtypes of breast cancer, or one's risk for being diagnosed at an earlier or more advanced stage (18,22). Social and physical contextual factors that affect breast cancer incidence rates overall or by specific subtype and stage are also depicted in this model, including socioeconomic factors, racial composition (as a crude measure of residential segregation), rural-urban status, mammography utilization, and provider density(10,15,20,25-27).

Data

The North American Association of Central Cancer Registries (NAACCR) Cancer in North America (CiNA) Deluxe File provided case data on all breast cancer cases diagnosed in LMDR states between 2012 and 2014(28). To be included in this dataset, data from central cancer registries must have 90+% case ascertainment, passing edits of 97% or better, and other quality indicators. These data are based on the NAACCR December 2016 data submission. Regulatory support for cancer registries is provided by the state, province or territory in which the registry is located while most funding is federal. In the U.S., registries also participate in the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) Program or the Centers for Disease Control and Prevention's National Program of Cancer Registries (NPCR) or both. In Canada, all registries submit data to the Canadian Cancer Registry maintained by Statistics Canada. Seven of the eight LMDR states provided active consent for their data to be included in this analysis (Alabama, Arkansas, Illinois, Kentucky, Louisiana, Mississippi, and Tennessee). Missouri data were not included as they did not consent for their data to be used.

All invasive female breast cancers were included (International Classification of Disease for Oncology 3rd Edition (ICD-O-3) of C500-C509), except for those with histology codes of 9050-9055 (mesothelioma), 9140 (Kaposi's sarcoma), 9590-9992 (leukemia and lymphoma), following the exclusion criteria used in a similar study (22). Cases who were missing on race/ethnicity and county of residence were 85 years of age or older, and/or were reported to their respective central cancer registry by way of a death certificate, autopsy report, or by nursing home or hospice were also excluded.

Germane to the current study, NAACCR CiNA Deluxe data file included age (19 groups), race/ethnicity, county of residence at diagnosis, collaborative staging site-specific factors, 1,2, and 15, which correspond to estrogen receptor (ER), progesterone receptor (PR), and Human epidermal growth factor 2 (HER2) statuses, respectively, and Surveillance Epidemiology and End Result (SEER) summary stage. County of residence at diagnosis was used to determine if a patient lived in the Delta or non-Delta Regions of these states. ER, and PR status were considered jointly and categorized a cancer case's hormone receptor (HR) status. HR+ cases included those that were ER+ or PR+ or borderline. HR- included those cases that were both ER- and PR-. For HER2 status, HER2+ and HER2- were categorized accordingly. Cases that were unknown on HR status and/or those cases with borderline or unknown HER2 status were considered to be of unknown subtype. Based upon these site-specific factors, molecular subtypes of breast cancer cases were approximated: 1) HR+/HER2-; 2) HR+/HER2+; 3)HR-/HER2+; 4) HR-/HER2- (triple negative); 5) unknown (18). Cases were also categorized by their SEER summary stage. As has been commonly used in similar studies, regional and distant cancers were categorized as late stage (29-31). Localized cancers were categorized as early stage. In situ and unknown/unstaged cancers were excluded from this analysis.

Age-adjusted Incidence Rates and Rate Ratio Calculations

Age-adjusted incidence rates (IR) and rate ratios (RR) with 95% confidence intervals for all early and late stage, respectively, invasive breast cancers combined and individually by molecular subtype and unknown subtype status to compare Delta and non-Delta Region rates. Analyses were also stratified by race/ethnicity, rural-urban status, and percent living in poverty. Early and late stage age-adjusted incidence rates and rate ratio calculations were performed to evaluate racial, rural-urban, and poverty level differences within the Delta Region specifically as

well. Rates were expressed per 100,000 population and were age-adjusted using the 2000 US standard population. Tiwari modifications were used in all analyses performed using SEER*Stat 8.4.3.

Multilevel Regression Models

Proc GLIMMIX in SAS 9.4 was used to construct multilevel regression models to calculate adjusted rate ratios for all breast cancers, each subtype individually, and breast cancers of unknown subtype as a means of comparing the Delta Region to the non-Delta Region overall and stratified by race/ethnicity, rural-urban status, and poverty level for both early and late-stage cancers. Similar analyses were performed examining solely Delta Region cases to assess race/ethnic, rural-urban, and poverty level differences within the Region.

Because counts were overdispersed for both early and late-stage cancers of all categorizations--all cancers combined, HR+/HER2+, HR+/HER2-, HR-/HER2+, triple-negative and unknown subtypes--multilevel negative binomial regression models were constructed. A three-level model in which analysis cells were nested within counties and counties were nested by state was initially tested, but models did not converge for all subtype analyses (Figure 3.2). Therefore, for consistency, a two-level model in which analysis cells were nested by county was used for all analyses. For these models, analyses cells were constructed containing the number of cases for each respective stage grouping in each county, which were divided by age (<50 years of age and 50+ years of age) and race/ethnicity (Non-Hispanic White, Non-Hispanic Black, Hispanic/Non-Hispanic Other). Analysis groups were divided at age 50 as it is the age at which estrogen receptor negative cancer rates peak, making 50 a good demarcation for risk, and because 50 years of age is the recommended starting age for mammography for women of average risk (32,33). Further, dichotomizing age optimizes the counts of each analysis cell,

especially for the rarer subtypes, compared to creating more groupings. County was included in the model as both a random and a fixed effect and analysis cells were considered in the model as fixed effects. Age and race/ethnicity-specific rates were calculated for the entire geographic area of our study to estimate the expected counts for each analysis cell. The natural log of these expected counts was included in each model as an offset variable.

Factors chosen for consideration in the regression model building process had been used in previous research as contextual factors that may affect breast cancer incidence and staging, as shown in Figure 3.1, and may explain any differences in incidence between the Delta and non-Delta Regions within the seven LMDR states. County-level data characterizing these social and physical contextual factors were pulled from the American Community Survey (ACS), National Cancer Institute (NCI) County Level Modeled Estimates of Mammography Utilization, United States Department of Agriculture (USDA), and the Area Health Resource File (34-36). The ACS is a continuous national survey that collects information on a myriad of factors, including county-level sociodemographic characteristics (34). 2010-2014 ACS county-level factors on % living in poverty, median household income, % with at least a high school education, and % of the population that identify as black were extracted. USDA's Rural-Urban Continuum Codes, which consider a county's population size and adjacency to a metropolitan area, were used to categorize counties as either urban or rural (36). A code of 1-3 was considered urban; a code of 4-9 was considered rural. The National Cancer Institute's State Cancer Profile provided county-level modeled estimates of the percentage of women aged 40+ who had a mammogram in the past two years (35). The Area Health Resource File provided data on the number of primary care physicians in each county for the years 2011 to 2014, which were used determine the average number of primary care physicians per 100,000 (i.e. provider density) for each county(37).

Ultimately, only one sociodemographic variable was considered in the model, poverty level, as these variables were highly correlated. Poverty level was chosen as it has been considered the most robust socioeconomic variable for measuring inequalities in cancer incidence (38). All other variables were considered in the analysis: rural-urban status, provider density, and mammography utilization. Provider density proved to non-significantly contribute to all models and caused poorer goodness of fit as measured by the Akaike Information Criterion, and therefore was excluded from inclusion in final models. Because of the important, but understudied, consideration of the interaction between race and rural context, particularly in the South (39), the cross-level interaction between rural-urban status and race were considered in all models and was retained if the interaction was statistically significant. Exponentials of coefficients estimated rate ratios. 95% confidence intervals were used to determine whether there were statistically significant differences in cancer incidence for early and late stages, respectively, between the Delta Region and non-Delta Region after accounting for the aforementioned potential confounders.

Results

Table 3.1 displays the age-adjusted IRs and RRs for the Delta and non-Delta Regions for all cancers, each individual subtype, and those of unknown subtype for all cases and for non-Hispanic whites and blacks. The age-adjusted incidence rate for early-stage breast cancer was lower in the Delta Region than the non-Delta Region (IR=70.4 and 76.4, respectively, RR=0.92, 95% CI=0.90-0.94). There was no statistically significant difference in late-stage rates. Rates among non-Hispanic whites and blacks followed a similar pattern, as both groups had lower early-stage rates in the Delta Region, but no differences in late-stage breast cancer. For HR+/HER2- cancers, the Delta Region had lower rates of both early and late stages. The

Delta/non-Delta Region difference was particularly stark for early-stage cancers (IR=44.6 and 52.7, respectively, RR=0.85; 95% CI=0.82-0.87). For the racial/ethnic stratification, only in non-Hispanic white women were there a Delta/non-Delta Region difference in late-stage HR+/HER2- (RR=0.92; 95% CI=0.87-0.96). Rates of both early and late stage triple negative breast cancers were higher in the Delta Region. The rate of early stage triple negative breast cancer was 9.9 per 100,000 in the Delta Region, compared to 8.7 per 100,000 in the non-Delta Region (RR=1.14, 95% CI=1.07-1.21). The rate of late-stage triple negative breast cancer was higher in the Delta Region compared to the non-Delta Region (IR=7.0 and 5.6, respectively, RR=1.24; 95% CI=1.16-1.34). Also of note, black women in the Delta Region had higher rates of late-stage triple-negative breast cancer than non-Delta black women (RR=1.15; 95% CI=1.03-1.29). Compared to women in the non-Delta Region, women in the Delta Region also had higher rates of both early and late-stage cancers of unknown subtype.

Table 3.2 displays the age-adjusted IRs and RRs stratified by rural and urban status in the Delta and non-Delta Regions for all cancers, each individual subtype, and those of unknown subtype for all cases. Both the rural and urban Delta Region had lower rates of early-stage breast cancer compared to their respective non-Delta Region counterparts. HR+/HER2- cancers showed a similar association, as both the rural and the urban Delta had lower rates of early-stage cancers than the non-Delta Region, but there was no difference in late-stage cancers. For HR-/HER2+ breast cancers, there was no difference in the rural Delta and non-Delta Regions for either early or late stage cancer. The urban Delta Region had higher rates of early-stage HR-/HER2+ breast cancer compared to non-Delta urban women (RR=1.18; 95% CI=1.03-1.35). There were no regional rural differences for late-stage triple-negative cancers. The urban Delta Region had higher rates of both early and late stage triple-negative breast cancer than non-Delta women. The

rate of early-stage triple-negative breast cancer in the urban Delta Region was 10.5 per 100,000 compared to 8.7 per 100,000 in the non-Delta Region. For late-stage triple-negative breast cancers, the rates in the Delta and non-Delta Regions were 7.3 and 5.6 per 100,000, respectively (RR=1.31; 95% CI=1.20-1.43). Both rural and urban Delta Regions had higher rates of both early and late stage breast cancer of unknown subtype compared to the non-Delta Region.

Table 3.3 displays the age-adjusted IRs and RRs stratified by poverty level in the Delta and non-Delta Regions. Women in the Delta Region who lived in counties with 20+% of the population living in poverty (i.e. high poverty) had higher rates of late-stage breast cancer compared to women in high poverty areas of the non-Delta (IR=43.9 and 41.0 per 100,000, respectively, RR=1.07; 95% CI=1.02-1.12). For HR+/HER2- breast cancer, women in high poverty counties in the Delta Region had higher rates of late-stage breast cancer than those in high poverty counties in the non-Delta Region (RR=1.07; 95% CI=1.01-1.14). For women in counties with less than 20% of the population in poverty, the Delta Region had lower rates of both early and late stage HR+/HER2- cancers. The Delta Region had higher rates of both early and late stage triple-negative breast cancers for both poverty stratifications compared to their non-Delta counterparts. Of particular note is the Delta/non-Delta Region difference in late-stage triple-negative breast cancers in high poverty counties (RR=1.26, 95% CI=1.12-1.42). Rates of both early and late stage breast cancers of unknown subtype are higher in the Delta Region than the non-Delta Region in counties with less than 20% of the population in poverty.

Table 3.4 displays the age-adjusted IRs and RRs for early and late stage breast cancers by subtype within the Delta Region stratified by race, rural-urban status, and poverty level. Black women in the Delta Region had lower rates of early stage breast cancer (RR=0.91; 95% CI=0.87-0.95) but higher rates of late-stage breast cancer (RR=1.34; 95% CI=1.28-1.41) compared to

white women. A similar relationship was seen for HR+/HER2- cancers, as black women had lower rates of early-stage cancer (RR=0.75; 95% CI=0.71-0.79), but higher rates of late-stage cancer (RR=1.10; 95% CI=1.03-1.18). For HR-/HER2+ cancers, black women had higher early (RR=1.33; 95% CI=1.08-1.64) and late stage cancer rates (RR=1.65; 95% CI=1.34-2.02) compared to white women in the Region. For triple-negative breast cancers, black women had higher rates of both early (RR=1.79; 95% CI=1.61-1.98) and late stage (RR=2.62; 95% CI=2.31-2.98) cancers as well. Rural women in the Delta Region had lower rates of early-stage breast cancer for all breast cancer cases combined (RR=0.89; 95% CI=0.85-0.92) and for each individual subtype, except HR+/HER2+ cases, compared to urban Delta residents. The rural Delta Region had lower rates of late-stage breast cancers of all subtypes combined (RR=0.94; 95% CI=0.85-0.92) and both HR+/HER2- and triple-negative cancers. Rural women had higher rates of both early and late stage breast cancer of unknown subtype. Women who live in higher poverty counties in the Delta Region have lower rates of early-stage breast cancer than less impoverished women for all breast cancers combined and for all subtypes individually except both HR- subtypes where there was no difference. Women in higher poverty Delta counties had higher rates of late-stage triple negative breast cancer (RR=1.20; 95% CI=1.06-1.36).

