Title: Stress Reactivity among African American Breast Cancer Survivors
PI: Chanita Hughes-Halbert, PhD

SPECIFIC AIMS

Dysregulation of the HPA has been suggested as a mechanism through which social and biological factors contribute to racial disparities in breast cancer outcomes. The HPA axis plays a central role in regulating the physiological stress response; a prolonged and elevated glucocorticoid response following a social stressor predicts tumor growth rates and the development of mammary cancer in rats that histologically and etiologically resembles human disease. Many African Americans experience stressful life events and circumstances, including economic, discriminatory, and other stressors. These psychosocial factors may contribute to an increased risk of advanced stage breast cancer among African American women, but not all African American women who are exposed to adverse psychosocial and social stressors develop advanced stage breast cancer and African American women who have a limited number of stressors also develop advanced stage breast cancer, regardless of early detection. This may be because stress reactivity (SR), or one’s physiological and psychological responses to a stressor, is highly individualized and dependent on psychological and social determinants. However, empirical data are not available on stress reactivity among African American breast cancer survivors (MBCS) and how these reactions vary among women based on their exposure to chronic stressors and psychological characteristics. Empirical data are also lacking on the association between stress reactivity and cancer control behaviors among MBCS even though prior studies have shown that these women are less likely than whites to engage in health behaviors that are important to cancer control and research is now being conducted to understand how stress affects these behaviors. For instance, Haushofer and colleagues are examining the association between stress reactivity, executive control, and health behaviors as part of the Science of Behavior Change Network. This research is testing the hypothesis that stress: (1) promotes temporal discounting; (2) has an adverse effect on self-efficacy, and (3) reduces executive control. However, stress reactivity, and the association between these responses and cancer control behaviors (e.g., diet, physical activity, and treatment compliance), have not been examined among MBCS. Prior studies have shown that African Americans have a dysregulated stress response as a result of persistent exposure to chronic and acute stressors; this may alter stress responses and result in high levels of allostatic load. In order to develop effective behavioral interventions for MBCS, an important first step is to verify that the mechanisms (e.g., temporal discounting, self-efficacy) involved in health behaviors for cancer control are associated with stress reactivity among these women. Therefore, in response to RFA-RM-17-028, Science of Behavior Change: Use-Inspired Research to Optimize Adherence, Behavior Change Interventions, and Outcomes (R21), we propose to examine the associations between social determinants and SR among MBCS and validate the association between these responses and targeted mechanisms of behavior change as part of a prospective exploratory study that will address the specific aims described below. Through this, we intend to establish the foundation for interventions (third generation) and policy changes in cancer prevention and the delivery of cancer care services (fourth generation studies).

Aim 1: Characterize the nature and distribution of stress reactivity among African American breast cancer survivors based on socioeconomic, clinical, and social stressors. We will compare stress reactivity following a validated laboratory social stress test among African American breast cancer survivors (AABCS) based on variations socioeconomic, clinical, and social stressors. We predict that AABCS who have chronic SES stressors (e.g., low income, education, financial strain), greater clinical stressors (e.g., advanced stage disease), and social stress (e.g., social isolation) will have greater stress reactivity compared to those who have fewer SES, clinical, or social stressors. We will also examine glucocorticoid sensitivity (e.g., percent of neutrophils, percent lymphocytes, percent monocytes, ratio of neutrophil/lymphocytes) as a potential predictor of stress reactivity to the Trier Social Stress Test (TSST).

In recognition of the potential for African Americans to have a blunted reactivity, we will also examine the frequency of dysregulated responses as part of Aim 1. Specifically, a dysregulated response will be indicated when cortisol does not return to baseline levels after the stressor has subsided or when the peak response is a small change from baseline levels. Secondary analyses for this aim will involve categorizing participants into dysregulated response groups (cortisol responder or cortisol non-responder) based on the magnitude of cortisol changes. Logistic regression models will then be used to identify factors (e.g., social isolation, glucocorticoid sensitivity) that are associated with whether women have a dysregulated or non-dysregulated response.
Aim 2: Examine the effects of stress reactivity on temporal discounting by comparing delayed discounting immediately versus longer after exposure to a social stressor among AABCS. We will randomize participants to complete the Kirby Delay Discounting Task immediately (10 minutes) or longer (20 minutes) after exposure to the TSST. We predict that delayed discounting will be greater immediately (10 minutes) following stress exposure compared to longer (20 minutes) after stress exposure. Path analysis will be used to examine the direct and indirect relationships between stress responses (e.g., high or low stress responders), delayed discounting, and cancer control and adherence behaviors.

Aim 3: Determine the extent to which active engagement with a stressor is associated with adherence to recommendations for cancer control (e.g., diet and physical activity) and treatment compliance among AABCS. Diet, physical activity, and treatment are important cancer control behaviors among breast cancer survivors. We will examine these behaviors following stress induction among AABCS. We predict that AABCS who have greater stress reactivity will be less likely to meet recommended guidelines for diet and physical activity and will be less compliant with treatment recommendations compared to those who have lower stress reactivity. We will also examine the relationship between adherence to cancer control behaviors and cognitive factors, self-efficacy, temporal discounting, and executive control.

