THE BIRTH OUTCOMES AND REPRODUCTIVE NEEDS OF PREMENOPAUSAL BREAST CANCER SURVIVORS: A MIXED METHODS STUDY

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A dissertation submitted to the faculty at the University of North Carolina at Chapel Hill in partial fulfillment of the requirements for the degree of Doctor of Philosophy in the Department of Maternal and Child Health in the Gillings School of Global Public Health.

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ABSTRACT

Kristin Zeneé Black: The Birth Outcomes and Reproductive Needs of Premenopausal Breast Cancer Survivors: A Mixed Methods Study
(Under the direction of Diane L. Rowley)

This mixed methods dissertation examined the risk of adverse birth outcomes, and the reproductive and sexual health needs of premenopausal breast cancer survivors in North Carolina. Using multivariable binomial regression, the first paper examined the prevalence of preterm birth (PTB) and low birthweight (LBW) according to breast cancer history prior to infant delivery and evaluated potential effect modification by race using statewide linked birth certificate files and Central Cancer Registry data from 1990-2009. A breast cancer history corresponded to 50-67% increases in risk of delivering a PTB or LBW infant compared to the general population, with greater increases among women who received chemotherapy or gave birth within two years of diagnosis. The higher prevalence of PTB and LBW associated with a breast cancer history was greater for white versus black mothers. The second paper explored the reproductive healthcare needs of breast cancer survivors by exploring the concordances and discordances of their reproductive and sexual health needs by post-diagnosis childbearing status and race. Seventeen North Carolinian women with a breast cancer history and diagnosed between the ages of 18-45 participated in a two-part, semi-structured interview. We utilized ResearchTalk's *Sort and Sift, Think and Shift*© Method, a multidimensional qualitative analysis approach. This approach, along with member checking the findings with a community advisory committee and participants, allowed us to identify the most salient themes from the data. The five overarching themes were that women with a breast cancer history: 1) received limited reproductive health information; 2) desired realistic expectations of conceiving post-cancer; 3)

made lifestyle choices based on family breast cancer history; 4) struggled with adjusting to their altered physical appearance; and 5) had menopause symptoms that led to sexual health and quality of life issues. Despite the many concordances in experiences, there were subtle discordances by post-diagnosis childbearing status and race. Women with a breast cancer history desire more education and resources to address their reproductive and sexual health concerns and would greatly benefit from receiving reproductive and sexual health counseling during breast cancer treatment and beyond.

To my husband, mother, sisters, friends, and mentors for being my ultimate cheerleaders and providing me with the love and encouragement I needed during every step of this journey.

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I feel fortunate that I was able to work with such a dynamic dissertation committee.

Their insightful feedback strengthened my research and their encouragement was comforting as I progressed through my dissertation. My Maternal and Child Health (MCH) advisor and dissertation chair, Dr. Diane L. Rowley and Epidemiology minor advisor, Dr. Hazel B. Nichols were especially attentive throughout my dissertation process. The countless number of meetings, phone calls, and email exchanges I had with them helped me put out a lot of fires and move forward at a steady pace. Furthermore, Drs. Jon Hussey, Eugenia Eng, and Vijaya K. Hogan were extremely responsive and accessible when I needed to tap into their expertise. The wisdom that I acquired from these five amazing faculty members over the years has developed me into a skilled researcher and knowledgeable public health professional. They are wonderful examples of dissertation committee members that take mentorship seriously.

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ART	assisted reproductive technologies
aOR	adjusted odds ratio
aPOR	adjusted prevalence odds ratio
BC	breast cancer
BRFSS	Behavioral Risk Factor Surveillance System
CDC	Centers for Disease Control and Prevention
CI	confidence interval
DAG	directed acyclic graph
ER	estrogen receptor
GA	Georgia
GnRHa	gonadotropin releasing-hormone agonist
HER	human epidermal growth factor receptor
LBW	low birthweight
MCH	maternal and child health
NC	North Carolina
NIH	National Institutes of Health
PI	principal investigator
PR	prevalence ratio
PR	progesterone receptor
PRAMS	Pregnancy Risk Assessment and Monitoring Survey
PTB	preterm birth
SES	socioeconomic status

CHAPTER 1: INTRODUCTION

Although breast cancer is considered a disease of the aging population, in 2013, 21.74% (64,560 out of 296,980) of women diagnosed with breast cancer were under the age of 50.(1) Due to the advancement of screening and treatment options for breast cancer, more women are able to live fruitful lives after a breast cancer diagnosis (2), yet for premenopausal breast cancer survivors little is known about the effects of the disease and treatment on their reproductive capacity and birth outcomes. With the co-occurrence of two trends, an increasing number of women delaying their first birth into their thirties and early forties (3,4) and the improvement of survival rates of women diagnosed with breast cancer before the age of 50 (5), there is a greater possibility that many young breast cancer patients have not yet started or completed their families at the time of diagnosis and may desire to have children after successful completion of their cancer treatment regimen.

Even though white women tend to have a higher incidence of postmenopausal breast cancer than black women, there is a dynamic crossover between black and white women when looking at premenopausal breast cancer.(6) In 2013, the age-adjusted incidence of breast cancer in women diagnosed under the age of 50 was 45.3 per 100,000, with black women under age 50 having an incidence of 41.5 and white women under age 50 having an incidence of 45.6. This black-white disparity is also evident in the 5-year relative survival rates. The overall 5-year breast cancer survival rate for women under the age of 50 at diagnosis is 90.7%; however, it is 81.7% for black and 92.0% for white women.(7)

Breast cancer diagnosed in young women is more likely to present at an advanced stage, be more aggressive, and have a poorer prognosis than breast cancer diagnosed in older women (8); moreover, young black women (when compared to white women, especially older white

women) are more likely to be diagnosed with basal-like tumors (i.e., ER-negative, PR-negative, HER2-negative, and either HER2-positive or CK 5/6-positive) (9,10), often referred to as triple-negative breast cancer (1,11), which is the most aggressive sub-type of breast cancer. Although a triple-negative breast cancer diagnosis is relatively rare, women diagnosed with triple-negative breast cancer have a poorer short-term prognosis than women with other types of breast cancer since triple-negative tumors are less responsive to treatment.(1)

In the general United States population, 9.6% of infants are delivered preterm (<37 weeks gestation) and 8.1% have a low birthweight (<2,500 grams). The preterm birth and low birthweight rates vary widely by race/ethnicity and maternal age. In 2015, black women were 40.5% more likely to deliver a preterm infant and 63.2% more likely to deliver a low birthweight infant compared to white women.(12) Mothers under the age of 15 or mothers aged 45 or older have a higher rate of delivering an infant before 37 weeks of gestation or less than 2,500 grams than mothers aged 25-34 years.(4)

There are clear black-white disparities in breast cancer incidence and 5-year survival rates, as well as birth outcomes since black women (when compared to white women) are more likely to be diagnosed with breast cancer before the age of 40 (1,6) and to deliver a preterm or low birthweight infant.(12) Additionally, the current literature is inconsistent about the potential risk of adverse birth outcomes among breast cancer survivors.(13–21) Considering the potential pregnancies that may occur among premenopausal breast cancer survivors, the specific aims of this study were to: 1) determine if premenopausal breast cancer survivors (ages 18-45) in North Carolina who had a live birth after their diagnosis have a greater prevalence of delivering a preterm or low birthweight infant (PTB; LBW) than women in North Carolina who had a live birth and have never been diagnosed with breast cancer; and 2) determine the unmet reproductive and preconception healthcare needs of premenopausal breast cancer survivors.

A mixed methods approach was used to explore the proposed aims. For Aim 1, a case-cohort study was conducted using a linked dataset of North Carolina cancer registry and birth

record data. The dataset includes about 2.3 million births that occurred between 1990-2009, including 512 births to breast cancer survivors. Aim 2 involved the collection of primary data by conducting two 45-60-minute in-depth, semi-structured interviews with 17 women with a history of breast cancer to learn about the reproductive health needs that may (or may not) have been met after their cancer diagnosis. The findings from the quantitative and qualitative methods were integrated to develop a more complete story about the reproductive health experiences of premenopausal breast cancer survivors.

Significance

Few published studies have examined the potential association between cancer and subsequent birth outcomes (16–18); a few notable studies have specifically focused on breast cancer and birth outcomes.(13–15,19–21) Yet, a majority of the studies of premenopausal breast cancer survivors have focused on pregnancy and survival rates after a pregnancy.(13–15,19,22) These types of studies do not provide a comprehensive perspective of the reproductive health experiences and challenges that premenopausal breast cancer survivors face. In order to understand the complexities surrounding the reproductive health issues of premenopausal breast cancer survivors, it is important to know about the biology of breast cancer in younger women, the effect of chemotherapy on reproductive health, the reproductive health concerns of young breast cancer survivors, risk predictors and factors for preterm birth and low birthweight, and the importance of preconception healthcare.