Table 3.5 displays the results of multivariable, multilevel negative binomial regression modeling for early and late stages of all breast cancer cases, individual subtypes, and cases of unknown subtype for all cases and stratification by race/ethnicity, rural-urban status, and poverty level. There is no difference between the Delta and non-Delta Regions in early or late stage cancers for all subtypes combined or any individual subtype across most stratifications when accounting for relevant first level and contextual confounders. Urban women in the Delta Region have higher rates of early stage triple negative breast cancer than non-Delta women after

adjusting for relevant factors (RR=1.10; 95% CI=1.01-1.21). Women in the Delta Region who lived in counties with less than 20% of the population in poverty had lower rates of HR+/HER2- cancers than non-Delta women after adjusting for relevant factors (RR=0.91; 95% CI=0.85-0.97). Unknown subtype rates were higher in the Delta vs. the non-Delta for the following groupings/stratifications: early and late stages of all breast cancers, early stage in white women, late stage in black women, early and late stage in rural women, early and late stage in women who lived in "low poverty" counties.

Table 3.6 displays the results of multivariable, multilevel negative binomial regression modeling for early and late stages of all breast cancer cases, individual subtypes, and cases of unknown subtype for all cases and stratification by race/ethnicity, rural-urban status, and poverty level within the Delta Region. Lower rates of early-stage cancers persisted in rural women for all subtypes combined, as well as HR+/HER2- and HR-/HER2+ cancers. Black women in the Delta Region had higher rates of all late-stage breast cancers (RR=1.10; 95% CI=1.04-1.15) and higher rates of triple-negative breast cancer (RR=1.17, 95% CI=1.00-1.33) compared to white women in the Region, even after accounting for age and relevant contextual factors. Higher rates of late-stage unknown subtypes persisted in the rural Delta after controlling for other factors.

Discussion

This present study utilized population-level cancer registry data to examine early and late-stage breast cancer incidence rate differences between the Delta and non-Delta regions of seven LMDR states for all breast cancers combined and stratified by subtype. There were no early and late stage incidence differences between the Delta and non-Delta Regions for all breast cancers combined. For both stage groupings, the Delta Region had lower rates of HR+/HER2- than non-Delta Region women but had higher rates of both early and late stage triple negative

breast cancers. Compared to their respective non-Delta women, rural Delta women had lower rates of early-stage HR+/HER2- breast cancer while urban Delta women had higher early and late stage triple negative breast cancers. Higher rates of unknown breast cancers of both staging groups tended to be higher in the Delta Region across most demographic stratifications. After adjusting for first and second level variables, any rate differences by stage were attenuated, except for some unknown subtype stratifications. In analyses of the Delta Region alone, black women had lower rates of early-stage breast cancer, but higher rates of late-stage breast cancer compared to white women. Black women also had higher rates of early and late stage HR- cancers. Rural Delta women had lower rates of both early and late stage breast cancers than their urban counterparts, an association that remained even after adjustment.

The overall rate of early-stage breast cancer was lower in the Delta Region than the non-Delta Region as were both early and late stage HR+/HER2- breast cancers. These lower rates across stages may be explained by the historically low levels of mammography utilization by women in the Delta Region (2,5). Ecological studies have shown that increased mammography utilization is correlated with high overall and HR+/HER2- breast cancer rates (22). Indeed, in the multivariable analysis of this study, the statistically significantly lower rates of overall and HR+/HER2- cancers for early and late stage were attenuated to statistical non-significance after accounting for factors like mammography utilization. HR+/HER2- is the subtype with the best prognosis, but it is also the most common subtype. Further, studies suggest that high rates of early-stage HR+/HER2- breast cancers may be indicative of overdiagnosis, which may occur in nearly one out of every three breast cancer diagnoses (22, 40). It is unclear how much the higher rates of early-stage HR+/HER2- breast cancers in the non-Delta Region are driven by overdiagnosis compared to a true excess of incident cases.

The lower rates of late-stage breast cancers and HR+/HER2- cancers may suggest that the higher mortality rates in the Delta Region may be driven by the less common, but more aggressive molecular subtypes (i.e. triple-negative), and/or by lower quality breast cancer treatment in the region. A study of breast cancer patients in Appalachia, a similarly socioeconomically disparate region with breast cancer mortality disparities, found that less than half of women who were eligible for post-surgical targeted therapy based upon subtype and staging actually did receive it, an indicator of poor treatment quality (41). However, there is a dearth of literature on cancer treatment quality in the Delta Region as a potential factor in the mortality disparity. This paucity of research provides an opportunity to further explicate the breast cancer mortality disparity in the Delta Region.

In the analysis of the Delta Region alone, black women had lower rates of early-stage breast cancer, but higher rates of late-stage breast cancer compared to white women for both all subtypes combined and for each individual subtype specifically, except the HR+/HER2+ subtype. Elevated rates of late-stage breast cancers among black women in the Delta Region remained for all subtypes combined and for the HR+/HER2- subtype specifically after accounting for age and contextual factors. These findings corroborate previous studies indicating higher rates of advanced stage breast cancer in black women compared to white women (8-10). Further, it underscores the importance of culturally component, tailored interventions to improve cancer screening rates and subsequently reduce the rate of late-stage cancers in black women in the Region. Several studies have shown that utilizing lay health advisors/community health advisors and/or faith-based settings can increase breast cancer screening among black women in Delta Region communities or other communities in the Deep South (42-45). One of these interventions includes Erwin's "Witness Project", which was developed and tested in the

Arkansas Delta and utilizes lay health advisors who are cancer survivors to educate black women on cancer screening in a faith-based setting (42,43). The Witness Project model has been identified as one of the NCI's Research-Tested Intervention Programs, a collection of effective, evidence-based programs that can be implemented targeted population groups or communities (46). Additionally, the American Cancer Society has successfully piloted a community health advisor program to improve cancer screening rates in black communities in the Deep South, which has some geographic overlap with the Delta Region (45). Scaling up these successful interventions and implementing them across the black communities within the Delta Region may help reduce the racial disparity in breast cancer staging through early detection. Because elevated rates of late-stage breast cancer were experienced among black women for all subtypes, it is important to note that different screening modalities will be more effective to detect each subtype. While typical X-Ray mammography may be effective for identifying HR+/HER2- breast cancers, ultrasound or MRI mammography are more effective for detecting triple-negative breast cancers (47-49). In fact, some organizations, such as the American Cancer Society and the National Comprehensive Cancer Network recommend breast MRI for women at particularly high risk (50-51). Interventions should also emphasize the effectiveness of different modalities to detect different subtypes, especially as triple-negative breast cancers are more common in black women.

The current study was not without limitations. First, data from one LMDR state, Missouri, were not included as they did not consent for their data to be used. While Missouri includes less than seven percent of the Delta Region population and is the Delta Region state with the largest percentage of white population, its omission may affect the study findings (1). For example, Delta Region disparities were identified for triple-negative breast cancers in urban

populations especially. The absence of data from non-Delta urban areas with a high proportion of black residents like St. Louis and Kansas City may alter the identified disparity. Finally, a three-level model proved to be too complex for the less common subtypes of breast cancer, especially with stratifications by stage. Thus state-to-state variability was unable to be accounted for. However, this study had several strengths. First, it utilized population-based cancer registry data, which includes all cancer cases that were diagnosed in the LMDR states during the study period. Second, it employed multilevel modeling to explore place-based effects on cancer staging, a method that has been underutilized in rural cancer research (52). Multilevel models assume the nonindependence of group membership (i.e. counties) and thus, produce less biased standard errors and reduce the risk of Type I errors. This study was the first to explore cancer staging differences across the multi-state Delta Region. Additionally, it was one of the first to explore staging differences in breast cancers stratified by the four molecular subtypes, rather than adjusting for subtype when assessing differences in stage.

Conclusions

Late stage breast cancer disparities between the Delta and non-Delta-Region were largely non-existent. This suggests that the higher rates of triple-negative breast cancer in the region and potential treatment disparities may be the key contributors to the Delta Region's breast cancer mortality disparities. Within the Delta Region, black women had higher rates of late-stage breast cancer across most subtypes. The Delta Region is rife with successful examples of community-based, culturally competent interventions to increase breast cancer screening uptake in black women. Scaling up these interventions throughout the Delta Region may help improve screening rates in black women and increase early detection. Further, it is important to ensure that

appropriate screening modalities be utilized to detect different breast cancer subtypes at an earlier, more treatable stage.

Figures and Tables

Figure 3.1: Conceptual Model for Elucidating Breast Cancer Disparities in the Delta Region

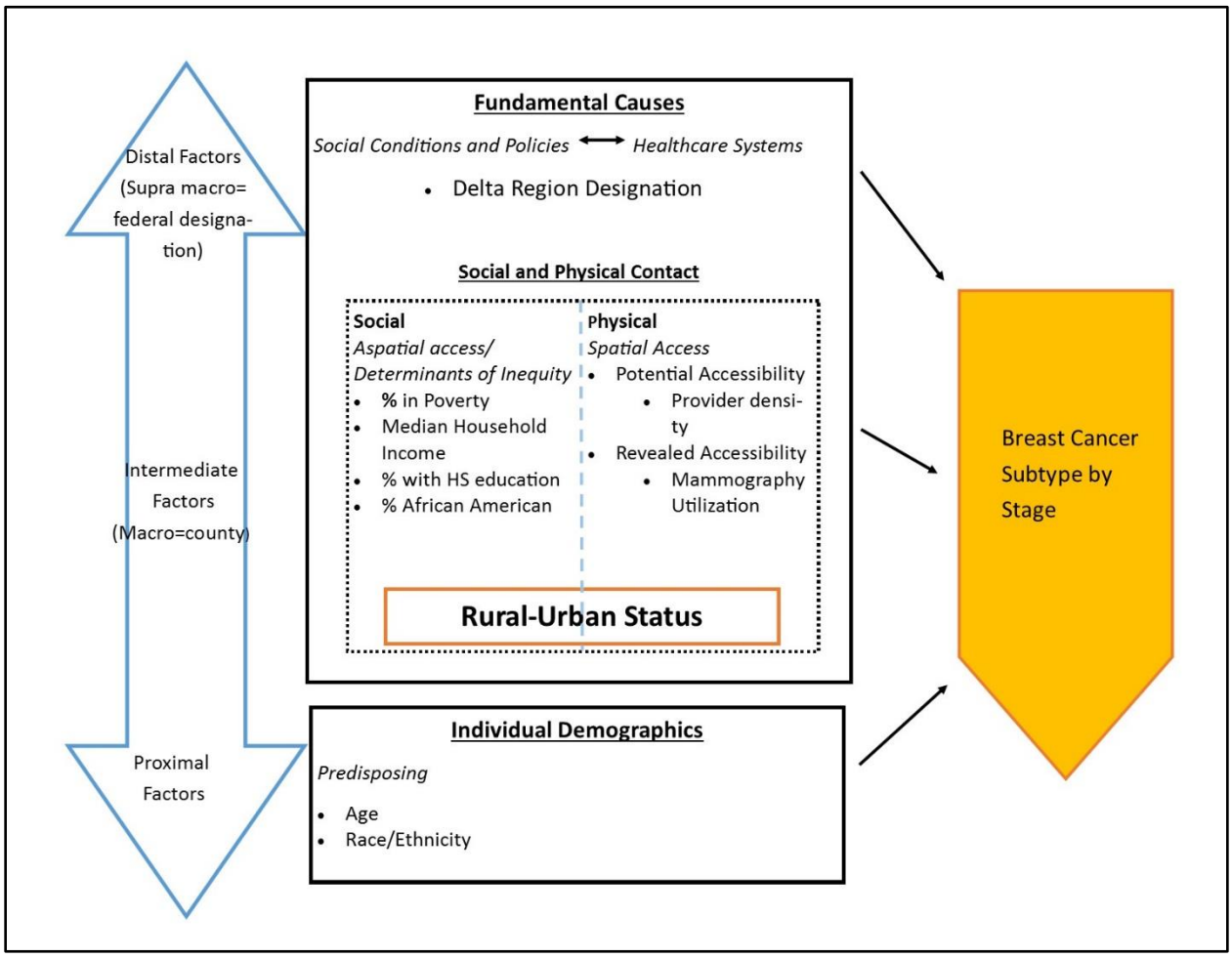

Figure 3.2: Diagram of Multilevel Regression Models

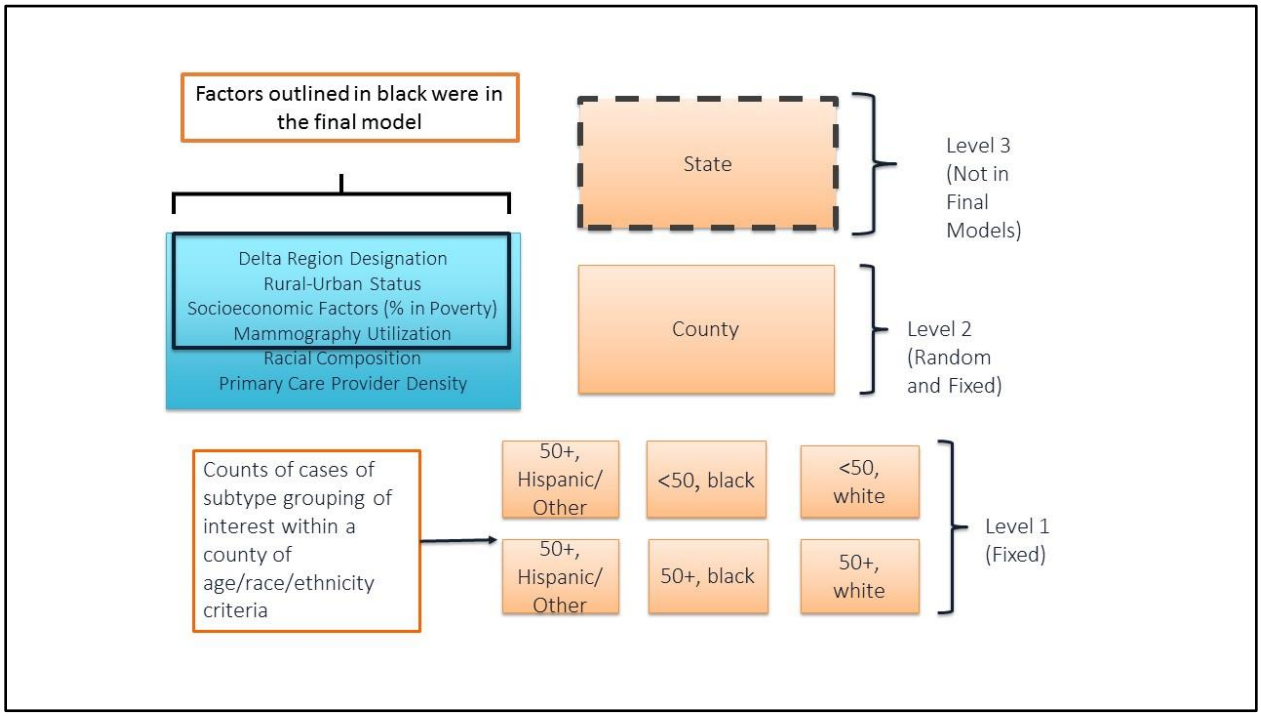

Table 3.1: Age-Adjusted Incidence Rate and Rate Ratios by Subtype and Stage and Race in the Delta and non-Delta Regions of the Lower Mississippi Delta Region States

