SOCIAL CONSTRUCTIONS, BIOLOGICAL IMPLICATIONS: A STRUCTURAL EXAMINATION OF RACIAL DISPARITIES IN BREAST CANCER SUBTYPE

by

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A dissertation submitted in partial fulfillment
of the requirements for the degree of
Doctor of Philosophy
(Health Behavior and Health Education)
in the University of Michigan
2014

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DEDICATION

To Claire and Nathaniel. Thank you for keeping me both grounded and inspired.

ACKNOWLEDGMENTS

This dissertation would not be possible without my committee members, my colleagues and friends, the Population Studies Center and Department of Health Behavior and Health Education, and my family. First and foremost, my committee chair, Arline Geronimus, changed the way that I look at public health research and the social world in which it is embedded. She opened up new and exciting areas for me to apply my previous skills, and she believed in both me and this new direction for my work when I needed that validation the most. For her wisdom, support, and encouragement, I will forever be thankful.

Each of my committee members used their talent and expertise to improve my work. While considering how to incorporate cortisol into my conceptual and analytical models, Rachel Snow pushed me to think more like an endocrinologist than a social scientist. Sharon Kardia shared valuable time and insight from her work as a genetic epidemiologist who appreciates the importance of the social patterning of risk factors. John Bound has guided me in my statistical methods and analyses. My work is stronger thanks to their collective efforts.

I have also been very fortunate to have received feedback and encouragement from wonderful colleague-friends. Annie Ro Rodriguez, Kurt Christensen, Amanda Simaneck, Lori Wallace, Linnea Evans, and Akilah Wise have all shared invaluable academic and social support through various stages of my dissertation development. Thank you all for your willingness to read, listen, and provide feedback throughout this process.

The steadfast support of the Population Studies Center has also been essential in getting me to the finish line. As a pre-doctoral trainee and recipient of a small grant for my dissertation work, I have received outstanding financial and academic support during the past 7 years. My research trajectory would certainly not be what it is today had I not been a part of the center.

The Department of Health Behavior & Health Education provided the early course work and professional development opportunities that inspired me to seek a career in academia. I am particularly thankful for the early mentorship and research support from Scott Roberts, and for being selected as a Richard Janz Memorial Fellowship recipient. With the help of this unexpected vote of departmental confidence and its associated research funding, I now find myself putting the final touches on my dissertation today.

Finally, I must thank my children, Claire and Nate, for being amazingly kind, patient, and empathetic kids, particularly when I was in my most frazzled dissertating moments. They must have inherited some of these wonderful traits from their equally amazing father, Keith, and grandparents, Marilyn and Sam Pastrovich. Thank you, everyone.

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ABSTRACT

The triple-negative subtype of breast cancer is etiologically and clinically distinct from the more common, less aggressive, and more treatable form of estrogen receptor-positive breast cancer. Numerous population-based studies have found that black women are 2 to 3 times more likely to develop triple-negative breast cancer than white women. Much of the existing research on racial disparities in breast cancer subtype has focused on identifying predisposing biological or genetic factors associated with African ancestry. However, this approach ignores growing multidisciplinary evidence suggesting that contemporary racial stratification shapes a wide range of environmental and social exposures that can subsequently impact cellular physiology and even gene expression patterns. Geronimus' weathering hypothesis provides a unique conceptual framework through which to consider how psychosocial and environmental stressors may structure the disruption of biological mechanisms according to race. Building upon this framework, my dissertation (1) integrates important findings from stress biology, breast cancer subtype, and health disparity research in the form of a critical literature review, (2) develops an alternative conceptual model for the examination of racial disparities in breast cancer subtype, and (3) tests aspects of the model in two empirical analyses, using a combination of state-wide cancer registry data, block group-level Census and American Community Survey data, individual-level reports of stress and discrimination, and daily cortisol decline, a purported biological measure of chronic stress exposure. My findings suggest that there are significant associations between neighborhood characteristics (i.e., socioeconomic status and racial

composition) and odds of more aggressive breast cancer subtypes, particularly within highly segregated metropolitan areas. However, these associations differ by race/ethnicity and across age groups. In a separate study population, the same neighborhood sociodemographic features are also associated with significant variation in daily cortisol decline. Taken together, this work demonstrates the potential for alternative sociobiological pathways linking race to the risk of triple-negative breast cancer, and suggests new avenues for research and public health action.

CHAPTER 1

Introduction

Breast cancer is the second most common type of cancer diagnosed in American women (Carol DeSantis, Siegel, Bandi, & Jemal, 2011). According to National Cancer Institute estimates, over 230,000 women will be diagnosed with breast cancer in 2014, and more approximately 40,000 women will die of the disease (*SEER Cancer Statistics Review, 1975-2011.*, 2014). While the overall breast cancer incidence rate remains higher among white women, black women of all ages are significantly more likely to die of the disease. The average annual age-adjusted breast cancer mortality rate for black women diagnosed between 2003 and 2007 was 32.4 deaths per 100,000, whereas 23.9 breast cancer related deaths were observed per 100,000 white women during that same period (Carol DeSantis et al., 2011). This inequality in breast cancer-related mortality rates becomes even more striking when considering the fact that, until the early 1980's, breast cancer mortality rates for white and black women were approximately equal (Smigal et al., 2006).

As with many public health problems, identifying and intervening on the fundamental causes of racial disparities in breast cancer mortality has proven to be quite difficult. Much of the research during the past two decades has focused on racial inequalities throughout the breast cancer continuum of care (Bigby & Holmes, 2005; Jones & Chilton, 2002; Newman & Martin, 2007). For example, when compared to white women, black women have lower levels of access

to quality mammography services (Hirschman, Whitman, & Ansell, 2007), experience longer diagnostic and treatment delays (Gorin, Heck, Cheng, & Smith, 2006; Kerner et al., 2003), and are more likely to receive suboptimal care once treatment is initiated (Bradley, Given, & Roberts, 2002). However, two studies conducted within the Department of Defense medical system indicated that even when white and black women have equal access to free medical care, black women still have a higher breast cancer-related mortality rate (Jatoi, Becher, & Leake, 2003; Wojcik, Spinks, & Optenberg, 1998). A recent review of clinical trial participants at a large cancer treatment center found that even when the treatment protocols are standardized and prognostic clinical factors are controlled for, black women with breast cancer still fare far worse than their white counterparts (Albain, Unger, Crowley, Coltman, & Hershman, 2009). Taken together, these finding suggests that unequal access to high-quality health care resources cannot fully explain the widening racial inequalities in breast cancer mortality.

Racial disparities in several clinical features of breast cancer are also well-documented, and are thought to contribute to the observed disparities in survival (Amend, Hicks, & Ambrosone, 2006; C. DeSantis, Jemal, & Ward, 2010). Differences in the distribution of breast cancer subtypes among white and black women are particularly intriguing. Numerous studies have found that, when comparing black and white breast cancer patients, black women are more likely to be diagnosed with tumors that have very low levels of specific hormone receptors (Gapstur, Dupuis, Gann, Collila, & Winchester, 1996; Hausauer, Keegan, Chang, & Clarke, 2007; Joslyn, 2002; Tarone & Chu, 2002). In fact, nearly 25% of black women who were diagnosed with breast cancer in California between 1999 and 2003 had tumors that lacked estrogen, progesterone, and human epidermal growth factor receptors – commonly referred to as triple-negative breast cancer, or TNBC – while less than 11% of white women in the same

cancer registry had triple negative tumors (Bauer, Brown, Cress, Parise, & Caggiano, 2007). This statistically significant disparity has meaningful clinical implications, as triple negative tumors are associated with larger and higher-grade carcinomas at the time of diagnosis and are not responsive to current endocrine treatments such as Tamoxifen and Herceptin (Kang, Martel, & Harris, 2008; Reis-Filho & Tutt, 2008). As a result, women diagnosed with triple-negative tumors have higher rates of five-year cancer-related mortality than women who are diagnosed with other types of breast cancer, regardless of the tumor stage at the time of diagnosis (Bauer et al., 2007).

The highly significant relationship between breast cancer subtype and five-year cancer-related mortality rate is one reason why breast cancer subtype is a valuable intermediate outcome to measure when assessing breast cancer inequalities. Because breast cancer subtype is thought to be determined at the time the tumor begins to develop, observed differences in subtype distribution across racial groups should not be influenced by access to breast cancer screening, diagnostic, and treatment resources (Morris & Carey, 2007; Perou et al., 2000; Zhu, Bernard, Levine, & Williams, 1997). Differences in the population-level distribution of breast cancer subtype can therefore be thought of as one of the initial sources of racial inequality in the breast cancer experience. As a result, identifying factors that influence the development of particular breast cancer subtypes may be critical to ascertaining upstream interventions that reduce racial disparities in breast cancer mortality.

Race: A Genotypic or Phenotypic Risk Factor?

Before embarking on research that explicitly explores biologic differences between racial groups, one must carefully consider exactly what race means in the context of these studies. For the purposes of this proposal, "black" refers to individuals who self-identify with this loosely

defined racial/ethnic group. My discussion of race will center on the social construction of majority and minority groups within the American culture, and in no way implies a biological basis for this stratification.

The operationalization of race in prior breast cancer disparities research is much less clear. Historical and cross-cultural perspectives on race (Smedley & Smedley, 2005), as well as thoughtful interpretations of the relationship – or lack thereof – between genetic ancestry data and race (Cooper, Kaufman, & Ward, 2003) strongly support the position that racial group is neither an objective nor biological variable. Accordingly, several authors explicitly state that race is not a biologically meaningful predictor of breast cancer outcomes, and suggest that race may be a proxy for other economic or psychosocial factors that are more directly responsible for the observed disparities (Brawley, 2002). However, virtually all research in breast cancer disparities has, at best, treated race as simple categorical risk factor. Some researchers have gone a step closer towards making race a biological entity by calling for the identification of inherited genetic risk factors that set black women with breast cancer apart from white women affected by the same disease (Hayanga & Newman, 2007). While these researchers may not espouse a biological construction of racial groups, their emphasis on searching for *inherited* risk factors that are common only among black women fails to consider the potential effects of the *acquired* biological changes that may result from differential exposure to social and physical environments across racial groups. Given the highly confounded relationships among race, socioeconomic position (SEP), and other psychosocial factors in the United States, this omission could be a critical mistake.

Incorporating a Guiding Theoretical Perspective and New Evidence

Geronimus has proposed the weathering hypothesis as one mechanism by which structural factors may lead to poor health outcomes among minority groups (Geronimus, 1992; Geronimus & Thompson, 2004). The weathering hypothesis emphasizes the role of social, political, and economic marginalization on health outcomes, particularly among younger black women (Geronimus, Hicken, Keene, & Bound, 2006). This theoretical perspective is particularly relevant in the case of racial disparities in breast cancer subtype, as premenopausal black women are at a particularly high risk of developing triple negative tumors (Kwan et al., 2009; Millikan et al., 2008; Parise, Bauer, Brown, & Caggiano, 2009; Trivers et al., 2009).

An emerging area of research may provide a useful empirical explanation for the relationship between the observed racial differences in the distribution of breast cancer subtypes and the well-documented differences in the economic and psychosocial experiences of American blacks and whites: human stress genomics (S. W. Cole, 2010). Researchers in this field are exploring the dynamic regulation of gene expression resulting from interactions with the social and physical environment. For example, recent human stress genomics research has demonstrated that certain gene expression patterns are associated with stressful experiences in the social environment such as social isolation and chronic interpersonal stress (Steven W. Cole, 2013; S. W. Cole et al., 2007). Human stress genomics research suggests that these sources of social stress trigger a series of biological signals that selectively increase or decrease gene transcription, particularly among genes involved with inflammatory or immune response systems (S. W. Cole, 2009). Transcription is an early and essential step in the process of creating active proteins from genes. As a result, alterations in the transcriptional control of a specific gene will change the gene's expression pattern, thereby modifying the amount of protein it produces.

Because the breast cancer subtypes are defined by whether or not the tumor expresses particular types of proteins, it stands to reason that similar mechanisms of transcriptional control may play an important role in the development of specific breast cancer subtype. Recent work by Ritter, Antonova, and Mueller (Ritter, Antonova, & Mueller, 2012) not only supports the hypothesized relationship between transcriptional control and breast cancer subtype, but also suggests that physiological responses to stress may be an important antecedent. The researchers' in vitro analysis of mouse and human mammary cell lines suggests that dysregulation of the stress-mediated cortisol feedback loop reduces the expression of the critical tumor suppressor gene, *BRCA1*.

To fully appreciate the implications of this finding, some context regarding both *BRCA1* and the stress-medicated cortisol feedback loop is needed. First, mutations in the *BRCA1* gene – which significantly disrupt the normal expression *BRCA1* or the function of its protein – are associated with a 50-80% chance of developing female breast cancer by age 70 (Antoniou et al., 2003; Chen & Parmigiani, 2007). Moreover, roughly 70% of *BRCA1* mutation-associated breast cancers are classified as triple-negative, whereas only 10-15% of breast cancers diagnoses among non-*BRCA1* mutation carriers are triple-negative (Atchley et al., 2008; Foulkes, Smith, & Reis-Filho, 2010; Mavaddat et al., 2012). There is a growing body of molecular research that supports the circumstantial evidence linking decreased *BRCA1* expression to increased risk of triple-negative breast cancer in particular (see Santarosa & Maestro (2012) for a more detailed review). Second, it is critical to note that the current population-based prevalence estimates for heritable *BRCA1* mutations among blacks (1.3-1.4%) are roughly half that of non-Ashkenazi Jewish whites (2.2-2.9%) (John et al., 2007; Malone et al., 2006). As a result, inherited mutations

in *BRCA1* are unlikely contributors to the increased prevalence of triple-negative breast cancer among black women relative to whites.

While blacks may have a lower risk of carrying a BRCA1 mutation, they may be at a significantly higher risk for exhibiting dysregulation of the stress-mediated cortisol feedback loop. When the cortisol feedback loop is functioning properly, it generates a typical pattern of cortisol secretion over a 24-hour period. This pattern, illustrated in Figure 1-1, is often described in terms of cortisol levels or changes in levels at certain times of day: the waking cortisol level; the change in cortisol from waking to its peak value 30-45 minutes later (the cortisol awaking response or CAR); the decrease in cortisol from either the peak or waking level to the bedtime level; and the total daily exposure to cortisol, as estimated by the area under the curve. Emerging research on population-level variation in diurnal cortisol patterns indicates that U.S. blacks and Hispanics from adolescence (A. S. DeSantis et al., 2007)and throughout adulthood (Karlamangla, Friedman, Seeman, Stawksi, & Almeida, 2013; Skinner, Shirtcliff, Haggerty, Coe, & Catalano, 2011) are more likely to exhibit lower levels of cortisol upon waking, smaller cortisol awakening responses, and flatter declines in cortisol levels throughout the day relative to whites. These racial/ethnic patterns remain significant even after adjusting for biobehavioral factors that are associated with cortisol levels (e.g., smoking, exercise, and obesity) and psychosocial characteristics such as cynical hostility, depression, emotional support, and chronic burden (A. S. DeSantis et al., 2007; Hajat et al., 2010).

Due in part to the lack of clear individual-level explanatory factors for the observed racial/ethnic variation in diurnal cortisol patterns, researchers have recently turned their attention toward neighborhood-level factors (Do et al., 2011; Karb, Elliott, Dowd, & Morenoff, 2012). With the long history of race-based residential segregation and the related economic and political

marginalization of minorities in this country, it is not surprising that neighborhoods are an increasingly common setting for research on the origins of racial/ethnic health disparities. However, the fact that different groups live in different areas may not always lead to worse social conditions for minority groups. There may very well be advantages for minorities who live in neighborhoods with higher percentages of same-minority residents, such as increased access to social support, less cultural isolation, and reduced exposure to class- and race-based prejudice (Keene & Geronimus, 2011; Pearson & Geronimus, 2011; Pickett & Wilkinson, 2008). These protective effects may be particularly salient in highly concentrated minority neighborhoods within metropolitan areas that have high levels of race-based residential segregation, a potential manifestation of entrenched racial ideologies (Geronimus, 2000). A nuanced, theory-driven and empirically-grounded approach is therefore needed when considering how neighborhood-level characteristics may relate to observed racial variation in the dysregulation of the stress-mediated cortisol feedback loop.

Taken together, these emerging lines of research regarding cortisol-related transcriptional control of *BRCA1* and racial/ethnic variation in observed diurnal cortisol patterns suggest a potential alternative mechanism for the origin of racial differences in breast cancer biology. It is therefore plausible that, rather than higher rates of heritable *BRCA1* mutations or other less penetrant genetic risk factors stemming from shared ancestry, dysregulation of the stress-mediated cortisol feedback loop could contribute to the significantly higher rates of triple-negative breast cancers diagnosed among black women via the cumulative impact of decreased *BRCA1* expression.

Dissertation Objectives

To begin testing this alternative pathway, I will address the following critical questions in three independent yet thematically linked papers: What is currently known – and not known – regarding the potential relationship between stress and racial disparities in breast cancer subtypes? Among women diagnosed with breast cancer, are neighborhood-level sociodemographic characteristics that are empirically or theoretically related to individual-level psychosocial stressors also associated with risk of triple-negative tumors? Are neighborhood- and/or individual-level stressors associated with a specific biological pathway that may increase the risk of developing triple-negative breast cancer?

Chapter 2 is a critical review of the empirical and theoretical evidence regarding how structural-, neighborhood-, and individual-level stressors may intersect with biological factors to contribute to racial disparities in breast cancer subtypes. A new conceptual model linking these multilevel factors is included in this paper. The conceptual model is built upon the theoretical framework of the weathering hypothesis, and the model serves as the basis for developing the empirical analyses proposed for second and third dissertation papers.

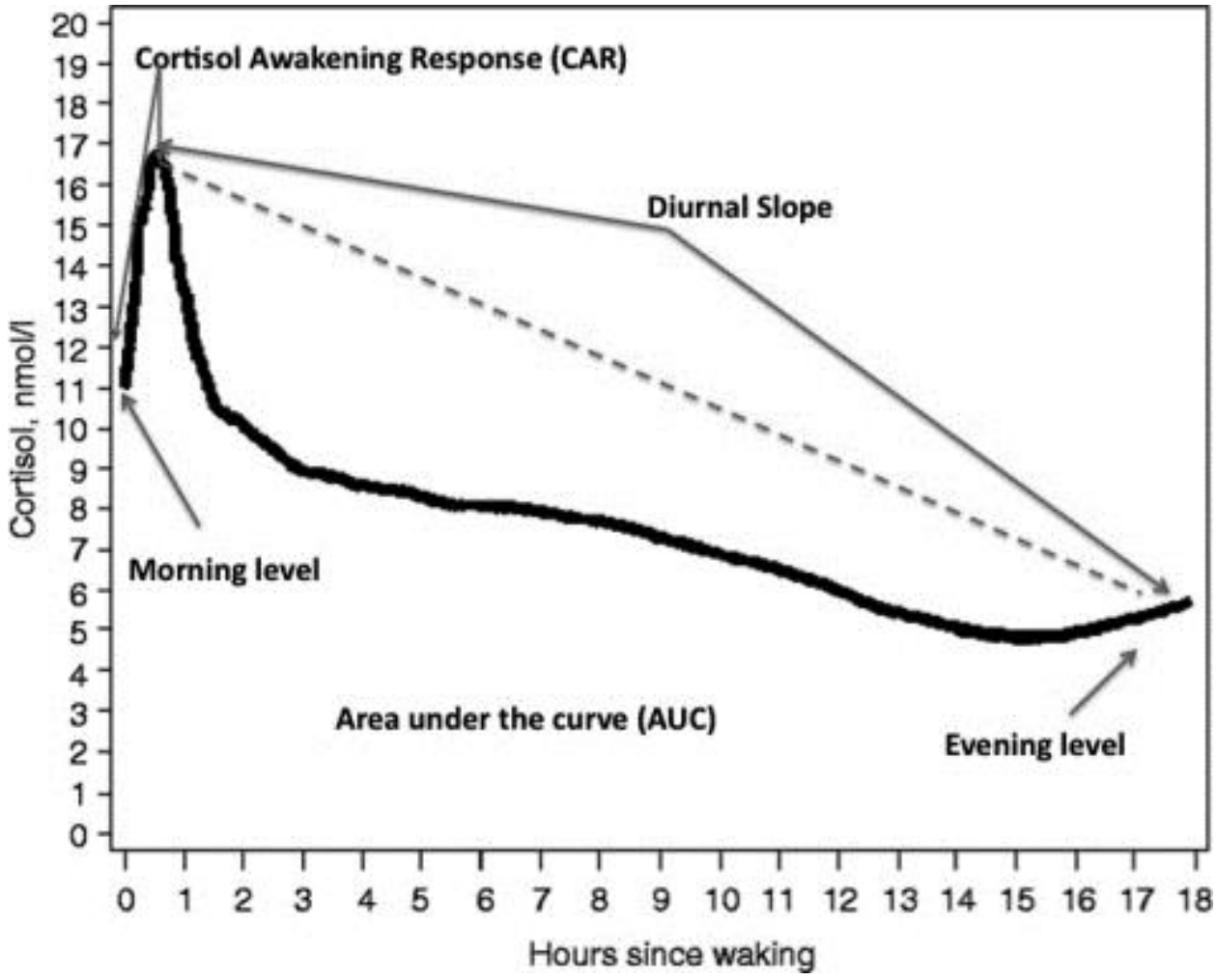
Chapter 3 focuses on the potential association between race-based residential segregation and the observed racial/ethnic variation in the distribution of breast cancer subtypes. As introduced here and elaborated upon in the first dissertation paper, exposure to chronic stressors within racially and economically segregated residential neighborhoods may contribute to racial variation in diurnal cortisol patterns (Do et al., 2011; Friedman, Karlamangla, Almeida, & Seeman, 2012; Merkin et al., 2009) and subsequent triple-negative breast cancer risk. Prior work by Warner and Gomez (Warner & Gomez, 2010) using California Cancer Registry (CCR) data provides an appealing model for exploring potential relationships between residential segregation

and breast cancer subtype. In this paper, I use the CCR data and linked California Neighborhoods Data System files to examine potential associations between race- and age-specific distributions of breast cancer subtype and 1) neighborhood-level racial composition, 2) neighborhood-level socioeconomic status, and 3) metropolitan-level race-based residential segregation.

To complement the population-level analysis described above, additional work is needed to deepen our understanding of potential neighborhood- and individual-level factors related to cortisol dysregulation. In Chapter 4, I use data from the Healthy Environments Partnership Wave 2 Community Survey and the Race/Ethnicity, Psychosocial and Environmental Stressors, and Telomere Length study to look for evidence of diurnal cortisol dysregulation via the average daily decline in cortisol levels, as well as associated stressors at the individual and neighborhood levels. I examine whether higher levels of perceived individual-level discrimination, neighborhood-level safety stress, and neighborhood-level social environmental stress will each independently predict flatter daily declines in cortisol levels after accounting for individual- and neighborhood-level sociodemographic characteristics.

There is little doubt that the fundamental causes of racial inequalities in breast cancer outcomes are complex. As Demicheli and colleagues (2007) note, the field is still lacking a "unifying hypothesis" that incorporates findings across multiple disciplines. The three proposed papers of this dissertation will help fill this gap by integrating diverse stress and breast cancer literatures, developing a unifying conceptual model for exploring racial variation in breast cancer subtypes, and testing two important components of the model via secondary data analyses.

Figure 1-1: Example of a diurnal cortisol pattern from Dowd, Simanek & Aiello (2009)



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CHAPTER 2

Black-White Disparities in Breast Cancer Subtype: The Intersection of Stress & Biology

Introduction

Racial disparities in several clinical features of breast cancer are well-documented (Amend, Hicks, & Ambrosone, 2006). However, differences in the distribution of breast cancer subtypes among white and black women are particularly troubling. Numerous studies have found that, when comparing black and white breast cancer patients, black women are more likely to be diagnosed with tumors that have very low levels of specific hormone receptors (Gapstur, Dupuis, Gann, Collila, & Winchester, 1996; Hausauer, Keegan, Chang, & Clarke, 2007; Joslyn, 2002; Tarone & Chu, 2002). In fact, nearly 25% of black women who were diagnosed with breast cancer in California between 1999 and 2003 had tumors that lacked estrogen, progesterone, and human epidermal growth factor receptors – commonly referred to as triple-negative tumors – while less than 11% of white women in the same cancer registry had triple negative tumors (Bauer, Brown, Cress, Parise, & Caggiano, 2007). A new report based on the National Cancer Data Base also found that, regardless of socioeconomic status, black women are nearly twice as likely to be diagnosed with triple-negative breast cancer than their non-Hispanic white counterparts (Sineshaw et al., 2014). This statistically significant disparity has meaningful clinical implications as triple negative tumors are associated with larger and higher-grade carcinomas at the time of diagnosis and are not responsive to current endocrine treatments such

as Tamoxifen and Herceptin (Kang, Martel, & Harris, 2008; Reis-Filho & Tutt, 2008). As a result, women diagnosed with triple-negative tumors have higher rates of five-year cancer-related mortality than women who are diagnosed with other types of breast cancer, regardless of the tumor stage at the time of diagnosis (Bauer et al., 2007).