Studies on Breast Cancer and Birth Outcomes

Out of six studies that have focused on the birth outcomes of premenopausal breast cancer survivors, three are population-based studies (19–21), two are cross-sectional retrospective survey studies (14,15), and one is a single-center case report.(13) There are four main limitations that are apparent throughout these six studies: 1) the inability to determine

which women are fertile and desire to have children (or not) (15,19–21); 2) the lack of maternal characteristics controlled for in the statistical analysis models (15,19,21); 3) the use of self-reported birth outcomes via survey instruments (14,15); and 4) relatively small study populations.(13,19) An additional issue to consider when focusing on the premenopausal breast cancer survivor population is the desire of these women to pursue motherhood and the potential selection bias introduced by the "healthy mother effect" that may be occurring since the "healthier" breast cancer survivors may be more fit and willing to become pregnant post-diagnosis and treatment.(19,23,24)

Three seminal, population-based studies that examined the birth outcomes of women diagnosed with breast cancer have been conducted in Denmark, Sweden, and western Australia (19–21) and these particular studies will serve as a model for the proposed study. These studies use linked cancer and birth registry data from nationwide healthcare data systems that have been active as early as the 1940s and collect data on every resident from birth to death. Despite having access to nearly complete, population-based data, these studies did not have consistent results on the potential risk of breast cancer survivors delivering preterm and low birthweight infants.

Langagergaard et al. (21) studied 216 births to breast cancer survivors with a median of 753 days (Range: 3-5965 days) from time of diagnosis until pregnancy (i.e., 1st day in last menstruation) and found no substantial increase in odds of low birthweight (aPOR: 1.3; 95% CI: 0.7-2.2) or odds of preterm birth (aPOR: 1.2; 95% CI: 0.4-3.8). When the analysis was stratified by type of breast cancer treatment, the overall results did not change. Infants born to breast cancer survivors had nearly the same mean birthweights as infants born to the comparison group of mothers who were not diagnosed with breast cancer.

The results of the Dalberg (20) study of 331 births to nulliparous women with a history of invasive breast cancer over a similar time period reached results that conflicted with the Langagergaard study. Dalberg et al. found that 11% of the infants born to women exposed to

breast cancer were delivered preterm compared with 5% of infants born to women not exposed to breast cancer. The odds of delivering an infant at less than 32 weeks of completed gestation for breast cancer survivors was 3.20 (95% CI: 1.70-6.03) times the odds for a woman not exposed to breast cancer. These odds were slightly lower when the infants were born between 32 and 36 weeks gestation (aOR: 1.53; 95% CI: 1.02-2.29). The odds of delivering an infant that weighed less than 1,500 grams for breast cancer survivors was 2.86 (95% CI: 1.41-5.78) times the odds for a woman not exposed to breast cancer.

The Ives (19) study used one of the most extensive population-based databases to examine fertility and birth outcomes among breast cancer survivors, since the public and private health records they used included data from the hospital morbidity database, birth and death registries, mental health services, cancer registry, and midwives' notifications. Out of the 2,539 breast cancer survivors between the ages of 15 and 44 in the study, 5% (n=123) had at least one pregnancy after diagnosis. These cases were compared to a control group that consisted of western Australian women who had at least one pregnancy between 1983-2004. Ives et al. found that the pregnancy rate was lower among the breast cancer survivors and they tended to be older than the general population. Fifty percent of the breast cancer survivors (n=62) had a birth within two years of their diagnosis date and there were only two preterm births reported.

This stark difference in the findings from these three population-based studies suggest that these past studies have not provided us with the full picture of the effects of breast cancer on subsequent birth outcomes. Therefore, there are still additional avenues that need to be explored in order to learn more about the birth outcomes among this specific population.

The persistent limitations in the current literature are mostly related to study design. The complexity of this topic signifies a need to conduct studies that employ quantitative and qualitative approaches, which includes using stronger epidemiological study methods with population-based samples, examining risk predictors and risk factors (e.g., maternal characteristics), and incorporating the personal insights of breast cancer survivors. The

National Institutes of Health (NIH) working group on developing best practices for mixed methods research recommends that mixed methods approaches are appropriately used in studies that aim to acquire a real life understanding of contextual or cultural influences on an identified outcome (25), which the proposed study aimed to achieve.

The Biology of Breast Cancer in Young Women

Breast cancer diagnosed in young women tends to present at an advanced stage, is more aggressive, and has a poorer prognosis than breast cancer diagnosed in older women.(8) Premenopausal breast cancer patients have poorer prognoses compared to older breast cancer patients, which may be due to the differences in biology of breast cancer in young women.(26,27) Factors that determine a patient's breast cancer prognosis, include tumor size, histologic tumor grade, nodal status, metastatic stage, immunohistochemical markers (e.g., estrogen receptor (ER), progesterone receptor (PR), human epidermal growth factor receptor (HER1, HER2), and cytokeratin (CK) 5/6 status), likelihood of recurrence, menopausal status, and age, among other things. Premenopausal women are more likely to be diagnosed with invasive breast cancers, such as infiltrating ductal carcinomas, to present with larger tumors (28,29), and have higher grade, ER-negative tumors.(30) One study found that when compared to premenopausal breast cancer patients aged ≥35 years, women aged <35 years were more likely to have tumors classified as ER-negative (38.8 versus 21.6%, *p-value*<0.001) and PR-negative (49.1 versus 35.3%, *p-value*<0.001).(30) About 60% of premenopausal breast cancer patients have ER-positive tumors, which are the tumors that are the most responsive to hormonal therapy.(31) However, when compared to older women, young women, especially young black women (9,32–34), are more likely to be diagnosed with basal-like tumors (i.e., ER-negative, PR-negative, HER2-negative, and either HER2-positive or CK 5/6-positive) (9,35), often referred to as triple-negative breast cancer (1,11), which is one of the most aggressive sub-types of breast cancer for all women, regardless of race/ethnicity.(10) Women diagnosed with

triple-negative breast cancer have a poorer short-term prognosis than women with other types of breast cancer since triple-negative tumors are less responsive to treatment (1), more likely to relapse within the first five years after diagnosis (36), and associated with higher mortality compared to the most common sub-type, luminal A (i.e., ER-positive or PR-positive and HER2-negative).(10) The classification of breast cancer sub-types is evolving, as indicated by O'Brien et al.'s (10) research and the current literature is not consistent on the use of basal-like versus triple-negative when classifying this specific sub-type of breast cancer. This is a particularly important issue to consider because premenopausal breast cancer patients are diagnosed with basal-like breast cancer at higher rates (31) and the O'Brien study (10) reported differences in the hazard ratios of breast cancer-related death when the usually all-inclusive triple-negative sub-type is teased apart into three sub-types (e.g., basal-like, HER-positive/ER-negative, unclassified). When breast cancer sub-types information is available, it should be well defined based on the current literature.

Effect of Cancer Treatment on Reproductive Health

Adjuvant endocrine therapy, which is the treatment of breast cancer with hormonal manipulation and/or cytotoxic therapies, is recommended for premenopausal breast cancer patients, because it improves the likelihood of relapse-free and overall survival by treating undetectable micrometastases.(31,37) Premenopausal breast cancer patients with hormone receptor-positive tumors are encouraged to receive adjuvant endocrine therapy that includes chemotherapy treatment and hormonal treatment (e.g., tamoxifen) for up to five years since it can reduce the 15-year death rate from breast cancer by 57% for women younger than 50 years old at time of diagnosis.(5) Tamoxifen does not improve recurrence or death rates for women with hormone receptor-negative disease; chemotherapy is beneficial for this group.(38)

Even though many of the side effects of chemotherapy are reversible once treatment is completed, the effects of this treatment on the ovaries can be irreversible.(39) Chemotherapy

has been shown to cause damage to female cancer patients' reproductive functioning by destroying mature ovarian follicles and causing ovarian toxicity. The resulting damage from chemotherapy treatment can range from temporary amenorrhea where menses returns post-treatment to complete ovarian failure or the early onset of menopause. Although it is highly likely that most women will experience menstrual cycle irregularity during chemotherapy treatment, it is expected that menstruation will return for premenopausal women within six months after the completion of the treatment. The type of chemotherapeutic agent, cumulative dose of the drug, duration of the treatment, age of the cancer patient, and pre-treatment ovarian reserve are all factors that determine a female cancer patient's likelihood of developing post-chemotherapy ovarian failure.(31,37,39,40) A longitudinal observational study assessing menstrual cycle maintenance and quality of life after breast cancer determined that after the completion of chemotherapy treatment, premenopausal breast cancer survivors under the age of 35 had an 85% recovery rate of their monthly menses. Breast cancer survivors ages 35 to 40 had a 45-61% recovery rate and those older than age 40 were the least likely to regain their menstrual cycle after the completion of treatment and during the study's follow-up period.(41) Yet, permanent amenorrhea may be desirable for some breast cancer patients since it is associated with increased survival. In a retrospective observational study of premenopausal breast cancer patients in Seoul, Korea, it was determined that 5-year disease-free survival was slightly higher for women who experienced chemotherapy-induced amenorrhea (88.0%) compared to women who did not (85%).(42)

It is recommended that breast cancer survivors, particularly those with hormone receptor-positive tumors, use non-hormonal birth control methods to decrease their risk of recurrence. They are also often asked to refrain from becoming pregnant while using tamoxifen, because it may have teratogenic effects on a fetus.(39) Premenopausal breast cancer patients with ER-positive tumors are highly encouraged to use tamoxifen for at least five years after the completion of chemotherapy and/or radiation treatment, since the use of this adjuvant

endocrine (hormonal) therapy decreases the risk of recurrence. The risk of becoming menopausal while taking tamoxifen increases with age. For tamoxifen users, less than 5% of women under age 40 become menopausal. This increases to 30% of women over age 40 and becomes as high as 84% of women who received chemotherapy and hormonal therapy.(43)

Although most studies conclude that in general breast cancer treatment is not associated with adverse birth outcomes (13–19,21), the Dalberg et. al (20) study did find that breast cancer survivors who have received chemotherapy treatment and have a subsequent pregnancy do have an increased risk of delivering a preterm or low birthweight infant.