	All					Non-Hispanic Black					Non-Hispanic White				
	Non-Delta		Delta			Non-Delta		Delta			Non-Delta		Delta		
	Count	IR†	Count	IR†	RR (95% CI)	Count	IR†	Count	IR	RR (95% CI)	Count	IR†	Count	IR†	RR (95% CI)
All Subtypes															
Early	40,184	76.4	11,853	70.4	0.92 (0.90-0.94)	4,973	70.7	3,304	66.5	0.94 (0.90-0.98)	33,092	79.9	8,294	73.1	0.91 (0.89-0.94)
Late	21,726	42.5	7,088	43.4	1.02 (0.99-1.05)	3,609	51.1	2,627	53.0	1.04 (0.98-1.09)	16,715	42.1	4,274	39.4	0.94 (0.90-0.97)
HR+/HER2-															
Early	27,941	52.7	7,583	44.6	0.85 (0.82-0.87)	2,866	41.1	1,801	36.5	0.89 (0.84-0.94)	23,691	56.5	5,610	48.7	0.86 (0.84-0.89)
Late	13,160	25.6	4,025	24.3	0.95 (0.92-0.99)	1,889	26.1	1,291	27.0	0.97 (0.90-1.04)	10,411	26.0	2,626	23.8	0.92 (0.87-0.96)
HR+/HER2+															
Early	3,526	6.9	1,035	6.2	0.90 (0.84-0.97)	461	6.4	292	5.8	0.91 (0.78-1.05)	2,813	7.1	721	6.5	0.92 (0.84-1.00)
Late	2,864	5.7	857	5.4	0.95 (0.88-1.03)	445	6.3	292	6.0	0.95 (0.81-1.11)	2,218	5.8	540	5.3	0.91 (0.82-1.00)

Table 3.1 (cont.)

	All					Non-Hispanic Black					Non-Hispanic White				
	Non-Delta			Delta		Non-Delta		Delta			Non-Delta			Delta	
HR-/HER2+															
Early	1,311	2.5	440	2.7	1.06 (0.95-1.19)	206	2.8	162	3.2	1.15 (0.93-1.43)	1,011	2.5	264	2.4	0.96 (0.83-1.10)
Late	1,360	2.6	425	2.6	0.99 (0.88-1.11)	253	3.5	183	3.6	1.03 (0.84-1.25)	991	2.5	234	2.2	0.86 (0.74-1.01)
Triple Negative															
Early	4,448	8.7	1,606	9.9	1.14 (1.07-1.21)	997	13.9	724	14.4	1.03 (0.93-1.14)	3,217	8.1	856	8.0	0.99 (0.91-1.07)
Late	2,836	5.6	1,107	7.0	1.24 (1.16-1.34)	754	10.6	605	12.2	1.15 (1.03-1.29)	1,920	5.0	476	4.6	0.94 (0.84-1.04)
Unknown															
Early	2,958	5.6	1,189	7.1	1.26 (1.17-1.35)	443	6.4	325	6.5	1.02 (0.88-1.19)	2,360	5.6	843	7.4	1.31 (1.21-1.43)
Late	1,516	2.9	674	4.0	1.38 (1.26-1.52)	268	3.8	256	5.1	1.36 (1.13-1.62)	1,175	2.8	398	3.5	1.25 (1.11-1.41)

Non-Delta Region is Reference Group; IR=Incidence Rate; RR=Rate Ratio; †Rates are expressed per 100,000 population

Table 3.2: Age-Adjusted Incidence Rates and Rate Ratios by Subtype and Rural-Urban Status in the Delta and non-Delta Regions of the Lower Mississippi Delta Region States

	Rural					Urban				
	Non-Delta		Delta			Non-Delta		Delta		
	Count	IR	Count	IR	RR (95% CI)	Count	IR	Count	IR	RR (95% CI)
All Subtypes										
Early	8,132	69.1	4,277	65.4	0.95 (0.91-0.98)	32,231	79.0	7,606	73.7	0.93 (0.91-0.96)
Late	4,679	41.3	2,617	41.9	1.01 (0.96-1.07)	17,134	43.0	4,488	44.6	1.04 (1.00-1.07)
HR+/HER2-										
Early	5,407	45.1	2,679	40.3	0.89 (0.85-0.94)	22,652	55.3	4,915	47.4	0.86 (0.83-0.88)
Late	2,671	23.5	1,446	22.6	0.96 (0.90-1.03)	10,537	26.3	2,585	25.5	0.97 (0.93-1.01)
HR+/HER2+										
Early	703	6.3	383	6.0	0.95 (0.83-1.08)	2,841	7.1	657	6.4	0.90 (0.82-0.98)
Late	631	5.7	323	5.4	0.95 (0.83-1.10)	2,250	5.8	535	5.4	0.94 (0.86-1.04)
HR-/HER2+										
Early	285	2.5	137	2.1	0.82 (0.66-1.02)	1,303	2.5	303	3.0	1.18 (1.03-1.35)
Late	315	2.8	147	2.4	0.85 (0.69-1.05)	1,039	2.6	278	2.7	1.06 (0.92-1.21)
Triple Negative										
Early	977	8.8	543	8.9	1.02 (0.91-1.13)	3,485	8.7	1,064	10.5	1.21 (1.13-1.30)
Late	648	5.9	385	6.6	1.12 (0.98-1.29)	2,198	5.6	726	7.3	1.31 (1.20-1.43)
Unknown										
Early	760	6.5	535	8.2	1.27 (1.13-1.42)	2,220	5.4	667	6.4	1.19 (1.09-1.30)
Late	414	3.5	316	4.9	1.41 (1.21-1.65)	1,110	3.5	364	2.7	1.29 (1.14-1.45)

Non-Delta Region is Reference Group; IR=Incidence Rate; RR=Rate Ratio; †Rates are expressed per 100,000 population

Table 3.3: Age-Adjusted Incidence Rate and Rate Ratios by Stage, Subtype, and Poverty Level in the Delta and non-Delta Regions of the Lower Mississippi Delta Region States

	20+% in Poverty					<20% in Poverty				
	Non-Delta		Delta			Non-Delta		Delta		
	Count	IR	Count	IR	IR	Count	IR	Count	IR	IRR
All Subtypes										
Early	6,485	67.2	6,279	67.1	1.00 (0.96-1.04)	33,699	78.5	5,574	74.4	0.95 (0.92-0.98)
Late	3,838	41.0	3,976	43.9	1.07 (1.02-1.12)	17,888	42.8	3,112	42.7	1.00 (0.96-1.04)
HR+/HER2-										
Early	4,271	43.6	3,975	42.1	0.96 (0.92-1.01)	23,670	54.8	3,608	47.7	0.87 (0.84-0.90)
Late	2,143	22.8	2,235	24.4	1.07 (1.01-1.14)	11,017	26.2	1,790	24.3	0.93 (0.88-0.97)
HR+/HER2+										
Early	590	6.4	538	5.8	0.90 (0.80-1.02)	2,936	7.0	497	6.7	0.96 (0.86-1.05)
Late	526	5.6	472	5.4	0.97 (0.85-1.10)	2,338	5.7	385	5.4	0.95 (0.85-1.06)
HR-/HER2+										
Early	229	2.4	244	2.7	1.14 (0.94-1.38)	1,082	2.5	196	2.6	1.03 (0.88-1.21)
Late	265	2.9	233	2.6	0.88 (0.73-1.06)	1,085	2.6	192	2.7	1.03 (0.87-1.21)
Triple Negative										
Early	777	8.4	905	10.0	1.19 (1.07-1.31)	3,671	8.7	701	9.7	1.11 (1.02-1.21)
Late	551	6.0	665	7.6	1.26 (1.12-1.42)	2,285	5.6	442	6.3	1.14 (1.02-1.26)
Unknown										
Early	618	6.4	617	6.6	1.03 (0.92-1.16)	2,340	5.4	572	7.7	1.41 (1.28-1.55)
Late	353	3.6	371	4.0	1.10 (0.94-1.28)	1,163	2.7	303	4.0	1.48 (1.30-1.69)

Non-Delta Region is Reference Group; IR=Incidence Rate; RR=Rate Ratio; †Rates are expressed per 100,000 population

Table 3.4: Age-Adjusted Incidence Rates in the Delta Region by Race, Rural-Urban Status, and County Poverty Level

	Race					Rural-Urban					Poverty Level				
	White†		Black			Urban†		Rural			Under 20%†		20+%		
	Count	IR‡	Count	IR ‡	RR (95% CI)	Count	IR‡	Count	IR	RR (95% CI)	Count	IR‡	Count	IR‡	RR (95% CI)
All Subtypes															
Early	8,294	73.1	3,304	66.5	0.91 (0.87-0.95)	7,606	73.7	4,277	65.4	0.89 (0.85-0.92)	5,574	74.4	6,279	67.1	0.90 (0.87-0.94)
Late	4,274	39.4	2,627	53.0	1.34 (1.28-1.41)	4,488	44.6	2,617	41.9	0.94 (0.89-0.99)	3,112	42.7	3,976	43.9	1.03 (0.98-1.08)
HR+/HER2-															
Early	5,610	48.7	1,801	36.5	0.75 (0.71-0.79)	4,915	47.4	2,679	40.3	0.85 (0.81-0.89)	3,608	47.7	3,975	42.1	0.88 (0.84-0.92)
Late	2,626	23.8	1,291	26.1	1.10 (1.03-1.18)	2,585	25.5	1,446	22.6	0.89 (0.83-0.95)	1,790	24.3	2,235	24.4	1.01 (0.94-1.07)
HR+/HER2+															
Early	721	6.5	292	5.8	0.89 (0.77-1.03)	657	6.4	383	6.0	0.93 (0.81-1.06)	497	6.7	538	5.8	0.87 (0.77-0.99)
Late	540	5.3	292	6.0	1.13 (0.97-1.32)	535	5.4	323	5.4	0.99 (0.86-1.15)	385	5.4	472	5.4	1.00 (0.87-1.15)

Table 3.4 (cont.)

	Race					Rural-Urban					Poverty Level				
	White†		Black			Urban†		Rural			Under 20%†		20+%		
	Count	IR‡	Count	IR ‡	RR (95% CI)	Count	IR‡	Count	IR	RR (95% CI)	Count	IR‡	Count	IR‡	RR (95% CI)
HR-/HER2+															
Early	264	2.4	162	3.2	1.33 (1.08-1.64)	303	3.0	137	2.1	0.70 (0.56-0.86)	196	2.6	244	2.7	1.02 (0.84-1.25)
Late	234	2.2	163	3.6	1.65 (1.34-2.02)	278	2.7	147	2.4	0.87 (0.70-1.07)	192	2.7	233	2.6	0.96 (0.79-1.18)
Triple Negative															
Early	856	8.0	724	14.4	1.79 (1.61-1.98)	1,064	10.5	543	8.9	0.85 (0.76-0.94)	701	9.7	905	10.0	1.03 (0.93-1.14)
Late	476	4.6	12.2	12.2	2.62 (2.31-2.98)	726	7.3	385	6.6	0.90 (0.79-1.02)	442	6.3	665	7.6	1.20 (1.06-1.36)
Unknown															
Early	843	7.4	325	6.5	0.88 (0.77-1.01)	663	6.4	526	8.1	1.26 (1.12-1.42)	572	7.7	617	6.6	0.86 (0.76-0.96)
Late	398	3.5	256	5.1	1.44 (1.22-1.70)	361	3.5	313	4.8	1.38 (1.18-1.62)	303	4.0	371	4.0	0.98 (0.84-1.15)

IR=Incidence Rate; RR=Rate Ratio; †Reference Group; ‡Rates are expressed per 100,000 population

Table 3.5: Multilevel Negative Binomial Regression Modeling of Early and Late Stage Invasive Breast Cancers by Delta Region Status and Stratified by Race/Ethnicity, Rural-Urban Status, and Poverty Level