The highly significant relationship between breast cancer subtype and five-year cancer-related mortality rate is one reason why breast cancer subtype is a valuable intermediate outcome to measure when assessing breast cancer inequalities. Because breast cancer subtype is thought to be determined at the time the tumor begins to develop, observed differences in subtype distribution across racial groups should not be influenced by access to breast cancer screening, diagnostic, and treatment resources (Morris et al., 2007). Differences in the population-level distribution of breast cancer subtype can therefore be thought of as one of the initial sources of racial inequality in the breast cancer experience. As a result, identifying factors that influence the development of particular breast cancer subtypes may be critical to ascertaining upstream interventions that reduce racial disparities in breast cancer mortality.

As with many public health problems, identifying and intervening on the fundamental causes of racial disparities in breast cancer mortality has proven to be quite difficult. Much of the research during the past two decades has focused on racial inequalities throughout the breast cancer continuum of care (Bigby & Holmes, 2005; Jones & Chilton, 2002; Newman & Martin, 2007). For example, when compared to white women, black women have lower levels of access to quality mammography services (Hirschman, Whitman, & Ansell, 2007), experience longer diagnostic and treatment delays (Gorin, Heck, Cheng, & Smith, 2006; Kerner et al., 2003), and are more likely to receive suboptimal care once treatment is initiated (Bradley, Given, & Roberts, 2002). However, two studies conducted within the Department of Defense medical

system indicated that even when white and black women have equal access to free medical care, black women still have a higher breast cancer-related mortality rate (Jatoi, Becher, & Leake, 2003; Wojcik, Spinks, & Optenberg, 1998). A review of clinical trial participants at a large cancer treatment center found that even when the treatment protocols are standardized and prognostic clinical factors are controlled for, black women with breast cancer still fare far worse than their white counterparts (Albain, Unger, Crowley, Coltman, & Hershman, 2009). Taken together, these finding suggests that unequal access to high-quality health care resources cannot fully explain the widening racial inequalities in breast cancer mortality. This conclusion further emphasizes the need to explore the origins of the observed racial differences in breast cancer subtype.

However, prior to embarking on research that explicitly explores biologic differences between racial groups, one must carefully consider exactly what race means in the context of these studies. For the purposes of this paper, "black" refers to individuals who self-identify with this loosely defined racial/ethnic group. My discussion of race will center on the social construction of majority and minority groups within the American culture, and in no way implies a biological basis for this stratification. But how has race been defined and operationalized in previous related research? Could race be a proxy for other economic or psychosocial factors that are more directly responsible for the observed population variation?

Historical and cross-cultural perspectives on race (Smedley & Smedley, 2005), as well as thoughtful interpretations of the relationship – or lack thereof – between genetic ancestry data and race (Cooper, Kaufman, & Ward, 2003) strongly support the position that racial group is neither an objective nor biological variable. Several authors explicitly state that race is not a biologically meaningful predictor of breast cancer outcomes (Brawley, 2002). However, other

researchers call for the identification of inherited genetic risk factors that set black women with breast cancer apart from white women affected by the same disease (Hayanga & Newman, 2007). While these authors may not espouse a biological construction of racial groups, their emphasis on searching for *heritable* risk factors that are common among black women fails to consider the potential effects of the *acquired* biological changes that may result from differential exposure to social and physical environments across racial groups. Given the highly confounded relationships among race, socioeconomic position (SEP), and other psychosocial factors in the United States, this omission could be a crucial mistake.

Geronimus has proposed the weathering hypothesis as one mechanism by which structural factors may lead to poor health outcomes among minority groups (Geronimus, 1992; Geronimus & Thompson, 2004). The weathering hypothesis emphasizes the role of social, political, and economic marginalization on health outcomes, particularly among younger black women (Geronimus, Hicken, Keene, & Bound, 2006). This theoretical perspective is particularly relevant in the case of racial disparities in breast cancer subtype, as premenopausal black women are at a particularly high risk of developing triple negative tumors (Kwan et al., 2009; Millikan et al., 2008; Parise, Bauer, Brown, & Caggiano, 2009; Trivers et al., 2009).

Two emerging areas of basic science research may provide a useful empirical explanation for the relationship between the observed racial differences in the distribution of breast cancer subtypes and the well-documented differences in the economic and psychosocial experiences of American blacks and whites: epigenetics and human stress genomics. Researchers from both fields are exploring the dynamic regulation of gene expression resulting from interactions with the social and physical environment, but via different molecular mechanisms. Epigenetic mechanisms have been described as "lying above the genome," in that they are not

necessarily heritable changes that are passed on from generation to generation, but they play a significant role in determining what proteins are made in specific cells under specific conditions (Berger, Kouzarides, Shiekhattar, & Shilatifard, 2009). In addition, recent human stress genomics research has demonstrated that certain gene expression patterns are associated with stressful experiences in the social environment such as social isolation (Cole et al., 2007; Sloan et al., 2010; Szyf, McGowan, & Meaney, 2008). Because the breast cancer subtypes are defined by whether or not the tumor expresses particular types of proteins, it stands to reason that epigenetic and other forms of transcriptional control play an important role in the determination of breast cancer subtype. Taken together, these two lines of research suggest a potential alternative mechanism for the generation of racial differences in breast cancer biology, and thus, mortality.

This paper will examine seminal findings in each of these disciplines and identify the limitations of the current literature. The weathering hypothesis and broader stress process theory serve as the theoretical basis for integrating epigenetic concepts into a novel interdisciplinary hypothesis. By using a multilevel, theory-based approach to examine the observed racial disparities in breast cancer mortality, I hope to identify new avenues for research and intervention that may also be relevant to other racial/ethnic health disparities.

Black-White Disparities in Breast Cancer Subtype

Breast cancer is now widely recognized as a highly heterogeneous disease. Among the first supporting pieces of molecular evidence came in the early 1970's when McGuire reported that some breast carcinomas have estrogen receptors (and are thus referred to as ER-positive cancers), while other, ER-negative breast cancers do not (McGuire, 1973). Since that initial

report, estrogen receptor status has been found to play an important role in the treatment and natural history of breast cancer. Not only are ER-negative cancers non-responsive to standard endocrine treatments such as tamoxifen, but they are also more likely to be diagnosed in pre-menopausal women, are associated with larger and higher-grade carcinomas at the time of diagnosis, and have a worse prognosis (W. Y. Chen & Colditz, 2007; Thorpe, 1988).

More recent research in the area of breast cancer hormone receptors has identified two additional receptors that have important clinical and prognostic implications: progesterone receptor (PR) and human epidermal growth factor receptor 2 (HER2). Tumors that express little to no ER, PR, or HER2 are commonly referred to as triple-negative tumors. Despite the prolific use of this term since inception 4 years ago, there are still no firm diagnostic guidelines as to exactly how little hormone receptor expression is needed in order to qualify as a triple-negative tumor (Foulkes, Smith, & Reis-Filho, 2010). Even with the heterogeneous application of the triple-negative categorization, studies have consistently found that approximately 15% of all invasive breast tumors fall into this category, and that they have many of the same clinically aggressive characteristics as ER-negative tumors (Foulkes et al., 2010).

The advent of DNA microarray technology has enabled scientists to rapidly examine the expression pattern of hundreds of genes – including the ER, PR, and HER2 genes – simultaneously. Investigations conducted in several different countries have identified at least four common sets of gene expression patterns, and therefore, four molecular subtypes of breast cancer (Carey et al., 2006; Perou et al., 2000; Sorlie et al., 2003). The most common molecular subtype, luminal A, expresses the estrogen receptor gene and thus is ER-positive. Basal-like breast cancers are the second most common subtype, and the estrogen receptor gene is not typically expressed in this group of carcinomas. As is the case with triple-negative tumors, basal-

like breast cancers are associated with more aggressive carcinoma progression and worse overall prognosis (Carey et al., 2006).

Triple-negative and basal-like subtypes of breast cancer are related in that they are both are largely defined by their ER-negative status. (Nielsen et al., 2004) However, several studies indicate that these categories are not completely equivalent on a biological or clinical basis. Figure 2-1 summarizes the current literature regarding the overlap and distinction between triple-negative and basal-like subtypes (S. Badve et al.; Bertucci et al., 2008; Linn & Van 't Veer, 2009; Olopade, Grushko, Nanda, & Huo, 2008; Perou, 2010; Schneider et al., 2008).

Despite incomplete concordance between triple-negative and basal-like subtypes, these two terms are sometimes used interchangeably in the literature. Strictly speaking, basal-like breast cancers are diagnosed using DNA microarray analysis to detect the complex gene expression patterns. However, several studies define the breast cancer molecular subgroups by the results from standard immunohistochemical (IHC) procedures: tumors that are ER-negative and PR-negative but also express cytokeratins (e.g., CK5/6) and may or may not express HER2 are deemed “basal-like” (Dunn, Agurs-Collins, Browne, Lubet, & Johnson, 2010). This technique circumvents the financial challenges of using the DNA-based methods of tumor categorization in large studies and produced accurate results in a sample of 21 genetically-identified tumors, but raises questions as to whether this may be yet another, subtly different breast cancer subgroup. (Nielsen et al., 2004) In addition, IHC testing algorithms were only recently standardized (Hammond et al., 2010). Earlier studies of repeated IHC testing across labs yielded different IHC results in up to 20% of the cases (S. S. Badve et al., 2008; Regan et al., 2006), which is indicative of considerable limitations in the breast cancer subtype literature (Foulkes et al., 2010).

While the classification criteria of ER- tumors, triple-negative tumors, and basal-like tumors varies, there is substantial evidence that black women diagnosed with breast cancer are more likely to have the more aggressive subtype, regardless of how that subtype is defined. Table 2-1 summarizes some of the largest and most recent studies of the distribution of breast cancer subtype among black and white women diagnosed with breast cancer. Among the papers that reported race-specific odds, black women were nearly 2 to 3 times more likely to be diagnosed with the aggressive breast cancer subtype under study. (Bauer et al., 2007; Carey et al., 2006; Gapstur et al., 1996; Parise et al., 2009; Stead et al., 2009; Trivers et al., 2009)

Recent epidemiological studies summarized in Tables 2-2 through 2-4 have identified additional factors that increase women's chances of developing more aggressive subtypes of breast cancer. The body of research has focused on the triple-negative subtype as the outcome of interest, primarily due to the relative ease of obtaining ER, PR, and HER2 receptor status data from cancer registries and medical records. While the cost of DNA microarray technology is falling, use of molecular profiling is not currently well-integrated into routine clinical care (Weigelt, Pusztai, Ashworth, & Reis-Filho, 2012).

The data presented in these tables and in the epidemiology of breast cancer subtype literature point to three important issues. First, the selection of an appropriate comparison group has differed across studies. To identify true causal risk factors, one would ideally need to follow a large population who is susceptible to the disease of interest, monitor each individual's level of exposure to suspected risk-increasing and risk-reducing factors, and then see who develops the disease over the course of the vulnerability period. This is certainly not a feasible methodological approach with complex diseases that may manifest at virtually any point in adulthood, as is the case with breast cancer. The majority of epidemiological studies in general

as well as those summarized in Tables 2-2 through 2-4 use a case-only approach and compare triple-negative or IHC defined basal-like cases to all other breast cancer cases diagnosed in the population of interest. Using this approach allows for risk factors that differ across breast cancer subtypes in either their magnitude or direction to be interpreted as indicators of etiologic heterogeneity (Troester & Swift-Scanlan, 2009). Results generated using case-only comparisons therefore cannot speak to overall, lifetime risk of developing specific breast cancer subtypes. This is an important distinction, particularly when considering population-level dissemination and interpretation of results.

Taking this case-only approach has revealed some significant differences when comparing triple-negative risk factors to those for breast cancers that are ER-positive. The most consistently significant factors associated with increased incidence of aggressive breast cancer subtypes have been black race and younger age of onset (Bauer et al., 2007; Carey et al., 2006; Gapstur et al., 1996; Kwan et al., 2009; Millikan et al., 2008; Parise et al., 2009; Setiawan et al., 2009; Trivers et al., 2009). Given that these factors reflect demographic features rather than a direct causal link to breast cancer subtype, analyses of biologically plausible risk factors are generally adjusted for both race and age (see footnotes following Table 2-4 for study-specific adjustments). Evidence for these biologically plausible risk factors is decidedly mixed. Some of the more interesting results highlighted in Table 2-3 are associations between aggressive breast cancer subtype, younger age at first birth, and greater number of live births. (Millikan et al., 2008; Trivers et al., 2009) These findings counter the widely held notion that the reduction in lifetime estrogen exposure afforded by having a first live birth before age 30 and/or more than one full-term pregnancy lowers one's overall breast cancer risk.

Little attention has been paid to the possibility that these less intuitive risk factors for aggressive breast cancer subtypes may be related to their social patterning across racial/ethnic groups. For example, 23.1% of black women who gave birth in 1990 were teenagers, while teenage mothers made up only 10.9% of all white women who gave birth that year (Bureau, 2009). It is possible that the relationship between aggressive breast cancer subtype and age at first birth is confounded by other unidentified exposures that may increase both black women's likelihood of giving birth at a younger age and their likelihood of developing an aggressive breast tumor. Previous research indicates that there may be advantages for black women to give birth at younger ages, as black women experience a faster and steeper health decline in later childbearing years (Geronimus, 1994; Geronimus & Korenman, 1993). Socially, there are additional benefits to having children earlier in life, such as the increased availability and better health of grandparents and other child care providers from older generations (Delaire & Kalil, 2002). This type of support may be particularly important to women who reside in low income neighborhoods and/or who do not currently have a committed partner to assist with child rearing and help provide financial support. As described later in this paper, these and other sources of social stress may also have an impact on the development of aggressive breast cancer subtypes. However, it is important to note that the racial difference in percentage of births to teenage mothers is shrinking, as teenage births represented 17.0% of all births to black women in 2007 and 9.4% of births to white women (U.S. Census Bureau, 2009). How this demographic shift may impact racial differences in aggressive breast cancer incidence rates remains to be seen.

Critical Analysis of Stark, et al (2010)

The conflation of race, biology, and social factors is not unique to breast cancer epidemiology, but it appears to be particularly pervasive in this literature. A study published this month in the highly-cited journal *Cancer* boldly suggests that the increased risk of triple-negative breast cancer observed among black American women is related to their shared genetic ancestry with "Ghanaian/African" women (Stark et al., 2010). The opening argument for such a link is that because 1) triple-negative breast cancers share some clinical similarities with breast tumors found in BRCA-1 and 2) black women are more likely to develop triple-negative breast cancer, there may be a genetic predisposition for this subtype that is more common among women of African ancestry. The authors present findings that, among white American, black American, and Ghanaian women diagnosed with advanced stage, poorly differentiated grade breast cancer, the percentage of triple-negative tumors were 15.4%, 41.9%, and 83.3%, respectively.

The authors admit that their results are limited by the fact that all of the Ghanaian breast cancer cases were diagnosed while palpated upon clinical examination and acknowledge that the average age at diagnosis was 12 to 14 years younger than American black and white women, respectively. This data combined with the fact that the average life expectancy of Ghanaian women is about 20 years less than that of American women and the afore mentioned younger age distribution of triple-negative breast cancer in the United States presents the possibility that the Ghanaian cases described in this study are either 1) not representative of the full range of breast cancer cases in Ghana, many of which may be slower growing, later presenting ER-positive tumors, or 2) Ghanaian women may be less likely to be diagnosed with later-onset ER-positive

tumors by virtue of the population's age structure rather than any genetic susceptibility to ER-negative disease.

While the work of Stark, et al, is certainly provocative, it suffers from several additional limitations that are pervasive in the breast cancer subtype disparities literature. First and foremost, the authors make a very broad and dubious assumption about the relationships among race, ancestry, and genetics. For their hypothesis to be true, the phenotype of skin color – and the racial categorization that comes along with it – must be an accurate, objective marker of a shared genetic ancestry. However, it is clear that race is neither objective nor biological data to begin with. Evidence for this claim can be found in historical and cross-cultural perspectives on race (Smedley & Smedley, 2005), as well as thoughtful interpretations of the relationship – or lack thereof – between genetic ancestry data and race (Cooper et al., 2003). Moreover, work by Parra, Kittles, and Shriver (2004) demonstrated that the correlation between skin color and ancestry informative genetic markers is highly variable across populations. Given this data and the history of racial/ethnic stratification in the United States, researchers should use caution when assuming that observed race/ethnicity is a strong indicator of ancestry-associated genetic risk.

While Stark and colleagues may not espouse a biological construction of racial/ethnic groups, their emphasis on searching for *heritable* risk factors that are theoretically more prevalent among black women fails to consider the potential effects of the *acquired* biological changes that may result from differential exposure to social and physical environments across racial groups. One major source of differential social and physical environmental exposures across racial groups, particularly in the United States, is poverty. White-black differences in most domains of socioeconomic position (SEP) are well documented (T. LaVeist, 2005). However,

Stark, et al (2010) dismisses any notion that race could be confounded by the effects of poverty with the following statement:

> "Data from international registries (in countries that have more homogeneous populations and therefore less opportunity for confounding between race/ethnicity and socioeconomic factors) fail to show any consistent association between poverty and frequency of ER-negative breast cancer." p. 4931

There are numerous flaws with this contention. First, the measurement of SEP in breast cancer registries is rudimentary at best (Baquet & Commiskey, 2000). Given the complex relationship between racial group and SEP that is shaped by the structural and community-level factors (D. R. Williams & Collins, 2001), careful attention must be paid to how these individual-level sociodemographic constructs are defined and measured in studies of breast cancer outcomes. Most studies of breast cancer incidence and mortality use data from large population-based samples, such as the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) registry. These local, state, and national tumor registries contain useful information on breast cancer subtype, tumor stage, and pathology, but they typically do not include any direct measures of individual-level SEP (Koh, Judge, Ferrer, & Gershman, 2005). To compensate for this lack of data, investigators frequently use small area measures (e.g., census tract-level median income) as proxies for the unavailable individual sociodemographic data (for one such example, see (Simon et al., 2006). However, this type of proxy approach to measuring SEP is not a methodological sound approach. Geronimus and Bound (1998, p.485) caution that, "… aggregate measures tap a more global construct than do microlevel measures and should not be interpreted as equivalent to microlevel constructs." Despite the widespread use of aggregate SEP measures in the breast cancer disparities literature, very few investigators have interpreted their findings in terms of a "more global construct."

Even if the current measures of SEP were robust, the authors specifically cite studies from foreign countries with more racially homogenous populations. What the authors fail to mention is that each of the countries cited are European nations with strong social welfare programs. As a result, having a lower SEP may not have the same degree of health and welfare implications as it does in the United States. Moreover, the authors imply that the racial homogeneity of these nations effectively controls for the non-genetic sources of variation in risk for aggressive breast cancer subtypes. Many studies have shown that the physical and mental health benefits of increasing SEP are not as robust among blacks as they are among whites in the United States (D. R. Williams, Mohammed, Leavell, & Collins, 2010). These findings strongly suggest that, at least in the United States, there are interactive effects between race and SEP. Simply looking at the association between breast cancer subtypes and SEP of the majority or dominant race in a nation fails to capture the full effect of that interaction. Finally, the authors fail to acknowledge that there are in fact several domestic studies of SEP and risk of aggressive breast cancer subtypes that have found significantly higher rates of aggressive disease among poor American women (Bauer et al., 2007; Gordon, 1995; A. Taylor & Cheng, 2003; Vona-Davis et al., 2008).

The rapidly expanding body of literature on aggressive breast cancer subtypes, their population distribution, and their associated risk factors has established that, among women diagnosed with breast cancer, black women are more likely than whites to have this more severe form of disease. What remains subject to much debate is *why* this is the case. Investigations into the role of African ancestry in breast cancer subtype are being pursued by Stark and colleagues as well as by prominent researchers from other institutions (Garner et al., 2008; Huo et al., 2009). By taking this genetic ancestry approach, these researchers are neglecting the fact that

race is a social construction. Skin color is a phenotype that may give some indication as to where one's ancestors lived prior to coming to the United States. However, skin color most certainly also has significant implications for the ways in which individuals are perceived and interact within other individuals and institutions during the course of their day-to-day lives. With recent advances in stress biology and a better understanding of its roles in health and disease, it is important that future research regarding breast cancer subtype consider the potential social origins of black-white disparities as well.

The following section will review the existing literature on the relationship between stress and breast cancer, with a focus on breast cancer incidence and development of metastatic disease. I will then introduce the theoretical basis for a new conceptual model that captures potential role of stress in the development and/or progression of the basal-like breast cancer subtype. Next, I will introduce recent evidence regarding the potential biological pathways from perceived stress to basal-like breast cancer relevant biological systems. The concluding section will focus on sources of stress that, on a population level, differ between black and white women. I will focus on neighborhood-level factors in particular, and offer suggestions for future areas of research and their broader health disparities and social policy implications.

Previous Investigations of the Relationship between Stress & Breast Cancer Risk

The theoretical and empirical relationship between stress and various health outcomes has been well documented, and the investigation of stress as a risk factor for breast cancer is also not a new proposition (Hill, Ross, & Angel, 2005; Pearlin, Schieman, Fazio, & Meersman, 2005; Wheaton, 1985). However, previous studies investigating the potential link between various types of psychosocial stressors and breast cancer risk have been underwhelming both in terms of

their methodology and the strength of their findings. From the 1960's onward, numerous studies tested this proposed relationship and reported conflicting results. Three meta-analyses published in 1999 and 2000 attempted to summarize and interpret the conflicting literature (Butow et al., 2000; McKenna, Zevon, Corn, & Rounds, 1999; Petticrew, Fraser, & Regan, 1999). Petticrew, et al, conducted the most rigorous analysis, which included a well-described method for evaluating the quality of the studies as well as their collective results.

Petticrew and colleagues identified 29 studies conducted between 1966 and 1997 that met their inclusion criteria for analysis. Of the 29 studies, only one was a prospective study, 14 were limited prospective studies in that the participants were surveyed after a breast lesion was discovered but prior to receiving a biopsy and diagnosis, and the remaining 14 studies were case-control trials. Case-control studies have methodological limitations in and of themselves, but they can be particularly problematic in stress research due to the fact that a case is, by definition, already affected by the outcome of interest, which may create a greater opportunity for recall bias when reporting previous stressful events. The limited prospective design may not be much better, as the participants may already know more about their health status than that investigator is aware of at the time of the survey.

Twelve of the 29 studies, including the prospective study, operationalized stress as bereavement, most commonly related to the loss of a husband. Only three of the 12 studies reported a statistically significant result that supported the hypothesis that stress in the form of bereavement was associated with an increased risk of developing breast cancer. All 28 of the limited-prospective and case-control studies evaluated the relationship between other types of stressors, including divorce (Kvikstad, Vatten, Tretli, & Kvinnsland, 1994), disturbing war experiences (Scherg, 1987), and threatening events (C. C. Chen et al., 1995). Only twelve of the

28 studies reported a statistically significant association between their specified non-bereavement stress and breast cancer risk.