1. SIGNIFICANCE

Biological Pathways to Racial Disparities in Breast Cancer Outcomes. Breast cancer is the second leading cause of cancer morbidity and mortality among African American women. For the first time, national data show that in addition to having greater rates of morbidity and mortality from breast cancer, the incidence of disease is comparable to the rates observed among white women. As more African American women are diagnosed with breast cancer, the risk of mortality is increased, thereby setting the stage for even greater racial disparities in breast cancer outcomes. One hypothesis about breast cancer disparities is that social conditions and physiological responses to social stressors influence biological processes that are important to the initiation and progression of disease. This hypothesis is based on data from animal studies which have shown that rats that are exposed to social stressors (e.g., isolation) are likely to develop mammary tumors that are histologically similar to those that develop among African American women. This research has demonstrated that the animal's physiological response to social stress is the mechanism through which mammary tumors develop; animals who have a dysregulated cortisol response in which hormonal levels do not decrease, or return to normal levels following stress exposure, are most likely to develop disease. Cortisol is the primary hormone that is responsible for the stress response; just as the HPA axis plays a central role in regulating the physiological stress response in animals, these mechanisms are also likely to be important to the initiation and progression of disease in humans. Our preliminary research and other studies show that AABCS experience several stressors following diagnosis and may be particularly vulnerable to stressors during the transition from active treatment to survivorship. These include chronic economic stressors (e.g., low income, financial strain) and living in in stressful social environments. Other work has shown that cumulative exposure to these types of stressors is associated with dysregulation of the HPA axis. For instance, Cohen et al. found that the diurnal rhythm of cortisol (e.g., peak levels shortly after wakening that are followed by a gradual decline throughout the day that results in low evening levels) differs between African Americans and whites. Compared to whites, African Americans had lower cortisol levels in the morning and higher hormonal levels at the end of the day. Racial differences in cortisol were independent of SES factors, but low SES (e.g., education and income) was associated with a dysregulated cortisol response that was characterized by higher levels of cortisol during the evening among African Americans. African Americans also have a significantly lower cortisol response to a laboratory-based psychosocial stress (cortisol reactivity) compared to whites. The proposed research will be the first to characterize SR among AABCS based on exposure to chronic and acute stressors.

Psychological Pathways to Breast Cancer Disparities. Cortisol responses following stress exposure are important to consider as biological mediators between social characteristics and cancer processes among AABCS, but these responses are expressed in a psychological context. That is, an individual's physiological stress response is mitigated by the strategies they use to adapt to or regulate their emotional responses. According to conceptual models of stress and coping, individuals engage in a series of cognitive strategies
following a stressful event to assess its potential threat or the amount of stress experienced (primary appraisal) and to evaluate their ability to cope with or manage these effects (secondary appraisal). These cognitive appraisals generate coping efforts that may be problem-focused (e.g., doing something to change the situation) or emotion-focused (e.g., learning to live with a situation). Together, these cognitive processes (appraisals and coping efforts) are hypothesized to contribute to behavioral outcomes that include cancer control behaviors (e.g., diet, physical activity). Our previous research has demonstrated that African American women at increased risk for developing breast cancer use religious beliefs and values to cope with cancer-related stressors, however, other cognitive factors may be important to cancer control behaviors among these women. For instance, African American women who had higher levels of future temporal orientation were most likely to participate in genetic counseling for inherited BRCA1/2 mutations whereas those who thought about the past a lot were most likely to perceive that they were at increased risk for developing breast cancer again. Luwago et al. also found that African American women who had high present temporal orientation had more barriers to mammography and were less likely to have had this screening compared to those who had low present temporal orientation. Other research has demonstrated that temporal orientation is associated with stress reactivity the likelihood of engaging in health behaviors decreased as both stress and temporal discounting increase. However, these relationships have not been examined among AABCS. We will extend our previous research on cognitive factors and temporal orientation among AABCS by examining the extent to which inducing a stress response is associated with cognitive factors that are intervention targets for health behavior change among AABCS.

Behavioral Pathways to Racial Disparities in Breast Cancer Outcomes. Examining SR among AABCS is important to understanding biological and psychological processes that contribute to racial disparities in breast cancer outcomes, but behavioral pathways also contribute to disparities in morbidity and mortality. According to Biobehavioral Models of Cancer Stress and Disease Outcomes, stress has a negative impact on health behaviors and compliance with treatment among survivors. Prior research has shown that AABCS are less likely than white breast cancer survivors to be compliant with recommended guidelines for physical activity. Similarly, AABCS are not compliant with recommended guidelines for intake of dietary fat, saturated fats, and sugars. While other studies have not found racial differences in the completion of primary or neoadjuvant treatment for breast cancer, a substantial minority of African American women did not complete primary treatment for inflammatory breast cancer. Using data from a population-based state cancer registry, White et al. found that 16% of African American women who had breast conserving therapy did not start adjuvant radiation therapy. Among those who had tumors that were larger than one centimeter, 16% of African American women started and 46.3% completed adjuvant chemotherapy. This study also found that women who lived in geographic areas with low SES were less likely to have a mastectomy or initiate radiation after breast conserving therapy. Other work has shown that stress and physiological reactions to stressors are associated with behavioral pathways that lead to cancer outcomes among women who have a personal history of breast cancer. In a sample that was composed primarily of white BC survivors, Karvinen et al. found that women who had lower physiological stress responses (e.g., heart rate variability) to a laboratory social stressor reported better compliance with medical appointments for follow-up cancer care. Our study will be the first to examine the extent to which activating a stress response is associated with compliance with recommendations for health behaviors that are important to cancer control among AABCS.