Delta vs. non-Delta Region (Reference Group)						
	All Breast Cancers IDR (95% CI)	**HR+/HER2+ IDR (95% CI)**	**HR+/HER2- IDR (95% CI)**	**HR-/HER2+ IDR (95% CI)**	**Triple Negative IDR (95% CI)**	**Unknown IDR (95% CI)**
All Cases[a]						
Early	0.99 (0.95-1.02)	0.96 (0.88-1.04)	0.95 (0.91-1.00)	1.00 (0.87-1.14)	1.03 (0.96-1.11)	1.21 (1.05-1.38)
Late	1.00 (0.96-1.04)	0.92 (0.84-1.01)	1.00 (0.95-1.05)	0.91 (0.80-1.04)	0.99 (0.90-1.09)	1.24 (1.06-1.44)
Non-Hispanic Whites[b]						
Early	0.98 (0.94-1.02)	0.98 (0.90-1.08)	0.94 (0.89-0.99)	0.98 (0.85-1.14)	1.00 (0.92-1.10)	1.25 (1.08-1.44)
Late	0.97 (0.93-1.01)	0.91 (0.81-1.01)	0.98 (0.92-1.03)	0.87 (0.74-1.02)	0.92 (0.82-1.04)	1.18 (0.99-1.39)
Non-Hispanic Blacks[b]						
Early	1.01 (0.94-1.09)	0.80 (0.63-1.01)	1.09 (0.89-1.07)	0.86 (0.67-1.11)	1.11 (0.98-1.25)	1.09 (0.82-1.45)
Late	1.02 (0.95-1.09)	0.81 (0.65-0.99)	1.02 (0.92-1.14)	0.88 (0.68-1.15)	1.00 (0.86-1.15)	1.49 (1.14-1.94)
Rural[c]						
Early	0.98 (0.94-1.03)	0.95(0.83-1.09)	0.95 (0.89-1.01)	0.87 (0.69-1.09)	0.92 (0.81-1.04)	1.26 (1.05-1.50)
Late	0.96 (0.91-1.01)	0.91 (0.78-1.06)	0.96 (0.89-1.04)	0.72 (0.58-0.90)	0.87 (0.75-1.01)	1.30 (1.07-1.56)
Urban[c]						
Early	0.99 (0.94-1.04)	0.93 (0.84-1.04)	0.95 (0.88-1.01)	1.10 (0.94-1.29)	1.10 (1.01-1.21)	1.11 (0.89-1.38)
Late	1.04 (0.99-1.09)	0.92 (0.82-1.04)	1.03 (0.95-1.11)	1.05 (0.89-1.25)	1.09 (0.96-1.24)	1.14 (0.88-1.48)
20+% in Poverty[d]						
Early	1.00 (0.95-1.05)	0.89 (0.78-1.01)	0.99 (0.93-1.05)	1.02 (0.84-1.26)	0.95 (0.84-1.07)	1.10 (0.92-1.32)
Late	0.97 (0.92-1.03)	0.89 (0.77-1.02)	1.00 (0.99-1.01)	0.75 (0.59-0.93)	0.91 (0.78-1.06)	1.11 (0.90-1.37)
<20% in Poverty[d]						
Early	0.97 (0.92-1.02)	0.98 (0.88-1.10)	0.91(0.85-0.97)	1.02 (0.85-1.21)	1.05 (0.96-1.15)	1.32 (1.09-1.61)
Late	1.01 (0.96-1.06)	0.93 (0.82-1.06)	0.96 (0.89-1.03)	1.06 (0.88-1.27)	1.03 (0.91-1.18)	1.39 (1.11-1.72)

Non-Delta Region is Reference Group; RR=Rate Ratio; [a] Adjusting for age, race/ethnicity, rural-urban status, poverty level, area mammography utilization, and race/rural-urban status interaction (if statistically significant);[b] Adjusting for race/ethnicity, rural-urban status, area mammography utilization, and race/rural-urban status interaction; [c] Adjusting for age, area mammography utilization, and poverty level; [d] Adjusting for age, race/ethnicity, racial composition, area mammography utilization, and poverty level; [e] Adjusting for age, race/ethnicity, area mammography utilization, rural-urban status, and race/rural-urban status interaction

Table 3.6: Multilevel Negative Binomial Regression Modeling of Early and Late Stage Invasive Breast Cancers in the Delta Region and Stratified by Age, Race/Ethnicity, Rural-Urban Status and Poverty Level

	All Breast Cancers RR (95% CI)	**HR+/HER2+ RR (95% CI)**	**HR+/HER2- RR (95% CI)**	**HR-/HER2+ RR (95% CI)**	**Triple Negative RR (95% CI)**	**Unknown RR (95% CI)**
Early Stage						
Race/Ethnicity						
Non-Hispanic White	Ref	Ref	Ref	Ref	Ref	Ref
Non-Hispanic Black	1.04 (0.99-1.10)	1.12 (0.77-1.64)	1.02 (0.96-1.09)	1.06 (0.85-1.32)	1.03 (0.92-1.14)	0.87 (0.75-1.00)
Rural-Urban Status						
Urban	Ref	Ref	Ref	Ref	Ref	Ref
Rural	0.94 (0.89-0.99)	0.99 (0.77-1.26)	0.91 (0.84-0.98)	0.74 (0.59-0.92)	0.92 (0.81-1.04)	1.26 (0.99-1.59)
Poverty Level						
<20% Below Poverty	Ref	Ref	Ref	Ref	Ref	Ref
20+% Below Poverty	0.94 (0.89-1.00)	0.85 (0.72-0.99)	0.97 (0.90-1.05)	1.01 (0.82-1.26)	0.90 (0.80-1.03)	0.86 (0.68-1.08)
Late Stage						
Race/Ethnicity						
Non-Hispanic White	Ref	Ref	Ref	Ref	Ref	Ref
Non-Hispanic Black	1.10 (1.04-1.15)	1.06 (0.91-1.25)	1.05 (0.96-1.15)	1.13 (0.87-1.47)	1.16 (1.00-1.33)	1.14 (0.96-1.36)
Rural-Urban Status						
Urban	Ref	Ref	Ref	Ref	Ref	Ref
Rural	0.99 (0.94-1.04)	1.02 (0.87-1.19)	0.90 (0.82-0.98)	0.86 (0.64-1.16)	0.97 (0.82-1.15)	1.36 (1.16-1.80)

Table 3.6 (cont)

	All Breast Cancers RR (95% CI)	HR+/HER2+ RR (95% CI)	HR+/HER2- RR (95% CI)	HR-/HER2+ RR (95% CI)	Triple Negative RR (95% CI)	Unknown RR (95% CI)
Poverty Level						
<20% Below Poverty	Ref	Ref	Ref	Ref	Ref	Ref
20+% Below Poverty	0.97 (0.92-1.02)	0.97 (0.83-1.13)	0.96 (0.89-1.04)	0.86 (0.68-1.10)	0.94 (0.79-1.12)	0.89 (0.71-1.10)

RR=Rate Ratio; All models also adjusted for age group, mammography utilization, and race-rural-urban status interaction (if significant)

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CHAPTER 4: SPATIAL ACCESSIBILITY TO MAMMOGRAPHY SERVICES IN THE LOWER MISSISSIPPI DELTA REGION STATES

Introduction

The Delta Region Authority (Delta Region) is a region along the Mississippi River that has been federally designated to improve economic opportunity (1). It comprises 252 counties and parishes in the eight Lower Mississippi Delta (LMDR) states, which include Alabama, Arkansas, Illinois, Kentucky, Louisiana, Mississippi, Missouri, and Tennessee, and contains nearly 10 million residents. The Delta Region is characterized by high poverty, high proportions of black residents, geographic isolation, and limited access to care (1,2). Further, it has higher rates of breast cancer mortality than both the rest of the country and the rest of the LMDR (3). Nine of the ten counties in the nation with the highest breast cancer mortality rates are in the Delta Region (4). Historically, women in the region have lower rates of mammography utilization than the rest of the country (2,5). Breast cancer disparities are even more striking among black women in the Delta Region (3). The interplay between spatial access to care and racial composition has been postulated as a contributing factor to breast cancer disparities (6,7). There are also fewer primary care physicians relative to the population (2). However, inequalities in spatial access to mammography services within the LMDR and between LMDR and non-LMDR areas of the Delta Region states have not been studied. Spatial accessibility considers the number of facilities that are accessible within a given distance or travel time (8). Determining and evaluating geographic variation in spatial access to mammography in the Delta Region may help explain why women in the Region have poorer rates of mammography utilization and higher breast cancer mortality rates.

There are numerous methods to assess spatial access to healthcare services such as mammography services (8-10). For example, the 2 Step Floating Catchment Area (2SFCA) method is a commonly used geographic information system (GIS) approach to evaluate the potential spatial accessibility of health care services (e.g. mammography facilities) by considering the supply of healthcare services relative to the population within a certain catchment area (11). Potential spatial access considers the "probable entry" into the health care system, not utilization itself, and takes into account distance or travel time to the healthcare service of interest. The 2SFCA method has multiple strengths. First, while it considers the distance to care, it does not assume that people utilize care at the location that is geographically closest. Rather, it assumes they seek care within a given travel time or distance (i.e. catchment area), and as such, may access multiple locations within the catchment area. However, it does not take into account distance decay, meaning, for example, it assumes that a resident who lives 29 minutes from a facility in a 30-minute catchment area has the same level of access as someone who lives 1 minute from a facility (i.e. it overestimates spatial access for those with long travel times). In order to mitigate that limitation, Luo and Qi developed an enhanced two-step floating catchment area (E2SFCA) method which applies weights to multiple zones within a catchment area that take into account distance decay (12). Both the 2SFCA and the E2SFCA methods have been used to characterize spatial access to mammography facilities in multiple studies in multiple geographic extents, including individual cities, states, and regions like the U.S. South and Appalachia (7,13-17).

Although 2SFCA and E2SFCA methods have been used to describe access to mammography in areas like Appalachia, they have not yet been used to characterize spatial access to mammography in other federally designated areas with significant health disparities

such as the Delta Region. Therefore, the objective of the present study is to use the E2SFCA method to evaluate spatial access to mammography in the eight Delta Region states to achieve the following aims:

1) To compare spatial accessibility to mammography services for women living in the Delta Region compared to those living in the non-Delta region of the LMDR states
2) To identify areas of low and high spatial access to mammography services in the Delta Region
3) To evaluate the relationship between racial composition and spatial access to mammography in the Delta Region

Methods

Spatial techniques were used to quantify spatial accessibility to mammography services in the LMDR states. Census tracts within the LMDR states were categorized as Delta Region or non-Delta Region based upon their location inside or outside the federally designated Delta Regional Authority (1). Spatial statistics were then used to assess whether or not spatial accessibility was clustered within the Delta Region and to identify areas of low and high spatial accessibility. Further, univariate analyses were performed to compare how accessibility varied between the Delta and non-Delta Regions and between rural and urban areas. Additionally, bivariate statistical and spatial analyses were used to assess the relationship between spatial access and racial composition.

Data Sources

To represent "supply" of mammography facilities, the FDA mammography facilities file was utilized. This file is a publicly available source of addresses of all facilities in the United States that have been approved by FDA-accredited entities to have a radiation emitting device

(i.e. mammography machines) in accordance with the Mammography Quality Standards Act (18). Data were obtained for the 8 LMDR states and all facilities in adjacent states that were within 60 minutes' drive time of an LMDR state. Facilities not accessible to the general public, including facilities affiliated with the Veterans' Administration, military bases, correctional facilities, and the Indian Health Service, were excluded. All addresses were geocoded using the U.S. Census Bureau's geocoder or GoogleMaps if the U.S. Census Bureau's geocoder was unable to generate a valid geocode.

To represent demand for mammography screening services, 2010-2014 data from the American Community Survey (ACS) were used. The ACS is an ongoing national survey performed by the U.S. Census Bureau that collects information on a variety of factors including data on census tract level population counts by age and gender (19). Data from the ACS on the number of women between the ages of 45-74 in the LMDR states were extracted. This age grouping was used as it includes the age categories available from the ACS that are most congruent with the ages recommended by the United States Preventive Services Task Force to receive regular mammograms (20).

United States Department of Agriculture (USDA) and ACS data characterized the rural-urban status designation and racial composition of each census tract. The USDA primary Rural-Urban Commuting Area (RUCA) codes were used to categorize census tracts in the MDR states as rural or urban. RUCA codes catalog census tracts according to their population density, urbanization, and daily commuting patterns (21). RUCA designations include 10 codes with 1 being the most metropolitan and 10 being the most rural. Codes 1-3 indicate a metropolitan area; codes 4-6 a micropolitan area; codes 7-10 small town or rural areas. These codes were collapsed into two groups: urban (Codes 1-3) and rural (4-10). ACS data were also used to determine the

racial composition of women in the LMDR by calculating the percent of women of recommended screening age who identified as black in each census tract (19).

Measuring Spatial Accessibility

The E2SFCA method was used to calculate a spatial accessibility score for every census tract in the eight LMDR states for all women aged 45-74. This method considers both the supply of and demand for healthcare services within a given catchment area. In keeping with similar studies assessing spatial access to mammography in large, mostly rural regions in the United States, a 60 minute drive time catchment area was used (13,15). The first step of this method creates a facility (S_j)-population (P_k) ratio (R_j) within a given catchment area taking into account distance decay in four smaller zones (i.e. a weight-W_r- for each zone-r) within the catchment area:

Step 1: $$R_j = \frac{S_j}{\sum_{r=1}^{4} \sum_{k \in (Distance\ (k,j) < d_0} P_k W_r}$$

The network analyst tool in ARCGIS was used to construct the four zones-- 0-10 minutes, 10-19 minutes, 20-29 minutes, 30-60 minutes' drive time—with the catchment area. A facility-population ratio was calculated within each zone considering slow and fast distance decay functions as proposed by McGrail and colleagues and applied for assessing access to care in large regions that include both rural and urban areas (22).