It is highly recommended that cancer care providers discuss fertility preserving options with their premenopausal breast cancer patients before beginning treatment, so that they are fully aware of the effect each treatment may have on their reproductive function.(39,40) This information is particularly important to discuss with women who have not started or completed their families, so they can make an informed decision about the most appropriate cancer treatment regimen for them and if there are any fertility preserving options they should pursue prior to the onset of treatment. The most popular and effective fertility preservation options are: 1) Pharmacologic treatment (e.g., gonadotropin releasing-hormone agonist (GnRHa) for ovarian protection, apoptotic inhibitors); 2) Ovarian transposition (oophorophexy); and 3) Assisted reproductive technologies (e.g., cryopreservation of embryos, cryopreservation of oocytes, ovarian tissue cryopreservation, artificial gametes).(31,39,40) According to Resolve, the National Infertility Association, the average cost of assisted reproductive technologies (ART) ranges from $865 to $8165 per cycle or procedure.(44) However, insurance companies usually do not cover fertility preservation or infertility treatments (39), which make these options unfeasible for many breast cancer patients who cannot afford the out-of-pocket expense for these treatments.

This body of knowledge suggests that breast cancer treatments may impact one's reproductive capacity, and therefore serve as a mediator in the relationship between breast cancer diagnosis and adverse birth outcomes.

Reproductive Health Concerns among Premenopausal Breast Cancer Survivors

The long-term reproductive impact of cancer treatments is a legitimate concern for premenopausal breast cancer survivors. There are three main reasons that a diagnosis of premenopausal breast cancer may negatively impact reproductive function: 1) the toxic effect of chemotherapy on ovarian follicles (31,37,39,40), as discussed above; 2) the common recommendation for breast cancer patients to delay pregnancy for at least two to three years post-diagnosis (31,39); and 3) the recommendation to not become pregnant during adjuvant endocrine therapy, which lasts for five (but up to ten) years post-diagnosis, which may contribute to an age-related decline in fertility.(31)

The two to three year time delay between a breast cancer diagnosis and becoming pregnant is recommended because there is a concern of the lingering toxic effects of treatment on growing oocytes and there is also the potential risk of recurrence during this period.(39) However, evidence exhibiting the benefit to patients of waiting more than two years post-diagnosis to become pregnant is limited, especially if the woman has a good prognosis and localized disease (19), adjuvant endocrine therapy has been completed (31), and the risk of recurrence is low.(39,45,46) Young women diagnosed with breast cancer often question if a pregnancy will increase their risk of breast cancer recurrence because breast cancer is hormone-dependent and pregnancy is a period when hormone levels are at an all-time high in a women's reproductive life-span. The main concern is that an increase in hormone levels during pregnancy may stimulate the growth of remaining breast cancer cells or dormant micrometastasis, which may in turn increase the risk of recurrence.(39) Yet, breast cancer survivors who become pregnant after the completion of treatment tend to have the same, if not

better survival rates (22,46,47) and are less likely to experience a recurrence of breast cancer (48) than women who do not become pregnant after a breast cancer diagnosis. In a study by Gelber and colleagues (22), the overall 5-year and 10-year survival rates for breast cancer survivors who became pregnant was 92% and 85%, while 5-year survival was 85% and 10-year survival was 74% for the matched non-pregnant breast cancer survivor control group. The results from this study support the healthy mother effect (19,23,24), which is a type of selection bias that may indicate that women who choose to and are able to become pregnant after a bout with breast cancer may be healthier in general compared to breast cancer survivors who choose not to or are not able to become pregnant.(24,31)

Since it is recommended that women take tamoxifen for a minimum of five years and up to ten years, this extends the period breast cancer survivors must wait to become pregnant, if they desire. Within this five- to ten- year waiting period, these women, particularly the older premenopausal breast cancer survivors, may become menopausal or suffer from infertility due to diminished oocyte reserves.(37,39)

The potential damaging effects of chemotherapy and hormonal therapy on reproductive function, as well as the age-related decline in fertility from delaying childbearing until the completion of treatment are all reproductive health issues that premenopausal breast cancer patients need to be informed of before, during, and after the completion of treatment so they are fully aware of the impact the cancer treatments may have on their plans to begin or complete their families. More information is needed to determine if these cancer treatments may have any influence on the birth outcomes of infants born to premenopausal breast cancer survivors.

Risk Predictors and Factors of Preterm Birth and Low Birthweight

The risk of delivering a preterm or low birthweight infant is known to vary by several maternal characteristics, including mother's age at time of pregnancy, race/ethnicity, and socioeconomic status.(49–51) Furthermore, studies that have focused on disparities in medical

treatment and health outcomes have demonstrated that racial/ethnic and socioeconomic status (SES) disparities are particularly apparent among cancer patients.(17,18,52–54) Therefore, maternal characteristics, race/ethnicity, and SES were important variables to include in this study's analytical models in order to determine if they are true effect measure modifiers or confounders in the association between premenopausal breast cancer and preterm birth or low birthweight. Many past studies that have focused on the association between breast cancer and birth outcomes may have not seen a strong correlation between these variables because they did not factor in relevant risk predictors and factors that may influence this relationship.

Preconception Health

Preconception health interventions aim to improve the health status and behaviors of women (and men) prior to conceiving a child with the ultimate goal of decreasing the risk of adverse pregnancy-related outcomes.(55) The preconception period in the life course often refers to the years in which one is of reproductive age, but also recognizes that a woman's preconception health status may be the result of negative exposures *in utero* or her mother's (or even maternal grandmother's) lifestyle behaviors or exposures. Since a majority of pregnancies are unplanned, there has been a growing emphasis on promoting healthy behaviors throughout the reproductive health period (e.g., smoking cessation, reduction in alcohol use, maintaining a healthy weight, consumption of essential vitamins and minerals) and not just during the prenatal period.(56)

In 2007, the Centers for Disease Control and Prevention (CDC) established a working group to develop a set of core state preconception health indicators, which were included in five population-based data systems, including the Pregnancy Risk Assessment and Monitoring Survey (PRAMS) and the Behavioral Risk Factor Surveillance System (BRFSS). The aim was to learn more about the preconception health status and behaviors of women in the U.S. These indicators were organized into eleven domains, which are: 1) general health status and life

satisfaction; 2) social determinants of health; 3) healthcare; 4) reproductive health and family planning; 5) tobacco, alcohol, and substance use; 6) nutrition and physical activity; 7) mental health; 8) emotional and social support; 9) chronic conditions; 10) infections; and 11) genetics/epigenetics.(57)

North Carolina is one of the original seven states that participated in the working group that developed these core indicators. Medical, state health department, and university-based entities in North Carolina have been dedicated to improving the preconception health of women and men in this state. In 2008, the North Carolina Preconception Health Coalition released a 2009-2013 strategic plan to promote intended pregnancy and healthy weight. The coalition's other priority areas are substance abuse, mental health, collaborative research on preconception-focused topics, and policy development and access to care.(58) This coalition is one example of how North Carolina is committed to educating women, men, and healthcare professionals about the importance of preconception health and is making strides towards providing more women in this state with access to preconception health services.

When applied to special populations, such as women diagnosed with and treated for premenopausal breast cancer, the preconception healthcare needs may differ from those prescribed to the general population of women of reproductive age. Therefore, it is important to learn more about the preconception health status and behaviors of special populations, so that the preconception health services referred to these women can be tailored to suit their specific reproductive health concerns that may be magnified by their health condition.

Conceptual Foundation

This study of the birth outcomes and reproductive needs of premenopausal breast cancer survivors provides additional insights into the lives and health of women after being treated for breast cancer. Improvements in treatment options and early detection have led to more survivors living for longer periods of time after breast cancer.(59) As breast cancer survivors

continue on with their lives, the medical and public health communities need to be prepared to address the health issues that may differ between breast cancer survivors and the general population.

In an effort to address gaps in the literature, the proposed study explored the association between a premenopausal breast cancer diagnosis and delivering a PTB or LBW infant, as well as the reproductive needs and concerns of young breast cancer survivors. Healthy mother effect bias (19,23,24), Lu's and Halfon's (60) life-course health development model, as well the biological effect of chemotherapy on reproductive function, served as the conceptual foundations for testing hypotheses regarding the effect of a breast cancer diagnosis on subsequent birth outcomes, as well as how this relationship is influenced by maternal characteristics and the length of time between breast cancer diagnosis and the date of first infant delivery post-breast cancer diagnosis. This study utilized quantitative and qualitative methods with the aim of providing a comprehensive synopsis of the reproductive health experiences of premenopausal breast cancer survivors. This information may assist medical and public health professionals with offering targeted preconception health services to this specific population in order to decrease their risk of experiencing an adverse birth outcome, as well as fully address their reproductive health concerns. A directed acyclic graph (DAG) that visually depicts the relationship between breast cancer and PTB/LBW from an epidemiological perspective is provided in Figure 1.1.

Not all of the pathways in the DAG were examined. The main causal pathway from breast cancer diagnosis to PTB/LBW was the foundation of the analysis with maternal age at infant delivery, education, marital status, parity, and smoking being controlled for as confounders, race/ethnicity being accounted for as a modifier, and chemotherapy accounted for as a mediator. In this study, chemotherapy was the main cancer treatment included in the analyses, due to its known negative effect on breast cancer patients' reproductive health and birth outcomes. Although fertility status (i.e., being premenopausal, peri-menopausal, or

menopausal after receiving cancer treatment) and body mass index are recognized in the DAG as important covariates on the pathway between the exposure and outcome, these variables are not available in the given dataset and therefore were not included in the analyses.