Impact of the Proposed Research and Relevance to the Science of Behavior Change Network. Despite advances in breast cancer treatment and increased access to early detection, African American women continue to experience disparities in morbidity and mortality from this disease. Based on data from animal studies, racial disparities in breast cancer outcomes are now being attributed to physiological stress responses to social stressors that activate biological processes that are involved in the initiation and progression of disease. Stress reactivity is a primary domain in the Science of Behavior Change Network (SOBC), but these responses have not been examined specifically among AABCS. AABCS are an
important population in which to examine the association between stress reactivity, cancer control behaviors, and treatment compliance because they are at increased risk for morbidity and mortality from this disease. Our exploratory research will be the first to use a biobehavioral model to examine stress reactivity in this high-risk population based on their exposure to chronic and acute stressors. The proposed exploratory research will also examine several of the key research questions in the SOBC in this novel population. First, we will activate a stress response in a novel population using a protocol from a SOBC study being conducted by Haushofer et al.7 to measure the relationship between stress reactivity and health behaviors. Second, we will measure several mechanisms (e.g., temporal discounting, executive control) that are important to health behavior change in response to exposing AABCS to a stressor that is being examined as part of the SOBC. Importantly, these mechanisms will be measured using assays that are being implemented in the SOBC in a novel clinical population. Lastly, we will determine the extent to which activating a stress response is associated with health behaviors for cancer control, treatment compliance, and the mechanisms that underlie these behaviors. By examining the extent to which compliance with recommendations for cancer control behaviors is based on stress reactivity and temporal discounting, self-efficacy, and executive control, the findings from the proposed research will identify novel intervention targets for enhancing compliance and reducing disparities in breast cancer outcomes among AABCS.

INNOVATION

In addition to being highly responsive to the objectives of RFA-RM-17-028, Science of Behavior Change: Use- Inspired Research to Optimize Adherence, Behavior Change Interventions, and Outcomes, and expanding the scope of research being conducted in the SOBC to a novel population, the proposed exploratory study has considerable innovation. First, our study will translate findings from animal studies on physiological reactions to social stress and breast cancer development to women who are most likely to experience poor outcomes from this disease. Our study will also generate novel empirical data on stress reactivity among AABCS and will examine the extent to which inducing a stress response is associated with cognitive intervention targets, health behaviors that are important to cancer control, and compliance with treatment recommendations. In addition to experiencing the clinical stress of being diagnosed with breast cancer, AABCS are at greater risk for experiencing economic stressors and living in stressful physical environments. Thus, AABCS are an important group to examine with respect to stress reactivity and the psychological and behavioral consequences of being exposed to stress. Further, an important first step to developing effective behavioral interventions for AABCS is to examine and understand the associations between stress reactivity, cognitive mechanisms that can be targeted as part of survivorship interventions, and behavioral outcomes. To our knowledge, the proposed exploratory study will be the first to characterize stress reactivity in AABCS and verify that the mechanisms (e.g., temporal discounting, self-efficacy) involved in health behaviors for cancer control and treatment compliance are associated with stress reactivity in a population of women that is at risk for disparities and poor outcomes.

2. RESEARCH DESIGN AND METHODS

Overview. The purpose of this exploratory study is to characterize the nature and distribution of stress reactivity among AABCS based on socioeconomic, clinical, and social stressors. We will also evaluate the relationship between stress reactivity and cognitive mechanisms that are central to adherence to recommendations for health behaviors for cancer control (e.g., cognitive appraisals, temporal discounting, self-efficacy). Lastly, we will examine the extent to which active engagement with a laboratory-based social stressor is associated with adherence to recommendations for cancer control and treatment compliance among AABCS. As shown in Figure 1, we will conduct a prospective laboratory study in which stress reactivity is measured among AABCS following exposure to a validated social stress test. We will also evaluate the association between these stress reactivity and compliance with recommendations for cancer control health behaviors and treatment recommendations.

Study Population. Subjects eligible to participate in this study include AABCS who were diagnosed with Stage I, II, or IIIa disease and have completed all breast cancer treatment. Women who are both acute and long-term survivors are eligible to participate in this study. For all women, patients must have been between the ages of 21-
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75 at diagnosis and diagnosed within the last 5 years. For those who are acute survivors, patients are eligible to participate in the study if they completed surgical treatment within the past three months, regardless of if they have initiated adjuvant therapy. Women who are not African American or Black, diagnosed with a later stage of breast cancer, and are not within the defined treatment parameters are not eligible to participate in this study. We considered enrolling women who were still receiving treatment since one of our outcomes is treatment compliance. However, we were concerned that the stress of undergoing active treatment would confound the effects of the social stress test. By abstracting data on treatment compliance (e.g., missed and completed post-treatment appointments) from medical records, we will be able to determine this variable among women in our proposed study population. Even if women are considered to have completed primary treatment (e.g., chemotherapy), they may miss appointments. Further, women are followed for several years following primary treatment to monitor side effects and determine recurrence status. Similar methods have been used in previous research to examine treatment compliance in breast cancer survivors. We also considered enrolling white breast cancer survivors and comparing racial differences in SR as part of the proposed research. We decided against this approach to focus the resources that are available in this exploratory study on conducting an in-depth analysis of stress reactivity among AABCS. AABCS are a priority population in terms of being at risk for experiencing disparities in morbidity and mortality. Developing a better understanding of the nature and distribution of stress reactivity, examining the association between stress reactivity and cognitive factors and mechanisms of behavior change, and evaluating the relationship between active engagement with a stressor and cancer control behaviors and treatment compliance will identify novel targets that can addressed as part of survivorship interventions among these women.