More recently, Chida, et al (2008) completed a meta-analysis of 83 prospective breast cancer studies that examined associations between stress-related psychosocial factors and cancer incidence, cancer-specific survival, and cancer mortality within community-based populations. While no association was seen between the psychosocial factors (e.g., stressors, stress-prone personality or poor coping style, poor social support, emotional distress or poor quality of life) and community-based breast cancer incidence or mortality, there was a significant negative relationship with breast cancer-specific survival (combined hazard ration 1.13, 95% CI = 1.05-1.21). (Chida, Hamer, Wardle, & Steptoe, 2008)

Some of the variation in both the individual studies' and the meta analyses' results may be attributed to limitations of common stress measurement approaches. Many of the studies used checklists such as the Social Readjustment Rating Scale created by Holmes and Rahe (1967). The use of such checklists presents several measurement issues, including the lack of event severity ratings and other contextual information about the events and the respondent. These are critical pieces of information, as being exposed to a stressor may not elicit distress, nor the same degree of distress, in every individual. Individual-level response to certain types of stressors may be dependent upon multiple exogenous factors such as baseline emotional resiliency, socioeconomic position, or the type and amount of available social support (Brown, Meadows, & Elder, 2007). The basic stress checklist approach also does not account for the fact that multiple events to be interrelated (ie., going through a divorce and experiencing a major change in financial state) and perhaps multiplicative in their effects, rather than simply additive. Similarly, some of the items on the checklist could actually occur as a result of experiencing the health

outcome under study, making interpretation of positive associations difficult to interpret. As discussed earlier, the latter issue is particularly problematic in case-control study designs.

In addition to concerns regarding the manner in which the many different types of stress were assessed, each of the reviewed studies varied widely in terms of the timeframe during which stress was measured. Some of the studies only asked participants to report stressful events that occurred within the past year, whereas other studies asked about stress over the course of the participants' lifetime. As with other late-onset, complex diseases, it is unclear how long an individual would need to be exposed to any one or more risk factors prior to developing breast cancer, thereby making it difficult to determine what the appropriate reporting timeframe should be.

Another methodological problem observed in several of the studies is the lack of adjustment for known breast cancer risk factors. For example, Cheang and Cooper's (1985) limited-prospective study found that the women who were diagnosed with breast cancer reported significantly more stressful life events and life events than the women who were diagnosed benign breast disease or who were healthy controls. However, they did not adjust for any confounders or baseline demographic variation. As a result, the cases in this study were, on average, 2.5 years older than the women in the benign breast disease group and 7.5 years older than the healthy controls. Not only do general risks for developing breast cancer increase with age, but with increasing years of life, one is also more likely to experience additional life events and stressful life event. Due to the high potential for confounding, these results should be taken with great caution.

While more recent studies have taken into account other breast cancer risk factors, virtually all of the existing stress-related research studies have treated breast cancer risk as a

single, uniform entity. With the relatively recent establishment of breast cancer subtypes, it has become quite clear that breast cancer is a heterogeneous set of conditions with distinct risk factors, etiologies, molecular signatures, natural histories (Sorlie, 2004). This heterogeneity has not been accounted for in the stress and breast cancer risk literature, as none of the studies in the four meta analyses described above stratified their cases by breast cancer subtype. This lack of subtype specificity may be a major contributor to the largely equivocal results, as the effects of stress on breast cancer subtypes may very well be different given the known effects of stress on the endocrine system. For example, chronic psychosocial stress can lead to disruption of the hypothalamic-pituitary-gonadal (HPG) axis, which in turn lowers the level of endogenous estrogen production (Chrousos, Torpy, & Gold, 1998). As a result, risk for ER-positive tumors could actually be reduced among individuals exposed to chronic stress, while ER-negative tumor risk may be unaffected or even increased via other stress-related neuroendocrine or telomere length pathways.

One recent randomized trial of an intensive group therapy intervention among women diagnosed with metastatic breast cancer did stratify the results by ER status, and provides the first empirical justification for stratifying by breast cancer subtype. Spiegel and colleagues (2007) found that the ER-negative women randomized to the experimental arm survived a median of 29 months compared to only 3 months in the control group, who received only educational materials. There was no significant difference in survival between ER-positive women randomized to the intervention or the control arm. While the intervention did not measure stress levels directly, the findings imply that reducing stress via intensive therapy has greater survival benefits for women with a more aggressive breast cancer subtype. This finding supports the hypothesis put forth by Chida, et al (2008) in that there may be several direct

physiological pathways that may link psychosocial stress to cancer survival, including: impaired DNA repair mechanisms, promotion of tumor migration and infiltration via changes in glucose uptake rates, and increased tumor vascularization. A more detailed account of these biological pathways as well as mouse model evidence to support the role of stress in activating these breast cancer-specific effects will be presented in the review of the conceptual model below.

Finally, another thought-provoking finding was cited in a recent analysis of stress and breast cancer incidence among participants in the Women's Health Initiative (Michael et al., 2009). Overall, the authors found that increased stress was associated with lower risk of post-menopausal breast cancer. However, participant reports of one "severely stressful life event" were associated with a small (but not statistically significant) increase in breast cancer risk only among black women. Melhem-Bertrandt & Conzen (2010) suggest that the theorized differential effects of stress on breast cancer subtype risk should be considered in addition to the "underlying population-based differences" in subtype risk (p. 133). Perhaps a better question may be whether the population-level differences in breast cancer subtype reflect population-level differences in exposure to – and physiological consequences of – chronic and severe stress.

An Alternative Hypothesis & Conceptual Model

Based on the literature reviewed thus far, an intriguing portrait of racial disparities in breast cancer subtype emerges. Relative to whites, black women are approximately 2 to 3 times more likely to develop a more aggressive subtype of breast cancer, no matter how that subtype is defined. This subtype, which will be referred to as basal-like breast cancer or BLBC for the duration of this paper, is clinically, epidemiologically, and molecularly distinct from the most common form of breast cancer, luminal A. These distinctions have not been accounted for in the

vast majority of prior research regarding the relationship between stress and breast cancer incidence and mortality. Similarly, racial differences in the exposure to stressors and the availability of coping resources have not been taken into account in the field of breast cancer health disparity research. In fact, much of the research as to why black women have significantly a higher rate of BLBC has focused upon possible genetic factors related to their African ancestry. Rather than continuing this overly simplistic search for risk factors in black women's *genotype*, I am proposing an alternative model that explores the implications of the *phenotype* of being black in America, particularly in regard to exposure to chronic stressors and strains. The following description of the conceptual model (Figure 3-2) will briefly introduce structural- and community-level factors that may serve as important sources of racial variation in exposure to key stressors and coping resources. The remainder of the model and this paper will focus largely on the individual-level factors, including a general overview of the three potential biological pathways that may connect stress to the incidence and progression of basal-like breast cancer.

The weathering hypothesis (Geronimus, 1992, 2001) provides the overall framework for translating structural- and community-level variables into the individual-level factors that are proximal to breast cancer subtype. The weathering hypothesis suggests that the cumulative impact of social and economic exclusion throughout the life course places individuals – especially black women – at a significantly increased risk of poor health outcomes, particularly in early and middle adulthood (Geronimus, 2001). This framework is especially appropriate given that the outcome of interest, incidence of the basal-like breast cancer subtype, occurs more frequently in pre-menopausal black women than in any other demographic group (Carey et al.,

2006). Aspects of Jackson and Knight's (2006) model of coping behaviors will also be included, as well as more general themes from Stokols' (1992) social ecological perspective.

Structural-level Factors

Structural-level factors are the broadest level of factors included in Stokols' (1992) social ecological perspective. In order to better understand and address the root causes of health disparities, these relevant structural factors must be taken into consideration (Link & Phelan, 1995). The proposed conceptual model focuses on historical and current political and economic inequalities as antecedent variables affecting breast cancer subtype.

Political and economic inequalities have had a strong influence on the residential patterns of many minority groups within the United States. Massey & Denton (1993) present a classic narrative on the origins of racial segregation and the urban ghetto in particular. According to the authors, some southern cities during the early 1900's created or reinforced race-based residential segregation patterns by passing ordinances that legally defined areas were white and black people could live. The authors also describe more subtle but equally effective tactics such as blockbusting, which decreased neighborhood property values, increased the percentage of black residents, and yielded real estate agents considerable profits by encouraging white homeowners to sell low and then re-selling the properties at above-market rates to incoming blacks. The use of discriminatory mortgage lending practices referred to as redlining has further limited the areas in which blacks have been able to live, most notably preventing many members of this population from living in well-resourced neighborhoods (Massey & Denton, 1993). While these and other sources of political inequality have contributed to the limited number of higher quality residential opportunities available to blacks, economic inequality also plays a significant role.

Black workers with similar educational backgrounds and employment experience continue to earn less income than their white peers (Wilson, 1996). This persistent race-based income inequality further limits blacks' housing options in many areas, and together with political inequality, contributes directly to the ongoing race-based residential segregation patterns in many America metropolitan areas.

Race-based residential segregation is another proposed structural antecedent of inequality in the distribution of breast cancer subtype. Residential segregation has been defined as "the extent to which individuals of different groups live in different neighborhoods within the region" (Reardon, 2006, p. 171). Massey & Denton (1993), among others, have argued that it is not the fact that different groups live in different areas that leads to worse social conditions for many minority groups, and for blacks in particular. Rather, it is the continuing unequal distribution of material, psychosocial, and other resources across neighborhoods that contribute to racial disparities in many aspects of American life, including health. Race-based residential segregation has been implicated in directly contributing to the observed racial disparities in health as well as perpetuating the complex relationship between race and low socioeconomic position (SEP), which is also widely believed to contribute to poor health outcomes (D. R. Williams & Collins, 2001). The implication of this dual relationship is that race-based residential segregation may be a significant confounder or fundamental cause of racial inequalities in health (Massey & Denton, 1993; Schulz, Williams, Israel, & Lempert, 2002). As a result, evaluations of health disparities such as those seen in breast cancer subtype need to carefully consider what roles residential segregation and SEP may have in the creation or propagation of observed racial difference in health outcomes. Previous studies of disparities in breast cancer subtype have not taken structural factors such as residential segregation into full consideration. The proposed conceptual model

attempts to elucidate how these larger structural factors may serve as antecedents to observed racial inequalities in breast cancer subtype.

Relationship between Structural Factors and Breast Cancer

Similarly, the impact of neighborhood socioeconomic status and/or race-based residential segregation on breast cancer outcomes has received relatively little attention. Three recent studies have made important contributions to this very small body of literature. Barrett, et al, (2008) examined potential associations between presence of a distant metastasis at diagnosis and neighborhood characteristics of concentrated disadvantage, concentrated affluence, and upward socioeconomic change among women who were diagnosed with breast cancer in Cook County, Illinois between 1994 and 2000 (Barrett et al., 2008). Each woman's home address at the time of her diagnosis was geocoded to the census tract level, which once again served as the community-level unit of analysis. Census-based measures of concentrated disadvantage and concentrated affluence were created based upon the work of Sampson, Morenoff, and Earls (1999). A new composite measure comparing 1990 and 2000 U.S. Census data on the value of owner-occupied housing, percent of civilian labor force employed in professional or managerial roles, and the percent of college-educated adults within a census tract was use create the upward socioeconomic change score. A multilevel logistic regression analysis identified concentrated affluence to be inversely related to distant metastasis at diagnosis (OR = 0.86, 95% CI = 0.79, 0.93) while both concentrated disadvantage (OR = 1.23, 95% CI = 1.12, 1.36) and upward socioeconomic change (OR = 1.09, 95% CI = 1.01, 1.18) were both directly associated with increased risk of distant metastasis at diagnosis.

Warner & Gomez (2010) looked at potential relationships between black-white residential segregation and stage at breast cancer diagnosis, breast cancer-specific and all-cause mortality in California between 1996 and 2004. (Warner & Gomez, 2010) Several notable findings were reported. First, when compared to residents of low segregated regions (e.g., the Bay Area), black women living in neighborhoods with low percentages of blacks within a highly segregated regions (e.g., Los Angeles County) had higher odds of being diagnosed with distant-stage cancer (OR = 2.11; 95% CI = 1.05-4.27). Moreover, black women who were diagnosed with breast cancer had lower levels of breast cancer specific (HR = 0.86; 95% CI = 0.76-0.97) and all-cause mortality (HR = 0.90; 95% CI = 0.82-0.99) when they lived in neighborhoods with at least 20% black residents. The authors note that "this protective neighborhood effect persisted across nearly all levels and most dimensions [evenness, concentration, exposure, centralization, and clustering] of segregation, and seemed to be more pronounced in more segregated regions." (p.401) While the authors had ER and PR status on approximately 70% of the included breast cancer cases, this information was only used to describe the overall study population and make statistical adjustments in the survival models. It would be interesting to see if the distribution of ER-negative/PR-negative breast cancers – when treated as an outcome in and of themselves – follow the same general pattern of distant-stage diagnosis and survival among black women living in various levels of neighborhood and regional segregation.

Research by Taylor, et al (2007) provides further evidence that discrimination may play a role in breast cancer among black women. The authors looked at measures of perceived discrimination among 49,161 women in the Black Women's Health Study and then examined the breast cancer incidence during a 6-year follow-up period. They found that women under the age of 50 who reported major discrimination in the workplace had an adjusted breast cancer

incidence rate ratio of 1.32 relative to women in the same age group who did not report workplace discrimination (95% confidence interval = 1.03-1.70). In addition, women under age 50 who reported that they had experienced all three domains of major discrimination – at the workplace, in housing, and by police – had a 1.48 adjusted incidence rate ratio relative to other women who had not experienced discrimination in any of those areas. Similar relationships were not seen among women ages 50 or older, which may indicate that younger women are particularly susceptible to the deleterious health effects of major discrimination as suggested in the weathering hypothesis. While the authors did adjust the incidence rate ratios for a large number of known and suspected breast cancer risk factors – age, BMI, education, age at menarche, menopausal status, use of hormone replacement therapy, age at first birth, oral contraceptive use, physical activity, alcohol use, and family history of breast cancer – they did not report on the hormone receptor status of the 593 self-reported breast cancer cases.

Taken together, these three sets of findings suggest social mechanisms such as gentrification, residential segregation, and racial discrimination are related to stage at breast cancer diagnosis, cancer-specific mortality and all-cause mortality, and breast cancer incidence, respectively. These larger structural issues may directly generate psychosocial stressors as illustrated in the conceptual model, but they may also work through important community level factors to initiate distress and activate harmful physiological mechanisms.

Community-level Factors

In keeping with the social ecological perspective, the community-level factors described in the conceptual model serve as an important intermediary between structural factors like race-based residential segregation and gentrification and the individual-level psychosocial,

behavioral, and biological factors that may directly increase a woman's risk of developing basal-like breast cancer. For the purposes of this model, each of the community factors will be conceptualized as characteristics of a neighborhood. Neighborhoods, in turn, will be conceptualized as the people and institutions that 1) reside within a defined geographical area and 2) are similarly influenced by the structural and cultural forces of the larger ecological systems (e.g., cities, states, nations) in which they are nested (Sampson, Morenoff, & Gannon-Rowley, 2002). It is important to note that defining meaningful neighborhood boundaries for public health research is one of several significant methodological challenges that remain in this field of research (Macintyre, Ellaway, & Cummins, 2002). Frequently, neighborhoods are operationalized in terms of administrative boundaries, such as school districts and census tracts, which may not accurately reflect the full scope of the neighborhood definition stated above (Sampson et al., 2002). Where appropriate, additional limitations of current neighborhood-level research methods will be cited, but a full review of the issues in this field are beyond the scope of this paper.

Just as there are many ways in which neighborhoods can be defined, there are also many potential mechanisms that could produce the reported associations between neighborhoods and health. I take the perspective that the association between neighborhoods and health reflects a dynamic interaction between both compositional (e.g., the characteristics of people who live in a neighborhood) and contextual (e.g., the characteristics and resources of the neighborhood itself) effects (Bernard et al., 2007; Cummins, Curtis, Diez-Roux, & Macintyre, 2007; Macintyre et al., 2002). From this vantage point, race-based residential segregation within a region and the underlying sociopolitical structures that support it have important implications in terms of the

social and physical environment in which they live. In turn, the social and physical environment may each affect the stressors and psychosocial buffers present within the neighborhood.

As described in the previous section, race-based residential segregation negatively impacts minority residents in several domains. However, there may also be some advantages for minorities who live in neighborhoods with higher percentages of same-minority residents. While these neighborhoods with higher ethnic group density may be economically and politically marginalized from a structural perspective, they may offer other community-level benefits (Pickett & Wilkinson, 2008). These benefits may derive from shared alternative cultural frameworks and experiences among neighborhood residents, offering a refuge from the dominant and often disapproving cultural forces (James, 1993) and racist attitudes (Becares, Nazroo, & Stafford, 2009). By sharing in and supporting alternative cultural frameworks, neighborhoods with high minority ethnic density may afford some health benefits (Bécares et al., 2012), even in the face of the higher poverty rates frequently associated with these neighborhoods (Bécares, Cormack, & Harris, 2013)

Large public housing projects may serve as an example of one type of neighborhood that historically had high percentages of minority residents and a high degree of economic, political, and social marginalization relative to the surrounding community. Two quotes from a New York Times article on life in the Cypress Hills Houses in Brooklyn illustrate the social complexity of life within public housing projects:

> If her mirror could grant her a wish, Ms. Lucas said, she would move them [her three children] far away, to a house with a porch. "A place," she said, "where you could have peace of mind."
>
> When asked about the good side of Cypress, he replied: "The friendships. When life is hard, people look out for each other here. When you don't got no money, they give you food, they give you shelter." He then motioned to his friend's couch, the one he has slept on many a night. (Brady, 2008)

These two residents succinctly capture popular notions of the dichotomous – yet by no means mutually exclusive – effects of living in urban public housing projects. On one hand, life in such disadvantaged areas may consist of daily struggles to keep children safe and physically as well as emotionally healthy, among other daily hassles and chronic strains. However, residents may be able to make it through tough times by drawing from the tangible and emotional support offered by neighbors and local kin networks who take on family-like roles. Recent work by Keene and Ruel (2013) which examines the experiences of older public housing residents who were recently relocated provides further qualitative evidence of the importance of these relationships to long-time residents.

Neighborhood tenure may be an important individual-level factor that also contributes to social integration, conceptualized here as access to social ties and social support (D. Keene, Bader, & Ailshire, 2013). Long-term residents of neighborhoods experiencing upward socioeconomic change may view the neighborhood through a different set of narrative frames (Small, 2004; Tach, 2009). In a recent study of a redeveloped, mixed income housing development in Boston, Tach (2009) found that longer-term residents had qualitatively different appraisals of their neighborhood than newcomers, and that these appraisals had a significant impact on their level of neighborhood engagement, and ostensibly their experience of social integration. In this particular neighborhood, residents with longer residential tenure viewed their current neighborhood conditions in a much more favorable light, whereas newcomers were less positive about their surroundings and thus less likely to engage with other members of their community.

It is important to note that, post-redevelopment, the neighborhood 1) remained almost entirely minority (1% white in 1990 vs. 3% white in 2000), 2) had a higher but still low median

household income ($11,044 in 1990 vs. $27,646 in 2000), and 3) had a significantly higher rental occupancy rate (78% in 1990 vs. 95% in 2000). These demographic changes do not reflect the stereotypical gentrified neighborhood, where the percentage of white residents, median income, and home ownership increase more dramatically. Subsequently, the impact of residential tenure on social integration may be different in these neighborhoods.

Relationship between Community Factors and Breast Cancer

Given the relationships among social integration, psychosocial stress response (Bolger, Zuckerman, & Kessler, 2000), and several health behaviors and health outcomes (Tay, Tan, Diener, & Gonzalez, 2013), it is reasonable to hypothesize that social integration could have an indirect effect on breast cancer subtype via chronic exposure to psychosocial stressors and the subsequent physiological and behavioral stress responses. As with most other community-level constructs, the relationship between social integration and breast cancer subtype has not yet been tested. However, the study by Barrett, et al (2008) described in the Structural Factors section provides some of the first empirically-based theoretical evidence for a relationship between neighborhood social networks and breast cancer disparities. The authors hypothesize that changes in neighborhood levels of social integration related to upward neighborhood socioeconomic change may contribute to the observed association between upward socioeconomic change and distant metastasis at diagnosis. This hypothesis implies that long-time black residents who remain in rapidly gentrified neighborhoods may suffer from worse breast cancer outcomes, due at least in part to the decreased social integration of the neighborhood. While the authors did report that black women also had a greater chance of having a distant metastasis at diagnosis (OR = 1.24, 95% CI = 1.03, 1.48), they did not discuss

the results of their neighborhood-level findings in terms of potential confounding with race due to race-based residential segregation, nor did they discuss whether whites and blacks might be equally affected by the neighborhood conditions measured. Further investigation of potential interactions among race, upward neighborhood socioeconomic change, social and physical order, and social integration within the context of breast cancer subtype is needed in order to test the relationships suggested in the conceptual model.

Individual-level factors

Demographic Factors

The pervasive influence of individual-level race, SEP, age, and residential tenure has already been noted in the previous sections of this paper and on all levels of the conceptual model (Figure 2-2). With regard to the conceptual model, two different types of relationships are indicated. The dashed arrows represent the direct association between race and breast cancer hormone receptor status that is typically reported in the literature. However, there are several limitations in the way that both race and SEP have been conceptualized and assessed. Much of the existing research has been conducted on an atheoretical basis, guided primarily by prevailing clinical, biological, and common wisdom. Moreover, most of the previously described research has treated race either a categorical variable and/or as a variable that requires statistical control. Statistically significant differences across racial groups are therefore typically interpreted as an indication that race is a significant predictor of the dependent variable (LaVeist, 1994). This is problematic in that the treatment of race as a simple categorical variable does not acknowledge the fact that race is, in fact, a complex construct that has significant implications for an individual's ability to access critical social, political, and economic resources due to prevailing

racialized ideologies in the United States (Geronimus & Thompson, 2004). The result of such racialized ideologies is that race and SEP remain tightly correlated within the United States, and structural factors such as race-based residential segregation help reinforce this troubling relationship (Schulz et al., 2002). The implications of these methodological weaknesses include the potential for research on the observed racial differences in breast tumor biology to be conducted and interpreted in a way that reinforces previously discredited notions of innate biological or genetic differences between racial groups, as demonstrated in the previously reviewed paper by Stark, et al (2010).

In response to these limitations, the dotted arrows found on the conceptual model depict alternative and more complex avenues by which sociodemographic characteristics may interact with key variables on multiple levels to generate the observed social patterning of breast cancer hormone receptor status. My focus is clearly on this set of demographic relationships, in an effort to provide greater context for those previously reported in the breast cancer literature. I will continue to integrate discussion of demographic factors through the remainder of this paper, but will not address them individually.

Psychosocial Stressors

Several authors have suggested that exposure to stressors associated with disadvantaged status increases the black population's vulnerability to mental and physical health problems (Geronimus & Thompson, 2004; Massey, 2004). Psychosocial stressors play a pivotal role in the conceptual model in that they may trigger biophysical responses leading to increased risk of basal-like breast cancer. In addition, exposure to psychosocial stressors may lead individuals to engage in health behaviors that, while alleviating or numbing some of the distress, also lead to

biophysical pathways related to development of basal-like breast cancer (Jackson & Knight, 2006).

Perceived social isolation is the psychosocial stressor with the most compelling theoretical and empirical evidence linking it to the intermediate biological factors and ultimate health outcome of interest. Social isolation has been repeatedly attributed to a wide variety of poor health outcomes, including increased risk of morbidity and mortality, although the precise mechanisms as to how social isolation impacts health remain unclear (Cacioppo & Hawkley, 2003). Of particular relevance to the proposed conceptual model, a study by McClintock, et al (2005) described a mouse model that linked social isolation to the development of breast cancer outcomes that are similar to basal-like breast cancer in humans. In this study, genetically identical female Norway rats – which naturally engage in many social behaviors such as sleeping in groups and co-rearing pups – were randomized to either normal group housing or socially isolated cages. All food and exercise conditions were held constant across both groups. However, the socially-isolated rats developed mammary carcinomas at a significantly higher rate than their group-housed counterparts. Interestingly, the tumors also developed at a much earlier age than what is typically seen in this particular breed.

More recent research in this area has been mixed. Williams, et al also found that females of the similarly sociable Sprague-Dawley mouse species suffered from increased rates of mammary tumor growth and tumor size when subjected to chronic stress in the form of social isolation (J. B. Williams et al., 2009). However, others have reported that a different bread of socially-isolated mice actually had lower numbers of mammary tumors than their group-housed counterparts (Hasen, O'Leary, Auger, & Schuler, 2010). Melhem-Bertrandt & Conzen theorize that because Hasen, et al used a mouse model that was a p53 knockout (e.g., all cells in the

mouse had reduced levels of p53 tumor suppressor gene function), their findings are difficult to interpret. If Melhem-Bertrandt & Conzen's argument is accepted, the sum of the limited mouse model findings suggest that the psychosocial stressor social isolation, which is also a stressor suspected to contribute to weathering in humans, is associated with increased rates of developing early-onset mammary tumors in rats. Determining whether a similar phenomenon occurs in human populations, particularly blacks or other disadvantaged groups, is an important public health questions that needs to be addressed.