To further exemplify the joint quantitative and qualitative analysis used in this study, the conceptual model in Figure 1.2 provides a more simplified depiction of the relationship between the aforementioned variables. The conceptual model is adapted from Lu's and Halfon's (60) life-course health development model to reflect the trajectories of premenopausal breast survivors from diagnosis to a subsequent pregnancy. The life-course health development model depicts how black and white women are differentially exposed to risk factors and protective factors over the life course and how this contributes to disparities in health outcomes.(60) The life-course health development model exhibits how black women have more cumulative exposure to risk factors (i.e., downward arrows) and less protective factors (i.e., upward arrows) than their white counterparts, which results in black women having lower reproductive potential over their life course. The conceptual model depicts how this situation may look for premenopausal breast cancer survivors.

There are a few key points represented in this conceptual model. The period in which women are undergoing chemotherapy is when both black and white women's reproductive potential exponentially declines, but this decline is more dramatic for black women than white women based on the hypothesis that black women have a greater cumulative exposure to risk versus protective factors compared to white women. Furthermore, the hormonal therapy-related and age-related decline in reproductive potential declines more slowly for white than black women based on the hypothesis that white women experience more protective versus risk factors compared to black women. It is also important to note that due to the healthy mother effect, the women who are able to become pregnant after a premenopausal breast cancer diagnosis are more likely to have a more positive prognosis and be represented in this model. The quantitative dataset allowed for an examination of how risk factors and protective factors

(e.g., maternal characteristics) differentially influence the birth outcomes of black and white women with and without a breast cancer history. Whereas, the qualitative dataset allowed for the further exploration of the reproductive potential of premenopausal breast cancer survivors by also including women who did not have children, either by choice or due to infertility issues.

Study Overview

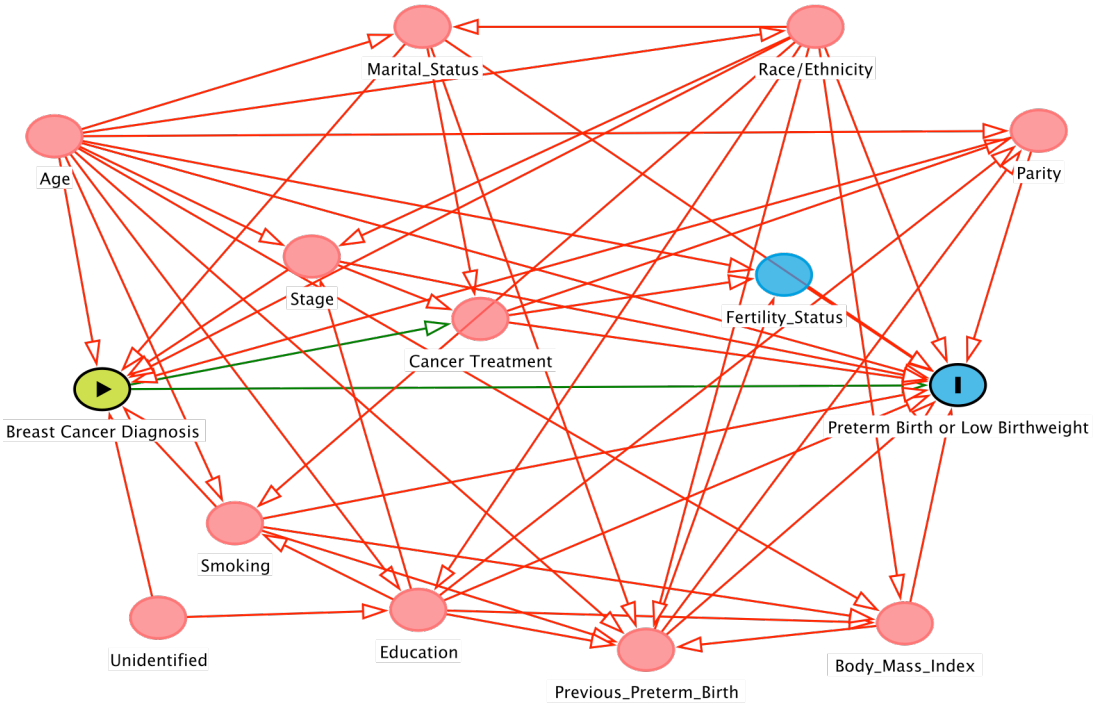
A mixed methods approach provides an avenue to explore the complex relationship between breast cancer and reproductive health through the lived experiences of premenopausal breast cancer survivors. In this study, the quantitative data provides an estimate of the prevalence ratios and confidence intervals of the association between a breast cancer history and preterm birth and low birthweight using linked cancer registry and birth record data from the North Carolina State Center for Health Statistics. The qualitative data provides an understanding of the reproductive health experiences and concerns of women with a breast history, in addition to similarities and differences in experiences by post-diagnosis birth status and race using in-depth interviews with premenopausal breast cancer survivors. The combined use of these methods sheds new light on this topic and provides a rich and more complex understanding of the reproductive health experiences of premenopausal breast cancer survivors.

As strategies for screening and treatment continue to advance, survival rates for breast cancer will simultaneously increase; therefore, the preconception health issues that arise for premenopausal breast cancer survivors need to be sufficiently addressed. Informed by the healthy mother effect bias theory (19,23,24), Lu's and Halfon's (60) life-course health development model, as well the biological effect of chemotherapy on reproductive function, this study adds to existing research by exploring additional factors that may influence the association between premenopausal breast cancer and subsequent birth outcomes for women in the United States. This study adds a layer to this pertinent discussion by highlighting the risk predictors and factors that may contribute to this complex issue, including maternal

characteristics and chemotherapy treatment. Furthermore, this study provides insights into the specific preconception health services and reproductive health counseling that women with a breast cancer history may benefit from prior to and after cancer treatment.

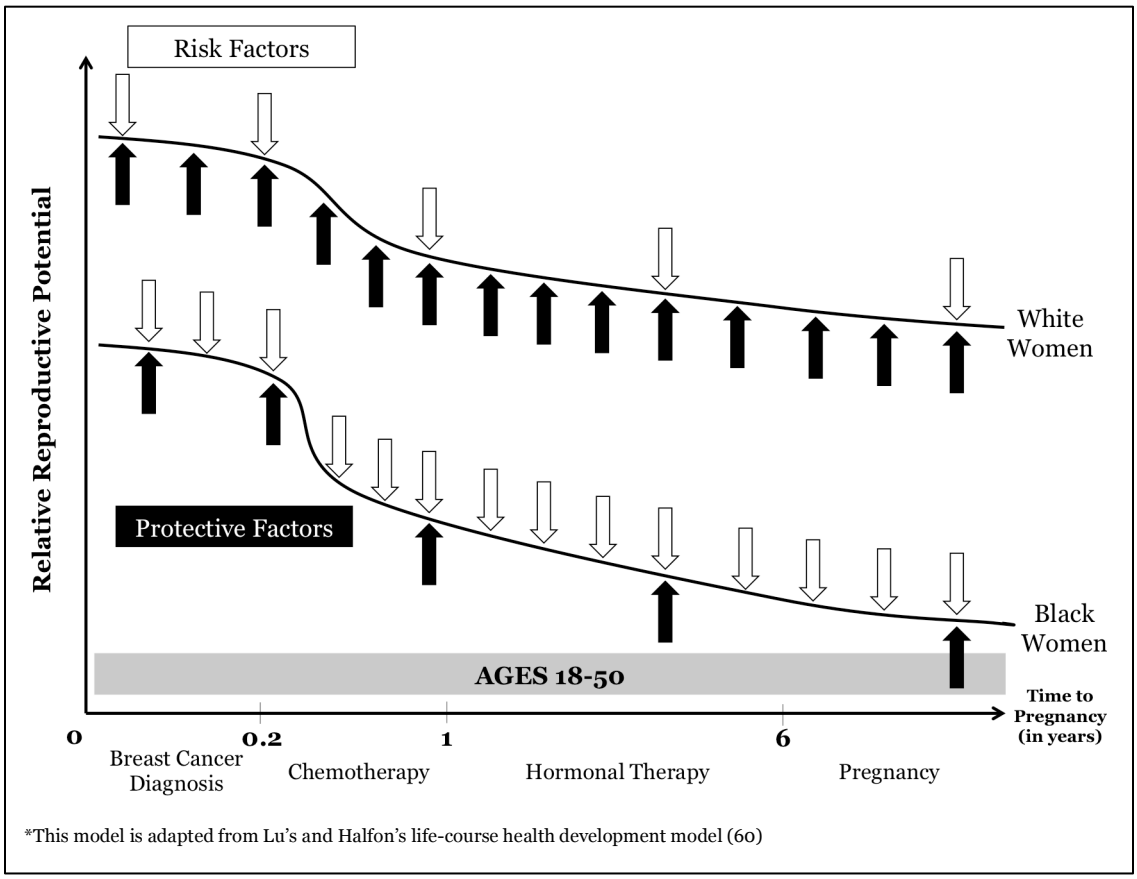
FIGURES

Figure 1.1. Directed Acyclic Graph (DAG) of the relationship between breast cancer diagnosis and preterm birth or low birthweight accounting for potential covariates



KEY:
*Green circle with play symbol is the exposure variable
†Blue circle with bold I is the outcome variable
♭Blue circles are the ancestors of the outcome variable
‡Red circles are covariates that are potentially associated with the exposure and outcome (i.e., confounders)
§Green line is the causal path
#Red lines are the bias paths

Figure 1.2. Conceptual model of how risk factors and protective factors differentially influence the relative reproductive potential of black and white women with a premenopausal breast cancer history



*This model is adapted from Lu's and Halfon's life-course health development model (60)

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CHAPTER 2: PREVALENCE OF PRETERM AND LOW BIRTHWEIGHT DELIVERY AFTER BREAST CANCER DIAGNOSIS: A POPULATION-BASED STUDY

Introduction

With an increasing number of women delaying childbearing (1,2) and improved breast cancer survival among women diagnosed before the age of 50 (3), many young breast cancer patients face decisions at the time of diagnosis that may influence their future reproductive health. Beyond the risk of infertility (4–7), other adverse birth outcomes including preterm birth and low birthweight may be more common among women with a prior breast history.(8) The potential risk of adverse birth outcomes among breast cancer survivors has not been studied in in the context of existing racial disparities in breast cancer incidence and birth outcomes in the United States.