Recruitment and Accrual. The procedures for the proposed research are based on the methods that have been used in our previous studies research that induced and measured stress reactivity in cancer survivors, and the methods and assays that are being examined as part of the SOBC. Subjects for this study will be identified from the oncology clinics at the Hollings Cancer Center (HCC). The HCC is the only NCI-designated cancer center in South Carolina. The HCC has a regional referral base that includes the entire state of South Carolina. About 250 new breast cancer cases are seen annually at the HCC and of these; we estimate that about 26% are African American. Patient information, including cancer diagnosis, race, and contact information are maintained in a centralized tumor registry that is maintained by the HCC. We will enroll 120 MBCS into the proposed research. To enroll eligible subjects, we will obtain waiver of written HIPAA Authorization in order to draw a random sample of MBCS patients from the HCC tumor registry. Following identification, permission will be obtained from the patient’s physician to invite them to participate in the study. MBCS will then be mailed an introductory letter explaining the study, the procedures involved in participation, and the informed consent form. The study invitation letter will include both the PI and provider’s signatures. The study will be introduced as a research project designed to develop a better understanding of how MBCS cope with their BC diagnosis. A toll-free telephone number and email address will be provided within the letter for women to use if they are not interested in being contacted for the study. Those that do not contact the research team within two weeks will be contacted by a professional telephone interviewer from the Medical University of South Carolina (MUSC). During this contact, the interviewer will review the information provided in the introductory packet. This will include reviewing the purpose of the study, the study procedures, and the potential risks and benefits of participating in the study. We will obtain approval for waiver of written informed consent to obtain verbal consent and conduct the screening interview and baseline survey among patients interested in participating in the study. The interviewer will complete a brief screening questionnaire that will assess SES (e.g., age, marital status, education level), cancer history (e.g., date of BC diagnosis, date of last cancer treatment), and current medical status (e.g., cancer recurrence status, co-morbid conditions). At the end of the screening questionnaire, eligible women will be invited to participate in the study. We have used this method to recruit MBCS and other cancer survivors in our previous research. We will draw random samples until 120 MBCS have completed the study procedures.

Baseline Telephone Interview. A 30-minute telephone interview will be conducted by a research assistant from MUSC to obtain SES and to measure social factors (e.g., perceived loneliness), perceived stress, and SES. We will also measure diet and physical activity behaviors during the baseline telephone interview. We considered alternative methods for collecting data for this study including mailed surveys. Our decision to collect data via a telephone interview is because the potential advantages of phone surveys (e.g., improved quality of data) outweigh the potential disadvantages of this approach. Our previous experience has shown that telephone
interviews are an effective method to collect data on SES, social factors, psychological functioning, and health behaviors among MCBS and that 30-minutes is a feasible length for a phone interview. Further, collectively, our investigative team has more than 20 years of experience in supervising data collection via telephone interview methods and procedures are in place to ensure that telephone interviewers are trained in proper survey administration and data entry. At the end of the baseline telephone interview, participants will be invited to participate in the laboratory assessments described below.

**Laboratory Assessments.** Two laboratory visits will be completed at the Clinical and Translational Research Center (CTRC) Research Nexus Laboratory and is described below.

Informed Consent Process. Written informed consent for participating in the laboratory visits and –month follow-up assessment will be obtained onsite prior to initiating the first laboratory visit. When the patient arrives for their first laboratory visit, they will be escorted to a private room to review the consent form. Once all questions from participants have been addressed, the patient will be instructed to sign the informed consent form. After obtaining written informed consent, laboratory assessments will be initiated.

**Pre-Challenge Visit.** Women will complete an in-person laboratory visit to obtain urine (from 12-hour urine recall) and blood samples prior to the Tier Social Stress Test (TSST). These biospecimens will be used to determine glucocorticoid sensitivity (e.g., % neutrophils, % lymphocytes, and % monocytes; ratio of neutrophil/lymphocytes) in our sample using the methods from previous research (see Cole et al., Social regulation of leukocyte homeostasis: the role of glucocorticoid sensitivity. Brain Behav Immun, 2008;22(7):1049-55). Height, weight, blood pressure, C-reactive protein levels, and IL-6 will also be determined using clinical measurements (i.e. height and weight scale) and blood samples. We will conduct a venipuncture to collect up to 4ml of plasma to assess IL-6 and CRP levels. Data from these biomarkers will be used to determine allostatic load among study participants. Following this clinical visit patients will be scheduled for their final clinic visit to complete the stress challenge.

**Stress Challenge Visit.** The TSST will be completed during a second laboratory visit after the pre-challenge visit. The TSST is a standardized psychological stress challenge which has been used extensively in research studies and is a method that is being used to induce a stress response in the SOBC. A meta-analysis demonstrates that it is the gold standard for evoking an HPA axis stress response in a laboratory setting. The ACTH and cortisol changes induced by the TSST reflect the sequence of HPA axis activity. That is, ACTH peaks first, at the end of the 15-minute stressor, and returns to baseline level within 40 minutes. Total plasma cortisol peaks 20 minutes after ACTH, and returns to baseline about an hour after initiation of the stressor. The experimental procedures and assessments for the TSST are collected at the same time point for each participant to control for changes in cortisol levels due to time of day (diurnal patterns) (see figure 1). After the TSST has been completed, the Kirby Delay Discounting Task will be administered according to participant’s randomization to the 10- or 20-minute delayed discounting group. In addition to collecting saliva samples as part of the TSST, saliva will be obtained before and after completing the delay discounting task.