Perceived discrimination is another social stressor that has been implicated in poor physical and mental health among minorities (Williams, Neighbors, & Jackson, 2003). As discussed in the Structural Factors section, perceived discrimination was associated with increased risk for breast cancer among black women under the age of 50 (T. R. Taylor et al., 2007). Breast cancer subtype was not included in their analysis, but because ER-negative breast cancers are more common among premenopausal black women than any other demographic group (Carey et al., 2006), it is reasonable to suggest that differences in the etiology and risk factors of ER-negative tumors are at least one reason why a similar increased risk of breast cancer among women 50 years old or older who perceived major discrimination was not observed. Further research is needed to test this hypothesis.

Finally, perceived neighborhood safety is another psychosocial stressor that has recently been implicated as a breast cancer risk factor. As conceptualized here, perceived neighborhood safety incorporates both perceptions of crime and unsafe housing within the neighborhood. Gelhert and colleagues have reported in conference settings and in personal communications that the number of neighborhood sexual assaults, personal experience of sexual assault, and poor neighborhood housing conditions were each associated with more aggressive breast cancer

subtypes, as defined by triple-negative hormone receptor status and glucocorticoid receptor-positive tumors (Gehlert et al., 2010). Full results of this study of 139 black women who lived in Chicago's South Side and were diagnosed with breast cancer are not yet available in manuscript form, but this novel finding linking specific types of psychosocial stressors to both biological measures of deregulated stress response (i.e., flat diurnal cortisol curves) and more aggressive breast cancer subtypes is particularly intriguing.

Psychological Distress

According to several stress process models, distress is an important mediator of both 1) the direct effects of community-level factors such as neighborhood disorder on health outcomes and 2) the indirect health effects of such community-level factors, as mediated by exposure to individual-level psychosocial stressors such as perceived social isolation (Hill et al., 2005; Pearlin, 1989; S. E. Taylor, Repetti, & Seeman, 1997). I will focus on the latter construction, which places distress as a key proximal factor to the physiological and behavioral responses that are thought to directly influence cellular changes responsible for determining breast cancer subtype. This distinction is important because, as discussed earlier, simply being exposed to various community-level factors or psychosocial stressors may not necessarily generate distress that results in the key physiological or behavioral responses described below. While a full review of individual coping resources and other potential moderators of the relationship between psychosocial stressors and resultant distress is beyond the scope of this paper, their role must still be acknowledged and considered when testing the individual-level relationships specified in the conceptual model.

Physiological Responses

When distress does occur, the hypothalamic–pituitary–adrenal (HPA) is activated. This well-designed neuroendocrine feedback system serves to prepare the body for immediate and effective responses to stressful situations, such as signaling for increased cortisol secretion in order to utilized stored energy and respond to physical threats (Traustadóttir, Bosch, & Matt, 2005). However, the inability to efficiently turn off the HPA axis following chronic exposure to stress – commonly referred to as allostatic load – has been associated with disregulation of glucocorticosteriods, neurotransmitters, and inflammatory cytokines (McEwen, 1998). Allostatic load is believed to have detrimental effects to existing cellular systems, including disregulation and acceleration of normal cellular aging process (McEwen & Wingfield, 2003). The cancer-related impact of these processes will be described in more detail in the Molecular Changes sections below.

Behavioral Response

Dietary behaviors represent a potentially important mediator on the pathway from community-level factors to breast cancer-related molecular changes. For example, neighborhoods with a high percentage of minority residents are less likely to have chain supermarkets located nearby (Morland, Wing, Diez Roux, & Poole, 2002). As a result, residents of these neighborhoods tend have limited access to good quality fresh fruits and vegetables (Moore & Diez Roux, 2006; Zenk et al., 2006). Minority neighborhoods also tend to have a greater number of small convenience stores, liquor stores, and fast food restaurants that sell relatively inexpensive, highly palatable foods of generally poor nutritional quality (Baker, Schootman, Barnidge, & Kelly, 2006). The combination of restricted availability of healthy

foods with the pervasive presence of less healthful comfort and fast foods has a significant impact on the dietary behaviors of local residents (Baker et al., 2006). In addition to the direct relationship between community-level material resources and dietary behaviors, eating comfort foods, which are typically high in fat and/or sugar, may also be an individual-level response to distress that actually helps dampen the stress response system that is activated via the HPA axis (Jackson & Knight, 2006; Jackson, Knight, & Rafferty, 2010).

One potential implication of these dietary behaviors is that black women who live in disadvantaged neighborhoods and are exposed to significant amounts of stress may not be getting enough folate in their diet. Folate, which is found in many green leafy vegetables and fruits, has an important role in the maintenance of proper DNA methylation patterns described in the following section (Cacioppo & Hawkley, 2003). With regards to breast cancer specifically, there is evidence that women who consume less folate in their diets are more likely to be diagnosed with estrogen receptor negative tumors (Zhang et al., 2005). Recent findings from the Black Women's Health Study also found that total vegetable intake was inversely associated with risk of ER-negative / PR-negative breast cancer, even after adjusting for 15 other known or suspected breast cancer risk factors, such as family history of breast cancer and use of hormone replacement therapy (Boggs et al., 2010). The authors also reported a trend towards a similar inverse relationship between cruciferous vegetables (e.g., broccoli, collard greens, cabbage) and ER-negative / PR-negative breast cancer, but it did not reach statistical significance. Perhaps even more importantly, the fact that no significant relationship between ER-positive breast cancers and vegetable intake was identified again suggests variation in the etiology and risk factors for breast cancer subtypes. Whether there is a similar relationship between basal-like breast cancers and vegetable and/or folate consumption remains to be determined.

Molecular Changes: The role of epigenetics

Stress-related responses such as allostatic load and food preference provide an empirical basis for connecting distress to racial disparities in the incidence of basal-like breast cancer via two molecular pathways: epigenetics and human stress genomics. Epigenetic regulation of gene expression takes place above the genome level – that is, epigenetic changes are not alterations in the DNA code, but rather changes in the molecular environment that either increase or decrease the production of proteins from specific genes (Petronis, 2010). The three major types of epigenetic alterations are changes in DNA methylation patterns, histone tail modifications, and changes in chromatin structure. I will focus on DNA methylation, as it is the best-understood epigenetic mechanism and has been the most researched epigenetic mechanism with regards to breast cancer.

While a detailed discussion of the DNA methylation process is beyond the scope of this paper, the basic principles can be described as follows: DNA methylation occurs when a group of molecules attach methyl groups to the specific areas of a gene's promoter region, thereby preventing the "reading" of the gene and the formation of the gene product. DNA methylation (and de-methylation) is a generally stable set of process that can be replicated from parent cell to daughter cell. However, an individual's DNA methylation patterns may also change over time.

Disruptions in the DNA methylation process are thought to be especially important in the development and proliferation of cancerous cells (Esteller, 2008; Gronbaek, Hother, & Jones, 2007). In order for cancerous cells to continue to grow and divide at a rapid pace, tumor suppressor genes need to be silenced via a deleterious gene mutation or gene-specific hypermethylation. Two recent studies have indicated that as cells age, chromosome instability

increases and hypermethylation of tumor suppressor genes is more prevalent (Ahuja, Li, Mohan, Baylin, & Issa, 1998; Issa, 2000). Additionally, tumor enhancing genes (also known as oncogenes) need to be turned on via general hypomethylation. The exact mechanisms that cause gene-specific hypermethylation and general hypomethylation in cancerous cells are not yet well characterized. However, there is increasing evidence that cellular aging, as well as elements of the physical and social environment, may play a role in this process (Szyf et al., 2008).

Some of the more interesting evidence for the relationship between cellular aging and hypermethylation comes from a study of monozygotic twins (Fraga et al., 2005). Monozygotic twins result from the early separation of a single egg into two genetically identical embryos. In this study, monozygotic twins who were less than 28 years old, and particularly those who were still in early childhood, exhibited very similar DNA methylation patterns. However, sets of twins who were older than 28, especially those who were middle aged and older, were found to have significantly different DNA methylation patterns across their genome. Whether the evolution of an individual's DNA methylation pattern is the result of more typical cellular aging processes or repeated environmental and/or psychosocial insults that are part of the weathering process has yet to be determined.

As noted by Joanovic, et al (2010), the primary epigenetic mechanism of interest with regards to estrogen receptor expression status has been DNA hypermethylation of the estrogen receptor alpha (ER-α) gene promoter region, *ESR1*. This focus is intuitive, as increased methylation of a promoter region results in the down regulation or silencing of gene's expression, which would thereby explain the lack of estrogen receptors in an ER-negative tumor. Indeed, in vitro laboratory work conducted in the mid-1990's supports this developmental pathway for ER-negative tumors. However, subsequent clinical studies have produced

conflicting results (Ferguson, Lapidus, Baylin, & Davidson, 1995; Weigel & deConinck, 1993). In one study, 76% of ER-negative breast cancers were found to have a methylated ER-α gene, while 22% of ER-positive tumors also demonstrated methylation of the ER-α gene (Wei et al., 2007). These results suggest that selective methylation of the ER-α gene plays an important, yet not necessary nor sufficient, role in the development of basal-like breast cancers. Most recently, Gaudet, et al (2009) found no clear association between promoter methylation levels and ER-α expression levels, but methylation of the progesterone receptor *PGR* promoter was associated with lower levels of ER-α expression.(Gaudet et al., 2009) Additional work is needed in this area to determine the true role of DNA methylation in the loss ER-α expression in ER-negative tumors.

Other types of epigenetic regulation may also be associated with the development of ER-negative and/or basal-like breast cancers. For example, ER-negative breast tumors display hypomethylation and subsequent over-expression of several breast cancer-related genes (Feng et al., 2007; Widschwendter et al., 2004). These more global patterns of hypo- and hypermethylation have recently been explored in breast cancer tumors. Christensen, et al (Christensen et al., 2010) recently tested 162 primary breast tumors found that triple-negative hormone status was significantly associated with altered DNA methylation patterns in a set of 130 cancer-related genes. When the researchers used an unsupervised clustering method to generate 8 distinct methylation-based classes of breast cancers, they also found trends towards increased methylation with increasing total dietary folate intake. However, none of the 8 methylation profiles were significantly associated with ER or triple-negative status, therefore no direct associations among hormonally-defined subtypes, methylation-defined subtypes, and folate intake can be made at this time. It is important to note though that this sample consisted of

primarily of white women (72.7% white, 8.1% black) and contained a higher percentage of ER-positive tumors (88%) than in the total Kiaser Permanente Northern California cancer registry (78%). A more diverse sample may yield different findings.

Molecular changes: The role of human stress genomics

Epigenetic mechanisms are but one way gene expression is modulated. Recently, there has been growing interest in exploring the role of neuroendocrine stress responses to changes in gene expression profiles. Cole (2010) provides an important review of pervious work in this area, which he refers to as "human stress genomics." He notes that early research on the expression of stress-related genes has been difficult to replicate for several reasons, including the high level of statistical noise that is due to both measurement error and true biological variability across time, individuals, and tissues within individuals. In addition, Cole argues that the prior conception of "stress genes" is faulty in that "it is unlikely that any gene is regulated solely and consistently by glucocorticoids or catecholamines, and thus constitutes a pure, reliable indicator of stress uncontaminated by other regulatory influences." (p.957)

In response to these limitations, Cole suggests in favor of taking an abstractionist approach to functional genomic data. This perspective focuses on the biological causes and consequences of gene expression, either in terms of the differential expression patterns of functionally-defined groups of genes (i.e., receptor activity genes), or in terms of the common regulatory pathways that lead to differential gene expression (i.e., decreased glucocorticoid receptor (GR)-mediated transcription). Cole argues that these abstractionist approaches have, and will continue to, yield more consistent results due to both the focus on more biologically stable targets of functional gene groups and regulatory pathways, as well as the statistical advantages of

looking at approximately 200 higher order gene function themes vs. approximately 22,000 individual level genes.

A recently published report provided the first evidence that individuals who have high self-reported levels of social isolation express genes that lead to over-activation of genes involved in the inflammatory response system, and under-activation of glucocorticoid response elements which are critical to the anti-inflammatory response system (Cole et al., 2007) While Cole and colleagues did not address the molecular mechanisms responsible for the up- and down-regulation of specific genes, a later paper put forth a helpful illustration (see Figure 2-3) of the potential pathways (Cole, 2009). The figure shows a dynamic flow of information from the social environment to protein formation, health, and behaviors via perceptions formed in the central nervous system, neuroendocrine responses, and transcriptional regulation of gene expression. This is a promising framework for exploring how exactly exposure to social stressors that more prevalent among black women may result in increased incidence of aggressive breast cancer subtypes within this population.

Not only is the general stress genomics framework developed by Cole and colleagues promising, but their specific findings regarding the potential social regulation of the glucocorticoid pathway may be of particular relevance to the subtype-specific risk of developing breast cancer.

Summary and Conclusions

Taken together, this suggests a potential biological mechanism that may at least partially explain why black women, who may have unique and/or additional exposure to neighborhood-level stressors, are at a greater risk for developing triple-negative breast cancers. Moreover, if this hypothesized relationship is accurate, it may add to our general understanding of the

complex ways in which neighborhoods and stress may contribute to health inequalities across racial groups.

Limitations of the Conceptual Model

The current conceptual model faces several limitations. At the individual level, personal attributes such as coping style and personality are not addressed. These factors may play a significant role in moderating an individual's perceptions of and response to stressful situations (Pruessner et al., 1997). However, most of the remaining empirical and theoretical questions reside at the community level of analysis. While each of the constructs described in the conceptual model have documented relationships with other health outcomes, the literature relating neighborhood factors to breast cancer subtype is virtually non-existent. This model is derived largely from indirect evidence of neighborhood effects on general stress and health processes, which themselves are not always well-defined.

Implications for Future Research

Numerous complex social and behavioral factors related to the stress and weathering processes may underlie the widely-reported racial inequality in breast cancer subtype. The proposed conceptual model provides one theoretically-driven structure by which these complex relationships may begin to be disentangled. Initiating interdisciplinary, theoretically-driven research projects to evaluate what mechanisms are plausible both at the social and biological level is essential in order to move this field forward and spur the develop of more effective intervention programs.

Policy makers, social advocates, and public health practitioners need to take special notice of this type of interdisciplinary health research, particularly as it relates to common biological processes that may impact other common complex diseases. For example, allostatic load-mediated cellular and DNA changes may be a common pathway for social conditions to differentially affect the health of disadvantaged minority populations. The implications of such a common pathway would go well beyond breast cancer and could contribute to broader health disparities.

Figure 2-1: Relationship between triple-negative and basal-like breast cancers

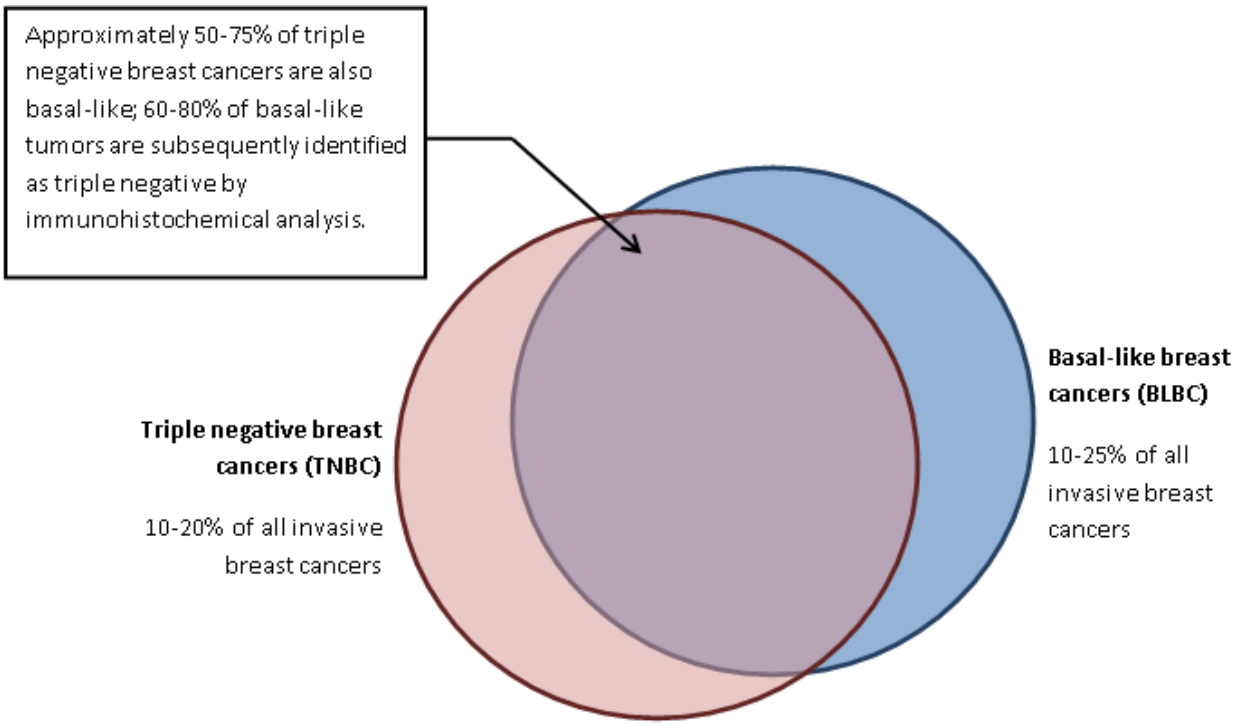


Table 2-1: Prevalence of estrogen receptor-negative, triple-negative and basal-like breast cancer subtypes among white and black women diagnosed with breast cancer

Breast cancer subtype	Geographic location & ascertainment period	Reference	Sample size:		% with specified subtype:		Black-White OR (95% CI)
			Black	White	Black	White	
Basal-like	North Carolina, 1993-1996	Carey et al. (2006)	196	300	26.5	16.0	2.1 (1.3-3.4)
	North Carolina, 1993-2001	Millikan et al. (2008)	581	843	20.1	12.2	n/a
Triple negative	Atlanta, 1990-1992 *	Trivers et al. (2009)	116	476	48.3	16.6	2.98 (2.12-4.20)
	California, 1999-2003	Bauer et al. (2007)	2,587	36,671	24.6	10.8	1.77 (1.59-1.97)
	California, 1999-2004	Parise et al. (2009)	2,936	39,501	27.0	11.5	1.88 (1.69-2.09)
	Single hospital, 1998-2006	Stead et al. (2009)	177	148	29.4	12.8	3.0 (1.6-5.4)
	California & Utah, 1997-2008	Kwan et al. (2009)	155	1,943	28.4	10.5	n/a
ER-, PR-	US hospital registries, 1990	Gapstur et al. (1996)	1,114	11,715	35.0	20.0	2.29 (1.99-2.64)
	Hawaii & LA, 1993-1996	Setiawan et al. (2009)	420	701	30.9	17.6	n/a
	SEER-11, 1992-1998	Tarone and Chu (2002)	8,870	101,140	34.4	19.4	n/a
	SEER-9, 1990-1997	Joslyn (2002)	7,332	85,377	33.7	18.9	n/a
	SEER-13, 1992-2004 **	Hausauer et al. (2007)	19,105	193,513	22.2	12.6	n/a

* Study population consisted only of women ages 20-54

** Study population consisted only of women ages 50 and older

Table 2-2: Sample of the sociodemographic risk factors for triple-negative breast cancer; statistically significant results in bold

	Trivers et al., 2009			Kwan et al., 2009			Millikan et al., 2008			Parise et al., 2009		
	Group	OR	95% CI	Group	OR	95% CI	Group	OR	95% CI	Group	OR	95% CI
Race	**Black**	**2.98**	**2.12-4.20**	**Black**	**3.14**	**2.12-4.66**	**Black**	**2.1**	**1.6-2.9**	**Black**	**1.88**	**1.69-2.09**
	White	---	reference	White	---	reference	White	---	reference	White	---	reference
Age at diagnosis, in years	**20–39**	**2.13**	**1.34-3.39**	**<50**	**2.78**	**1.99-3.90**	**< 40**	**4.5**	**2.7-7.3**	**< 50**	**1.21**	**1.14-1.29**
	40–49	1.09	0.72-1.64	50-64	1.99	0.85-1.62	**40-49**	**2.6**	**1.7-3.9**	≥ 50	---	reference
	50–54	---	reference	≥ 65	---	reference	**50-59**	**1.8**	**1.1-2.8**			
							≥ 60	---	reference			
Education	< College grad	1.35	0.97-1.89	*Not measured*			*Not measured*			*Not measured*		
	College grad +	---	reference									
SES	≤200% PI*	1.22	0.77-1.93	*Not measured*			*Not measured*			**SES 1 – low**[†]	**1.12**	**(1.01-1.24)**
	201–700% PI	---	reference							**SES 2**	**1.11**	**(1.01-1.21)**
	>700% PI	1.06	0.71-1.57							**SES 3**	**1.09**	**(1.01-1.19)**
										SES 4	**1.09**	**(1.01-1.18)**
										SES 5 - high	---	reference
Insurance status	Private	---	reference	*Not measured*			*Not measured*			*Not measured*		
	Public/ none	1.51	0.91-2.53									

Table 2-3: Sample of the reproductive risk factors for triple-negative breast cancer; statistically significant results in bold

	Trivers et al., 2009			**Kwan et al., 2009**			**Millikan et al., 2008**			**Phipps et al., 2008**		
	Subgroups	OR	95% CI	Subgroups	OR	95% CI	Subgroups	OR	95% CI	Subgroups	OR	95% CI
Age at menarche, in years	**< 12**	**1.55**	**1.08-2.23**	*Not measured*			< 13	1.3	0.9-1.7	< 13	1.1	0.7-1.7
	12+	---	reference				≥ 13	---	reference	≥ 13	---	reference
Age at first birth, in years	Nulliparous	---	reference	Nulliparous	---	reference	Nulliparous	---	reference	< 20	---	reference
	< 18	**2.83**	**1.30-6.14**	< 26	1.28	0.90-1.82	**< 26**	**1.9**	**1.2-3.0**	20-24	1.1	0.6-2.1
	18+	0.99	0.67-1.48	≥ 26	0.93	0.63-1.38	≥ 26	1.2	0.7-2.1	25-29	1.3	0.6-2.8
										≥ 30	0.7	0.2-2.3
Number of full-term births	0	---	reference	0	---	reference	0	---	reference	1	---	reference
	1–3	0.98	0.65-1.45	1-2	1.11	0.78-1.58	**1-2**	**1.6**	**1.0-2.7**	2	0.8	0.3-1.7
	≥ 4	**2.40**	**1.24-4.64**	≥ 3	1.18	0.81-1.72	**≥ 3**	**1.7**	**1.0-2.9**	≥ 3	0.8	0.3-1.7
Time since last birth, in years	Nulliparous	---	reference	*Not measured*			*Not measured*			*Not measured*		
	≤ 5	**2.25**	**1.16-4.36**									
	> 5	0.95	0.64-1.42									
Breastfeeding duration, in months	Never	---	reference	Never	---	reference	Never	---	reference	Never	---	reference
	<12 mo.	1.02	0.70-1.48	0-3 mo.	1.04	0.71-1.52	0-3 mo.	1.1	0.7-1.9	< 6 mo.	0.9	0.5-1.6
	≥12 mo.	0.83	0.48-1.43	≥ 4 mo.	0.78	0.59-1.03	≥ 4 mo.	0.7	0.5-1.1	**≥ 6 mo.**	**0.5**	**0.3-0.9**
Age at menopause, in years	*Not measured*			*Not measured*			*Not measured*			< 45	---	reference
										45-54	0.9	0.4-2.0
										≥ 55	1.2	0.5-3.0

Table 2-4: Sample of additional biobehavioral risk factors for triple-negative breast cancer; statistically significant results in bold

	Trivers et al., 2009			**Kwan et al., 2009**			**Millikan et al., 2008**			**Setiawan et al., 2009**		
	Groups	OR	95% CI	Groups	OR	95% CI	Groups	OR	95% CI	Groups	RR	95% CI
Body mass index (BMI)*	< 25	---	reference	< 25	---	reference	< 25	---	reference	< 25	---	reference
	25.0-29.9	**1.90**	**1.27-2.85**	25-29	1.33	0.98-1.81	**25-29**	**1.4**	**1.0-2.2**	25-<30	0.98	0.79-1.21
	≥ 30	**1.89**	**1.22-2.92**	≥30	1.04	0.75-1.45	≥30	1.3	0.8-1.9	≥ 30	0.79	0.60-1.03
BMI, pre-menopausal women	*Not measured*			< 25	---	reference	< 25	---	reference	*Not measured*		
				25-29	**1.82**	**1.03-3.24**	**25-29**	**1.7**	**1.0-3.1**			
				≥30	**1.97**	**1.03-3.77**	≥30	1.6	0.9-2.7			
BMI, post-menopausal women	*Not measured*			< 25	---	reference	< 25	---	reference	< 25	---	reference
				25-29	1.08	0.73-1.59	25-29	1.2	0.7-3.0	25-<30	1.00	0.77-1.30
				≥30	0.76	0.49-1.17	≥30	1.0	0.5-1.7	**≥ 30**	**0.69**	**0.49-0.98**
Hormone replacement therapy use**	*Not measured*			Never	---	reference	Never	---	reference	Never use	---	reference
				Ever	0.97	0.72-1.31	Ever	0.8	0.5-1.3	Former use	1.11	0.81-1.51
										Current (1)	1.21	0.79-1.85
										Current (2)	1.11	0.82-1.51
Alcohol use	Never	---	reference	Never	---	reference	Never	---	reference	0 drinks/day	---	reference
	<7 drinks per week	0.72	0.50-1.04	Ever	0.98	0.73-1.30	Ever	0.9	0.6-1.2	< 2 drinks per day	1.21	0.99-1.48
	≥7 drinks per week	0.72	0.44-1.17							**≥ 2 drinks per day**	**1.71**	**1.19-2.46**

* BMI values are associated with the following clinical designations: <25 = under- to normal weight; 25 – 29.9 = overweight; ≥30 = obese
** Type of hormone replacement therapy is indicated by: (1) = estrogen only therapy; (2) = estrogen-progestin therapy

Footnotes for Tables 2-4:

Trivers et al., 2009:

Odds ratios are weighted, compared to the ER/PR+, HER2- subtype and are adjusted for race, age and stage (race models are adjusted for age & stage; age models are adjusted for race & stage; stage models are adjusted for age & race)

Kwan et al., 2009:

Case-only odds ratios adjusted for age at diagnosis, race/ethnicity except in models with age at diagnosis or race/ethnicity as main predictors

Parise et al., 2009:

Adjusted odds ratios.