Black women are more likely than their white counterparts to be diagnosed with breast cancer during their reproductive years (9) and deliver preterm or low birthweight infants. Breast cancer diagnosed in young women, especially young black women, is more likely to be more aggressive and have a poorer prognosis than breast cancer diagnosed in older women and young white women.(10–12) In the general U.S. population, 9.6% of infants are delivered preterm (PTB; <37 weeks gestation) and 8.1% have a low birthweight (LBW; <2,500 grams).(2) Rates of PTB and LBW increases with maternal age and vary by race/ethnicity. For example, mothers aged 45 or older compared to those aged 25-34 years have a higher portion of PTB (24.2 vs. 9.1%) and LBW (20.4 vs. 7.4%) deliveries.(13) At the same time, black women are 40.5% more likely to deliver a PTB infant and 63.2% more likely to deliver a LBW infant compared to white women.(2)

A breast cancer diagnosis and its treatment may have long-lasting effects on reproductive health outcomes. Alkylating agent-based chemotherapies can cause ovarian toxicity (5), including loss of mature ovarian follicles. During chemotherapy treatment, premenopausal women may experience temporary chemotherapy-related amenorrhea or premature ovarian failure.(4–7) After completion of chemotherapy, a 5- to 10-year course of adjuvant endocrine therapy is recommended for hormonally-responsive tumors to improve relapse-free and overall survival.(6,7,14) Pregnancy is not recommended during the course of adjuvant endocrine therapy; therefore, some women may choose to not initiate or to interrupt endocrine therapy to achieve pregnancy.(15)

Black-white disparities in breast cancer incidence rates and birth outcomes raise concerns about potential disparities in the reproductive health of premenopausal breast cancer survivors. Most previous studies have focused on survival rates among breast cancer survivors with a post-diagnosis pregnancy compared to those without.(16–18) Survival does not appear to be adversely affected by post-diagnosis pregnancy; however, this may be partially attributable to a "healthy mother effect."(16,19,20) Few published studies have examined infant outcomes after a breast cancer diagnosis.(8,16,18,21–23) Our study examined the prevalence of PTB and LBW according to breast cancer history prior to infant delivery in a population-based study in North Carolina (NC) and evaluated potential effect modification by race.

Methods

This study was reviewed and approved by the University of North Carolina at Chapel Hill's IRB and Office of Human Research Ethics (#14-1394).

North Carolina Central Cancer Registry

The primary exposure for this analysis was breast cancer history prior to delivery. We identified breast cancer diagnoses during the study period (1990-2009) within the state-

mandated North Carolina Central Cancer Registry (NC-CCR).(24) The NC-CCR is a gold-certified North American Association of Central Cancer Registries (NAACCR) cancer registry within the Centers for Disease Control and Prevention's National Program of Cancer Registries. We used topography site code C50 from the International Classification of Disease-Oncology, 3rd Edition (25) to identify first primary breast cancer diagnoses at ages 18-45. Additional NC-CCR variables included date of diagnosis, age at diagnosis, and receipt of treatment (e.g., surgery, chemotherapy, radiation, endocrine therapy).

North Carolina Birth Certificate Files

The study population for this analysis was comprised of all live, singleton births to NC residents during 1990-2009 (n=2,325,229). Within ten days of a delivery, a hospital administrator or person attending a non-hospital delivery (e.g., midwife) must file a birth certificate to the Department of Health and Human Services. The NC State Center for Health Statistics houses and manages these vital statistics records.(26) Further eligibility criteria included maternal ages 18-50 years (n=2,213,487), and maternal ethnicity and race designated as non-Hispanic Black or White (n=1,916,998). Latinas and other races/ethnicities were excluded because there was not sufficient power to examine these racial/ethnic categories independently. Women who experienced a stillbirth, miscarriage, or other adverse pregnancy outcome that did not result in a live birth are not included because they are not systematically captured in vital records data. We also excluded mothers who delivered infants at less than 20 weeks gestation or weighing less than 500 grams because they were outside of the age and weight of viability. After these exclusions, 1,912,269 births contributed to the LBW analysis and 1,910,014 births contribute to the PTB analysis (2,255 births were missing gestational age).

Information abstracted from the birth certificate files included number of weeks of gestation at time of delivery, infant's weight in pounds and ounces, maternal number of years of education, marital status at time of delivery, number of living children, race, ethnicity, number

of cigarettes smoked per day during pregnancy, maternal age at delivery, and date of infant delivery.

North Carolina Central Cancer Registry and Vital Records Linkage

Birth certificate files were linked with the NC-CCR for the period of January 1, 1990 through December 31, 2009, by the NC State Center for Health Statistics. The linkage protocol applied a probabilistic algorithm using names and social security numbers in Link Plus (CDC; Atlanta, GA). Identifying information was redacted from the final dataset. Breast cancer history prior to infant delivery was defined as a maternal breast cancer diagnosis recorded in the NC-CCR that preceded the date of delivery in the birth certificate files. Two births by mothers with a breast cancer history were excluded because the diagnosis date was not available and the diagnosis age was above 45 years.

Covariates

The risk of delivering a PTB or LBW infant is known to vary by several maternal characteristics, including mother's age at time of pregnancy, race/ethnicity, and socioeconomic status (SES).(27–29) Studies that have focused on disparities in medical treatment and health outcomes have demonstrated that racial/ethnic and SES disparities are particularly apparent among cancer patients.(30–34) Therefore, maternal characteristics, race/ethnicity, and SES were important covariates to include in this study's analytical models. Each covariate included in analytical models is described below.

Preterm birth was defined as gestational age 20 to <37 weeks at delivery. Infant weight was calculated by converting weight in pounds and ounces to grams. Low birthweight was defined as <2,500 grams. Maternal years of education were categorized as less than high school (≤11 years), high school diploma (12 years), at least some or graduated college (13-16 years), and professional/graduate degree (≥ 17 years). Mother's marital status was abstracted from the

birth certificate (married or not married). Number of living children was used to determine parity status as primiparous (i.e., no infant delivery prior to the current birth) or multiparous (i.e., a previous delivery in addition to the current birth). Maternal race/ethnicity is composited using the race and Hispanic ethnicity variables on the birth certificate. Number of cigarettes smoked per day during pregnancy was dichotomized as smoked during pregnancy (yes/no). Receipt of chemotherapy is derived from the first listed date of chemotherapy treatment or otherwise categorized as no chemotherapy. Length of time between diagnosis and infant delivery was calculated using the mother's breast cancer diagnosis date and the date of infant delivery and categorized as <2, 2-4.9, and ≥5 years. Maternal age at infant delivery in years was included in the analysis as a continuous variable.

Statistical Analysis

Multivariable binomial regression was used to calculate prevalence ratios (PR) and 95% confidence intervals (CI) for the association between breast cancer history and birth outcome (i.e., PTB and LBW). We assessed and identified additional covariates as an effect measure modifier using likelihood ratio tests (e.g., race/ethnicity) with the *a priori* significance criteria set at 5% or as a confounder using 5% change in estimate tests (e.g., maternal age at infant delivery, education, marital status, parity, and smoking) for inclusion in multivariable models. We assessed statistical interaction between breast cancer history and race on the additive (common referent) and multiplicative (stratified) scales using relative excess risk due to interaction (RERI) with 95% CIs (35) and cross-product interaction terms (36), respectively. All analyses were performed using SAS statistical software version 9.3 (Cary, NC).

Results

Of the 1,912,269 eligible live births in NC during 1990-2009, 512 births were linked to mothers with a breast cancer history. The mean age at breast cancer diagnosis was 31.8 years

(SD=4.7) and the average time from diagnosis to delivery was 3.3 years (SD=2.8). Nearly half (49.4%) of mothers with a breast cancer history had a record of starting chemotherapy (Table 2.1).

Overall, 10.8% of infants were PTB and 8.8% were LBW. Among all births, 72.3% were to white women and 27.7% to black women. Compared to the general population of reproductive age mothers, mothers with a breast cancer history were older at the time of infant delivery, and more likely to have attended college, be married, and not smoke during pregnancy (Table 2.1).

We observed an increased risk of PTB and LBW for births to women with a breast cancer history, especially for women who received chemotherapy treatment or gave birth within two years of their diagnosis date. After multivariable adjustment for maternal age, education, marital status, parity, race, and smoking, the PR associated with breast cancer history was 1.67 (95% CI: 1.42-1.97) for PTB and 1.50 (95% CI: 1.23-1.84) for LBW. The PR of PTB among births to mothers with a breast cancer history that received chemotherapy treatment was 2.17 (95% CI: 1.79-2.63) compared to the general population. The corresponding PR for LBW was 1.92 (95% CI: 1.50-2.45). The PR of PTB among births that occurred within two years of the mother's diagnosis date was 2.58 (95% CI: 2.12-3.15) compared to the general population. The corresponding PR of LBW was 2.16 (95% CI: 1.64-2.85) (Table 2.2).