<table>
<thead>
<tr>
<th>TIME</th>
<th>EXPERIMENTAL PROCEDURE</th>
<th>STRESS ASSESSMENT</th>
</tr>
</thead>
<tbody>
<tr>
<td>4:00-4:15pm</td>
<td>Accclimation period (15 minute duration)</td>
<td>Patient arrives and given relaxation tools (i.e. spa video, magazine, nature scenes)</td>
</tr>
<tr>
<td>4:16 Baseline (immediately following accclimation period)</td>
<td>Laboratory Stress measurements</td>
<td>Take cortisol, BP, HR, and assess SUD</td>
</tr>
<tr>
<td>4:28pm</td>
<td>Laboratory Stress measurements</td>
<td>Take cortisol, BP, HR, assess SUD, and explain the task and give participant paper to write notes</td>
</tr>
<tr>
<td>(5 minutes following 2nd lab measurements)</td>
<td>TSST</td>
<td></td>
</tr>
<tr>
<td>5 minutes</td>
<td>Interview task</td>
<td></td>
</tr>
<tr>
<td>5 minutes</td>
<td>Arithmetic task</td>
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<tr>
<td>Post TSST stress assessments (12 minute increments)</td>
<td></td>
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</tr>
<tr>
<td>4:46pm</td>
<td>Post TSST (2 minutes following TSST)</td>
<td>Post-TSST Assessment</td>
</tr>
<tr>
<td>12 mins post TSST</td>
<td>Post-TSST Assessment</td>
<td>Cortisol, BP, HR, SUD</td>
</tr>
<tr>
<td>5:10pm</td>
<td>Final Post-TSST Assessment</td>
<td>Cortisol, BP, HR, SUD</td>
</tr>
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Note: Patients more than 15 minutes late are unable to participate in the TSST and would need to be rescheduled.

**Outcome Assessment.** We will measure stress reactivity using saliva samples that are collected prospectively during the TSST. Specifically, saliva samples will be obtained prior to the TSST to measure baseline levels of cortisol. A saliva sample will be obtained throughout the TSST to measure cortisol during stress exposure. We
will also measure heart rate variability (HRV) and blood pressure using standard medical equipment and procedures during the TSST. We will also measure compliance with recommendations for cancer control behaviors (e.g., diet and physical activity) 1-month after the TSST by telephone follow-up to measure short-term health behaviors following engagement with the stressor. To determine treatment compliance, we will abstract data on missed and completed oncology appointments from the HCC clinic records.

**Measures.** The measures described below will be obtained by self-report at baseline to characterize chronic SES stressors and compliance with recommendations for cancer control behaviors prior to stress exposure. First, we will measure chronic SES stressors in terms of income, employment status, and financial strain. The Life Events Questionnaire (LEQ) is a validated measure that captures life events across multiple areas. The Health, Work (e.g., difficulty finding a job); Residence (e.g., difficulty finding housing), and Financial subscales of the LEQ will be used for the purposes of the current study. In addition, the Perceived Stress Scale and the Everyday Discrimination Scale will be used to capture perceived stress and discriminatory stress, respectively. We will use the short form of the Loneliness Scale and Interpersonal Support Evaluation List (ISEL) to measure social isolation and support, respectively. Financial strain will be measured by a validated Likert-style item that asks participants if they have some, just enough, or not enough money left over at the end of the month. Cancer-related stressors will be measured in terms of intrusion and attempts to avoid cancer-related thoughts and feelings using the Short-Form of the Impact of Events Scale (IES) and perceived risk and control about breast cancer recurrence. Perceived risk and control will be measured using items from our Dr. Hughes-Halbert's previous research on cancer recurrence among AABCS. Cognitive appraisals will be measured using items from Dr. Hughes-Halbert's previous research. These items ask women to indicate how much stress they have experienced about their cancer diagnosis and treatment (primary appraisal) and how confident they are that they can manage stressors related to their diagnosis and treatment (citations). Clinical stressors will be measured in terms of breast cancer stage and grade and the presence of treatment-related side effects. For instance, AABCS will be asked about their reproductive history and whether or not they have entered menopause naturally or as a result of breast cancer treatment.

We will use assays from the SOBC to measure cognitive mechanisms that are important to health behaviors. These include temporal discounting, executive control, and self-efficacy. Specifically, we will use the Consideration for Future Consequences to measure temporal discounting and the Behavior Rating Inventory of Executive Function-Adult to measure executive control. Lastly, we will use the Generalized Self-Efficacy Scale to measure the extent to which participants are confident in their ability to manage stressful situations and events. These mechanisms will be measured at baseline during the telephone interview and during the 1-month follow-up telephone interview after women have been exposed to the social stressor.

Our outcome variables include stress reactivity in terms of cortisol, HRV, blood pressure responses and compliance with recommendations for diet, physical activity, and breast cancer treatment. Specifically, salivary cortisol will be measured during the TSST to determine peak activity and recovery using samples that are collected at baseline, immediately after the speech stressor, and at 15-minute intervals after completion of the speech stressor. Saliva will be collected using Salivette sampling devices (Sarstedt, Numbrecht, Germany) and will be assessed using the Active-Cortisol ELISA (Diagnostic Systems Laboratories, Webster, TX). We will use intra-individual differences between baseline and post-TSST salivary cortisol levels in the analysis. We will use the Dietary Risk Assessment questionnaire to measure the quality of dietary behaviors based on intake of fruit, vegetable, fiber, and fat. Physical activity will be measured using the Seven-Day Physical Activity Recall (PAR) questionnaire. The PAR measures the intensity and frequency of physical activity during the past week. We will also use Likert-style items from the NCI's HINTS to measure adherence to recommended guidelines for fruit and vegetable intake and physical activity. We have used these NCI items to measure adherence to guidelines in our previous research with community-based samples of African Americans.