Millikan et al., 2008:

Case-only odds ratios compare basal-like to luminal A breast cancer. Age odds ratio is adjusted for race; race odds ratio is adjusted for age, and all remaining odds ratios are adjusted for both age and race.

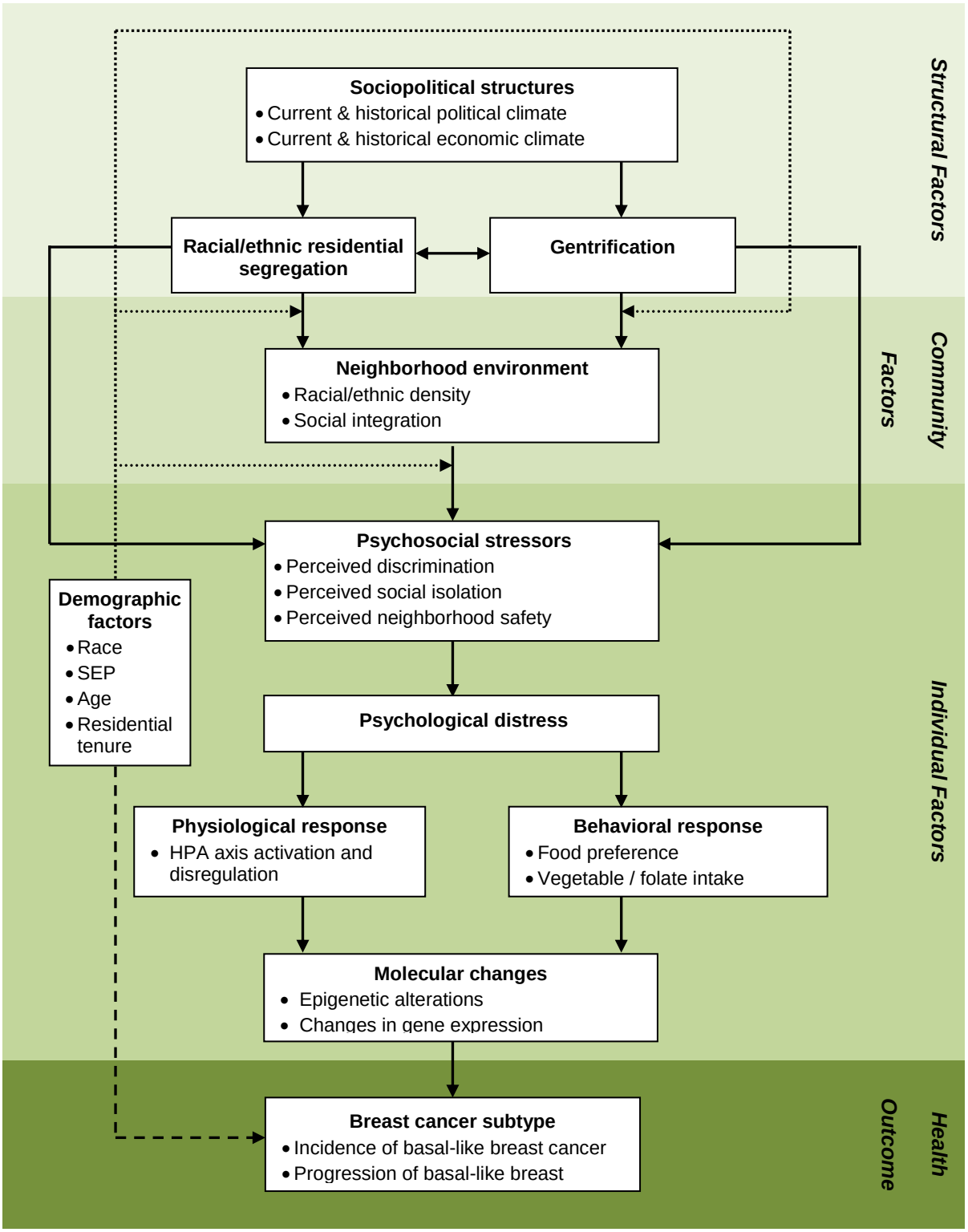
Phipps et al., 2008:

Odds ratios are adjusted for age and diagnosis/reference year. Number of live births, age at first live birth, and breastfeeding were coadjusted for each other.

Setiawan et al., 2009:

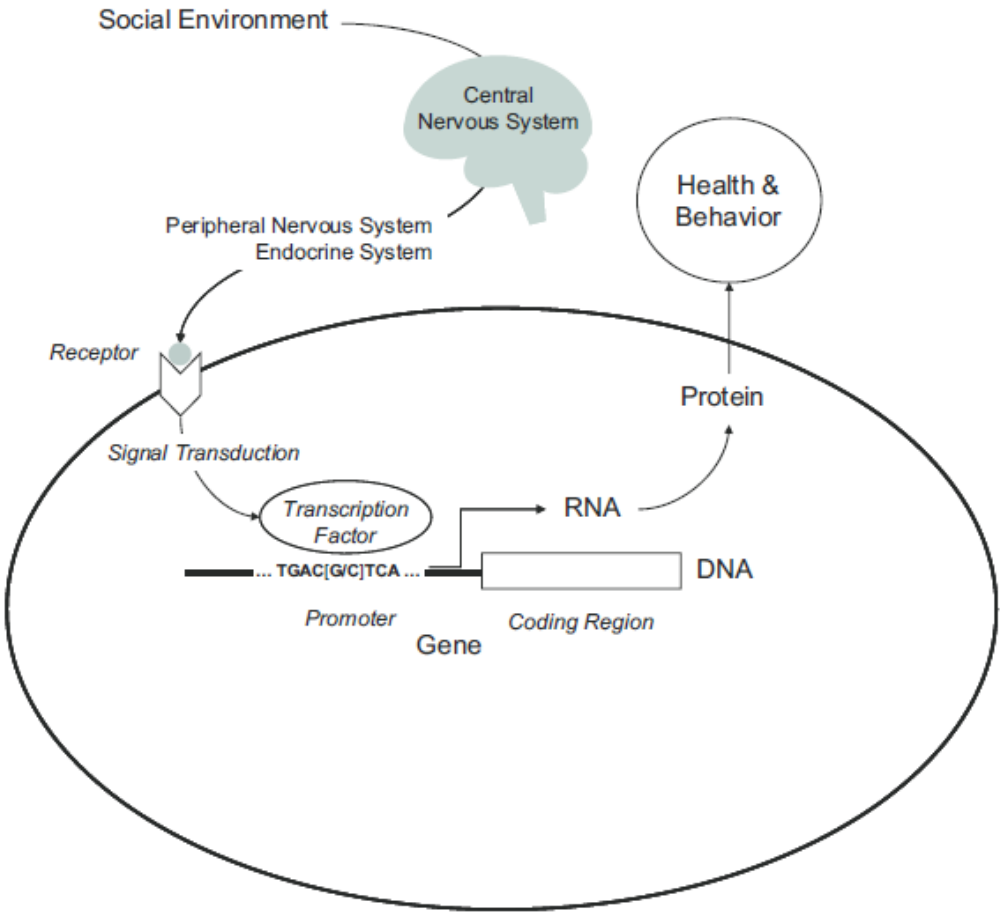
Authors report that "Results were stratified on age at recruitment, year of recruitment, race/ethnicity, type of menopause, and study center and were mutually adjusted for age at menarche, age at first birth, number of children, BMI, alcohol intake, duration of hormone therapy, and family history of breast cancer."

Figure 2-2: Conceptual model of the relationship between stress and basal-like breast cancer



Solid arrows = direct (box to box) or moderating (box to arrow) relationships
Heavy dashed arrow = direct association between race and breast cancer subtype typically reported in the literature.
Dotted arrows = alternative avenues by which sociodemographic factors may interact with key constructs

Figure 2-3: Illustration of social signal transduction set forth in Cole, S. W. (2009). Social Regulation of Human Gene Expression. Current Directions in Psychological Science, 18(3), 132-137.



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CHAPTER 3

Neighborhood Sociodemographics and Hormone Receptor Status among California Women Diagnosed with Breast Cancer

Introduction

Racial/ethnic disparities have been well documented across the breast cancer continuum (Bigby & Holmes, 2005; Jones & Chilton, 2002; Newman & Martin, 2007). When compared to white women, black women have lower levels of access to quality mammography services (Hirschman, Whitman, & Ansell, 2007), experience longer diagnostic and treatment delays (Gorin, Heck, Cheng, & Smith, 2006; Kerner et al., 2003), are more likely to receive suboptimal care once treatment is initiated (Bradley, Given, & Roberts, 2002), and are more likely to die of the disease (Albain, Unger, Crowley, Coltman, & Hershman, 2009; Jatoi, Becher, & Leake, 2003; Wojcik, Spinks, & Optenberg, 1998).

Disparities in several clinical features of breast cancer are also well-documented (Amend, Hicks, & Ambrosone, 2006; DeSantis, Jemal, & Ward, 2010), and the differential distribution of breast cancer subtypes are particularly noteworthy. While breast cancer subtype is ideally defined directly via gene expression profiles of tumor tissue, routinely collected immunohistochemical markers such as the concentration of three specific hormone receptors are frequently used as proxy measures (Won et al., 2013). Numerous studies have found that, relative to whites, black women with breast cancer are more likely to be diagnosed with tumors that express very low levels of estrogen receptors (ER), progesterone receptors (PR), and human epidermal growth factor receptors (HER2) (Gapstur, Dupuis, Gann, Collila, & Winchester, 1996;

Hausauer, Keegan, Chang, & Clarke, 2007; Joslyn, 2002; Tarone & Chu, 2002). Commonly referred to as triple negative breast cancer, this particular subtype is associated with larger and higher-grade carcinomas at the time of diagnosis (Parise, Bauer, Brown, & Caggiano, 2009), and these aggressive tumors are not responsive to current adjuvant treatments such as Tamoxifen and Herceptin (Kang, Martel, & Harris, 2008; Reis-Filho & Tutt, 2008). As a result, triple negative tumors are associated with lower 5-year survival rates even after adjusting for other clinical features, such as stage at diagnosis and tumor grade (Bauer, Brown, Cress, Parise, & Caggiano, 2007; Boyle, 2012). Because breast cancer subtype is thought to be determined at the time the tumor begins to develop, observed differences in subtype distribution across groups should not be influenced by access to breast cancer screening, diagnostic, and treatment resources (Morris et al., 2007).

Differences in the population-level distribution of breast cancer subtype are therefore an early, clinically-meaningful source of inequality in the breast cancer experience, but the origins of this disparity remain unclear. Women from low socioeconomic areas also appear to have higher rates of triple-negative tumors (Gordon, 1995; Vona-Davis & Rose, 2009), but little work has been done to disentangle the associations among race, socioeconomic status (SES), and the differential distribution of breast cancer subtypes. The few studies that have examined SES in relation to breast cancer subtype have been limited by the conceptualization and measurement of SES (Dunn, Agurs-Collins, Browne, Lubet, & Johnson, 2010). State and national cancer registry data are frequently used in these types of analyses, but given the lack of individual-level socioeconomic data collected by the cancer surveillance systems, researchers frequently resort to using area based socioeconomic information as proxy measures. This approach is problematic, as the area-based measures capture more than just approximate individual-level SES (Geronimus &

Bound, 1998). As a result, broader structural issues that are 1) related to both the racial and socioeconomic composition of the area, and 2) could independently contribute to the observed disparities status in breast cancer subtype cannot be adequately addressed using this approach.

Residential segregation is one such structural factor that reinforces the complex relationship between race and SES within the United States (Schulz, Parker, Israel, & Fisher, 2001; Williams & Collins, 2001), and it is receiving increasing attention in the breast cancer disparity literature. Recent work from Warner and Gomez (2010) suggests that black women living in metropolitan areas with high levels of race-based residential segregation were significantly more likely to be diagnosed with advanced stage breast cancer and die of the disease if they lived in a block group with more non-black residents. The relationship remained significant after adjusting for neighborhood-level socioeconomic status, suggesting that factors other than material resources may contribute to this risk. Warner and Gomez posit that one such factor may be reduced access to social support within neighborhoods consisting of fewer co-ethnic residents. Other work suggests that blacks living in more integrated neighborhoods may also be subjected to greater levels of discrimination (Hunt, Wise, Jipguep, Cozier, & Rosenberg, 2007; Welch, Sigelman, Bledsoe, & Combs, 2001) which has also been identified as a potential risk factor for the development of breast cancer among black women (Taylor et al., 2007).

The weathering hypothesis (Geronimus, 1992; Geronimus & Thompson, 2004) provides a useful theoretical framework for exploring the potential role of these and other neighborhood-related psychosocial factors related to breast cancer disparities, as it emphasizes the role of social, political, and economic marginalization on health outcomes, particularly among black women in early to middle adulthood (Geronimus, Hicken, Keene, & Bound, 2006). In this study, I use the weathering framework to explore the distribution of *double negative* (estrogen and

progesterone receptor negative, also abbreviated as ER-/PR-) breast cancers across the same study population as Warner and Gomez and determine whether the social patterning of this breast cancer subtype is similar to the patterns reported for stage at diagnosis and mortality. HER2 receptor status was excluded from this analysis for several reasons. First and foremost, The American Society of Clinical Oncology and the College of American Pathologists did not recommend routine testing for HER2 receptor status in invasive breast cancers until 2007 (Wolff et al., 2007), and the NCI Surveillance, Epidemiology and End Results (SEER) Program Central Cancer Registries were not required to collect this data until 2010 (Reichman et al., 2010). As a result, nearly 50% of the otherwise eligible cases are missing HER2 data. Despite the large percentage of missing HER2 data, I elected to retain the 1996-2004 sampling frame used by Warner & Gomez to build off of their findings. This sampling frame also brackets the extensive residential segregation data available from the 2000 Census. To my knowledge, metropolitan and micropolitan residential segregation data are not yet available for the 2010 Census, nor for any of the five-year American Community Survey data sets. Due to these methodological considerations, I chose double negative breast cancer as the primary subtype of interest for this analysis, using the double positive (ER+/PR+) subtype as the reference category. Additional information regarding the missing HER2 data and plans for related exploratory analyses are provided in the Measures section.

I hypothesize that at the population level, both black and Hispanic women with breast cancer will have lower proportions of ER-/PR- disease with increasing concentrations of co-ethnic neighborhood residents. I anticipate that this relationship will be robust to adjustment for neighborhood socioeconomic status, and will be more pronounced 1) within metropolitan areas that have high levels of race-based residential segregation, and 2) among younger women.

Methods

Study Subjects

Cases for this analysis were drawn from the California Cancer Registry (CCR). The CCR has been tracking cancer cases across the state of California since 1988 and has received gold certification status from the North American Association of Central Cancer Registries (NAACCR) for data quality and completeness. The individual-level CCR data has been geocoded to the 2000 Census block group level and linked to the 21,390 California census block groups that are currently included in the California Neighborhoods Data System (CNDS). The CNDS was developed by researchers at the Cancer Prevention Institute of California (CPIC) to aid in the area-based analysis of cancer risk factors and survival (Gomez et al., 2011). The CNDS is a collection of neighborhood characteristics derived from the 2000 Census as well as other types of local information, such as 15 unique measures of racial/ethnic residential segregation from the RAND Center for Population Health and Health Disparities ("Segregation Indices Data Series," 2000).

Matching the catchment period used by Warner and Gomez (2010) and centered on the 2000 decennial census, all non-Hispanic white and non-Hispanic black female residents of California who were diagnosed with a first primary, invasive breast cancer between January 1, 1996 and December 31, 2004 were eligible for the study. A total of 124,852 women met these initial criteria. Women whose address could not be directly geocoded to a census block group (n = 5,807; 4.7%) or lived in a block group outside of the 25 California metropolitan statistical areas or MSAs (n = 4,279; 3.4%) were removed from the sample. Of the 114,766 remaining eligible women, 25,124 (21.9%) were missing estrogen and/or progesterone receptor data and

14,400 (12.5%) had complete data but were not classified in either the reference (ER+/PR+) or outcome (ER-/PR-) categories. These women were also excluded. A total of 75,242 women met the final eligibility criteria and were included in the following analyses.

Both the University of Michigan Health and Behavioral Sciences Institutional Review Board and the California Health and Human Services Agency's Committee for the Protection of Human Subjects reviewed and approved the study protocol.

Measures

Individual-level variables

Breast cancer subtype. While much of the current literature on breast cancer subtype uses the three hormone receptor definition, the primary outcome measure for this analysis is based on estrogen receptor and progesterone receptor (commonly abbreviated ER/PR) only. The CCR has been collecting ER and PR status since 1990, but only began collecting information on the third hormone receptor, HER2, in 1999. For the first few years after HER2 data collection began, the rate of missing data was quite high. As a result, only 38,863 (51.7%) of the 75,242 otherwise eligible cases have complete data on all three hormone receptors. While not completely concordant, the ER-/PR- subtype is a reasonable approximation of distribution of triple-negative breast cancer.

Race/Ethnicity. Individual race/ethnicity data as reported in the CCR is first included as an independent variable to model differences in breast cancer subtypes and their predictors across the racial/ethnic groups. Racial/ethnic categories are subsequently used to stratify the sample for within-group analyses. In this analysis, the two racial/ethnic groups are mutually exclusive, representing non-Hispanic whites (hereafter referred to as whites) and non-Hispanic

blacks (hereafter, blacks). Race/ethnicity information is derived from patients' medical records, and have been shown to be of good quality (Clegg et al., 2007; Gomez & Glaser, 2006).

Age. Age at the time of diagnosis is included as a continuous variable in all models. Additionally, to assess for possible variation in ER-/PR- odds ratios across the adult lifespan, age-stratified models were also constructed. The three stratifying age groups were constructed such that the middle age group – women between the ages of 45 and 64 – could be compared to both younger and older groups of women diagnosed with breast cancer. This middle age group is of particular importance from a weathering perspective, as the premature onset of age-related illness and disability quickly accumulate among minority group members during this period (Geronimus et al., 2006; Geronimus & Snow, 2013).

The designated age groups also allow for a crude proxy measure of menopausal status. Menopausal status is not included in the CCR records, but the designated age groups roughly correspond to pre-menopausal (under age 45), peri- and post-menopausal (ages 45 to 64), and elderly (ages 65 and older) status in Western cultures (Gold, 2011; Hill, 1996). Approximation of menopausal status may be important, as multiple studies have found that the risk of hormone receptor negative breast cancer is greater among pre-menopausal women (Forshee, Storey, & Ritenbaugh, 2003; Tarone & Chu, 2002)

Year of diagnosis. To account for the increase in ER and PR reporting rates over the course of the study, the year of diagnosis was included. This variable also adjusts for the widely reported decline in ER+/PR+ cancers diagnosed among white women following the 2002 release of Women's Health Initiative data linking use of hormone replacement therapy to increased risk of breast cancer (DeSantis, Howlader, Cronin, & Jemal, 2011; Ravdin et al., 2007).

Marital status. Standard demographic categories of single never married, separated, divorced, widowed, and unknown are compared against the reference group of married women.

Payer source at diagnosis. Data regarding the primary payer source at the time of breast cancer diagnosis was categorized into five groups: private insurance; uninsured or self-pay; publicly funded (e.g., Medicare, Medicaid, Indian Health Service, or county-funded); military sponsored (e.g., TriCare or Veterans Administration); and unknown. While representing only one dimension of socioeconomic status, primary payer at diagnosis is the CCR variable that may best approximate individual-level socioeconomic status (Chan, Gomez, O'Malley, Perkins, & Clarke, 2006).

Tumor characteristics. Given the previously reported relationships between tumor stage, tumor grade, and ER/PR subtype (Boyle, 2012; Parise et al., 2009) both clinical factors were controlled for in all analyses. Tumor stage was assessed using the SEER 1977/2000 summary stage categories of local, regional, distant, and unknown. Tumor grade was categorized into four groups of increasing severity as well: I, II, III/IV, and unknown.

Metropolitan- and neighborhood-level variables

Residential racial segregation. The black-white entropy index (H) was selected as the primary measure of metropolitan-level racial segregation. Also known as the information theory index or Theil's H, the black-white entropy index is a measure of what Massey and Denton (1989) refer to as "evenness," or the degree to which the selected racial groups present in an area (i.e., MSA) are evenly distributed across its component parts (i.e., census tracts). The measure is similar in concept to the more widely used dissimilarity index, but is considered to be the superior due to its spatial properties and its ability to be mathematically decomposed into

meaningful parts (Reardon & Firebaugh, 2002). Scores on this measure range from 0, meaning all census tracts have the same racial composition as the entire MSA, to 1, which means that each census tract is comprised of only one racial/ethnic group (Iceland, 2004). The black-white entropy index scores for the 25 California MSA scores into tertiles. MSA's in the highest tertile were categorized as highly segregated MSA's, whereas the bottom two tertiles became the low segregation comparison group.

Neighborhood racial concentration. Complementing the MSA-level measures of segregation, measures of neighborhood (block group) racial/ethnic concentration are also included in the analyses. These measures are also derived from the 2000 decennial census and capture the percent non-Hispanic black residents living within block groups comprised of approximately 1,000 residents. Notably, the neighborhood racial concentration measures are assessed at a smaller geographical unit than the roughly 4,000-resident census tracts that are component parts of the entropy indices.

Neighborhood-level socioeconomic status. The CNDS includes several single-variable measures of block group-level socioeconomic status (SES) from the 2000 Census, as well as a previously validated composite measure of socioeconomic status comprised of block group-level education, employment, income, and housing indicators (Yost, Perkins, Cohen, Morris, & Wright, 2001). Given previously identified conceptual and statistical issues with composite area-based socioeconomic measures (Geronimus & Bound, 1998), block group median household income was chosen as the primary indicator of neighborhood socioeconomic status. Secondary analyses replacing median household income with the composite measure – of which median household income is one component – were also conducted.

Data analysis

Descriptive statistics of the full study population and each racial/ethnic subgroup are reported in Tables 1 – 3. Means and standard deviations were calculated for the continuous variables, while frequencies are listed for each categorical measure. Statistically significant differences between racial/ethnic subgroups were assessed for each independent variable using unadjusted t-tests and chi-square tests, respectively. Inter-group differences with p-values ≤ 0.05 are noted in the tables and highlighted in the results section.