In our data, nearly half of the infants with adverse birth outcomes were both PTB and LBW (47.3% overall; 46.6% of births to mothers with a breast cancer history). Preterm birth may be on the causal pathway from breast cancer history to LBW, making co-adjustment for these factors inappropriate.(37) Therefore, we further examined LBW models restricted to term pregnancies (≥37 weeks gestation; N=404 births to women with a breast cancer history). In this analysis, the PR for LBW associated with mother's breast cancer history was 1.68 (95% CI: 1.09 to 2.59) (Table 2.3).

In analyses stratified according to maternal race, the PR for PTB associated with breast cancer history was 1.31 (95% CI: 1.00-1.72) for black mothers and 2.06 (95% CI: 1.67-2.54) for white mothers. The corresponding PRs for LBW were 1.49 (95% CI: 1.14-1.94) for black mothers and 1.53 (95% CI: 1.12-2.08) for white mothers. There is evidence of statistical interaction between breast cancer history and race for PTB (*P*-interaction=0.01), but not for LBW (*P*-interaction=0.9) on the multiplicative scale (Table 2.4). The interaction between breast cancer history and race was not statistically significant on the additive scale for the risk of PTB (RERI: -0.61; 95% CI: -1.28-0.07) or LBW (RERI: 0.36; 95% CI: -0.50-1.23). Compared to white mothers in the general population, the PR for PTB was 2.06 (95% CI: 1.67-2.54) for white mothers with a breast cancer history, 1.45 (95% CI: 1.44-1.47) for black mothers without a breast cancer history, and 1.90 (95% CI: 1.45-2.50) for black mothers with a breast cancer history. The PR for LBW was 1.53 (95% CI: 1.12-2.08) for white mothers with a breast cancer history, 1.82 (95% CI: 1.80-1.84) for black mothers without a breast cancer history, and 2.71 (95% CI: 2.08-3.54) for black mothers with a breast cancer history, compared to white mothers without a breast cancer history (Table 2.5).

In analyses restricted to births to women with a breast cancer history, receipt of chemotherapy was associated with a PR of 1.78 (95% CI: 1.25-2.53) for PTB and 1.68 (0.94-3.03) for LBW compared to no chemotherapy. The PR of PTB among births that occurred within two years of the mother's diagnosis date was 2.04 (95% CI: 1.44-2.90) compared to births that occurred two years or more after the mother's diagnosis date. The corresponding PR of LBW was 1.78 (95% CI: 0.93-3.41) (Table 2.6).

Discussion

Women with a premenopausal breast cancer diagnosis may not have started or completed their families at the time of diagnosis. Our findings indicate that a breast cancer history may correspond to 50-67% increases in risk of delivering a PTB or LBW infant compared

to the general population, with greater increases in risk observed among women who received chemotherapy or gave birth within two years of diagnosis. Examination of the prevalence of adverse birth outcomes within race showed that both black and white mothers with a breast cancer history had a significant increase in risk (31-49% and 53-106%, respectively) of delivering a PTB and LBW infant compared to mothers without a breast cancer history within their racial group. Yet, the prevalence of PTB and LBW was greater for white mothers compared to black mothers in these analyses. This may be due, in part, to the cumulative exposure to risk factors for PTB and LBW (38,39) influencing the health status of black women such that the added health implications of being diagnosed and treated for breast cancer does not have the same level of effect on their reproductive health outcomes as it does for white women. When white mothers in the general population is used as the common referent, white mothers with a breast cancer history have the highest prevalence of PTB, but black mothers with a breast cancer history have the highest prevalence of LBW. The interaction between breast cancer history and race was significant on the multiplicative scale in the within race analyses when examining PTB, but not on the additive scale when white women in the general population was used as the common referent. This attests to the importance of examining racial disparities using a common referent other than the white unexposed group.(40)

Three population-based studies of birth outcomes of women diagnosed with breast cancer have been conducted in western Australia, Sweden, and Denmark.(8,16,23) These studies linked cancer and birth data from nation-wide registries, yet have discordant results. In Australia during 1982-2003, 5% (n=123) of women with a breast cancer history conceived after their diagnosis, 50% (n=62) of them had a birth within two years of their diagnosis date, and only two PTB (<36 weeks gestation) were reported.(16) In Sweden during 1973-2002, women with a breast cancer history (when compared to the general population) had greater odds of delivering an early PTB (<32 weeks gestation; aOR: 3.20, 95% CI: 1.70-6.03) or very LBW (<1,500 grams; aOR: 2.86, 95% CI: 1.41-5.78) infant.(8) This increase was not observed in

Denmark during 1973-2002, where the odds of delivering a PTB (<37 weeks gestation; aPOR: 1.2, 95% CI: 0.4-3.8) or LBW at term (<2,500 grams and ≥37 weeks gestation; aPOR: 1.3, 95% CI: 0.7-2.2) infant were not significantly different between women with a breast cancer history and the general population.(23)

The magnitude of our effect estimates were consistent with the Danish study (23) and used the same cut point for PTB. The Swedish study (8) used lower cut points for PTB and LBW. We reanalyzed our data using the same cut points as the Swedish study (8), but our results were not statistically significant. The Danish study (23) conducted stratified analyses by sex of child and type of treatment, but did not see a substantial change in the overall effect estimates. Our analysis reinforces that racial group is an important consideration for evaluating adverse birth outcomes in the U.S.

Some limitations of our analysis must be considered. Information on breast cancer hormone receptor status, stage, use of endocrine therapy, and chemotherapy agents, dose, and cycle were either not available or frequently missing and therefore not analyzed. We were not able to account for multiple births to the same mother. Pregnancies that result from assisted reproductive technology (ART) cannot be identified and tend to have a higher prevalence of multiple births, as well as PTB and LBW deliveries. Only about 1.5% of infants born in the U.S. general population are conceived via ART.(41)

Strengths of our analysis include the use of a population-based dataset to address a 20-year period with approximately two million births overall. With persistent racial disparities in cancer care and birth outcomes in the U.S., the added exploration of race as a modifier of the association between breast cancer history and adverse birth outcomes is an important contribution. Our analyses that examined receipt of chemotherapy and time between diagnosis date and delivery provide additional insights into factors along the breast cancer trajectory that may contribute to increased risk of adverse birth outcomes among mothers with a breast cancer history. In our data, it is not possible to distinguish pregnancies that co-occur with breast

cancer diagnosis or the active treatment period. Future longitudinal studies that follow breast cancer patients from diagnosis to birth will be critical to disentangle potential differences between women who are diagnosed with breast cancer during pregnancy from those who conceive after the active treatment period.

Breast cancer treatment has long-term implications on the health and quality of life of women. Understanding the effects of breast cancer treatment on future reproductive health outcomes is an important concern for premenopausal women. They may benefit from targeted preconception health services and reproductive health counseling prior to and after cancer treatment. Furthermore, qualitative research may reveal a deeper understanding of breast cancer survivors' decision-making process regarding their treatment regimen as it relates to their post-treatment childbearing goals.

TABLES

TABLE 2.1. CHARACTERISTICS OF LIVE BIRTHS ACCORDING TO MOTHER'S BREAST CANCER HISTORY AT TIME OF DELIVERY, NORTH CAROLINA 1990-2009

	Breast cancer history *(N=512)*		**General population** *(N=1,911,757)*	
	N	*%*	N	*%*
Preterm Birth				
Term (≥37 weeks gestation)	404	*78.9*	1,703,476	*89.1*
Preterm (<37 weeks gestation)	108	*21.1*	206,026	*10.8*
Missing	0	*0.0*	2,255	*0.1*
Low Birthweight				
Healthy weight (≥2,500 grams)	436	*85.2*	1,743,325	*91.2*
Low birthweight (<2,500 grams)	76	*14.8*	168,432	*8.8*
Missing	0	*0.0*	0	*0.0*
Education				
Less than high school (≤11 years)	19	*3.7*	266,180	*13.9*
High school diploma (12 years)	123	*24.0*	662,969	*34.7*
Some or graduated college (13-16 years)	282	*55.1*	814,843	*42.6*
Professional/graduate degree (≥17 years)	87	*17.0*	164,664	*8.6*
Missing	1	*0.2*	3,101	*0.2*
Marital Status				
Married	404	*78.9*	1,320,768	*69.1*
Not married	108	*21.1*	590,559	*30.9*
Missing	0	*0.0*	430	*0.02*
Parity				
Primiparous (1 birth)	153	*29.9*	787,261	*41.2*
Multiparous (≥ 2 births)	359	*70.1*	1,124,496	*58.8*
Missing	0	*0.0*	0	*0.0*
Race/Ethnicity				
White, non-Hispanic	324	*63.3*	1,382,978	*72.3*
Black, non-Hispanic	188	*36.7*	528,779	*27.7*
Missing	0	*0.0*	0	*0.0*
Smoking				
Non-Smoker	463	*90.4*	1,605,661	*84.0*
Smoker	46	*9.0*	296,037	*15.5*
Missing	3	*0.6*	10,059	*0.5*
Maternal Age at Infant Delivery (in years)				
Mean *(Standard Deviation)*	34.6 *(4.7)*		27.1 *(5.7)*	
Range	20.0-48.0		18.0-50.0	
Age at Breast Cancer Diagnosis (in years)				
Mean *(Standard Deviation)*	31.8 *(4.7)*			
Range	18.7-44.3			
Chemotherapy				
Didn't receive chemotherapy	259	*50.6*		
Received chemotherapy	253	*49.4*		
Missing	0	*0.0*		
Length of Time between Diagnosis & Infant Delivery				
< 2 years	195	*38.1*		
2 ≤ years < 5	197	*38.5*		
≥ 5 years	120	*23.4*		
Missing	0	*0.0*		