**Statistical Considerations.** The data analysis for this exploratory study is designed to address our specific aims and is essentially descriptive and correlational. First, descriptive statistics will be generated from baseline data to characterize the study sample in terms of SES, clinical history, and psychosocial factors (e.g., life stress events, social isolation). Frequencies will also be generated to characterize stress reactivity, cancer control behaviors, and
treatment compliance. We will then conduct bivariate analyses (e.g., Chi Square Tests of Association, T-Tests) to examine the relationships between baseline data on SES, clinical stressors, experiences with social stressors, and stress reactivity (specific aim 1). We will also generate correlation coefficients to evaluate the relationship between stress reactivity and mechanisms of behavior change (e.g., temporal discounting, self-efficacy, executive control) (specific aim 2). Next, we will use discriminant analysis to classify participants as high or low stress responders based on changes in cortisol, blood pressure, and heart rate during the TSST.25 Using high and low stress responder group as the predictor variable, analysis of variance (ANOVA) will be conducted to examine differences in cancer control behaviors and treatment compliance (specific aim 3). Additional analysis will be conducted to examine associations between stress reactions (e.g., high versus low cortisol, high versus low heart rate) and cancer control behaviors and treatment compliance. The purpose of this analysis is to determine if behavioral outcomes vary based on indicators of stress reactivity. Bivariate analyses (e.g., T-Test, correlation analyses) will be conducted to examine the relationship between SR and mechanisms of behavior change (e.g., temporal discounting, self-efficacy, executive control). Last, we will use multivariate regression analysis to evaluate the independent associations between SR and cancer control behaviors and treatment compliance while controlling for SES factors, clinical stressors, and experiences with social stressors. A total of 120 participants will be enrolled into this study. This sample size will ensure that all hypothesis tests of interest will have sufficient (>80%) power, assuming 2-sided testing, an alpha level of 0.05, and a general linear model framework for comparing the independent and dependent variables. With a sample size of n=120, we will have 80% power to detect medium effect sizes when comparing the SES groups (e.g. lower vs. higher education, financially strained vs. not strained, etc.), equivalent to 0.5 to 0.6 standard deviation units, depending on the proportion in each group.

Scientific Relevance and Future Applications. Although findings from animal studies are providing insights about biological mechanisms that are important to cancer health disparities, these mechanisms are not being examined among individuals at the greatest risk for morbidity and mortality. Dysregulation of the HPA has been identified as a possible mechanism through which social and biological factors contribute to racial disparities in breast cancer outcomes; this exploratory study will examine HPA stress responses among MBCS based on individual variation in perceived stress, social factors, and clinical stressors using a laboratory model of stress reactivity that is a key component of the SOBC. Stress reactivity is a primary domain in the SOBC, but these responses have not been examined specifically among MBCS. The proposed exploratory research will be the first to also examine several of the key research questions in the SOBC in this novel population. As part of generating novel empirical data that expands the scope of the research being conducted in the SOBC, this exploratory study will identify novel intervention targets that can be used to improve compliance in a population that is at risk for non-compliance with recommendations for diet and physical activity that are important to quality of life and survivorship outcomes. The findings from this research will be used to develop interventions that improve quality of life and survivorship among MBCS by targeting both biological and psychological mechanisms that are important to adherence to recommendations for health behaviors that are important to cancer control and treatment compliance.
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PROTECTION OF HUMAN SUBJECTS

Human Subjects Involvement and Characteristics. The purpose of the proposed research is to: (1) characterize the nature and distribution of stress reactivity among African American breast cancer survivors; (2) examine the relationship between stress reactivity and cognitive factors and mechanisms of behavior change (e.g., self-efficacy, temporal discounting, and executive control); and (3) evaluate the association between stress reactivity and adherence to recommendations for cancer control behaviors and treatment compliance.

Inclusion and Exclusion Criteria. Individuals eligible to participate in this study are African American or Black women who have a histologically confirmed stage of I, II, or IIIa breast cancer. To be eligible, women have to be between the ages of 21-75 at diagnosis, and have been diagnosed within the last 5 years. Women who are not African American or Black, diagnosed with a later stage of breast cancer, and are not within the defined treatment parameters are not eligible to participate in this study.

Sources of Materials. Study data will be collected through oncology and clinical record data, medical chart abstraction, self-report through telephone interviews, and laboratory measurements. Specifically, detailed clinical information will be abstracted from the participant's medical record to be able to control for factors that could impact HPA axis functioning in our statistical analyses. As part of this, we will determine if participants have been prescribed medications that could influence cortisol responses (Granger et al., Psychoneuroendocrinology, 2009) and if they have a history of co-morbid conditions. We will also obtain the participant's current age and age at diagnosis, their height and weight, disease characteristics (e.g., biopsy date, stage and grade of disease), treatment information (e.g., surgery completion date, type of adjuvant treatment), and pre-diagnosis risk information (e.g., age at menarche, family history) during the medical abstraction. Physiological responses to a laboratory-based social stress test will be obtained through saliva samples. All data that is collected for this study will be strictly for research purposes.

Recruitment Procedures and Informed consent. The research activities that will be completed during the study are designed to characterize the nature and distribution of stress reactivity in order to understand the complex ways in which these reactions differ based on sociodemographic, psychological, and behavioral factors. We will conduct telephone interviews and laboratory-based assessments to characterize stress reactivity and to evaluate the association between stress reactivity, cognitive mechanisms, and cancer control behaviors and treatment compliance among African American breast cancer survivors. Specifically, participants will be recruited using the procedures described below.

Patient Identification and Screening. We will identify African American breast cancer survivors who have completed treatment using the oncology clinic and cancer registry databases at the Medical University of South Carolina Hollings Cancer Center (MUSC/HCC). Specifically, we will identify patients who meet eligibility criteria from these databases and following identification, permission will be obtained from the patient's physician to invite them to participate in the study. Patients will then be mailed an introductory letter explaining the purpose of the study, the procedures involved in participation, and the informed consent form. The study will be introduced as a research project designed to develop a better understanding of how African American breast cancer patients cope with their diagnosis. A self-addressed reply card will be included for women to return if they are not interested in being contacted for the study and those who do not return the reply card within two weeks will be contacted by a professional telephone interviewer from the MUSC/HCC. During this contact, the interviewer will review the information provided in the introductory packet. This will include reviewing the purpose of the study, procedures involved in participation, and the potential risks and benefits of participation. After reviewing the purpose of the study and obtaining verbal informed consent, the interviewer will complete a brief screening questionnaire that will assess cancer history (e.g., date of diagnosis, date of surgical treatment), race, and age. Eligible women will then complete the baseline telephone interview and be invited to participate in the laboratory procedures. Those who are not eligible will be thanked for their time and no further contact will be made.