- Fast decay weights: 1, 0.60, 0.25, 0.05
- Slow decay weights: 1, 0.80, 0.55, 0.15

The population of any census tract whose centroid fell within a respective zone was included in the ratio. The decay function represents the fact that spatial access to mammography declines as travel time to the facility increases, thus facility-population ratios in zones further away from the

facility carry successively less weight (i.e. populations further away from a facility are less likely to use this facility). Because results can be sensitive to the choice of decay function weights and the appropriate weights for mammography services in the LMDR are unknown, two sets of weights, designated as "fast" and "slow" were used. Compared to slow functions, fast decay functions apply smaller weights to each travel time zone, reflecting a steeper decline in mammography access as travel time increases. Facility-to-population ratios were computed using each set of weights, as noted in Table 4.1.

The second step of the E2SFCA method involves constructing similar travel time zones around the centroid of each individual census tract (*k*) and summing the facility-population ratios (R_j) by applying the appropriate weights. The sum represents the spatial accessibility score (A_i^f) for each census tract.

Step 2: $$A_i^F = \sum_{r=1}^{4} \sum_{j \in (Distance(i,j) \leq d_0} R_j W_r$$

Rural-urban designations, racial composition, and fast and slow decay spatial accessibility scores in the Delta Region were mapped using ARCGIS 10.4.1. These maps displayed racial composition and spatial accessibility scores in five groups using natural jenks classification, which identifies natural breaks in score values to maximize variance between groups and minimize variance within groups. Global and Local Moran's I statistics were calculated in ARCGIS 10.4.1 for both spatial accessibility scores to determine if these scores were spatially clustered and where clusters of low and high spatial accessibility scores exist. To quantify spatial relationships among census tracts, a 100-kilometer distance and a minimum of 2 neighbors were used, following previous studies that have analyzed spatial clusters over a large

geographic area (23). These statistics were calculated for both the slow and fast decay accessibility scores.

The Local Moran's I identified local spatial clusters of census tracts according to four pattern types: low access clusters, high access clusters, low-high spatial outliers, high-low spatial outliers (24). Low-access clusters are concentrated geographic areas of low accessibility scores; high-access clusters are concentrated geographic areas of high accessibility scores. Low-high spatial outliers are areas where tracts with low accessibility scores are surrounded by tracts with high accessibility scores; high-low spatial outliers identify tracts with high spatial access that are surrounded by tracts with low accessibility scores. Census tracts that do not fall into any of these four categories represent areas where there is no statistically significant spatial clustering of accessibility scores.

Correlation analysis was used to assess the association between racial population composition and spatial accessibility scores. Because racial composition and spatial accessibility scores are not normally distributed, Spearman's rank coefficients were used. These values were calculated for the entire Delta Region and separately for each state as well by rural-urban status. Bivariate Local Moran's I analysis using GeoDa was performed to identify areas where census tracts with high black population percentages are surrounded by tracts with high (or low) spatial access to mammography. Similar to the univariate Local Moran's I, this analysis identifies four spatial patterns: low access-high black population proportion; high access-high black population proportion; low access-low black population proportion; and high access-low black population proportion. Of greatest interest is identifying areas with low access and high black population proportions.

Descriptive, Univariate, and Bivariate Statistical Analysis

Summary statistics (mean, standard deviation, median) were calculated for accessibility scores for both weights for the Delta Region compared to the non-Delta Region in the 8 LMDR states combined and for each state individually. Because accessibility scores were overdispersed, Wilcoxon Two-Sample Tests were performed to determine if Delta/non-Delta Region spatial accessibility scores differed significantly. Additionally, accessibility scores were compared by rural-urban status. In sum, the following comparisons were made for both sets of distance decay weights: urban vs. rural Delta Region; rural Delta Region vs. rural non-Delta Region; and urban Delta Region vs. urban non-Delta Region.

Results

Choropleth Maps of Rural-Urban Status and Racial Composition

Figure 4.1A displays the rural-urban distribution of census tracts within the Delta Region. Most of the Delta Region was rural with the exception of large urban centers in Memphis, Tennessee; Little Rock, Arkansas; and New Orleans, Louisiana and smaller urban centers scattered throughout the Region. Figure 4.1B shows the percentage of women aged 45-75 within each census tract who are black. Generally speaking, there was a north-south gradient, with higher proportions of black women of recommended screening age in Mississippi, Alabama, and southern Arkansas.

Choropleth Maps and Spatial Analysis of Spatial Accessibility Scores

Choropleth maps of both the fast and slow weighted spatial accessibility scores in the Delta Region show that spatial access to mammography varies considerably, with areas of high spatial access generally concentrated in the northern and Alabama portions of the Delta region (Figure 4.2). Global Moran's I statistics for both fast and slow decay weights indicate moderate

clustering of spatial accessibility scores in the Delta Region, Moran's I of 0.35 and 0.43, respectively (Table 4.1). Local Moran's I analysis for both weights shows large clusters of high accessibility scores in the Illinois and Kentucky portions of the Delta Region with smaller clusters of high accessibility scattered throughout the rest of the Region. Large clusters of low accessibility scores are found in the Missouri, Arkansas, and Tennessee portions of the Region, with particular clustering immediately surrounding Memphis, Tennessee.

Univariate Analysis of Spatial Accessibility Scores

Based on a Wilcoxon test, there was no statistically significant difference in fast decay spatial accessibility score by Delta Region designation, with median scores of 0.000175 and 0.000161 in the Delta Region and non-Delta designations, respectively ($p=0.40$) (Table 4.3). Median fast decay scores in the Delta Region ranged from 0.000138 in Arkansas to 0.000243 in Illinois. Illinois and Louisiana were the only states with statistically significant differences in median fast decay spatial accessibility scores between Delta and non-Delta regions. The median spatial accessibility score was higher in the Illinois Delta Region compared to the non-Delta Region part of the state (0.000243 and 0.000156, respectively, $p<0.001$). The median spatial accessibility score in the Louisiana Delta Region was lower than in the non-Delta part of the state (0.000178 vs. 0.000203; $p<0.001$).

Findings for the slow decay spatial accessibility scores were somewhat similar to the fast decay scores. Overall, there were no differences in median spatial accessibility scores between the Delta and non-Delta Regions (0.000181 and 0.000166, respectively; $p=0.50$). There were no statistically significant differences in Delta and non-Delta Region slow decay spatial accessibility scores by state, except for Illinois, Kentucky, and Louisiana. In Illinois, the median slow accessibility score is higher in the Delta compared to the non-Delta region (0.000244 and

0.000159, respectively; p<0.0001). Similarly, the Delta Region of Kentucky had a higher median slow decay spatial accessibility score than the non-Delta Region part of the state (0.000220 and 0.000214, respectively; p=0.01). However, the Delta Region part of Louisiana had lower median slow decay spatial accessibility score than the non-Delta part of the state (0.000178 and 0.000237, p<0.001).

Spatial accessibility scores also did not differ significantly between the rural and urban Delta and between the urban Delta and non-Delta designations for fast decay scores (Table 4.3). However, median spatial access was slightly higher in the rural DRA vs. the non-DRA (0.000171 vs. 0.000170, p=0.02). For the slow decay score, however, census tracts in the rural Delta Region had a lower median slow decay spatial accessibility score (0.00171) than the urban Delta Region (0.000186) (p=0.0006). Rural census tracts in the Delta Region had a higher median slow decay spatial accessibility score than rural census tracts in the non-Delta Region (0.000171 and 0.000168, respectively; p=0.04). Urban census tracts in the Delta Region also had a higher median slow decay spatial accessibility score than the non-Delta urban census tracts (0.000186 and 0.000165, respectively; p=0.0007).

Bivariate Analysis of the Relationship between Spatial Accessibility Scores and Racial Composition

For both the fast and slow decay scores, racial composition and accessibility showed a weak, but statistically significant, positive correlation for the Delta Region as a whole (Spearman's rho=0.107 and 0.0856; p<0.001, respectively) (Table 4.4). In Alabama, the slow decay score showed a moderate, negative correlation between racial composition and spatial accessibility (Spearman's rho=-0.237; p<0.01). In Arkansas and Missouri, both fast and slow decay scores were moderately correlated with racial composition while in Louisiana, Mississippi,

and Tennessee, there was weak, positive correlation between racial composition and both fast and slow decay spatial accessibility scores. There was no statistically significant correlation between racial composition and spatial accessibility in Illinois, nor when stratifying the Delta Region by rural and urban status.

Bivariate Moran's I analysis showed low spatial clustering of racial composition and fast decay spatial accessibility scores (Moran's I=0.036). In total, 86 census tracts scattered throughout Alabama, Arkansas, Tennessee, Mississippi, and Louisiana had a high proportion of black women of screening age and low spatial accessibility scores in nearby census tracts (Figure 4.3A). The Bivariate Moran's I analysis showed similar low spatial clustering of racial composition and slow spatial accessibility scores (Moran's I=0.049). The spatial pattern is very similar to that for the fast accessibility scores, with 90 census tracts scattered throughout Alabama, Arkansas, Tennessee, Mississippi, and Louisiana showing a high proportion of black women of screening age and low spatial accessibility scores in neighboring census tracts (Figure 4.3B).

Discussion

This study found no difference in tract-level spatial accessibility to mammography facilities between the Delta and non-Delta Regions overall considering both decay weights. However, when scores were stratified by state, access was higher in the Delta Region of Illinois compared to the non-Delta area of the state while the Delta Region part of Louisiana had lower spatial accessibility than the non-Delta part of the state. The Kentucky Delta Region had higher spatial accessibility scores than the non-Delta part for slow accessibility weights. Global Moran's I showed moderate clustering for both decay speeds. Local Moran's I showed clusters of high spatial accessibility in the Delta Region of Illinois and the westernmost part of the

Kentucky Delta. Low spatial access was clustered in much of the Arkansas Delta and parts of Tennessee and Mississippi (i.e. a cluster of low spatial access around Memphis). Smaller clusters of low spatial access were seen in southern Louisiana as well. These findings reveal uneven patterns of spatial access to mammography within the Delta Region and notable areas of low spatial access in central and southern areas where mammography facilities are underdeveloped.

There was weak to moderate positive correlation between racial composition (% of screening aged women in the census tract who are black) and spatial accessibility scores for the Delta Region as a whole and within most individual states. These positive correlations indicate that in some states, mammography facilities are more spatially accessible to tracts where black women make up a larger proportion of the local population. However, the slow decay score in the Alabama Delta Region was weakly, negatively correlated with racial composition. For both decay scores, there were census tracts scattered throughout the southern part of the Delta Region with high black racial composition and low neighboring spatial accessibility scores.

These findings suggest that there is little difference in spatial access to mammography in the Delta Region compared to the non-Delta Region within the LMDR states. However, there was intrastate variability by Delta Region designation in Illinois, Kentucky, and Louisiana, with Louisiana being the only state with lower spatial access in the Delta Region. Further, median spatial accessibility scores varied by state within the Delta Region with the lowest scores in Arkansas and the highest scores in Illinois. This geographic variation points to inequalities in spatial access despite the overall availability of mammography services at levels comparable to non-Delta regions of the LMDR states.

In sum, these findings have two key public health implications. First, the overall lack of spatial accessibility differences in the Delta vs. non-Delta Region suggests that lower utilization

of mammography screening and higher breast cancer mortality in the region may not be due to disparities in spatial access to care. Instead, low mammography utilization may be due to aspatial factors such as financial, knowledge, and psychosocial barriers to screening services. Continued interventions are needed to address these nonspatial barriers to mammography utilization in the Delta Region (25,26). Additional research is needed to elucidate the factors associated with the breast cancer mortality disparity in this region, such as breast cancer staging and subtype. Recent studies have shown higher rates of the most aggressive breast cancer subtypes (i.e. triple-negative) in several LMDR states, but it is unknown if the Delta Region specifically has higher rates (27,28). Second, identified state-to-state variability in spatial access may provide guidance for resource allocation of federal funds targeted for the Delta Regional Authority, such as the USDA's Delta Health Services Grant, to those areas with particular disparities compared to the non-designated part of the state or compared to other areas within the Delta Region.

In addition to the findings of the univariate statistics, the findings of the spatial analysis help identify clusters of low access to mammography services which may help guide resource allocation and interventions. Clusters of low spatial access were identified in large parts of Arkansas and Missouri as well as smaller clusters in Tennessee, Mississippi, and Louisiana for both decay speeds. Arkansas also had the lowest spatial accessibility with the Delta Region of all states. These findings add to the growing body of literature suggesting that using spatial methods to assess access to screening services may guide the allocation of resources and identify service shortage areas (13,17). These methods can be extended in two ways. First, GIS-based measures can be applied to the evaluation of other providers of cancer screening services (e.g. gastroenterologists who perform colonoscopies or lung cancer screening locations). Second, they can be used in combination with spatial methods that identify clusters of high late-stage cancers

or cancer mortality. Many studies have suggested that using spatial methods to visually display and/or identify clusters of low screening rates, late-stage cancers or cancer deaths may guide screening interventions (23,29,30). However, there is limited research that simultaneously considers the geographic clustering of areas with both low access to services and high rates of late-stage cancers or mortality or low screening rates. Evaluating the clustering of both low access and high risk or low utilization may more effectively target interventions to areas most in need of screening services.