N=total number; %=percentage

TABLE 2.2. PREVALENCE RATIOS AND 95% CONFIDENCE INTERVALS FOR PRETERM BIRTH AND LOW BIRTHWEIGHT ACCORDING TO BREAST CANCER HISTORY, CHEMOTHERAPY, AND LENGTH OF TIME BETWEEN DIAGNOSIS AND DELIVERY

	Preterm Birth			Low Birthweight		
	N <37 weeks	Age Adj.[a] *PR (95% CI)*	Multivariable[b] *PR (95% CI)*	*N <2,500 grams*	Age Adj.[a] *PR (95% CI)*	Multivariable[b] *PR (95% CI)*
Breast cancer history						
No	206,026	1.00	1.00	168,432	1.00	1.00
Yes	108	1.89 (1.60-2.24)	1.67 (1.42-1.97)	76	1.76 (1.43-2.16)	1.50 (1.23-1.84)
Chemotherapy[c]						
No	38	1.31 (0.98-1.76)	1.17 (0.87-1.56)	28	1.28 (0.90-1.82)	1.10 (0.78-1.55)
Yes	70	2.48 (2.03-3.03)	2.17 (1.79-2.63)	48	2.24 (1.73-2.89)	1.92 (1.50-2.45)
Time between diagnosis & delivery[c]						
< 2 years	62	2.86 (2.33-3.52)	2.58 (2.12-3.15)	38	2.29 (1.72-3.04)	2.16 (1.64-2.85)
2 ≤ years < 5	30	1.36 (0.98-1.90)	1.20 (0.86-1.66)	20	1.20 (0.79-1.82)	0.98 (0.65-1.47)
≥ 5 years	16	1.19 (0.75-1.87)	1.04 (0.66-1.63)	18	1.79 (1.17-2.74)	1.49 (0.98-2.26)

Adj.=adjusted; PR=prevalence ratio; CI=confidence intervals

[a] Adjusted for mother's age at infant delivery

[b] Adjusted for mother's age at infant delivery, education, marital status, parity, race/ethnicity, and smoking

[c] Includes only women with a breast cancer history (n=512 for preterm and low birthweight)

TABLE 2.3. PREVALENCE RATIOS AND 95% CONFIDENCE INTERVALS FOR LOW BIRTHWEIGHT AT TERM ACCORDING TO BREAST CANCER HISTORY

	Low Birthweight at Term[a]		
	N <2,500 grams	Age Adj.[b] *PR (95% CI)*	Multivariable[c] *PR (95% CI)*
Breast cancer history			
No	47,083	1.00	1.00
Yes	19	2.03 (1.31-3.15)	1.68 (1.09-2.59)
Chemotherapy[d]			
No	8	1.57 (0.79-3.09)	1.29 (0.66-2.54)
Yes	11	2.59 (1.46-4.58)	2.14 (1.22-3.76)
Time between diagnosis & delivery[d]			
< 2 years	10	3.14 (1.73-5.70)	2.93 (1.63-5.27)
2 ≤ years < 5	3	0.78 (0.25-2.39)	0.60 (0.20-1.83)
≥ 5 years	6	2.58 (1.19-5.61)	2.12 (0.98-4.56)

Adj.=adjusted; PR=prevalence ratio; CI=confidence intervals
[a] Infants delivered weighing <2500 grams and at ≥37 weeks gestation
[b] Adjusted for mother's age at infant delivery
[c] Adjusted for mother's age at infant delivery, education, marital status, parity, race/ethnicity, and smoking
[d] Includes only women with a breast cancer history (n=404)

TABLE 2.4. PREVALENCE RATIOS AND 95% CONFIDENCE INTERVALS FOR PRETERM BIRTH AND LOW BIRTHWEIGHT STRATIFIED BY RACE/ETHNICITY ACCORDING TO BREAST CANCER HISTORY

Race/Ethnicity	Breast Cancer History	Preterm Birth		Low Birthweight	
		N <37 weeks	*PR (95% CI)*[a]	*N <2,500 grams*	*PR (95% CI)*[a]
Black, non-Hispanic	No	75,286	1.00	71,159	1.00
	Yes	40	1.31 (1.00-1.72)	41	1.49 (1.14-1.94)
White, non-Hispanic	No	130,740	1.00	97,273	1.00
	Yes	68	2.06 (1.67-2.54)	35	1.53 (1.12-2.08)
		P-interaction=0.01		*P-interaction=0.9*	

PR=prevalence ratio; CI=confidence intervals

[a] Adjusted for mother's age at infant delivery, education, marital status, parity, and smoking

TABLE 2.5. PREVALENCE RATIOS AND 95% CONFIDENCE INTERVALS FOR PRETERM BIRTH AND LOW BIRTHWEIGHT BY INTERACTION BETWEEN BREAST CANCER HISTORY AND RACE/ETHNICITY

	Preterm Birth			**Low Birthweight**		
		Breast Cancer History			Breast Cancer History	
Race/Ethnicity	*N <37 weeks*	No *PR (95% CI)*[a,b,c]	Yes *PR (95% CI)*[a,b,c]	*N <2,500 grams*	No *PR (95% CI)*[a,b,d]	Yes *PR (95% CI)*[a,b,d]
White, non-Hispanic	130,808	1.00	2.06 (1.67-2.54)	97,308	1.00	1.53 (1.12-2.08)
Black, non-Hispanic	75,326	1.45 (1.44-1.47)	1.90 (1.45-2.50)	71,200	1.82 (1.80-1.84)	2.71 (2.08-3.54)

PR=prevalence ratio; CI=confidence intervals; RERI=relative excess risk due to interaction
[a] Adjusted for mother's age at infant delivery, education, marital status, parity, and smoking
[b] RERI = PR11 – PR10 – PR01 + 1; 95% CI for RERI estimated using Hosmer and Lemeshow (35)
[c] RERI= 0.61 (95% CI: -1.28-0.07)
[d] RERI= 0.36 (95% CI: -0.50-1.23)

TABLE 2.6. PREVALENCE RATIOS AND 95% CONFIDENCE INTERVALS FOR PRETERM BIRTH AND LOW BIRTHWEIGHT IN WOMEN WITH A BREAST CANCER HISTORY ACCORDING TO CHEMOTHERAPY, LENGTH OF TIME BETWEEN DIAGNOSIS AND DELIVERY, RACE/ETHNICITY, AND PARITY

	Preterm Birth			Low Birthweight		
	N <37 weeks	Age Adj.[a] *PR (95% CI)*	Multivariable[b] *PR (95% CI)*	*N <2,500 grams*	Age Adj.[a] *PR (95% CI)*	Multivariable[b] *PR (95% CI)*
Chemotherapy						
No	38	1.00	1.00	28	1.00	1.00
Yes	70	1.86 (1.31-2.64)	1.78 (1.25-2.53)	48	1.85 (1.21-2.83)	1.68 (0.94-3.03)
Time between diagnosis & delivery (2-year cut point)						
≥ 2 years	46	1.00	1.00	38	1.00	1.00
< 2 years	62	2.14 (1.52-3.00)	2.04 (1.44-2.90)	38	1.84 (1.22-2.76)	1.78 (0.93-3.41)
Time between diagnosis & delivery (5-year cut point)						
≥ 5 years	16	1.00	1.00	18	1.00	1.00
< 5 years	92	1.58 (0.97-2.56)	1.60 (0.97-2.64)	58	1.06 (0.65-1.73)	0.92 (0.54-1.55)
Race/Ethnicity						
White, non-Hispanic	68	1.00	1.00	35	1.00	1.00
Black, non-Hispanic	40	1.00 (0.71-1.42)	0.97 (0.65-1.45)	41	2.02 (1.33-3.05)	1.76 (1.08-2.86)
Parity						
Primiparous (1 birth)	28	1.00	1.00	22	1.00	1.00
Multiparous (≥ 2 births)	80	1.27 (0.86-1.86)	1.10 (0.74-1.64)	54	1.09 (0.69-1.72)	0.78 (0.47-1.27)

Adj.=adjusted; PR=prevalence ratio; CI=confidence intervals

[a] Adjusted for mother's age at infant delivery

[b] Adjusted for mother's age at infant delivery, education, marital status, parity, race/ethnicity, and smoking

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CHAPTER 3: THE OTHER SIDE OF THROUGH: YOUNG BREAST CANCER SURVIVORS' SPECTRUM OF REPRODUCTIVE AND SEXUAL HEALTH NEEDS FROM DIAGNOSIS TO SURVIVORSHIP