To test the hypothesized relationships among neighborhood racial/ethnic concentration, metropolitan-level racial segregation, and odds of ER-/PR- breast cancer subtype, two-level population average generalized estimating equation models were constructed using the XTGEE command in Stata 13 (StataCorp, 2013), specifying a binomial distribution, logit link, exchangeable correlation structure, and robust standard errors. This statistical approach takes into account the clustering of individual cases within census block groups, but avoids the modeling and distribution assumptions that underlie multilevel mixed effects models (Hubbard et al., 2010). Given the large number of clusters (block groups), the relatively small number of cases per cluster (mean = 4.3 cases per block group in the full sample; range = 1 to 67), and the conceptual emphasis on the effects of cluster-level predictors, population average models are well-suited for addressing the current research questions (Hosmer, Lemeshow, & Sturdivant, 2013). The odds ratios generated by population average models are interpreted in a similar manner as standard logistic regression models, with the parameter estimates describing the effect of each predictor averaged across all block groups.

To examine the intersecting relationships (Kelly, 2009) among individual race/ethnicity, neighborhood- and MSA-level characteristics, and ER/PR subtype, the two-level population

average models were first constructed for the full study sample, then stratified by race/ethnicity. Each of the full and racial/ethnic subsamples were then further stratified by 1) MSA-level black-white entropy index, and 2) individual-level dichotomous categories for age at diagnosis. A two-sample t-test was used to examine whether the observed differences in the magnitude of the regression coefficients across strata were statistically significant.

Results

Descriptive statistics

Tables 1 through 3 illustrate the unadjusted demographic characteristics of the study sample across all individual, neighborhood, and metropolitan-level variables. Compared to white women, the mean age at diagnosis was significantly lower for blacks ($p < 0.01$). Black women in this sample were less likely than white women to be: married ($p < 0.01$); have private health insurance ($p < 0.01$); be diagnosed with an early stage ($p < 0.01$), low grade ($p < 0.01$), or ER+/PR+ tumor ($p < 0.01$). The median neighborhood household income for black women was significantly lower than that of whites ($p < 0.01$), while the mean percentage of black ($p < 0.01$) neighborhood residents was much greater than that of white women ($p < 0.01$). Black women were more likely to reside in a highly-segregated metropolitan area than white women ($p < 0.01$).

Multivariable analyses

Given the significant variation across racial/ethnic groups described in Table 1, all models adjusted for individual-level sociodemographic characteristics (age, marital status, insurance status, and race/ethnicity in the non-stratified models) as well as clinical features (year of diagnosis, stage at diagnosis, and tumor grade). In both the total population and within

race/ethnicity, age at diagnosis was inversely associated with the odds of having ER-/PR- breast cancer (data not shown). Increasing year of diagnosis, stage at diagnosis, and tumor grade were each associated with substantially higher odds of ER-/PR- cancer across all racial/ethnic subgroups (data not shown). In the total population and among white women only, being single was associated with approximately 10% lower odds of ER-/PR- subtype relative to married women ($p < 0.01$; data not shown), while having military-sponsored health insurance rather than private insurance was associated with a nearly 40% increase in odds of ER-/PR- ($p = 0.01$; data not shown).

The covariates most central to the aim of this study were measured at the neighborhood (block group) and MSA levels. As such, the odds ratios for only these variables are reported in Tables 4 through 6. Previously documented racial/ethnic disparities in the odds of ER-/PR- breast cancer were observed in the full study sample. Relative to white women and holding all other individual- and neighborhood-level variables constant, the odds of having ER-/PR- breast cancer was 94% higher for blacks ($p < 0.01$; see Table 4, Model 3). Neighborhood socioeconomic status was also significantly associated with breast cancer subtype in the fully-adjusted model, as every $10,000 increase in block group median household income was associated with a 2.6% decrease in the odds of ER-/PR- breast cancer ($p < 0.01$). In addition, each 10-point increase in the percentage of black neighborhood residents was modestly associated with a 1.7% decrease in the odds of ER-/PR- breast cancer ($p = 0.09$).

Different patterns emerged when the full study sample was stratified by race/ethnicity (Table 5). Among whites, a 10% increase in the block group percentage of black residents resulted in a 3.9% increase in the odds of ER-/PR- diagnosis ($p = 0.02$), but this relationship was completely attenuated by the addition of block group median household income to the model

(OR = 1.01, p = 0.42). As observed in the full sample, increasing block group median household income was significantly associated with lower odds of ER-/PR- subtype among white women.

This relationship between neighborhood SES and ER/PR subtype was not found among blacks (Table 5). Instead, bock group percentage of black residents was a statistically stronger predictor, with every 10% increase in black concentration resulting in a 2.7% decrease in odds of ER-/PR- subtype in the fully-adjusted model (p = 0.03). Unlike the results for the white subsample, the relationship between percentage of black neighborhood residents and odds of ER-/PR- breast cancer was even stronger when neighborhood SES was taken into account (OR = 0.97, p = 0.01). The difference in the coefficients for the neighborhood racial composition variable between the white subpopulation and the black subpopulation was statistically significant (p < 0.01)

When the racial/ethnic subpopulations were further stratified by metropolitan-level segregation (Table 6) and age at diagnosis (Table 7), differences were observed across strata for black women, but were largely absent within the white subpopulation. For example, black women living in highly segregated MSAs had lower odds of ER-/PR- breast cancer with increasing neighborhood black percentage (OR = 0.97, p = 0.04), and to a lesser extent, increasing neighborhood SES (OR = 0.97, p = 0.10). However, these relationships were not statistically significant among black women living in less segregated areas (SES OR = 0.99, p = 0.80; percent black OR = 0.99, p = 0.80). This difference in odds ratio across MSA segregation levels was not statistically significant.

Unique age group-specific patterns were seen within the black subpopulation. For example, black women diagnosed with breast cancer before age of 45 had 7.2% lower odds of ER-/PR- breast cancer with each $10,000 increase in block group median household income (p =

0.03), but did not benefit from increasing percentages of black neighborhood residents. The opposite relationships were seen among black women diagnosed at age 65 or above, as they had a 8.4% lower odds ($p < 0.01$) with every 10% increase in neighborhood percentage of black residents, but no significant change in odds relative to neighborhood SES. Among black women in the primary age group of interest (ages 45 to 64), neither the neighborhood SES or neighborhood racial/ethnic composition variables were significantly related to odds of ER-/PR- breast cancer. While neighborhood median household income and the percentage of black residents within the neighborhood were significantly related to odds of ER-/PR- breast cancer within the youngest and oldest age groups, respectively, comparisons of the coefficients across age groups indicate that they are not significantly different from one another.

When the analysis was restricted to whites, the both the segregation level- (Table 6) and age-stratified models (Table 7) yielded the same general patterns that were observed in the full white subpopulation. At both segregation levels and across all three age groups, increasing neighborhood median household income was associated with significantly lower odds of ER-/PR- breast cancer. The difference in coefficients across segregation level and age group strata were not statistically significant. Also as seen in the full white subpopulation, the percentage of black residents within the block group was positively associated with the odds of having ER-/PR- breast cancer among white women in both more- and less-segregated MSAs and among white women diagnosed between the ages of 45 and 64. However, as in the full white sample, this association was no longer significant in any stratified white subgroup once neighborhood median household income was included in the model, and the difference in coefficients across age groups was not significant.

Discussion

Among black women diagnosed with breast cancer, living in neighborhoods with greater concentrations of black residents reduced the odds of being diagnosed with ER-/PR- breast cancer. As hypothesized, the risk-reducing effects were particularly strong within metropolitan areas that were among the most racially segregated areas in California, based on the black-white entropy index. In both the full sample of black breast cancer patients and among black residents of highly-segregated areas, the relationship between black residential concentration and ER/PR status became even stronger when neighborhood socioeconomic status was accounted for. These findings build upon the results of Warner & Gomez (2010), who found similar relationships among racial concentration, stage at diagnosis, and mortality among black Californian women diagnosed with breast cancer during the same time period. Taken together, these findings suggest that, for black women with breast cancer, the benefits of living in more densely black neighborhoods may operate through non-socioeconomic pathways that may potentially include reduced exposure to racial discrimination (Hunt et al., 2007; Welch et al., 2001), greater acceptance of alternative cultural frameworks (James, 1993) and/or greater opportunities for social support (Das-Munshi, Becares, Dewey, Stansfeld, & Prince, 2010; Keene & Geronimus, 2011).

While this finding and the potential explanations are consistent with the conceptual model, the significant racial concentration-associated reduction in odds of ER-/PR- subtype seen only among black women ages 65 and over ran counter to my hypothesis. One plausible biological explanation is that the ER-/PR- breast cancers diagnosed in younger women may have a stronger genetic contribution. Mutations in the *BRCA1* gene are thought to be responsible for roughly 10% of pre-menopausal breast cancers (Lakhani et al., 2002; Mavaddat et al., 2012), and

approximately 70% of tumors diagnosed among *BRCA1* mutation carriers are triple-negative (Atchley et al., 2008; Foulkes, Smith, & Reis-Filho, 2010; Mavaddat et al., 2012). The higher prevalence of *BRCA1* mutation associated breast cancers may thus partially obscure the relationship between ER-/PR- and other non-inherited risk factors.

From a more socially-oriented perspective, the impact of psychosocial exposures within a neighborhood may change over the life course, with older black women potentially deriving greater benefits from living among more co-ethnic neighbors. What remains to be examined is how these benefits may be accrued, and if the benefits vary across various levels of residential tenure, residential stability, and neighborhood poverty. Two studies conducted in the Chicago metropolitan area are worth noting. Keene, Bader, and Ailshire (2013) found that the positive relationship between residential tenure and available social support was even stronger in more impoverished Chicago neighborhoods. Barrett and colleagues (2008) found that women living in Cook County, Illinois census tracts that experienced upward socioeconomic change between 1990 and 2000 actually had higher risks of being diagnosed with late-stage breast cancer. Considering that increasing neighborhood-level socioeconomic status commonly coincides with decreasing percentages of minority residents (i.e., gentrification; see Goetz, 2011) it would be important to further disentangle how neighborhood racial/ethnic composition and socioeconomic status may relate to neighborhood tenure, and how these relationship may be of particular import to the availability of social support and the subsequent health and well-being of elderly black women.

The lack of neighborhood tenure and other social-contextual data needed to disentangle these complex relationships is one of several study limitations. The analytic plan for this study was built around the availability of block group-level sociodemographic data and metropolitan-

level racial/ethnic segregation data generated from the 2000 Census. Choosing this source of sociodemographic information was essential for addressing the research questions at the optimal geographic levels and developing a data set that closely relates to that used by Warner and Gomez. However, the resulting limitations on the California Cancer Registry catchment period meant that a more coarse approximation of breast cancer subtype would be needed. Future studies that make use of block group level data from later 5-year American Community Survey estimates and calculate new black-white entropy indices from the 2010 Census are needed to have a sufficient number of cases with data on all three hormone receptors.

Data limitations at the individual level are also worth noting. The large number of women missing either ER or PR information could introduce bias into study sample. The single point of measurement for neighborhood-level characteristics could mask the importance of duration and/or critical period exposure to neighborhood-level factors. The lack of life course residential and socioeconomic histories could prove to be problematic if 1) a particular threshold level of exposure to neighborhood-level factors must be met before the individual-level psychosocial, behavioral, and biological processes more proximal to specific breast cancer subtypes take hold, or if 2) there is a critical developmental period for neighborhood-level exposures during the life course other than immediately prior to diagnosis of breast cancer. The importance of the duration and timing of neighborhood-level exposures to the development of specific breast cancer subtypes is not yet known, thus the impact of these data limitations cannot be fully evaluated. Finally, the dearth of individual-level biopsychosocial data prevents the analysis of potential pathways linking neighborhood-level factors to the two breast cancer subtypes.

Despite these limitations, this study makes an important contribution to the breast cancer disparities literature: the increased risk of more aggressive breast cancer subtypes routinely

observed among black women may be at least partially mediated via social-structural mechanisms. Research that focuses solely on ancestry-based genetic risk factors for breast cancer subtypes fails to address how the phenotype of being a minority in America shapes ones lived experiences, and how those lived experiences may in turn shape the odds of developing a specific breast cancer subtype. The psychosocial and physiological effects of increased exposure to racial/ethnic discrimination and/or decreased support and acceptance for individuals whose sociocultural identities are outside of the dominant norms may represent two pathways by which neighborhood factors influence the development of triple-negative breast cancer. To properly investigate these and other complex, dynamic relationships, additional research guided by current empirical evidence and theory in multiple disciplines ranging from molecular cancer biology to social epidemiology is needed.

Tables

Table 3-1. Individual-level descriptive statistics, by race/ethnicity

	Total sample		White cases		Black cases	
N (%)	75,242	100%	69,614	92.5%	5,628	7.5%
Age (years):						
mean, SD	60.3	± 14.1	61.6	± 13.9	56.8	± 13.9
Marital status:						
Single, never married	9,226	12.3%	7,904	11.4%	1,322	23.5%
Married	42,328	56.3%	40,115	57.6%	2,213	39.3%
Separated	706	0.9%	527	0.8%	179	3.2%
Divorced	8,598	11.4%	7,706	11.1%	892	15.8%
Widowed	13,158	17.5%	12,292	17.7%	866	15.4%
Unknown	1,226	1.6%	1,070	1.5%	156	2.8%
Primary insurer:						
Uninsured / self-pay	648	0.9%	542	0.8%	106	1.9%
Private	48,044	63.9%	44,707	64.2%	3,337	59.3%
Public	22,551	30.0%	20,647	29.7%	1,904	33.8%
Military	676	0.9%	604	0.9%	72	1.3%
Unknown	3,323	4.4%	3,114	4.5%	209	3.7%
Summary stage:						
Localized	47,655	63.3%	44,670	64.2%	2,985	53.0%
Regional	24,781	32.9%	22,519	32.3%	2,262	40.2%
Remote	2,347	3.1%	2,037	2.9%	310	5.5%
Unknown	459	0.6%	388	0.6%	71	1.3%
Grade:						
I	16,226	21.6%	15,652	22.5%	574	10.2%
II	29,008	38.6%	27,288	39.2%	1,720	30.6%
III & IV	23,923	31.8%	21,033	30.2%	2,890	51.4%
unknown	6,085	8.1%	5,641	8.1%	444	7.9%
ER-PR status:						
ER+ / PR+	58,673	78.0%	55,401	79.6%	3,272	58.1%
ER- / PR-	16,569	22.0%	14,213	20.4%	2,356	41.9%

Table 3-2. Neighborhood-level sociodemographic measures: means and standard deviations for the 17,477 study neighborhoods, by individual cases' racial/ethnic group

	White cases		Black cases	
Neighborhood socioeconomic indicator:				
Median household income, 1999 US dollars	$63,170	± 29,429	$44,063	± 21,421
Mean Yost index	0.518	± 0.927	-0.320	± 0.844
Neighborhood racial concentration:				
Mean % non-Hispanic White	65.3%	± 22.0%	25.6%	± 24.8%
Mean % non-Hispanic Black	3.4%	± 06.1%	29.2%	± 26.4%

Table 3-3. Metropolitan-level measures of racial residential segregation: counts and percentages of study cases residing in each tertile of the black-white entropy index, by individual race/ethnicity

	White cases		Black cases	
n (%) residing in a metropolitan statistical area within:				
Lowest black-white entropy index tertile	12,121	17.4%	135	2.4%
Middle black-white entropy index tertile	15,666	22.5%	936	16.6%
Highest black-white entropy index tertile	41,827	60.1%	4,557	81.0%

Table 3-4. Adjusted[1] odds ratios (and 95% confidence intervals) for the association between ER-/PR- vs. ER+/PR+ subtype and individual-level race, neighborhood-level median household income and neighborhood racial concentration, California Cancer Registry 1996-2004

	ER-/PR- vs. ER+/PR+ Subtype OR (95% confidence intervals)		
	Model 1	Model 2	Model 3
Individual race:			
White (ref.)	1.00	1.00	1.00
Black	1.86 (1.74-1.99)	1.96 (1.81-2.13)	1.94 (1.78-2.11)
Block group level demographics:			
Median household income[2]	0.98 (0.97-0.98)		0.97 (0.97-0.98)
% Black[3]		0.99 (0.98-1.01)	0.98 (0.96-1.00)

[1] Adjusted for age at diagnosis, year of diagnosis, marital status, insurance status, stage at diagnosis, and tumor grade

[2] units = $10,000 (1999 U.S. dollars)

[3] units = 10-point change in percent of racial/ethnic group

Table 3-5. Race/ethnicity specific adjusted[1] odds ratios (and 95% confidence intervals) for the association between ER-/PR- vs. ER+/PR+ subtype and neighborhood-level median household income & racial/ethnic concentration, California Cancer Registry 1996-2004

	ER-/PR- vs. ER+/PR+ Subtype OR (95% confidence intervals)		
	Model 1	Model 2	Model 3
White women:			
Median household income[2]	0.97 (0.97-0.98)		0.97 (0.97-0.98)
% Black[3]		1.04 (1.01-1.07)	1.01 (0.98 -1.05)
Black women:			
Median household income	0.99 (0.96-1.02)		0.98 (0.95-1.01)
% Black		0.97 (0.95-1.00)	0.97 (0.95-0.99)

[1] Adjusted for age at diagnosis, year of diagnosis, marital status, insurance status, stage at diagnosis, and tumor grade

[2] units = $10,000 (1999 U.S. dollars)

[3] units = 10-point change in percent of racial/ethnic group

Table 3-6. Segregation level stratified, race/ethnicity specific adjusted[1] odds ratios (and 95% confidence intervals) for the association between ER-/PR- vs. ER+/PR+ subtype and neighborhood-level median household income & racial/ethnic concentration, California Cancer Registry 1996-2004

	ER-/PR- vs. ER+/PR+ Subtype OR (95% confidence intervals)		
	Model 1	Model 2	Model 3
White women			
Residing in highly segregated MSAs:			
Median household income[2]	0.98 (0.97-0.99)		0.98 (0.97-0.99)
% Black[3]		1.05 (1.01-1.09)	1.02 (0.99-1.07)
Residing in less segregated MSAs:			
Median household income	0.97 (0.96-0.99)		0.98 (0.96-0.99)
% Black		1.09 (1.01-1.18)	1.06 (0.99-1.15)
Black women			
Residing in highly segregated MSAs:			
Median household income	0.98 (0.95-1.01)		0.97 (0.94-1.00)
% Black		0.98 (0.95-1.00)	0.97 (0.95-1.00)
Residing in less segregated MSAs:			
Median household income	0.99 (0.93-1.06)		0.99 (0.92-1.06)
% Black		0.99 (0.88-1.11)	0.99 (0.87-1.11)

[1] Adjusted for age at diagnosis, year of diagnosis, marital status, insurance status, stage at diagnosis, and tumor grade

[2] units = $10,000 (1999 U.S. dollars)

[3] units = 10-point change in percent of racial/ethnic group

Table 3-7. Age stratified, race/ethnicity specific adjusted[1] odds ratios (and 95% confidence intervals) for the association between ER-/PR- vs. ER+/PR+ subtype and neighborhood-level median household income & racial/ethnic concentration, California Cancer Registry 1996-2004

	ER-/PR- vs. ER+/PR+ Subtype OR (95% confidence intervals)		
	Model 1	Model 2	Model 3
White women			
Age at diagnosis < 45 years:			
Median household income[2]	0.96 (0.94-0.98)		0.96 (0.94-0.98)
% Black[3]		1.03 (0.95-1.12)	0.99 (0.91-1.08)
Age at diagnosis = 45 to 65 years:			
Median household income	0.97 (0.96-0.98)		0.98 (0.96-0.99)
% Black		1.06 (1.00-1.11)	1.03 (0.98-1.08)
Age at diagnosis ≥ 65 years:			
Median household income	0.98 (0.97-1.00)		0.98 (0.97-1.00)
% Black		1.01 (0.96-1.07)	1.00 (0.94-1.06)
Black women			
Age at diagnosis < 45 years:			
Median household income	0.94 (0.88-1.00)		0.93 (0.87-0.99)
% Black		0.97 (0.92-1.03)	0.96 (0.90-1.02)
Age at diagnosis = 45 to 65 years:			
Median household income	0.98 (0.95-1.02)		0.98 (0.95-1.02)
% Black		1.01 (0.97-1.04)	1.00 (0.97-1.04)
Age at diagnosis ≥ 65 years:			
Median household income	1.04 (0.98-1.10)		1.01 (0.95-1.08)
% Black		0.90 (0.86-0.95)	0.91 (0.86-0.95)

[1] Adjusted for age at diagnosis, year of diagnosis, marital status, insurance status, stage at diagnosis, and tumor grade

[2] units = $10,000 (1999 U.S. dollars)

[3] units = 10-point change in percent of racial/ethnic group

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CHAPTER 4

Individual and Neighborhood Characteristics, Perceived Unfair Treatment, and Diurnal Cortisol Patterns among Adults in Detroit

Introduction

Perceived discrimination or unfair treatment has been linked to a wide range of conditions, including: depressive symptoms during pregnancy (Ertel et al., 2012), weight change (Cozier, Wise, Palmer, & Rosenberg, 2009), obesity (Hunte & Williams, 2009), high blood pressure (Dolezsar, McGrath, Herzig, & Miller, 2014), physical and mental health recovery after an injury (Sullivan, Scott, & Trost, 2012), and even breast cancer incidence (Taylor et al., 2007). However, the psychological, behavioral, and biological mechanisms by which perceptions of unfair treatment may contribute to these conditions remain an area of considerable research interest (Gibbons et al., 2014; Williams & Mohammed, 2009).

Researchers have suggested that, as a form of chronic or acute stress, perceptions of unfair treatment may repeatedly activate the hypothalamic-pituitary-adrenal axis (HPA), eventually leading to its dysregulation and a cascade of harmful downstream physiological consequences (Skinner, Shirtcliff, Haggerty, Coe, & Catalano, 2011). Measurement of salivary cortisol levels over the course of one or more days is one way to approximate HPA axis activity with relatively low participant burden (Kraemer et al., 2006). Current evidence suggests that alterations in the typical diurnal pattern of salivary cortisol secretion – namely, the shallow decrease in salivary cortisol levels between morning wake-up and evening bedtime – may reflect dysregulation of the HPA axis negative feedback loop (Spiegel, Giese-Davis, Taylor, &

Kraemer, 2006), and that these alterations are associated with a similar set of negative physical and mental health outcomes as perceived unfair treatment (Hajat et al., 2013; Kjolhede, Gustafsson, Gustafsson, & Nelson, 2014; Marchand, Durand, Juster, & Lupien, 2014). However, the casual relationships driving these associations have not been established, and it is possible that some of the physical and/or mental health outcomes could be influencing salivary cortisol levels, either directly or indirectly via other biopsychosocial mechanisms.

With these limitations in mind, very few studies that have directly examined potential relationships between perceived unfair treatment and daily cortisol decline. Fuller-Rowell, Doan, and Eccles (2012) found that increasing levels of perceived discrimination was associated with a more shallow daily cortisol decline among white study participants. The opposite was true among black participants, as they exhibited a steeper and presumably more healthy daily cortisol decline when reporting higher levels of perceived discrimination. In their study of Mexican American adolescents, Zeiders, Doane, and Roosa (2012) found no significant relationship between daily cortisol decline and perceived discrimination, although they did observe significant associations with other aspects of the diurnal cortisol pattern.

Despite the current lack of published significant relationships between daily cortisol decline and perceived discrimination among minority group members, previous research has found that the daily cortisol decline is typically flatter among members of minority racial/ethnic groups (Cohen et al., 2006; DeSantis et al., 2007; Hajat et al., 2010; Karlamangla, Friedman, Seeman, Stawksi, & Almeida, 2013), and individuals with lower levels of socioeconomic status, whether it is measured in terms of education (Dowd et al., 2011) or an index of income and wealth (Hajat et al., 2010). However, these sociodemographic patterns are not consistently

observed across all studies, probably due in some part to the wide variation in salivary cortisol sampling protocols and methods of statistical analysis (Dowd, Simanek, & Aiello, 2009).