In addition to simultaneously evaluating access and risk, it is also important to consider the relationship between access and area level demographic characteristics that may play a role in cancer disparities, like racial composition (6,7). Racial composition (i.e. the percentage of the female population of screening age who were black) proved to be positively, but only weakly correlated with spatial access. There was slight variation at the state level, as the slow decay score in Alabama was negatively and weakly associated with racial composition; however spatial accessibility scores were positively, and moderately correlated for most other states. The bivariate LISA analysis revealed scattered small clusters of tracts containing high proportions of black populations surrounded by tracts with low spatial access to mammography. These tracts are home to large concentrations of black women who are at higher risk for late breast cancer diagnosis and mortality, yet mammography screening facilities are in short supply in nearby areas. Such places may be good sites to target screening interventions to those who might be at high risk for poor cancer outcomes in the Delta Region. Other studies have suggested similar approaches In Toronto, Canada, Lofters and colleagues considered clustering of primary care physicians and racial/ethnic groups to help target cancer screening interventions (29). Similarly, Towne and colleagues assessed access to screening services among American Native and Alaska

Natives (31). However, neither of these studies used bivariate Local Moran's I analysis as the present study did. This method may be effective to identify areas with dual risk factors for poor cancer outcomes: sociodemographic composition and access to screening services.

All analyses were performed using both fast and slow decay weights. For the most part, fast and slow decay scores yielded fairly similar results in univariate and bivariate analysis and in spatial analyses, which is consistent with other studies that test different sets of weights applied to the E2SFCA method to evaluate spatial access to health care services (11,17,22). However, the slow decay was more sensitive in identifying rural-urban differences within the Delta Region states and in the Delta Region, respectively. This is consistent with McGrail's findings which indicate that implementing a decay function of any sort, even with additional rules, affects rural and urban accessibility scores differently (22). While the choice of decay score is arbitrary, Luo suggests that a faster decay score be utilized for more common health care services like pharmacies, while a slower decay score be used for scarcer services like cancer care services (11). Mammography services are less available than pharmacies but more available than cancer treatment facilities, making it unclear which decay function would be more appropriate. Additional research should explore what decay weights, proposed by Luo or others, may be most accurate to determine spatial access based upon the ubiquity of a given service, especially when applied to geographically large regions that are largely rural, but also have some urban centers. Alternatively, a continuous or variable decay function could be further assessed for its utility in assessing spatial access to services as the rural-urban gradient (15,22,32).

Limitations and Strengths

This study has certain limitations—both in characterizing supply and demand for mammography services. To characterize supply of mammography, only facility locations were

considered, not the number of machines at each facility, as that information was not publicly available. This may mean that spatial accessibility is underestimated. To characterize demand for services, ACS population estimates were used. ACS data are meant to describe, not estimate, populations. Unlike the census which theoretically accounts for the entire U.S. populations, the ACS is a sample, and therefore subject to both sampling and nonsampling errors. Further, population estimates were for women aged 45-74, the age category available in ACS that is most congruent with recommended screening ages. However, many women who utilizing screening are younger or older than recommended screening age (33). Thus, the population estimates used are representative of theoretical demand, not practical demand.

Despite these limitations, this study has many strengths. First, the E2SFCA method was used, which, compared to other methods, more appropriately considers accessibility relative to distance traveled. Further, an understudied region that experiences significant health and access to care disparities was examined. This study was one of the first to use a variation of the 2SFCA method to consider how access to care may vary by racial composition. The findings identify gaps in spatial access to mammography that should be targeted in creating new facilities, including mobile and fixed site services, and in planning educational and informational programs.

Conclusions

The E2SFCA method was used to evaluate access to mammography services in the Delta Region. Access to services did not vary between the Delta and non-Delta Region within the eight states of interest. There was state-level variation in access, and spatial statistics found that there were clusters of low access in especially in Arkansas, Mississippi, and Louisiana. The relationship between racial composition and spatial access was explored but found no notable

relationship between a high proportion of black residents and low spatial access was identified. Relevant to the Delta Region, the identified areas of low access may be targets for resource allocation and public health interventions. Relevant to health services research, broadly speaking, the approaches used in this study could be applied to other screening services, and research could explore the overlapping relationship between sociodemographic characteristics and access to care.

Figures and Tables

Figure 4.1: Rural-Urban Designation (A) and Racial Composition (B) in the Delta Region

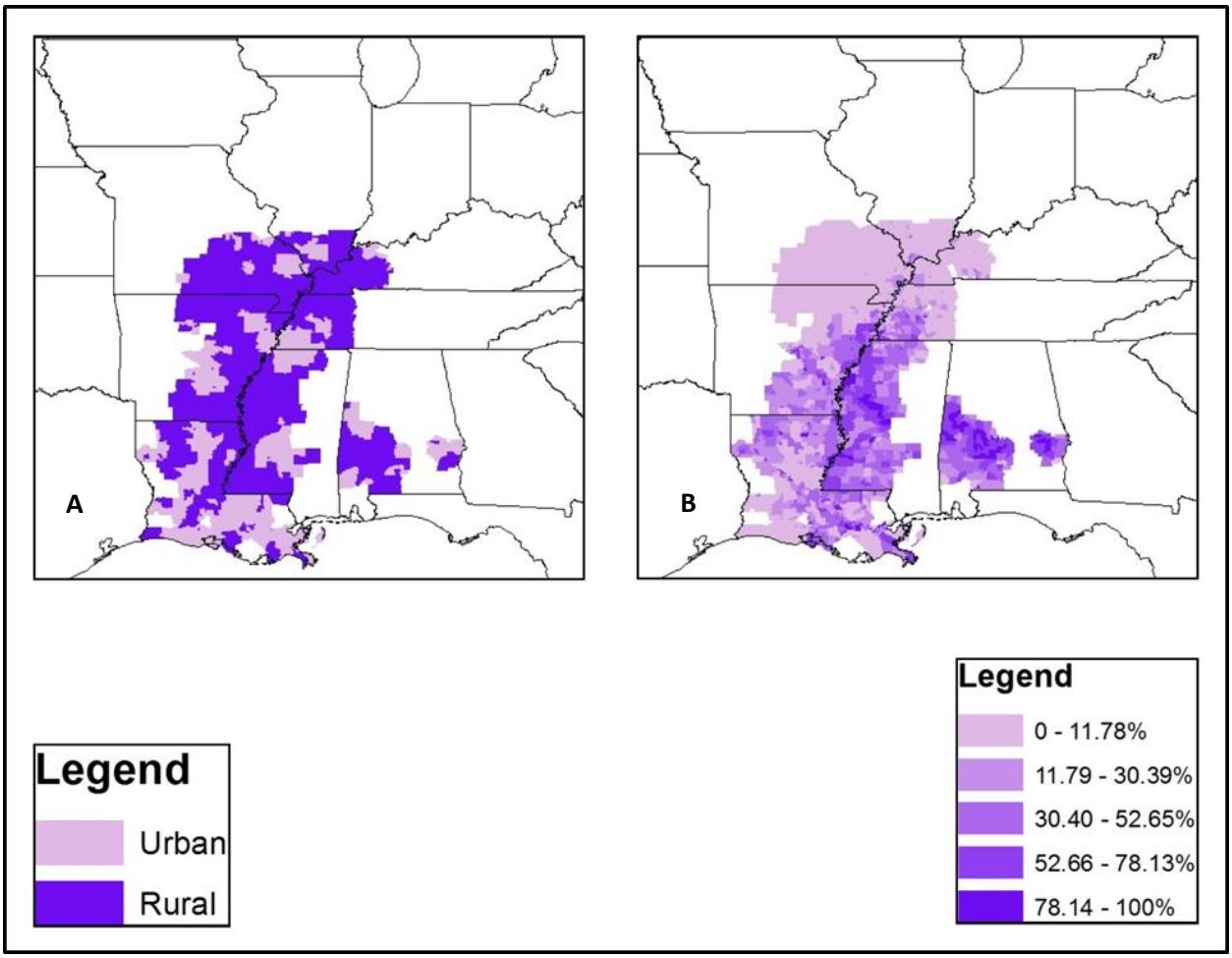

Figure 4.2: Spatial Accessibility Scores, Fast (A) and Slow (B) Decay

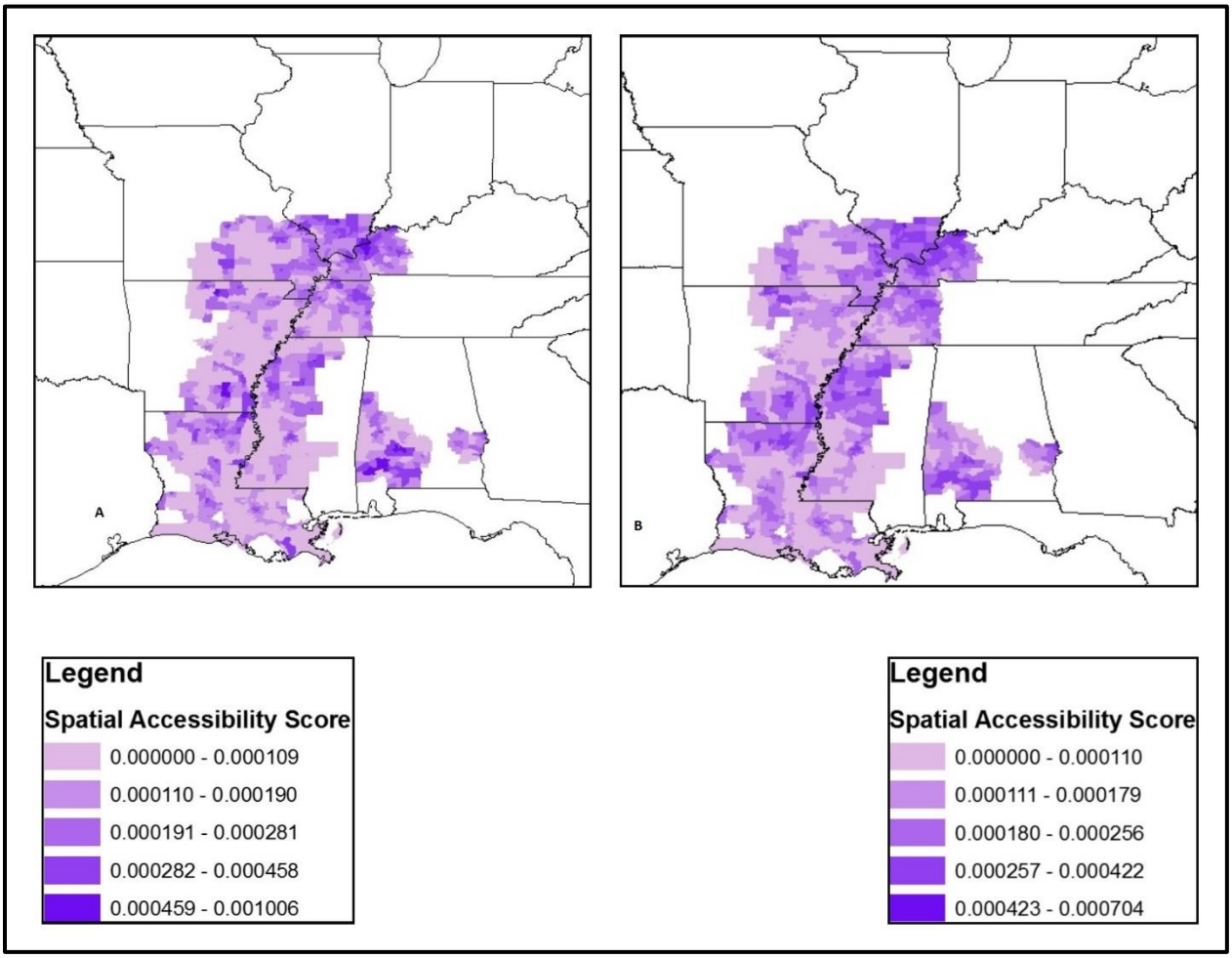

Figure 4.3: Local Moran's I for the Delta Region, Fast Decay (A) and Slow Decay (B)

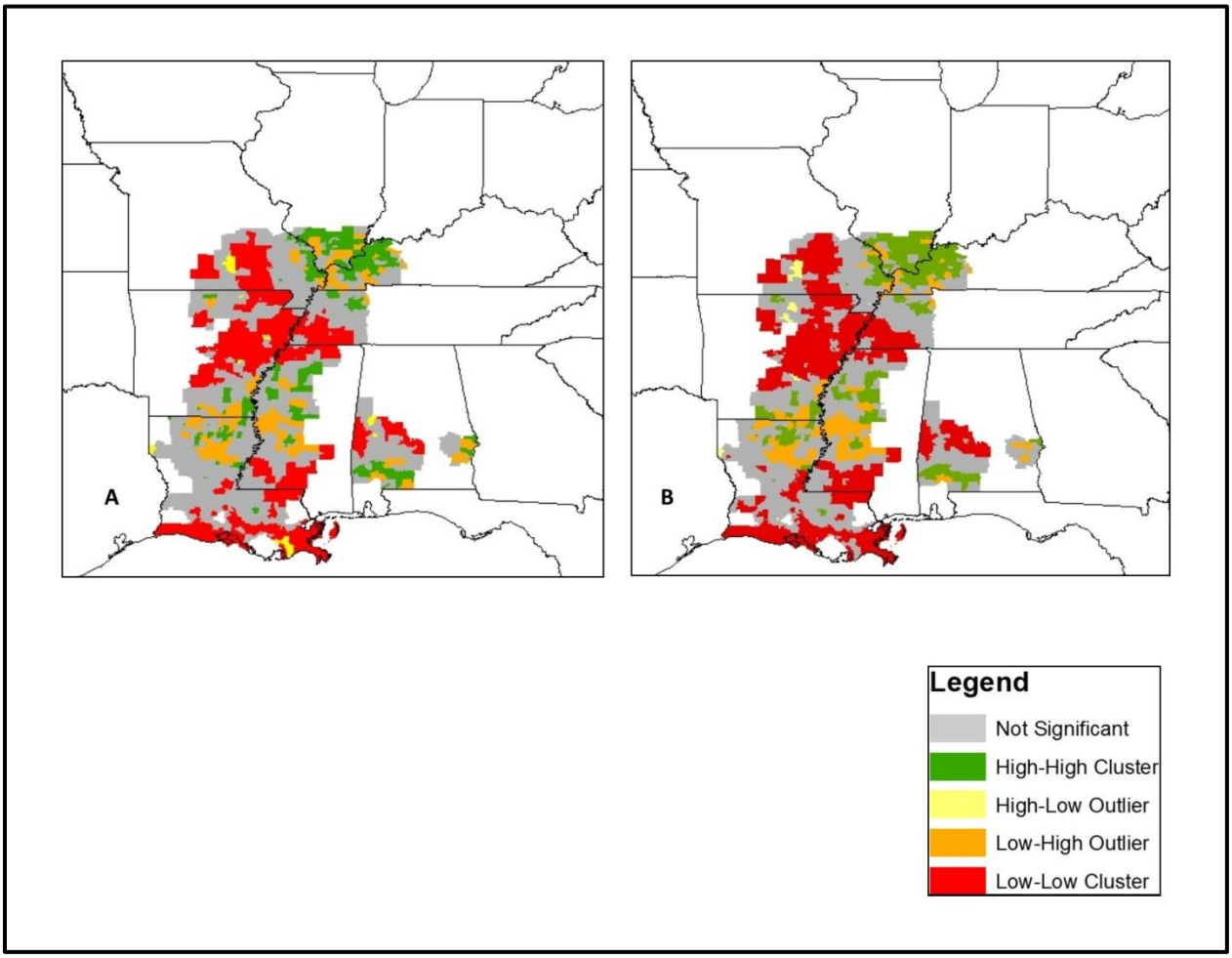

Figure 4.4: Bivariate Local Moran's I; Racial Composition and Spatial Accessibility