Baseline Telephone Interview and Laboratory Assessments. At the end of the screening, eligible women will complete a structured baseline telephone interview. The baseline telephone interview will assess sociodemographic characteristics and measure social (e.g., perceived loneliness) and psychological (e.g., perceived stress) stressors, SES stressors, emotional regulation, and cancer control (e.g., diet and physical
activity) behaviors. Participants will also be asked about their exposure to trauma and the timing of these events during the baseline telephone interview. At the end of the baseline telephone interview, participants will be invited to participate in the laboratory assessments.

Laboratory Assessments. Two laboratory visits will be completed as described below.

Written informed consent will be obtained prior to completing the first laboratory visit. To obtain informed consent, the information provided in the consent form will be reviewed with participants. Once all questions from participants have been addressed, written informed consent will be obtained. After obtaining written informed consent, laboratory assessments will be initiated.

Pre-Challenge Visit. Women will complete an in-person laboratory visit TSST to obtain urine (from 12-hour urine recall) and blood samples prior to the TSST. These biospecimens will be used to determine glucocorticoid sensitivity (e.g., % neutrophils, % lymphocytes, and % monocytes; ratio of neutrophil/lymphocytes) in our sample using the methods from previous research (see Cole et al., Social regulation of leukocyte homeostasis: the role of glucocorticoid sensitivity. Brain Behav Immun, 2008;22(7):1049-55). Height, weight, blood pressure, C-reactive protein levels, and IL-6 will also be determined using clinical measurements and blood samples. Data from these biomarkers will be used to determine allostatic load among study participants.

Stress Challenge Visit. The TSST will be completed during a second laboratory visit after the pre-challenge visit. After the TSST has been completed, the Kirby Delay Discounting Task will be administered according to participant’s randomization to the 10- or 20-minute delayed discounting group. In addition to collecting saliva samples as part of the TSST, saliva will be obtained before and after completing the delay discounting task.

Follow-Up Telephone interviews. Participants will be contacted at 1-month after the laboratory visit to re-assess cancer control behaviors. Verbal informed consent will be obtained for completing the 1-month follow-up telephone interview. Participants will receive a financial incentive to reimburse them for travel expenses and to compensate them for the time needed to complete study procedures.

Potential Risks. There is a slight risk that participants may experience adverse psychological reactions such as anxiety or stress as a result of discussing issues related to their breast cancer diagnosis, personal health behaviors, and social and psychological stressors during the baseline telephone interview. We will minimize this risk by ensuring that telephone interviewers are trained to detect increased anxiety and how to intervene accordingly. Also, participants will be given rest breaks as needed throughout the telephone interviews, and if warranted, any referrals for follow-up psychological care will be made as needed.

There are also minimum risks associated with the laboratory assessments. Patients may experience some mild physical discomfort from the venipuncture to retrieve the blood sample. Participants will be exposed to a psychological stressor (giving a speech and arithmetic task) to induce a stress response. It is likely that the stress test will produce a certain amount of stress and may cause an increase in blood pressure and increased heart rate. We do not anticipate that the laboratory stressor would provoke any significant adverse reactions that are not usually encountered on a day-to-day basis. The Research Assistant conducting the in-person laboratory assessment will be highly trained in administering the laboratory stress test. As part of this training, she/he will be trained to determine if participants are experiencing any adverse reactions and will terminate the assessment immediately. If warranted, referrals for follow-up psychological care will be made as needed. Our study team includes a Clinical Psychological (Carla Kmett Danielson, PhD) who has extensive experience administering the Trier Social Stress Test, monitoring responses, and making referrals to psychological services as needed.

Participants may also potentially experience a loss of privacy as a result of providing information about their past medical history and personal health behaviors for cancer control. However, we are using items that have been tested and validated and are commonly used in clinical settings and it is likely that participants would have been exposed to similar types of questions through their routine medical care. Therefore, we do not anticipate that participants will feel that their privacy has been violated. Also, we will obtain permission from the IRB to obtain informed consent over the telephone prior to initiating any study activity. Eligible patients will be required to verbally agree to participate in the study during the initial scripted telephone call after the invitations letters have been mailed out. Only patients that express interest in participating will be administered the baseline
telephone survey. Written informed consent will be obtained prior to conducting the laboratory assessments. We will also give participants the option to opt out of being contacted if they do not want to be contacted about participating in the study. Participants will be informed that their participation is voluntary and that they can withdraw their participation at any time without any adverse consequences.

**Protection Against Risks.** We will take every precaution to protect the privacy and autonomy of participants and to assure that the consent is truly informed. As we described above, verbal informed consent will be obtained for screening, study enrollment and completion of the baseline and 1-month follow-up interviews. As part of the verbal informed consent process, the purpose of the study will be explained orally and the right to refuse to answer all or some of the questions will be emphasized. It will also be stressed that they can start or stop their participation at any time throughout the duration of the study. Participants who refuse to complete the laboratory assessment or those who withdraw from the study will be thanked and all further contacts will be terminated. We will also obtain written informed consent prior to conducting the laboratory assessments. As part of obtaining written informed consent, we will review the purpose, procedures, duration of participation, and their rights for being a research participant. Participants will be given the opportunity to ask questions before signing the informed consent form and proceeding with the laboratory assessments.