Another potential source of ambiguity is the fact that the social patterning of exposures that may be associated with chronic stress and subsequent daily cortisol decline have not been fully examined. Three recent population-based studies have used multilevel modeling techniques to begin looking at the relationship between diurnal cortisol patterns and both individual- and neighborhood-level stressors. Using data from the Multi-Ethnic Study of Atherosclerosis (MESA) Stress Study, Hajat et al (2010) found that black and Hispanic participants had lower waking cortisol levels relative to whites, and that these differences remained statistically significant after adjusting for known health behaviors (e.g., smoking) and psychosocial factors (e.g., cynical hostility) that have been previously associated with cortisol levels. Black participants also had flatter rates of late-day cortisol decline compared to whites, and this finding was also robust to adjustment for health behaviors and psychosocial factors.

Do and colleagues used the same data set but focused their analyses on neighborhood-level covariates derived from the MESA Community Survey (Do et al., 2011). Reports of higher levels of neighborhood violence were associated with lower cortisol levels at wake-up and slower rates of morning cortisol decline among residents enrolled in the MESA Stress study. Lower levels of social cohesion and higher levels of disorder were also associated with a trend toward lower waking cortisol levels, but these patterns were less consistent than those associated with neighborhood violence. Do and colleagues reported that the black and Hispanic participants in the MESA Stress study were much more likely to reside in neighborhoods that were in the lowest tertile for social cohesion and the highest tertiles for violence and disorder.

Race/ethnicity was controlled for in the multilevel models and was not reported as a separate predictor of cortisol levels.

It is important to note that the MESA Community Survey was comprised of a separate set of respondents who lived within one mile of each MESA Stress Study participant and were sampled via random digit dialing or list-assisted methods. While this design allows for an independent assessment of neighborhood-level conditions, it cannot directly assess how individual perceptions of one's neighborhood may relate to individual diurnal cortisol patterns. Additionally, it is not known how the interaction between individual- and neighborhood-level sociodemographic characteristics may influence individual perceptions of the neighborhood, and how this interplay may relate to diurnal cortisol patterns.

The third population-based study to use a multilevel approach for modeling diurnal cortisol patterns utilized data from the Chicago Community Adult Health Study (CCAHS). Karb et al (2012) reported that participants living in areas with higher levels of perceived neighborhood stress exhibited a flatter slope for cortisol decline over the course of the day. Similar cortisol patterns were found when examining objective measures of neighborhood stressors derived from the study's systematic social observation protocol, Census data, and Unified Crime Reports. Individual-level characteristics including gender, educational attainment, depression, alcohol use, and physical activity were also associated with various aspects of the diurnal cortisol pattern, but the neighborhood level effects remained statistically significant after adjusting for these factors. Notably, Karb and colleagues did not find any significant relationships between race and waking cortisol level, morning cortisol increase, or daily cortisol decline.

As with the MESA Study, it is important to note how the subjective neighborhood level variables were generated in the CCAHS. Karb et al report that their perceived neighborhood stress measure was comprised of five scales – perceived disorder, perceived violence, neighborhood safety, physical hazards, and quality of neighborhood services – that were included in the CCAHS resident surveys and aggregated up to create standardized neighborhood-level scores. In this case, the originally measured individual perceptions of the neighborhood stressors may be more closely related to individual changes in diurnal cortisol patterns than an aggregated measure of perceived stress from multiple neighborhood residents. Thus, it may be more appropriate to treat each of these scales or even the composite perceived neighborhood stress measure as an individual-level covariate rather than a true neighborhood-level variable.

While findings from the MESA Stress Study and CCAHS provide an interesting first look at the relationships among individual-level stress, neighborhood-level stressors, and diurnal cortisol patterns, many questions still remain. Of particular importance to the conceptual model developed in Chapter 2 and the findings reported in Chapter 3 is the question of how individual- and neighborhood-level sociodemographic factors may shape individual's exposure to the stressors. More specifically, do minority residents who live in neighborhoods with a greater percentage of co-ethnic minorities exhibit *less* dysregulated cortisol profiles, net of objective neighborhood-level socioeconomic factors? If so, can this relationship be at least partially explained lower levels of perceived unfair treatment?

The purpose of this study is to examine contextual factors (i.e., individual sociodemographic characteristics, neighborhood sociodemographic characteristics) which may be associated with: 1) individual perceptions of acute and everyday unfair treatment, 2) average

daily decline in salivary cortisol levels, and 3) the potential relationship between perceived unfair treatment and daily salivary cortisol decline. To begin addressing these issues, I use data from the Healthy Environments Partnership (HEP) Wave 2 Community Survey and the Race/Ethnicity, Psychosocial and Environmental Stressors, and Telomere Length examine potential individual- and neighborhood-level covariates of cortisol dysregulation.

Methods

Data Sources

Data for this analysis came from three sources. Information regarding individual-level sociodemographics and perceived unfair treatment were collected as part of the Health Environments Partnership (HEP) Wave 2 Community Survey. The HEP Wave 2 Community Survey was conducted in 2008 as a follow-up to the initial survey launched in 2002. The first HEP survey was a stratified two-stage probability sample of Detroit residents living in one of three areas that were chosen for their relative sociodemographic diversity (Schulz et al., 2005). The 2008 Wave 2 survey attempted to re-contact original survey respondents and collect additional information regarding their perceptions of the neighborhood physical and social environment, stressful experiences, physical activity, other health behaviors, and current cardiovascular health status. Of the 919 Wave 1 HEP Community Survey participants, 219 were successfully enrolled into the Wave 2 survey. An additional 241 residents living on the same block as unreachable respondents from the Wave 1 survey were enrolled into the study, for a total of 460 participants.

Salivary cortisol samples were collected from a subset of the HEP Wave 2 Community Survey participants as part of the Race/Ethnicity, Psychosocial and Environmental Stressors, and

Telomere Length study, which will subsequently be referred to as the Telomere Study. The 460 HEP Wave 2 participants represent the universe of eligible individuals for the Telomere Study. During the course of the HEP Wave 2 interview, participants were given a brief overview of the Telomere Study aims, participation requirements, and payment for study participation. If the HEP Wave 2 participant indicated that he or she was interested in learning more about the Telomere Study, their contact information was forwarded to the Telomere Study assistant project director for follow-up. Of the 262 HEP Wave 2 participants who were contacted by the assistant project director and expressed interest Telomere Study enrollment, 241 individuals completed the study interview and provided either blood (n = 2), saliva (n = 12), or both blood and saliva (n = 227) samples for analysis. Because the cortisol levels were obtained via saliva samples, the two participants who only provided blood samples were ineligible for the current analysis.

Finally, Telomere Study participants' street addresses were used to geocode the data set and link it to the 2010 U.S. Census block group definitions for the city of Detroit. Block groups are used to represent each participant's neighborhood of residence at the time of their enrollment in the Telomere Study. Between the time of the HEP Wave 2 survey and enrollment into the Telomere Study, five participants moved from a block group that was within one of the three HEP-defined study areas (i.e., Eastside, Northwest, or Southwest Detroit) to a block group that was outside of the study area boundaries. These participants were excluded from the current analyses, as the answers that they provided during the HEP Wave 2 survey reflect different neighborhoods than those in which they were living in at the time of the Telomere Study's cortisol sample collection. Following the merger of the HEP Wave 2 survey, Telomere Study cortisol results, and 2010 Census block group data, the total of 234 individuals were initially eligible for this study.

The Telomere Study was approved by the University of Michigan Health Sciences and Behavioral Sciences Institutional Review Board and the HEP Steering Committee. Members of the HEP Steering Committee's Data Use Subcommittee reviewed the proposal for the current analysis and granted permission for the secondary use of their data set.

Cortisol collection & measurement

Approximately four to seven days prior to their Telomere Study clinic appointment or home visit, enrolled participants received a set of nine numbered saliva collection tubes. On the three weekdays immediately prior to their scheduled clinic appointment or home visit, participants were instructed to remove the cotton roll from the sequentially numbered tubes, chew on the cotton roll for approximately one minute, return the cotton roll to the tube without touching the cotton, and record the time of the sample collection on the sheet provided. The instructions also specified that the saliva collection should take place at three particular time points on each of the three days: immediately after waking up and before getting out of bed; 30 minutes after waking up and before eating, brushing teeth, or smoking; and immediately before going to bed in the evening, at least 30 minutes after eating, brushing teeth, or smoking. The set of nine saliva collection tubes were returned to the assistant project director during the clinic appointment or home visit. All samples were logged and stored at -80 ºC in the Central Ligand Assay Satellite Services (CLASS) laboratory of the University of Michigan School of Public Health until being shipped on dry ice to the University of Trier Psychobiology Laboratory for analysis. The laboratory's salivary cortisol assay procedures are described in detail elsewhere (Dressendorfer, Kirschbaum, Rohde, Stahl, & Strasburger, 1992). Each cortisol sample was run in duplicate and the intra-assay coefficients of variation (CV) were recorded. The laboratory

received no identifying or sociodemographic information about the participants and provided results linked to the unique randomly-generated identification number assigned to each participate upon enrollment in the Telomere Study.

As illustrated in Figure 1-1 and described in Kudielka et al (2012), cortisol secretion occurs in a time dependent, pulsatile pattern over the course of 24-hour period. While other studies have examined multiple components of this daily pattern, I chose to focus on the daily cortisol decline for four reasons. First and foremost, the decline in cortisol levels over the course of the day – sometimes referred to as the diurnal slope – is thought to be less dependent on the circadian light cycle than the post-waking rise in cortisol levels, commonly referred to as the cortisol awakening response or CAR (Kudielka et al., 2012). Thus, measuring the daily decline in cortisol values from wake-up to bedtime excluding the CAR should yield a measure that is less prone to bias related to circadian control (Smyth, Hucklebridge, Thorn, Evans, & Clow, 2013), differences between workdays and non-workdays (Schlotz, Hellhammer, Schulz, & Stone, 2004) , and error introduced by mistimed sample collection (Smyth, Clow, Thorn, Hucklebridge, & Evans, 2013). In addition, recent work has noted that while there is still considerable intra-individual variation over long periods of time, daily cortisol decline is more stable than the CAR (Ross, Murphy, Adam, Chen, & Miller, 2014), is more closely related to other aspects of the diurnal cortisol pattern (Clow, Hucklebridge, Stalder, Evans, & Thorn, 2010; Golden et al., 2013), and is more conceptually relevant to the biological assessment of chronic stress exposure (Hellhammer, Wüst, & Kudielka, 2009). Perhaps owing to this increased intra-individual stability and conceptual relevance, previous empirical findings related to sociodemographic characteristics have been most consistent when examining patterns of daily

cortisol decline rather than other aspects of the diurnal pattern (i.e., waking levels, bedtime levels, or CAR) (Dowd et al., 2009).

While no professional societies have established precise guidelines, several review papers have set forth basic principles for the collection and analysis of salivary cortisol samples (Hellhammer et al., 2009; Kudielka et al., 2012; Smyth, Hucklebridge, et al., 2013). Following these recommendations, participants were excluded from the analysis if, on all three study days, the wake-up saliva sample was collected before 4 AM or after 11 AM. Participants were also excluded if all three days of bedtime saliva samples were collected less than 12 hours or more than 20 hours after the wake-up sample. Together, these saliva sampling time criteria resulted in the removal of 9 participants from the analysis (see Table 4-1).

To estimate the daily cortisol decline in this study, the waking cortisol level was subtracted from the bedtime cortisol level and divided by the number of hours between the two sample collection times. This process was repeated for each available day of eligible cortisol data. Of the 184 eligible participants, 124 (67.4%) had valid daily cortisol decline data for all three sampling days. Forty-eight participants (26.1%) had valid cortisol data for 2 of the 3 sampling days, with the remaining 12 participants (6.5%) only having a valid daily cortisol decline for one sampling day. Following a range check of the otherwise eligible cortisol data, one participant was removed from the analysis due to intra-assay coefficient of variance values greater than 20% and three participants were removed due to cortisol values that were both greater than three standard deviations above the study's mean and outside the expected physiological range. All remaining available daily cortisol decline data were used to create an individual-specific mean daily cortisol decline measure. This measure served as the primary outcome measure representing individual-level biological stress response.

Other studies have used more complex models such as multilevel linear splines to approximate the daily cortisol decline (Karb et al., 2012; Sanchez, Wu, Raghunathan, & Diez-Roux, 2012). However, that approach requires setting at least one knot for the splines. Given that the Telomere Study only collected saliva at three time points across the day, and that the second time point was selected to measure the CAR, using a multilevel linear spline approach would have required incorporating the CAR into the daily cortisol decline model. I chose not to use this approach given the prior discussion regarding the potential for CAR and daily cortisol decline to be subject to different source of physiologic regulation. This decision follows the precedent set by DeSantis, et al (2007).

Even if one or more additional cortisol measures were available in the Telomere Study, the only day-specific information that was collected was the time of the saliva sample. As such, adding a third, collection day-specific level nested within the current two-level regression model would have yielded only one additional covariate (i.e., collection time) to address the intra-individual variation in daily cortisol decline. Fortunately, Kraemer and colleagues (2006) found that the daily cortisol decline calculated from two cortisol measures (wake-up and evening) were highly correlated with a four sample measure of daily cortisol decline. Based on their findings and to reduce bias related to the previously discussed CAR, issues the 30 minute post-awakening samples were excluded from the slope calculation.

Demographic and survey measures

Perceived unfair treatment

Previously validated measures of everyday and acute unfair treatment were used in the HEP Wave 2 survey, with some minor modifications (Williams, Yu, Jackson, & Anderson,

1997). The *acute unfair treatment* scale ascertained whether participants had experienced unfair treatment in one of seven domains within the past 12 months: unfair treatment at work, from police or immigration officials, at school, while getting housing or other resources, while seeking health care, or while obtaining other services. One point was assigned for each affirmative response. The scores from the seven items were summed and then divided by seven to yield a possible maximum score of 1. Because acute unfair treatment is central to the study questions, the two individuals who did not respond to this portion of the survey were excluded from the analyses.

The *everyday unfair treatment* measure asked participants to report, on a 5-point scale from "never" to "always," how frequently they experienced five less severe interactions: being treated with less courtesy or respect, receiving poorer service, being treated as if not smart, acting afraid of you, or feeling threatened or harassed. Scores from the five items were summed and divided by five to yield a range of scores from 0 to 5.

Individual-level sociodemographics

Race/ethnicity. Due to the hypothesized importance of the relationship between individual race/ethnicity and neighborhood racial/ethnic composition, the analysis will be limited to participants who report their racial/ethnic background as non-Hispanic white, non-Hispanic black, or Hispanic. Two individuals who reported their race to be "Other, non-Hispanic" and one individual of an unspecified multiracial background were excluded from the study.

Gender. Previous studies have been inconsistent, as some report flatter daily cortisol declines among females (Hajat et al., 2010; Karb et al., 2012), others report males are worse off (Karlamangla et al., 2013; Kumari et al., 2010), and still others have found no significant gender

differences (DeSantis et al., 2007; Skinner et al., 2011). Nevertheless, gender is included in the models.

Age was operationalized as a continuous variable. Previous research has indicated that the daily cortisol decline is flatter with increasing age (Karlamangla et al., 2013; Kumari et al., 2010; Nater, Hoppmann, & Scott, 2013), therefore age was controlled for in all analyses.

Poverty-to-income ratio (PIR) was dichotomized, with participants reporting an annual household income level below that of the federal, household size-adjusted poverty level (i.e., PIR < 1) as the group of interest. Twenty-one participants were excluded from the analysis due to missing data PIR data.

Highest level of education was divided into four categories: less than a high school degree, high school degree or GED, some college or an associate's degree, and college degree or higher. Four participants reported "other" as their highest level of education and were excluded from this analysis.

Neighborhood-level sociodemographics

Neighborhood racial/ethnic concentration was measured for non-Hispanic whites, non-Hispanic blacks, and Hispanics of all racial backgrounds at the census block group level using data from the 2007-2011 American Community Survey estimates. The 5-year period of the ACS data set completely encompasses the Telomere Study data collection period (2008-2010), as well as the recent recession and housing crises.

Neighborhood socioeconomic status was assessed using the percentage of block group households with a poverty-to-income ratio (PIR) of less than one. This is the same type of SES

measure that was used at the individual level, but was derived from the 2007-2011 ACS estimates rather than an aggregation of the individual-level data from HEP participants residing within the same block group.

Potential confounders of the stress-cortisol relationship

Current medications. Given prior research linking variation in cortisol levels to steroid medications (Granger, Hibel, Fortunato, & Kapelewski, 2009), I examined current medication usage as reported during the Telomere Study interview. The medication listings were reviewed and dichotomized as currently taking / not currently taking steroid medications. Seven participants were removed from the analysis due to report of their self-report of currently taking a corticosteroid medication that could influence the salivary cortisol measurement.

Body mass index (BMI) has also been associated with cortisol secretion (Ranjit, Young, Raghunathan, & Kaplan, 2005). However, BMI may also be associated with stress via a number of mechanisms including stress-related eating (Torres & Nowson, 2007) or reduced physical activity (Moore-Greene, Gross, Silver, & Perrino, 2012). BMI was thus included in the regression models, and was coded into the three standard categories of normal (< 25), overweight (25-29.9), or obese (≥ 30).

Finally, *smoking* has been previously associated with flatter daily cortisol declines (Kumari et al., 2010), and is frequently considered to be stress-related health behavior (Cohen et al., 2006; Ranjit et al., 2005). To account for the potential confounding relationships, HEP survey measures of current smoking status (yes/no/former smoker) was used to account for individual level variation in tobacco use.

Sample Demographics

The final sample for this study consisted of 184 participants living within one of 49 census block groups in the three HEP study areas. A summary of the various exclusion criteria and the number of HEP Wave 2 participants omitted from the analysis can be found in Table 4-1.

The basic demographics of the study sample are reported in Table 4-2. Reflecting the recent economic challenges facing many Detroiters, the nearly half of our sample reported annual household incomes that are below the federal poverty level, adjusted for household size. The almost uniformly disadvantaged socioeconomic status of the study population across racial/ethnic groups may have important implications for the interpretation and generalizability of the study results.

Compared to those with complete data on all measures, cortisol-eligible individuals who were missing data on one of the key covariates reported significantly lower levels of both acute (0.12 vs. 0.24; $p = 0.02$) and everyday unfair treatment (1.47 vs. 1.87; $p < 0.01$). Individuals with missing data were also somewhat more likely to be Hispanic (23.4% of individuals with missing data vs. 9.4% of the study population; $p = 0.07$) and to have a flatter daily cortisol decline (-0.255 vs. -0.393; $p = 0.07$). These differences between the included and excluded participants could introduce bias into the study findings.

Analysis

Descriptive statistics, univariate regression models, multivariate linear regression models, used to assess the patterning of perceived acute and everyday discrimination within the study population. To maximize the available multi-day cortisol data and provide a more nuanced

analysis of contextual factors at both the individual- and neighborhood-level, I used two-level random coefficient models, nesting individuals within block groups with the xtmixed command in Stata 13.

Results

Everyday unfair treatment as an outcome

As anticipated, black participants reported significantly higher levels of everyday unfair treatment relative to whites. Everyday unfair treatment levels were highest and most statistically significant among black participants with poverty-to-income ratios above 1. Hispanic participants also reported higher levels than whites but lower levels than black participants. Neither the Hispanic-white nor the Hispanic-black differences reached statistical significance

In multivariate models, higher everyday unfair treatment levels were associated with younger age, being male, and having a college degree. The ICC for the fully adjusted individual-level models indicate that almost 9% of the variation in everyday unfair treatment was attributable to variation at the block group level. Block group-level racial/ethnic concentration and SES, as measured by the percentage of households with PIR < 1, were not associated with everyday unfair treatment. However, including either the percentage of black neighborhood residents or the percentage of white neighborhood residents modestly reduced the statistical significance of the difference between black and white participants.

Acute unfair treatment as an outcome

Surprisingly, descriptive statistics indicated that there was no statistically significant difference in levels across racial/ethnic groups. In multivariate models, higher acute unfair

treatment levels were associated with being male and having a college degree. In the fully adjusted individual-level models, 13% of the variation in acute unfair treatment was attributable to variation at the block group level. Neither block group percentage of black residents, percentage of Hispanic residents, nor block group SES were associated with acute unfair treatment. However, the block group percentage of white residents was significantly and *negatively* associated with acute unfair treatment. The addition of percent white residents also reduced the variation in acute unfair treatment attributable to block group-factors from 13% to 8%.

Daily cortisol decline

The mean daily cortisol decline was significantly less among Black participants. In exploratory analyses that subdivide white, black, and Hispanic participants by PIR level, the relationship with daily cortisol decline appears to be strongest among black participants with PIR < 1. Hispanic participants also significantly flatter daily cortisol decline compared to whites, but it is still greater than the mean decline among blacks.

In multivariate models, lower daily declines in cortisol levels were associated with older age, having a high school degree (relative to having a college degree), being a current smoker, and reporting higher levels of everyday unfair treatment. Reporting higher levels of acute unfair treatment also had a modest but consistent effect throughout out the models.

Adding block group-level variables to the model yielded several statistically significant results. First, higher percentages of neighborhood households with PIR < 1 was associated with a less steep mean daily cortisol decline. The addition of black neighborhood racial concentration resulted in a more complex set of relationships. Overall, higher percentages of black

neighrbohood residents were associated with a significantly less steep daily cortisol decline. However, the decrease in the magnitude of the cofficient for black study participants indicates that, when black neighborhood racial concentration is incorporated into the model, the black-white difference in mean daily cortisol decline becomes smaller, yet is still statistically significant (Table 4-5, model 5 vs. model 6). In addition, the coefficient for acute life events is not statistically significant once the neighborhood percentage of black residents is added to the model. Incorporating the percentage of Hispanic neighborhood residents has the opposite result, as higher percentages of Hispanic residents are associated with greater mean daily cortisol declines (Table 4-5, model 7). Again, the coefficients for both black and Hispanic study participants are attenuated in with the addition of this neighborhood composition measure, but they are still significantly different from whites. The percentage of white residents had no significant effect on daily decline, nor on other covariates within the model. In the full individually-adjusted model, the amount of block group attributable variation in cortisol daily decline was nearly 14%. Adding the block group –level covariates reduced this figure to ~9%

Discussion

The sociodemographic patterning of everyday and acute unfair treatment is similar in terms of gender and education, but differs with respect to the associations with individual race/ethnicity, depressive symptoms, and block group percentages of white residents. The flatter mean daily cortisol decline observed among black participants may be an indicator of biological stress response dysregulation and/or greater levels of cortisol exposure throughout the day. Each of these underlying affects may be detrimental to one's health.

One counterintuitive finding is that while individuals with a college education and black participants with higher PIR report higher levels of unfair treatment, they also have more robust or "healthier" daily cortisol declines. While these two findings may not be causally related to one another, it is possible that having additional financial or other forms of supportive resources associated with having a college education or higher PIR help mitigate the otherwise detrimental biopsychosocial effects of perceived unfair treatment. It is also possible that the relationship could work in the opposite direction: having greater access to various resources associated with higher levels of education or PIR may also lead to a more conscious understanding of unfair treatment when it occurs, and as such, more active and effective coping with the situation.

Finally, the measured neighborhood sociodemographic features are of greater statistical significance to daily cortisol declines than the two unfair treatment measures. This suggests that there may be unexplored aspects of the neighborhood social or physical environment that are both related to neighborhood socioeconomic status and/or racial composition and diurnal cortisol patterns. Post-hoc exploratory analyses of several types of neighborhood perceptions, including sense of community, neighborhood social environment, neighborhood physical environment, and neighborhood satisfaction yielded largely non-significant findings. The one exception was a five-item measure assessing negative aspects of the neighborhood social environment, including gang activity and loitering: higher scores on this measure were associated with flatter daily cortisol decline. Additional exploration of this and other perceptions of the neighborhood environment may identify actionable aspects of the neighborhood environment that could improve diurnal cortisol patterns and potentially improve residents' health.

There are several limitations to this study, starting with the small sample size. With less than 40 participants in the white and Hispanic subpopulations, the stratified sub-analyses lack the

power to detect more subtle predictors of unfair treatment and daily cortisol decline. In addition to the small sample size, there are several limitations to conducting a post-hoc, cross-sectional analysis. First, there non-random sources of measurement error could have been introduced via the cortisol assay process. While all samples were collected in the same manner and were analyzed by the same laboratory using standard protocols, the samples varied in the length of time they were frozen prior to analysis, with the Day 3 samples remaining in storage for the longest period of time. This issue is partially addressed by averaging of the cortisol values across all eligible study days. There was also a varying degree of lag time between the completion of the HEP Wave 2 survey and the collection of the saliva samples as part of the Telomere Study. This lag time ranged from less than a month to nearly two years, with the average time between survey completion on saliva collection being 6 months. Given the recently-published evidence regarding the modest intra-individual correlation of repeated daily cortisol decline measures, the results described in this paper could be strengthened if the cortisol and survey measurements were completed at the same time (Ross et al., 2014).