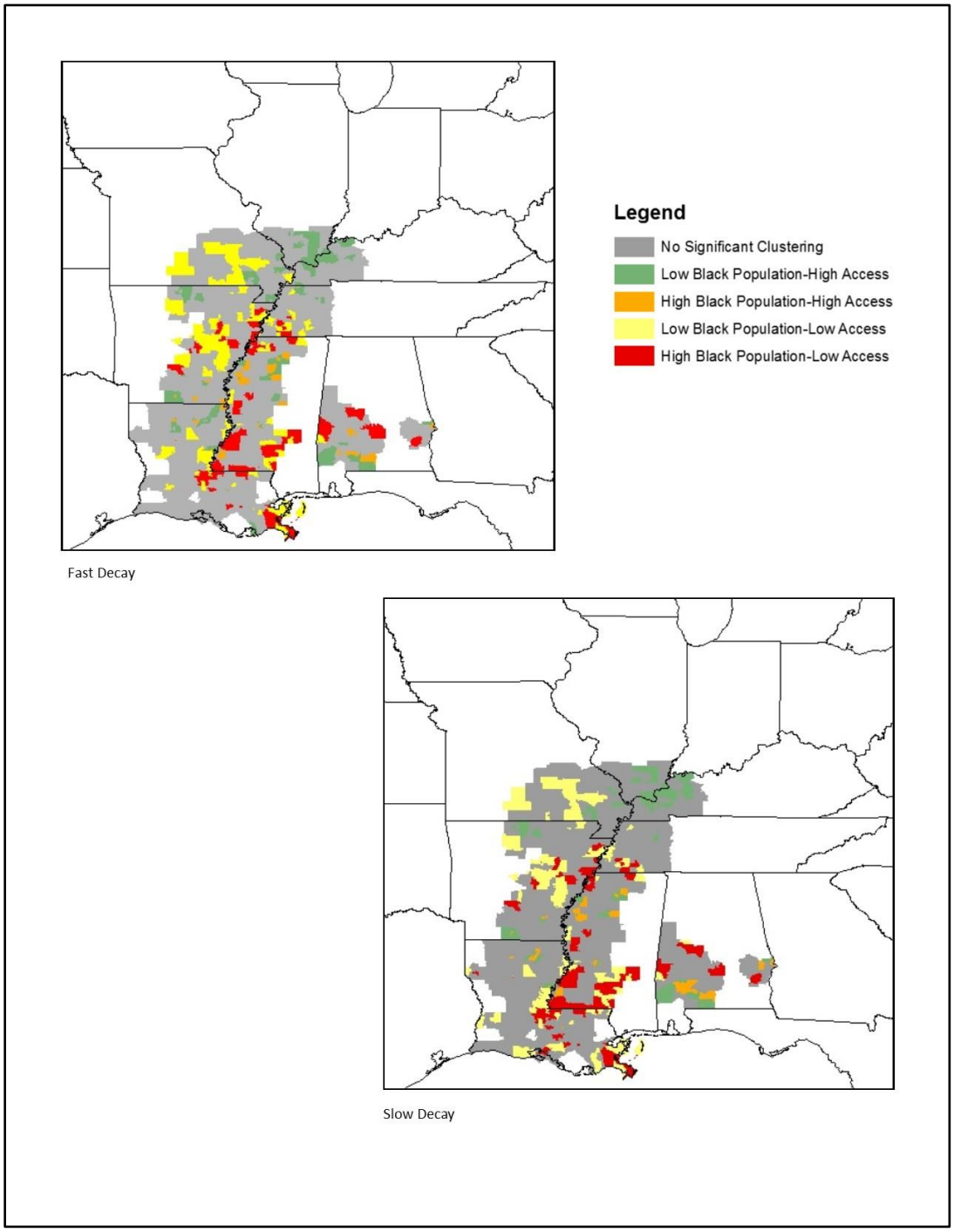

Table 4.1: Global Moran's I Results

	Decay Speed	**Moran's I**	**Z Score**	**P Value**
Delta Region	Fast	0.35	102.82	<0.001
	Slow	0.43	125.8	<0.001

Table 4.2: Spatial Accessibility to Mammography in the Lower Mississippi Delta by State and Delta Designation

	Delta		Non-Delta		
	Mean (SD)	**Median**	**Mean (SD)**	**Median**	**P-value†**
Fast Decay					
All	0.000181 (0.000101)	0.000175	0.000207 (0.000251)	0.000161	0.40
Alabama	0.000213 (0.000173)	0.000168	0.000195 (0.000287)	0.000136	0.07
Arkansas	0.000146 (0.000091)	0.000138	0.000189 (0.000202)	0.000136	0.26
Illinois	0.000248 (0.000085)	0.000243	0.000194 (0.000214)	0.000156	<0.001
Kentucky	0.000254 (0.000150)	0.000222	0.000232 (0.000170)	0.000202	0.06
Louisiana	0.000174 (0.000168)	0.000168	0.000282 (0.000203)	0.000203	<0.001
Missouri	0.000178 (0.000105)	0.000188	0.000235 (0.000298)	0.000164	0.24
Mississippi	0.000184 (0.000112)	0.000166	0.000191 (0.000094)	0.000183	0.14
Tennessee	0.000179 (0.000067)	0.000186	0.000204 (0.000341)	0.000160	0.16
Slow Decay					
All	0.000181 (0.00008)	0.000181	0.000209 (0.000241)	0.000166	0.50
Alabama	0.000197 (0.000131)	0.000162	0.000198 (0.000278)	0.000157	0.66
Arkansas	0.000147 (0.000065)	0.000144	0.000187 (0.000188)	0.000135	0.91
Illinois	0.000244 (0.000057)	0.000244	0.000195 (0.000244)	0.000159	<0.001
Kentucky	0.000252 (0.000119)	0.000220	0.000233 (0.000151)	0.000214	0.01
Louisiana	0.000176 (0.000063)	0.000178	0.000274 (0.000199)	0.000237	<0.001
Missouri	0.000173 (0.000078)	0.000181	0.000237 (0.000290)	0.000169	0.16
Mississippi	0.000187 (0.000086)	0.000184	0.000187 (0.000072)	0.000185	0.97
Tennessee	0.000178 (0.000049)	0.000190	0.000204 (0.000331)	0.000167	0.25

SD=standard deviation; † Wilcoxon Two-Sample Test

Table 4.3: Spatial Accessibility Scores by Rural-Urban Status

	Rural		Urban		
Fast Decay					
	Mean (SD)	**Median**	**Mean (SD)**	**Median**	**P-value†**
Delta Region	0.000183 (0.000111)	0.000171	0.000180 (0.000094)	0.000175	0.61
	Delta		**Non-Delta**		
Rural	0.000183 (0.000111)	0.000171	0.000243 (0.000363)	0.000170	0.02
Urban	0.000180 (0.000094)	0.000175	0.000198 (0.000206)	0.000160	0.47
Slow Decay					
Delta Region	0.000175 (0.000082)	0.000171	0.000185 (0.000076)	0.000186	0.0006
	Delta		**Non-Delta**		
Rural	0.000175 (0.000082)	0.000171	0.000238 (0.000347)	0.000168	0.04
Urban	0.000185 (0.000076)	0.000186	0.000199 (0.000195)	0.000164	0.0007

SD=standard deviation; † Wilcoxon Rank Two-Sample Test

Table 4.4: Correlation between Spatial Accessibility and Racial Composition in the Delta Region

	Fast Decay Spatial Accessibility Score	**Slow Decay Spatial Accessibility Score**
All	0.107020†	0.08565†
Alabama	-0.13783	-0.23700‡
Arkansas	0.25786†	0.26536†
Illinois	-0.14645	-0.19792
Kentucky	0.22022*	0.05157
Louisiana	0.19113†	0.17955†
Missouri	0.39701†	0.42192†
Mississippi	0.19640†	0.20512†
Tennessee	0.16037†	0.17629†
Rural Delta Region	-0.00760	-0.05282
Urban Delta Region	0.21253	0.18202

†p<0.0001;‡p<0.01;*p<0.05

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CHAPTER 5: DISCUSSION AND CONCLUSIONS

The Delta Regional Authority is a federal-state partnership aiming to improve socioeconomic conditions in 252 counties and parishes in the eight-state region along the Mississippi River and in the Alabama Black Belt. The Delta Region's sociodemographic composition put it at a three-pronged risk for health disparities. First, it has a high proportion (32.4%) of black residents (1). Second, more than one in five residents live in poverty, and more than forty percent of the counties are persistent poverty counties (1). Third, although there are some metropolitan areas like Memphis, Little Rock, and New Orleans, the Region is largely rural. Because of these risks, the Delta Region experience cancer and access to care disparities. Compared to the nation as a whole, residents in the region have higher rates of all causes of death, cancer mortality, and breast cancer mortality (2-4). Breast cancer mortality rates are also higher among black women in the region compared to white women (2). Residents of the Delta Region have limited access to primary care physicians and federally qualified health centers (5, 6). Additionally, a lower proportion of women in the Delta Region utilize mammography (5, 7). Both of these factors may be indicative of less access to mammography services and increased risk of late-stage breast cancer. Some of the risk factors for the triple-negative breast cancer subtype—which is the most aggressive and least treatable subtype-- and more advanced cancer staging are more prevalent in this region, including a higher proportion of blacks, geographic location in the South/Midwest, rurality, and low income (1,8-9). However, there is limited research on what specific cancer factors—subtype, staging, and access to mammography—may exist in this region that contribute to these higher breast cancer mortality rates. This dissertation explored differences in subtype, staging, and access to mammography to help explain the mortality disparities in the Delta Region. This chapter briefly summarizes the findings of this

dissertation and how these findings might the guide development of preventive interventions, regional policies, resource allocation, and future research efforts.

Chapter 2 of this dissertation addressed breast cancer subtype differences and identified higher rates of triple-negative breast cancer in the Delta Region compared to the non-Delta Region. Although this elevated rate of triple-negative breast cancer in the Delta Region was attenuated in multivariable analyses, the elevated rate was maintained in urban areas. Black residents in the Delta Region had higher rates of hormone receptor negative cancers than white women in the Region. Chapter 3 of this dissertation examined the difference in breast cancer staging by subtype and found that no particularly notable differences in late-stage between the Delta and non-Delta Regions. However, black women in the Delta Region had lower rates of early-stage breast cancer, but higher rates of late-stage breast cancers than their white counterparts. Chapter 4 examined spatial access to mammography in the Lower Mississippi Delta Region states and found that, for the most part, women in the Delta Region had similar access to mammography services as non-Delta Region women. However, clusters of low spatial access in areas within the Delta Region were identified.

Broadly speaking, the findings of this dissertation have public health implications for community-based intervention, state-level policy change, and regional resource allocation. Additionally, these findings provide the foundation for further research to continue to explore breast cancer disparities in the Region, to examine regional disparities for other cancer types, and to promote collaborative academic partnerships across the Delta Region.

Public Health Implications

This dissertation identified regional and racial disparities in the breast cancer subtype and staging. The Delta Region, particularly black women and those living in urban areas, had higher rates of triple-negative breast cancer. There are few modifiable risk factors for triple negative breast cancers, but increasing breastfeeding initiation and duration among black, Delta Region women may be one way to reduce triple-negative breast cancer rates (10). Additionally, within the Delta Region, black women had lower rates of early stage breast cancer and higher rates of late-stage breast cancer, indicating that mammography utilization rates may be lower among black women in the region. Successful, community-based efforts in pockets of the Delta Region could be scaled up and broadly disseminated to continue to educate black women on screening and increase screening rates. Further, there are state-level policy changes that may be helpful to improve breast cancer disparities. Finally, Delta Region-specific resources from the Health Resource and Service Administration (HRSA), the United States Department of Agriculture (USDA), and general federal appropriations for the Delta Region may be allocated to improve breast cancer prevention efforts and to make mammography services more available for underserved residents.