We will also take extensive precautions to protect the privacy of the participants. Personal health identifiers (e.g., name, address) will not be used to identify participants in study databases or on laboratory materials. We will use a confidential subject identification number to identify all participant data in research databases and on study documents (e.g., baseline telephone interview), and laboratory materials (i.e. biospecimen tubes). Cortisol saliva kits and plasma tubes will be labeled with the study identification number. A key containing each participant's name, study identification number, and telephone number will be kept in a locked file cabinet until study procedures have been completed and the data have been checked for completeness and accuracy. At that time, this identifying information will be destroyed. Thus, we will retain no identifying information in the study data files. Moreover, all computerized study databases for questionnaire data will be housed on a secure, password-protected network server. All personal contact information will be kept in a database that will be housed separately from the database containing questionnaire data. There will be limited access to study files and study databases throughout the duration of the study; only pertinent study staff will have access to study information.

Securing of participant identifying information will be accomplished through several means. All study documents including screeners, consents, assessments and call logs will be kept in a locked file cabinet in a locked office. The data management system for the proposed research will be designed to achieve the major elements of the study including: (1) determination of study eligibility, (2) monitoring recruitment and accrual, (3) generation of study materials, and (4) storage of data from telephone interviews. This type of system has been developed as part of Dr. Hughes-Halbert's previous studies and we will use these existing data management systems as the model for developing the data management system for the proposed study. All data collected as part of this study will be stored on a secure password-protected network server. Moreover, access to the server will be monitored by the PI and limited to pertinent study personnel.

**Protection against Adverse Reactions.** To minimize the risk of experiencing adverse emotional reactions and loss of privacy, Research Assistants will be trained in how to administer interview questions in a sensitive manner. They will also be trained in how to detect signs of extreme anxiety and participants who show signs of extreme distress will be referred to local clinical psychologists or counselors when warranted. Since we are using standardized questionnaires that have been used extensively in general population samples without adverse events, we anticipate that psychological injury will be infrequent, if at all. Additionally, a highly trained Research Assistant, who is experienced in psychological testing, will deliver the in-person laboratory psychological stress assessment. The Research Assistant will be trained on the assessment tool and will be supervised through weekly discussions about the laboratory-based assessments. A licensed nurse will administer the venipuncture and vital sign assessments (heart rate and blood pressure). As described above, study data will be entered into research databases using a confidential subject identification number.
Potential Benefits of the Proposed Research to Subjects and Others. There are no direct clinical benefits to participating in this study. The potential risks associated with study participation are minimal and the information that is learned through this research is likely to have significant benefits. African American women continue to experience disparities in breast cancer outcomes. Dysregulation of the hypothalamic-pituitary-axis (HPA) axis is a mechanism that contributes to the initiation and progression of mammary cancers in animals. Characterizing stress reactivity and determining the ways in which these responses are associated with cognitive mechanisms that are important to health behaviors, meeting recommended guidelines for health behaviors that are important to cancer control, and treatment compliance is critical for identify mechanisms that that contribute to racial disparities in breast cancer outcomes among African American women. This information is needed to identify novel intervention targets for African American women who have a personal history of breast cancer. Women who participate in this study may experience positive emotions as a result of contributing to research that may ultimately help to improve the quality of survivorship among African American women. Lastly, research on factors involved in stress reactivity among African American breast cancer patients is necessary to develop tailored, personalized approaches to improve cancer control behaviors and treatment compliance in women who have a personal history of disease.

Importance of the Knowledge to be Gained. Disparities in breast cancer morbidity and mortality continue to exist among African American women despite increased early detection and the availability of more effective therapies. Stress responses have been shown to impact pathways that are activated during the initiation and progression. This study will be the first to examine stress reactivity among African American breast cancer survivors and understand the complex ways in which these reactions are associated with cancer control behaviors and treatment compliance among these women. Our research will move beyond black-white comparisons in incidence and survival by examining why and how African American breast cancer patients experience poor outcomes using a biobehavioral model in this population. Ultimately, the results of this research will provide greater insights into psychological and biological mechanisms that contribute to racial disparities in breast cancer outcomes and will generate novel empirical data that can be translated into targeted interventions to improve breast cancer outcomes among African American women.

INCLUSION OF WOMEN AND MINORITIES

Only women will be eligible to participate in this study. We are examining stress reactivity among breast cancer survivors. Men who develop breast cancer have a different pathophysiology than women, and therefore, will not be included in this sample.

Only individuals who self-identify as being African American or Black are eligible to participate in this study. Our decision to only include African Americans/Blacks in this study is because they to continue to have poor breast cancer outcomes. Thus, these individuals are an important priority for cancer control research.

INCLUSION OF CHILDREN

Children under age 18 are not eligible to participate in this study because the goal of this research is to examine stress reactivity, adherence to recommendations for health behaviors that are important to cancer control, and treatment compliance among adult women with a past diagnosis of breast cancer. Children under age 18 are not included in this research because they are at low risk for developing breast cancer.

RESOURCE SHARING PLAN

The purpose of this study is to describe the nature and distribution of stress reactivity among African American breast cancer survivors based on sociodemographic, clinical, and psychosocial stressors and to
evaluate the relationship between stress reactivity and cognitive mechanisms that are important to health behaviors that are important to cancer control. We will also examine the association between stress reactivity and adherence to recommendations for health behaviors that are important to cancer control and treatment compliance. The study protocols (e.g., baseline and follow-up telephone interviews) and procedures for completing the laboratory stress test will be made available to other investigators in the Science of Behavior Change Network (SOBC) through the program website. This resource is also publically available to investigators; therefore, our study materials will also be available to investigators who are not a part of the SOBC. Data (e.g., datasets that are generated for statistical analysis) that are generated through the proposed exploratory study will also be made available through the SOBC and will be made available to investigators upon request.