Second, as is the case in most secondary data analyses, the measures that are available from the combined HEP-Telomere data set may not be the optimal measures of the constructs of interest within the conceptual model that is guiding the analysis. The HEP Wave 2 survey did use slightly modified versions of two previously-validated measures of unfair treatment, but these measures only capture the perceived or acknowledged occurrence of specific events. As with other stressors, individuals may be subjected to unfair treatment and have a physiological response to the unfair treatment even if they do consciously acknowledge the discrimination for what it is. Other researchers have posited that recognizing and actively coping with experiences of racial discrimination may help reduce its deleterious psychological effects (Williams &

Mohammed, 2009). Moreover, recent work by Hicken and colleagues suggests that the *anticipation* of race-related discrimination is associated with hypertension prevalence (Hicken, Lee, Morenoff, House, & Williams, 2014) and sleep difficulty (Hicken, Lee, Ailshire, Burgard, & Williams, 2013) among blacks. When considering the circadian influences on cortisol release and the previously described relationship between flattened daily cortisol decline and hypertension, one could make the argument that the modest association between acute unfair treatment and daily cortisol decline may belie a potentially more important relationship between race-related vigilance and daily cortisol decline.

Finally, within the broader context of the conceptual model presented in Chapter 2, this population and study design does not allow for a more direct test of the relationship between cortisol dysregulation and subtype-specific breast cancer risk. A much larger, prospective study would be necessary to adequately assess that potential relationship. The combined results from my studies may, at best, merely suggest that this proposed pathway be explored further.

Table 4-1: Summary of study exclusion criteria and final sample size

Total number of HEP 2008 Community Survey participants:	460
Number of participants excluded based on the following criteria:	
Did not participate in the Telomere study	222
Home address at the time of saliva collection was outside of the HEP study areas	5
Key variables with incomplete data (unfair treatment, PIR) or designated as "other" (race/ethnicity, education)	30
Did not meet one or more of the saliva sample collection standards on all 3 collection days	9
Unreliable or unrealistic cortisol values for all 3 collection days	3
Self-report of relevant steroid medication usage during the past week	7
Total number of eligible participants:	**184**

Table 4-2: Participant characteristics

	Full sample:	White:	Black:	Hispanic:
Number of respondents (% of total)	184	38 (20.7%)	103 (56.0%)	43 (23.4%)
Mean age (SD)	49.7 (12.1)	54.8 (12.5)	50.1 (11.0)	44.2 (12.5)
Sex:				
Female (%)	131 (71.2%)	25 (65.8%)	77 (74.8%)	29 (67.4%)
Male (%)	53 (28.8%)	13 (34.2%)	26 (25.2%)	14 (32.6%)
Poverty-to-income ratio < 1 (%)	88 (47.8%)	19 (50%)	49 (47.6%)	20 (46.5%)
Highest education level:				
Less than high school degree (%)	57 (31.0%)	13 (34.2%)	22 (21.3%)	22 (51.2%)
High school degree or GED (%)	46 (25.0%)	5 (13.2%)	31 (30.1%)	10 (23.3%)
Some college (%)	63 (34.2%)	12 (31.6%)	42 (40.8%)	9 (20.9%)
College degree or higher (%)	18 (9.8%)	8 (21.1%)	8 (7.8%)	2 (4.7%)
Smoking status:				
Never smoked (%)	73 (39.7%)	12 (31.6%)	38 (36.9%)	23 (53.5%)
Current smoker (%)	59 (32.1%)	14 (36.8%)	38 (36.9%)	7 (16.3%)
Former smoker (%)	52 (28.3%)	12 (31.6%)	27 (26.2%)	13 (30.2%)
Body mass index (BMI):				
Normal (18.0 - 24.9) (%)	32 (17.4%)	8 (21.1%)	22 (21.4%)	2 (4.7%)
Overweight (25.0 - 29.9) (%)	50 (27.2%)	9 (23.7%)	29 (28.2%)	12 (27.9%)
Obese (>= 30) (%)	102 (55.4%)	21 (55.3%)	52 (50.5%)	29 (67.4%)
Current medication usage:				
Using psychotropic medication (%)	11 (6.0%)	6 (15.8%)	5 (4.9%)	0
Using HRT or oral contraceptives (%)	4 (2.2%)	2 (5.3%)	2 (1.9%)	0

Table 4-3: Block group characteristics

	Full sample:	**White:**	**Black:**	**Hispanic:**
Number of respondents (% of total)	184	38 (20.7%)	103 (56.0%)	43 (23.4%)
Number of unique block groups	49	18	39	14
Mean % of block group with PIR < 1 (SD)	44.7% (17.9)	49.3% (14.7)	43.8% (19.1)	44.0% (14.9)
Block group (BG) racial/ethnic composition:				
Mean % BG non-Hispanic white alone (SD)	9.9% (10.1)	16.2% (8.3)	9.1% (10.0)	15.9% (10.6)
Mean % BG non-Hispanic black alone (SD)	69.2% (35.6)	38.0% (38.5)	77.4% (28.5)	21.8% (31.0)
Mean % BG Hispanic (SD)	18.8% (31.1)	44.5% (38.1)	11.2% (22.5)	60.7% (29.5)

Table 4-4: Unadjusted distribution of key variables across racial/ethnic groups

	Full sample:	**White:**	**Black:**	**Hispanic:**
Number of respondents (% of total)	184	38 (20.7%)	103 (56.0%)	43 (23.4%)
Mean # depressive symptoms (SD)	2.72 (0.52)	2.71 (0.51)	2.73 (0.54)	2.69 (0.48)
Unfair treatment / discrimination:				
Mean acute unfair treatment (SD)	0.24 (0.26)	0.23 (0.22)	0.28 (0.28)	0.17 (0.21)
Mean everyday unfair treatment (SD)	1.87 (0.69)	1.66 (0.49)	**1.97 (0.72)**	1.81 (0.74)
Diurnal cortisol measures, nmol/L:				
Mean wake-up cortisol level (SD)	10.17 (6.09)	12.68 (6.72)	**9.19 (6.47)**	**10.28 (3.42)**
Mean bedtime cortisol level (SD)	4.46 (4.41)	4.11 (5.30)	5.09 (4.57)	3.26 (2.61)
Mean hourly cortisol decline (SD)	- 0.39 (0.40)	- 0.62 (0.45)	**- 0.27 (0.38)**	- 0.49 (0.28)

* Bolded statistics indicate unadjusted, statistically significant difference from white participants' results ($p \leq 0.05$)

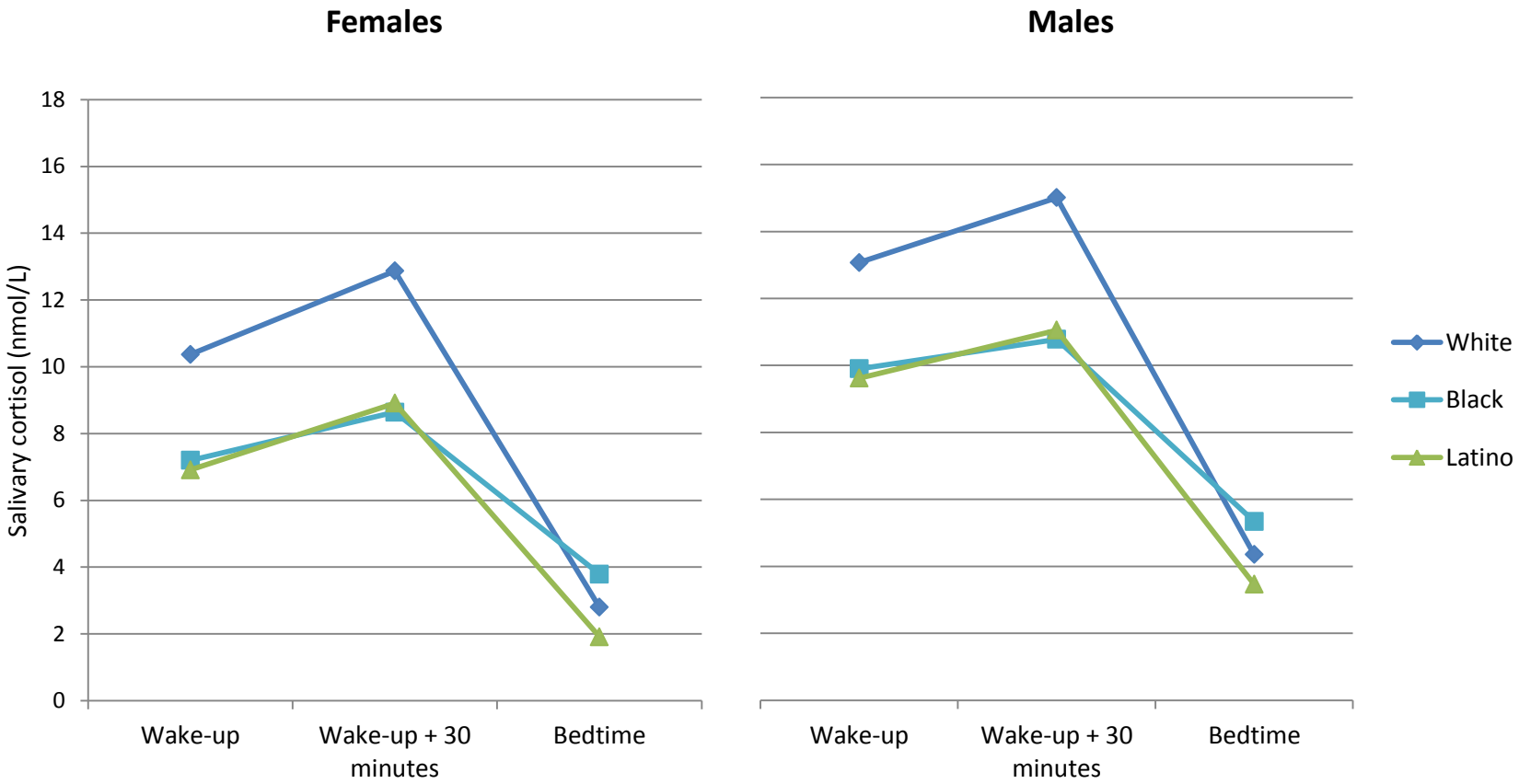
Table 4-5: Two-level models of mean hourly decline in salivary cortisol levels & acute unfair treatment (n = 184)

	Model 1	Model 2	Model 3	Model 4	Model 5	Model 6	Model 7	Model 8
Level 1 coefficients								
Race: [ref = White]								
Black		0.336**	0.318**	0.325**	0.338**	0.227**	0.213**	0.347**
Hispanic		0.150^	0.149^	0.192*	0.196*	0.229**	0.238**	0.194*
Poverty-to-Income Ratio < 1		-0.050	-0.047	-0.047	-0.045	-0.034	-0.026	-0.045
Age (in years)		0.004^	0.004	0.003	0.002	0.002	0.002	0.002
Female		0.011	0.034	0.061	0.068	0.072	0.079	0.069
Education: [ref = college]								
Less than high school		0.214*	0.260*	0.188^	0.148	0.131	0.130	0.150
High school degree / GED		0.248*	0.297**	0.236*	0.208*	0.195^	0.193^	0.209*
Some college		0.138	0.157	0.116	0.079	0.072	0.063	0.079
Acute unfair treatment			0.213^	0.196^	0.190^	0.172	0.178^	0.194^
Smoking status: [ref = never]								
Current smoker				0.151*	0.166*	0.181**	0.180**	0.164**
Former smoker				0.091	0.095	0.095	0.093	0.095
BMI: [ref = normal]								
Overweight				-0.009	-0.018	-0.006	-0.002	-0.019
Obese				0.070	0.066	0.074	0.082	0.067
Level 2 coefficients								
% residents with PIR < 1					0.005**	0.004**	0.004**	0.005**
% Black residents						0.003*		
% Hispanic residents							-0.003**	
% White residents								0.001
Residual variance, $\hat{\theta}$	0.135	0.121	0.119	0.112	0.110	0.107	0.108	0.111
Conditional variance, $\hat{\psi}$	0.025	0.013	0.013	0.016	0.012	0.011	0.009	0.011
Composite error, $\hat{\xi}$	0.160	0.134	0.132	0.128	0.122	0.118	0.117	0.122
ICC	0.158	0.096	0.095	0.128	0.097	0.094	0.075	0.091

Table 4-6: Two-level models of mean hourly decline in salivary cortisol levels & everyday unfair treatment (n = 184)

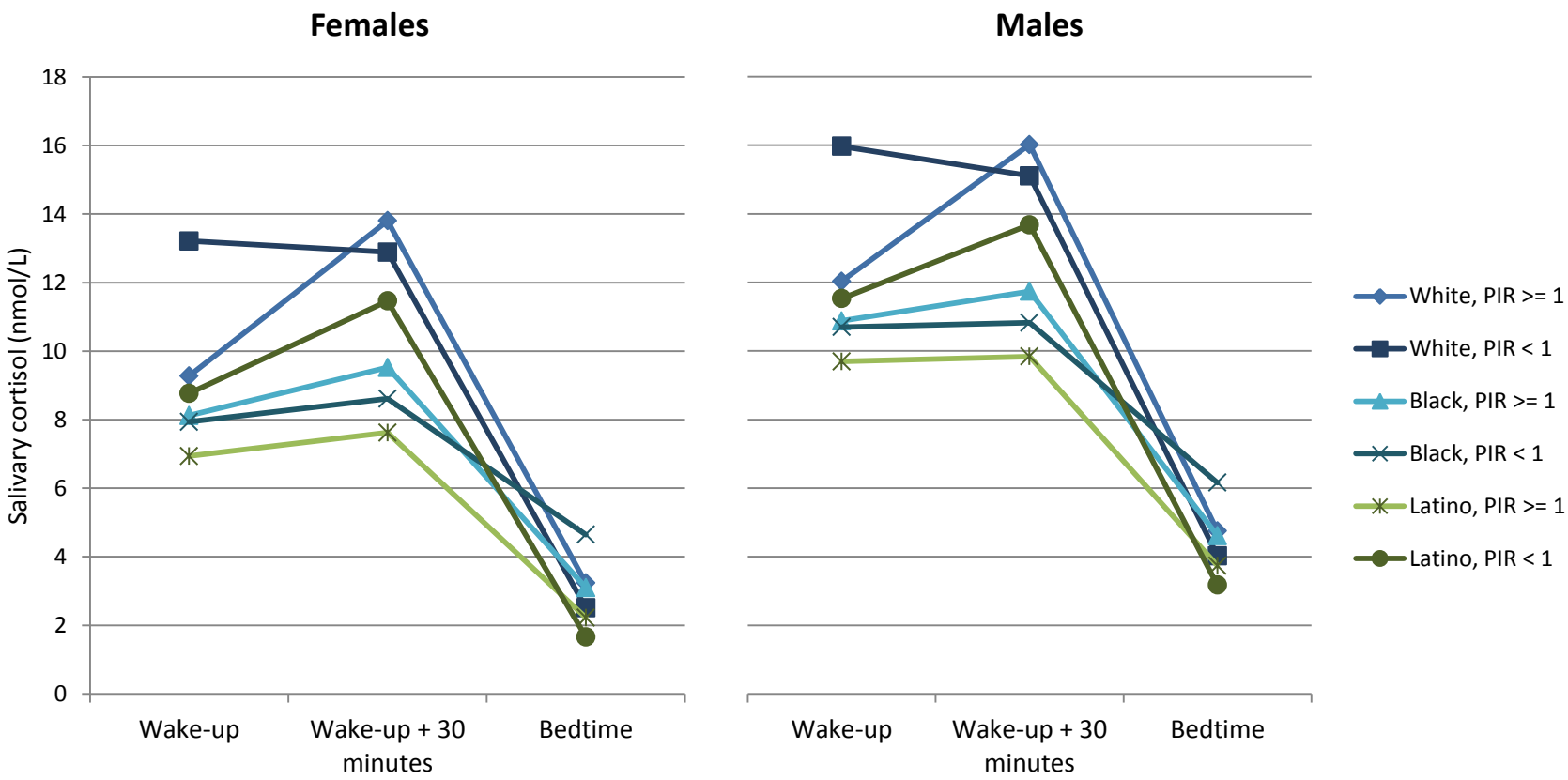
	Model 1	Model 2	Model 3	Model 4	Model 5	Model 6	Model 7	Model 8
Level 1 coefficients								
Race: [ref = White]								
Black		0.336**	0.317**	0.325**	0.337**	0.218*	0.205*	0.340**
Hispanic		0.150^	0.146^	0.187*	0.188*	0.224**	0.232**	0.188*
Poverty-to-Income Ratio < 1		-0.050	-0.049	-0.049	-0.047	-0.035	-0.026	-0.047
Age (in years)		0.004^	0.004^	0.004	0.003	0.003	0.003	0.003
Female		0.011	0.025	0.051	0.059	0.065	0.072	0.059
Education: [ref = college]								
Less than high school		0.214*	0.232*	0.160	0.123	0.109	0.108	0.123
High school degree / GED		0.248*	0.254*	0.195^	0.170	0.161	0.158	0.170
Some college		0.138	0.151	0.108	0.073	0.067	0.058	0.073
Everyday unfair treatment			0.068^	0.057	0.060	0.061	0.063	0.060
Smoking status: [ref = never]								
Current smoker				0.148*	0.163*	0.178**	0.177**	0.162*
Former smoker				0.097	0.099	0.099	0.097	0.100
BMI: [ref = normal]								
Overweight				0.005	0.005	0.009	0.013	-0.005
Obese				0.075	0.072	0.080	0.088	0.072
Level 2 coefficients								
% residents with PIR < 1					0.005**	0.005**	0.005**	0.005**
% Black residents						0.003**		
% Hispanic residents							-0.004**	
% White residents								0.000
Residual variance, $\hat{\theta}$	0.135	0.121	0.118	0.112	0.111	0.108	0.108	0.111
Conditional variance, $\hat{\psi}$	0.025	0.013	0.014	0.017	0.012	0.011	0.008	0.012
Composite error, $\hat{\xi}$	0.160	0.134	0.132	0.129	0.123	0.119	0.116	0.123
Residual interclass correlation	0.158	0.096	0.103	0.132	0.096	0.091	0.072	0.094

Figure 4-1: Predicted mean cortisol levels, by gender and race/ethnicity



Margins set for high school graduate, non-smokers with a normal BMI and mean values for all other covariates

Figure 4-2: Predicted mean cortisol levels, by gender, race/ethnicity, and PIR status



Margins set for high school graduate, non-smokers with a normal BMI and mean values for all other covariates

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Chapter 5

Conclusions

The triple-negative subtype of breast cancer is etiologically and clinically distinct from the more common, less aggressive, and more treatable form of estrogen receptor-positive breast cancer. Numerous population-based studies have found that black women are 2 to 3 times more likely to develop triple-negative breast cancer than white women. Much of the existing research on racial disparities in breast cancer subtype has focused on identifying predisposing biological or genetic factors associated with African ancestry. However, this approach ignores growing multidisciplinary evidence suggesting that contemporary racial stratification shapes a wide range of environmental and social exposures that can subsequently impact cellular physiology and even gene expression patterns.

Chapter 1 of this dissertation introduces how a multidisciplinary, multilevel framework rooted in current empirical evidence and structurally oriented theory may provide some new insight into the persistence of racial/ethnic disparities in breast cancer subtype. Chapter 2 greatly expands upon this argument via the synthesis and critique of current evidence regarding subtype-specific breast cancer epidemiology, the purported role of African ancestry as a breast cancer risk factor, and potential relationships between stress and breast cancer risk. With this evidence in mind, I then introduce several theoretical perspectives that guide the integration of the empirical data into a new conceptual model of the potential origins of racial/ethnic disparities in

breast cancer subtypes. Among the various theories, Geronimus' weathering hypothesis provides a particularly useful analytic framework through which to consider how psychosocial and environmental stressors may structure the disruption of biological mechanisms according to race. Building upon this framework, I suggest that the ways in which structural forces shape neighborhood social environments may play an important – and as of yet untested – role in the biopsychosocial pathways that could ultimately impact gene expression patterns. Specific alterations in gene expression patterns may subsequently increase the risk of the more aggressive forms of breast cancer that are more prevalent among black American women.

I begin testing parts of the conceptual model in Chapter 3. Using data from the California Cancer Registry, the California Neighborhood Data System, and the 2000 U. S. Census, I identified significant variation in the odds of ER-/PR- breast cancer across racial/ethnic groups. More importantly, I found that the racial/ethnic groups also vary in terms of how neighborhood socioeconomic status and racial/ethnic concentration relate to ER-/PR- odds ratios, and that this neighborhood level patterning itself varies between highly segregated and less segregated metropolitan areas. While white women in every segregation and age group strata have lower odds of ER-/PR- breast cancer with increasing neighborhood socioeconomic status (SES), only younger black women appear to benefit from higher levels of neighborhood SES. Conversely, while black women as a whole had significantly lower odds of ER-/PR- breast cancer when living in neighborhoods with a higher percentage of black residents, this relationship was statistically significant only among older black women when the group was stratified by age at diagnosis. These findings indicate that much more work needs to be done in order to unpack the complex relationships among age (as it relates to both neighborhood tenure and more general life course phases), neighborhood characteristics (particularly the interplay between residential

stability and neighborhood sociodemographics), and biopsychosocial pathways that facilitate the observed association between neighborhood characteristics and odds of having a more aggressive subtype of breast cancer.

In Chapter 4, I begin to explore one potential biopsychosocial pathway that could link race-related stressors to racial variation in odds of being diagnosed with an ER-/PR- breast cancer. Previous work suggests that exposure to chronic stressors within racially and economically segregated residential neighborhoods may contribute to dysregulation of the cortisol feedback loop (Do et al., 2011; Karb, Elliott, Dowd, & Morenoff, 2012). Recent work by Ritter, Antonova, and Mueller (2012) suggests that dysregulation of the stress-mediated cortisol feedback loop reduces the expression of the critical tumor suppressor gene, BRCA1. Current evidence suggests that there are several molecular pathways by which loss of BRCA1 function may lead to the TNBC subtype (Santarosa & Maestro, 2012). It is therefore plausible that dysregulation of the stress-mediated cortisol feedback loop could increase the risk of developing TNBC via the cumulative impact of decreased BRCA1 expression.

In order to examine the relationships among perceived unfair treatment, neighborhood sociodemographic features, and daily cortisol decline, I conducted a multilevel of analysis of daily cortisol decline among residents of three Detroit areas. The results of this study suggest that perceived acute unfair treatment may have a modest association with flatter – presumably less well-regulated and thus less healthy – diurnal cortisol patterns. Neighborhood socioeconomic status and racial/ethnic concentration may also be related to variation in daily cortisol decline, but perhaps not in the direction that was expected based on the findings of my first empirical paper or prior salivary cortisol research.

Taken together, this work is just the beginning of an interdisciplinary, contextual examination of the potential social and biological mechanism that link institutional racism to risk of specific breast cancer molecular subtypes. Future steps in building this area of research may include: the study of longitudinal, nuanced residential histories in terms of exposure to racially structured psychosocial exposures and subtype-specific breast cancer incidence; gene-environment correlation studies that incorporate single nucleotide polymorphisms (SNPs) associated with specific breast cancer subtypes into analyses of race-related social exposures; and examinations of whether the previously reported positive association between percentage of African ancestry informative genetic markers and risk of triple negative breast cancer may be due to gene-environment correlation rather than ancestral genotype. Each of these research approaches are geared toward elucidating whether the association between breast cancer subtype and 1) putative risk-increasing SNPs, and/or 2) African genetic ancestry may be indirect, driven by the correlation between the *phenotype* of African ancestry – i.e., skin color – and socially patterned elements of the environment – i.e., race-related stress.

Through such structurally mindful research programs, the nascent field of social genomics may help unpack the multifaceted relationship between not only race/ethnicity and breast cancer subtype, but perhaps also other persistent racial/ethnic health disparities in the United States. Ultimately, results from these types of studies could be used to help identify policy or community actions to that address structural inequalities that contribute to worse health outcomes for racial/ethnic minority populations.

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