To decrease triple-negative breast cancer rates, interventions to increase breastfeeding initiation and duration, particularly among multiparous black women in urban areas of the Delta Region, may prove to be effective. A 2005 study found that the East South Central Region, which includes several Delta Region states, were least likely to identify the health benefits of breastfeeding and were less likely to have a positive opinion about breastfeeding in public (11). However, there is reason to be optimistic about efforts reduce women's risk for triple-negative breast cancer in the Delta Region. For example, Memphis, Tennessee, which may be particularly

at risk for high rates of triple-negative breast cancer due to its racial composition, high birthrates, and low breastfeeding rates, has made particular strides in attitudes and efforts related to breastfeeding (11). There are groups like the Shelby County Breastfeeding Coalition that aim to promote breastfeeding in the County (12). Further, a 2015 study by Nouer and colleagues found that attitudes toward breastfeeding and understanding of its health benefits have improved in women of all races in Memphis (13). Continued coalition-building efforts, increased knowledge, and improved attitudes toward breastfeeding may have long-term effects on the diagnosis of triple-negative breast cancer.

Additionally, to reduce late-stage breast cancer diagnoses in black women in the Delta Region, there is an opportunity to scale up and disseminate effective, community-based education interventions throughout the Region to increase screening rates and improve early detection. Indeed, while previous studies have shown that Delta Region women are less likely to be up-to-date with screening recommendations, this dissertation found that women in the Delta Region had similar spatial access to mammography services as those outside of the Region. This suggests that aspatial barriers to mammography (e.g. psychosocial and/or financial barriers) may play a role. Interventions utilizing lay health advisors/community health advisors have been shown to effectively increase breast cancer screening among black women Delta Region communities or other communities in the Deep South (14-17). Erwin's "Witness Project" was developed and tested in the Arkansas Delta and utilized lay health advisors who are cancer survivors to educate black women on cancer screening in a faith-based setting (15-16). This program has been identified as one of the National Cancer Institute's (NCI) Research-Tested Intervention Programs (18). Additionally, the American Cancer Society has successfully piloted a community health advisor program to improve cancer screening rates in black communities in

the Deep South, which has some geographic overlap with the Delta Region (17). In the Mississippi Delta of the state of Mississippi is a particularly stellar example of community-based work is the work spearheaded by Freddie White-Johnson through the Fannie Lou Hamer Cancer Foundation (FLHCF) and the University of Southern Mississippi's Mississippi Network for Cancer Prevention & Control (19). The work led by Ms. White-Johnson in her role at the University of Southern Mississippi uses community health advisors to educate community members in nine counties in western Mississippi. Her work funded by the FLHCF included cancer education, outreach, and advocacy in the Region. For these efforts, the FLHCF and Ms. White Johnson received the Eugene Washington PCORI Engagement Award. The wealth of effective efforts can provide models for other communities in the Delta desiring to educate women on breast cancer screening and improve breast cancer mortality rates.

In addition to community-based interventions, there are policy-based efforts that may be helpful in improving breast cancer outcomes in the Delta Region. First, during this dissertation's study period (2012-2014), only three of the eight Delta Region states (Arkansas, Illinois, and Kentucky) had expanded Medicaid, a provision of the Affordable Care Act that broadened the eligibility criteria for Medicaid coverage (20). While this has since increased to four states, as Louisiana has expanded coverage, further expansion in Alabama, Missouri, and Mississippi would help provide coverage for the most vulnerable populations to receive coverage for mammography and cancer treatments, which would indeed help the prognosis for cancer patients. Studies have shown that cancer screening rates among low-income individuals were higher in states that expanded Medicaid compared to those that did not, and states that did not expand Medicaid, especially in the South, had higher breast cancer mortality-incidence ratios and lower screening rates (21-22). Because the Affordable Care Act's Medicaid expansion criteria

broaden the income level for which people are eligible, expansion may be particularly beneficial for people in the Delta Region, who experience significant economic challenges. Additionally, it is important to ensure that Breast and Cervical Cancer Screening programs are appropriately funded. These programs provide cancer screening to low-income women who are uninsured or underinsured. However, according to the American Cancer Society's Cancer Action Network, only two Delta Region states (Arkansas and Illinois) have state appropriations at or above 100% of the CDC-funding levels (23). Three states are below 33% of the CDC-funding levels (Alabama, Kentucky, and Missouri), and three states are between 33% and 99% of the CDC-funding levels (Louisiana, Mississippi, and Tennessee). Much like Medicaid expansion, adequately funding programs for early detection, navigation services, and connections to needed treatment are vital to reducing disparities.

There are several Delta Region-specific grant mechanisms and programs that may be utilized to improve access to mammography services in the Delta Region. The USDA disseminates funds through the Delta Health Services Grant mechanism that aims to address "unmet health needs" in the region in the form of healthcare services, health education programs, healthcare job training, or expansion of healthcare infrastructure (24). Past grant awards have gone to telemedicine expansion or simulation training and equipment (25-26). Findings from this dissertation provide the evidence for potential grant applicants who may be interested in address breast cancer disparities to develop applications for increasing mobile mammography efforts, building infrastructure for free-standing mammography centers, and training cancer registrars. All of these potential applications could provide and/or facilitate healthcare services in the region while improving occupational and economic opportunities in the Delta Region.

Future Research Directions

The findings of this dissertation help explain why women in the Delta Region have higher breast cancer mortality rates than women in the non-Delta Region. Additionally, these findings help explicate why black women in the Region have higher rates white women in the Region and black women outside of the Region. There are three areas particularly important research avenues to consider to better understand the cancer disparities in the Delta Region. One, there is a need to continue to explicate the Delta Region's breast cancer disparities, both in etiology and treatment. Second, there are additional areas of cancer disparities in the Region that are also understudied that need to be explored. Third, there is an opportunity to develop partnerships across the Region to synergize research efforts and reduce disparities.

Continued Elucidation of Delta Region Cancer Disparities

While the current study helped to identify higher rates of triple-negative breast cancer rates as a contributing factor to the high breast cancer mortality rates in the Delta Region, these higher rates do not fully explain these mortality disparities. In addition to the higher triple-negative breast cancer rates in the Delta Region, this dissertation found that black women in the Delta Region had higher overall breast cancer incidence rates than white Delta Region women. It is important to understand the contributing factors to breast cancer among black women. A current cohort study, the Southern Community Cohort Study (SCCS), has the potential to be an important data source to further explore the cause of breast cancer in the black women in the Delta Region if appropriate geographic data are available for research purposes (26-27). The NCI-funded SCCS began in 2001 and enrolled roughly 85,000 participants in twelve southern states, six of which are Delta Region states. Recruitment stopped in 2009, and participants are being followed prospectively. More than a two-thirds of participants are black. The baseline

questionnaire for this study asks extensive questions about demographics, personal health history, family health history, health care utilization, nutrition and physical activity habits, occupational history, and other topical areas. Participants also provided a blood or buccal swab sample. The rich data from this study may provide insight into factors put black women at greater risk for breast cancer in this region. Future research should utilize these data to explore additional factors that may help explicate additional factors that may explain the breast cancer disparities in this region.

In addition to exploring disparities risk factors, it is important to understand how disparities in breast cancer treatment may contribute to the mortality disparities in the Delta Region. A study utilizing Surveillance Epidemiology and End Results (SEER) data found that black women were less likely to receive guideline-concordant treatment across most subtypes (28). A study in the Delta Region city of Memphis found that black breast cancer patients were less likely to receive surgery, radiation, chemotherapy, and endocrine therapy than white women, but the study did not stratify or control for subtype (29). With the appropriate dataset with appropriate geographic coverage (e.g. Medicare data), research could explore certain aspects of treatment within the Delta Region population. Additionally, healthcare systems data from systems in the Delta Region, like data used in the Vidal study, may be a good source of data to explore treatment disparities in smaller geographic areas of the Delta Region.

Breast cancer is not the only area of cancer disparities in the Delta Region. Studies have indicated notable mortality disparities in colorectal, cervical, lung, and prostate cancers (2,30-32). These cancers, in particular, are important because they are the greatest contributors to the overall cancer mortality rate (e.g. lung and colorectal cancers) and/or there is significant opportunity to intervene with preventive and screening interventions (e.g. colorectal and cervical

cancers). Indeed, there have been studies that have explored these disparities, such as human papillomavirus vaccination uptake (which can prevent cervical cancer), at a regional level (33). There have also been community-based interventions to address colorectal cancer screening within pockets of the Delta Region (34). Continued regional epidemiological studies and community-based interventions should be undertaken to further elucidate and reduce regional disparities.

To be sure, there are challenges to addressing disparities across a multi-state region. A 2008 report from the University of Tennessee Health Science Center and the Mississippi State Department of Health Data identified the state-to-state variability in demographic, socioeconomic, health behavior, and health outcomes data as a particular challenge to address the region's disparities (35). However, there are some national level avenues for data acquisition that may be fruitful. For example, this dissertation utilized cancer surveillance data from the North American Association of Central Cancer Registries (NAACCR) Cancer in North America Deluxe File. NAACCR members may request multi-state cancer data that includes the county of residence which would allow for identification of Delta Region counties. This data source includes population-based, individual-level information on the demographic, tumor, treatment, and survival characteristics of all cancer cases within the requested geographic area, contingent upon state consent. Federal data sources on demographics, healthcare workforce, and health behaviors and outcomes include the American Community Survey, the Area Health Resource File, and the CDC's WONDER data. These data sources provide information at a county level, or smaller in the case of the American Community Survey, but there are limitations in the type of analyses that can be performed. For the most part, utilization of these data sources will limit researchers to ecological analyses. However, these sources are still important and effective

resources. Administrative data from Medicare is another source of data to assess cancer disparities within the Delta Region. A strength of this data source is that it includes individual-level data, but a weakness is that it is primarily limited to individuals 65 years of age and older.

Regional Collaborations to Reduce Disparities

There is an enormous opportunity to develop collaborative academic research opportunities throughout the Delta Region to capitalize on resources and expertise that exist at academic institutions who serve the Delta Region. Work that is being done in the context of the similarly designated Appalachian Regional Commission can be a model for the more recently designated Delta Regional Authority. Several academic institutions are currently doing health disparities in pockets of the Delta Region. Coordinating and/or collaborating on efforts across academic institutions can help leverage the expertise and resources of each institution.

Appalachia was federally designated in 1965, 35 years before the Delta Region received its designation. With this history, the Appalachian region has been able to develop networks to address cancer disparities within its region. One example is the Appalachian Community Cancer Network, which is one of NCI's Community Network Program Centers (36). The Network is headquartered at the University of Kentucky but includes additional regional offices at Ohio State University, Pennsylvania State University, Virginia Tech University, and West Virginia University. Additionally, this Network has active community advisory boards in Kentucky, Ohio, Pennsylvania, Virginia, and West Virginia. This network was built upon nearly a decade of work from a previous NCI-funded Appalachian Leadership on Cancer which mobilized 1,800 community leaders who built coalitions in 71 counties in the Region (37). The work done in Appalachia provides a successful framework for the Delta Region to model. While developing a multi-state, regional network to facilitate cancer disparity efforts would indeed take a decade,

there already are single state networks, innumerable coalitions, and multiple academic institutions are actively engaged in research throughout the region.

Some of the active community-based work led by academic institutions in Arkansas and Mississippi has already been discussed in this chapter. However, Illinois provides a multi-faceted example of the collaborative work that is being done within the Delta Region of the state. In 2008, the Healthy Southern Illinois Delta Network was formed (38). This Network brought together Southern Illinois University's Center for Rural Health and Social Service Development, Southern Illinois Healthcare, and several coalitions from local health departments in the Region. The formation of this Network enabled local health departments and other organizations to join forces on grant applications and initiatives. Additionally, there are currently at least three academic institutions working with healthcare systems and public health departments in the Delta Region of Illinois on cancer disparity efforts. Southern Illinois University School of Medicine and Washington University School of Medicine in St. Louis have funding from an NCI grant to address rural cancer disparities in both central and southern Illinois (39). Much of this work is being done in the Delta Region of southern Illinois. Additionally, the University of Illinois-Chicago is working with one of the local health departments in the Delta Region to address cancer disparities through community-engaged research (40). Indeed, this is just a snapshot of the work being done in a single state. There are similar Networks and academic research being done to address cancer disparities throughout the Delta Region.

In April 2015, the Delta Research Consortium was launched at a summit meeting at Arkansas State University (41). This meeting brought together representatives from many of the 46 institutions of higher education in the Delta Region. Although the meeting was not specific to health research, one of the emerging interest groups at the event centered on "biomedical/public

health" research. Although the next steps of this consortium remain unclear, re-visiting the efforts of this meeting may provide the foundation for develop of collaborative research efforts in the Delta Region. This chapter introduces only a fraction of the collaborations and research efforts of communities and academic institutions in the Delta Region. In order to reduce and eliminate the disparities in the Region, it will take all of these coalitions and institutions working together.

Conclusions

This dissertation identified disparities in breast cancer subtype, staging, and access to mammography services in the Delta Region. In particular, women in the Delta Region had higher rates of triple-negative breast cancer than non-Delta women. Rates of triple-negative breast cancer remained higher in urban Delta women, even after accounting for age, race, and contextual factors. Further, black women had higher rates of breast cancer in the Delta region than white women. While disparities in breast cancer staging in the Region were minimal, black women in the Delta Region had higher rates of late-stage breast cancer compared to their white counterparts. There were few differences in spatial access to mammography services in the Delta Region compared to the non-Delta Region. However, clusters of low access were identified throughout the Region. To address these disparities, several recommendations are summarized:

- interventions to increase breastfeeding uptake and mammography utilization
- state-level policy improvements to increase access to screening services
- dissemination of Delta Region-specific federal funding to increase access to screening services
- continued breast cancer disparities research to elucidate the etiology of breast cancer and to understand treatment disparities in the Delta Region

- new avenues of epidemiological and health services research to explore disparities in other cancer types in the Delta Region
- development of a region-wide research network, similar to Appalachia, for academic institutions and other partners to address the Delta Region's cancer disparities

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