Background

The long-term reproductive health impact of cancer treatments is a justifiable concern for premenopausal women with a breast cancer history. There are several reasons that a diagnosis of premenopausal breast cancer may negatively impact reproductive function. Chemotherapy can be directly toxic to ovarian follicles and result in transient or permanent amenorrhea, depleted ovarian reserve, and a shorter reproductive window.(1–4) Indirectly, delays in childbearing plans can contribute to an age-related decline in fertility.(1) For example, breast cancer patients are often encouraged to delay pregnancy for at least two to three years after diagnosis (1,3), and to not become pregnant during adjuvant endocrine therapy, which may be prescribed for five years or more. Hence, chemotherapy and adjuvant endocrine therapy may cause other reproductive health issues due to gynecological and vasomotor symptoms, changes in sexual function, and an earlier onset of menopause.(5,6) Additionally, the potential side effects of menopause brought on by chemotherapy and adjuvant endocrine therapy, including vaginal dryness and low libido may restrict women's desire or ability to be sexually intimate with their partners.(7,8) Whether or not women desire to conceive after the breast cancer treatment, all premenopausal women may experience treatment-related reproductive or sexual health issues that have the potential to affect their quality of life in survivorship.(9)

A two- to three-year time delay between a breast cancer diagnosis and becoming pregnant is recommended because of concern about the lingering toxic effects of cancer treatment on growing oocytes and the potential risk of cancer recurrence is highest during this period.(3) However, evidence of the benefit to patients waiting more than two years after

diagnosis to become pregnant is limited, especially if the woman has a good prognosis and localized disease (10) and the risk of recurrence is low.(3,11,12) Young women diagnosed with breast cancer often question if a pregnancy will increase their risk of breast cancer recurrence because breast cancer is hormone-dependent and pregnancy is a period when hormone levels are at an all-time high in a women's reproductive life-span. The main concern is that an increase in hormone levels during pregnancy may stimulate the growth of remaining breast cancer cells or dormant micrometastasis, which may in turn increase the risk of recurrence.(3) Yet, breast cancer survivors who become pregnant after the completion of treatment tend to have the same, if not better survival rates (12–14) and are less likely to experience a recurrence of breast cancer (15) than women who do not become pregnant after a breast cancer diagnosis. In a study by Gelber and colleagues (13), the overall 5-year and 10-year survival rates for breast cancer survivors who became pregnant was 92% and 85%, while 5-year survival was 85% and 10-year survival was 74% for the matched non-pregnant breast cancer survivor control group. The results from the Gelber et al. (13) study are potentially due to a healthy mother effect (10,16,17), i.e., women who choose and are able to become pregnant after breast cancer may be healthier in general compared to breast cancer survivors who choose not to or are not able to become pregnant.(1,16)

The American Society of Clinical Oncology highly recommends that cancer care providers discuss the possibility of infertility and fertility preserving options with their premenopausal cancer patients (or refer them to a reproductive specialist) before beginning treatment.(18) Yet, less than half of U.S. physicians are following these guidelines.(19) It is critically important for breast cancer patients to receive information on the potential effects of each cancer treatment option on their reproductive and sexual function, so they are fully aware of how the treatments may affect intimacy with their partners, as well as plans to begin or complete their families. Receipt of this information will allow breast cancer patients to make an informed decision about their cancer treatment regimen and determine if they should receive

fertility preservation treatment (e.g., cryopreservation of embryos, cryopreservation of oocytes, ovarian tissue cryopreservation, artificial gametes) prior to the onset of cancer treatment. According to Resolve, the National Infertility Association, the average cost of fertility preservation/infertility treatment ranges from $865 to $8165 per cycle or procedure.(20) However, insurance companies usually do not cover fertility preservation or infertility treatments (3), which make these options unfeasible for many breast cancer patients who cannot afford the out-of-pocket expense for these treatments.

Preconception health interventions aim to improve the health status and behaviors of women (and men) prior to conceiving a child with the ultimate goal of decreasing the risk of adverse pregnancy-related outcomes.(21) The preconception period in the life course often refers to the years in which one is of reproductive age, but also recognizes that a woman's preconception health status may be the result of negative exposures *in utero* or her mother's (or even maternal grandmother's) lifestyle behaviors or exposures. Since a majority of pregnancies are unplanned, there has been a growing emphasis on promoting healthy behaviors throughout the reproductive health period (e.g., smoking cessation, reduction in alcohol use, maintaining a healthy weight, consumption of essential vitamins and minerals) and not just during the prenatal period.(22)

There have been national and international efforts to track and improve the preconception and maternal health status of women. The CDC/ATSDR Preconception Care Work group worked with a select panel of experts in 2006 to develop a strategic plan that provided recommendations on how to improve the preconception health status of women in the United States, as well as enhance how preconception care services are rendered.(21) This call to action led to the development of 45 core state preconception health indicators that are now tracked via national surveillance systems, such as the Pregnancy Risk Assessment Monitoring System.(23) Furthermore, *Healthy People 2020* acknowledges preconception health as an important strategy for improving the pregnancy and overall health outcomes of women.(24)

The Millennium Development Goal (MDG) framework has expanded MDG5 on improving maternal health from solely focusing on maternal mortality to also including reproductive and sexual health as important contributors to maternal health.(25) In general, there is a growing recognition that women's health is much broader than maternal health. Improving the lives of girls and women not only has positive implications for their future pregnancy outcomes (if they choose to conceive), but can also enhance their health status and wellbeing in general.

The preconception healthcare needs of women diagnosed with and treated for premenopausal breast cancer may differ from those prescribed to the general population of women of reproductive age. Furthermore, known racial disparities in breast cancer incidence rates and birth outcomes raise concerns about potential disparities in the reproductive and sexual health outcomes of premenopausal breast cancer survivors since black women are more likely than their white counterparts to be diagnosed with breast cancer during their reproductive years (26) and experience adverse birth outcomes.(27) Therefore, it is important to learn about the preconception health status and behaviors of special populations (and their sub-groups), so that preconception health services for these women can be tailored to suit their specific reproductive health concerns that may be magnified by their health condition.

This study aimed to determine the reproductive healthcare needs of premenopausal breast cancer survivors by exploring the concordances and discordances of participant identified reproductive and sexual health needs between: 1) women who did/desired and did not have a child after their breast cancer diagnosis; and 2) women of color and white women.

Methods

Institutional Review Board Approval

The University of North Carolina at Chapel Hill's IRB and Office of Human Research Ethics reviewed and approved this study (#14-1394).

Study Design, Approach, and Positionality

We explored the reproductive healthcare needs of premenopausal breast cancer survivors via in-depth semi-structured interviews. Since reproductive/sexual health and breast cancer are sensitive topics and we wanted to explore each woman's distinct personal experiences in order to make comparisons, in-depth interviews were the best qualitative data collection method for acquiring the information we needed to address our study's aim. In order to build rapport with participants, we conducted each interview in-person over the course of two sessions.

The study's principal investigator (PI) was cognizant that her positionality as a researcher was influenced by her race/ethnicity (non-Hispanic black), gender (female), educational status (PhD graduate), health status (non-breast cancer patient), and other factors. Recognizing that her positionality may affect how she identified subtle and explicit disparities in the interview data, she made a conscious effort throughout this study to be aware of her preconceived notions, while also carefully listening to what the data was revealing. Her community advisory committee and interviewees were influential in holding her accountable to the data.

Community Advisory Committee

An advisory committee of two breast cancer survivors and two advocates was convened to incorporate a community perspective into the recruitment, data collection, and analyses processes. The committee met during the initial stages of study development and provided feedback on the interview guide, as well as recruitment materials and sources. The committee met a second time to discuss and refine the preliminary list of themes. Two committee members attended the group sessions with interview participants and two served as co-authors on this paper. The community advisory committee's contributions to the development of the study and analysis of the data greatly enhanced the overall quality of the study. Their perspective as breast

survivors and long-term advocates allowed them to provide additional insights on the study from an experienced lens that the study's PI did not possess.

Study Population and Recruitment

From October 2015 to March 2016, the PI recruited women with a breast cancer history, diagnosed between the ages of 18 and 45, and living in North Carolina. An effort was made to recruit a racially diverse pool of women with a breast cancer history who had the following reproductive health experiences: 1) had a live birth after breast cancer diagnosis; 2) wanted to have child(ren) after breast cancer diagnosis, but was not able to become pregnant; or 3) never desired to have child(ren) or decided not to have child(ren) after breast cancer diagnosis.

To identify and connect with young women with a breast cancer history, the PI utilized three recruitment sources: 1) community- and cancer center-based breast cancer support group meetings; 2) cancer center-based listservs for young breast cancer survivors; 3) referrals from the community advisory committee. At support group meetings, the PI gave a brief presentation of the study, disseminated study brochures, and collected the contact information from women interested in being interviewed. Leaders of cancer center-based young breast cancer survivor support groups emailed fact sheets about the study via listservs designated for current and former support group members. Community advisory committee members provided a list of local foundations for young breast cancer survivors and the PI contacted the foundations via email or phone to inform them about the study. The PI contacted each woman that expressed interest in participating in the study, either at support group meetings or via email responses to listserv postings, via phone to confirm her interest in being interviewed, collect demographic information, determine eligibility, address any questions, and schedule the first interview.

Data Collection

Each participant was interviewed in-person at a private location that was convenient for her (e.g., local library, her home) and the PI conducted all interviews. All participants provided written consent before starting the interview. Since discussing breast cancer diagnosis and treatment, as well as reproductive health may be sensitive topics for some women, we made efforts to ensure that the interview questions would cause minimal emotional trauma to the participants. The PI asked the participants if they desired to pause or stop the interview when they appeared to be emotionally distressed, but every woman completed the interview. At the conclusion of the first interview, each participant received $25 cash for participating in the study, a resource guide of relevant cancer, emotional, and reproductive health support services, and a thank you card. At the conclusion of the second interview, each participant received $35 cash. Participant recruitment continued until a saturation point was reached where the interviewees' responses addressed the established questions and began to overlap to the point where new insights ceased to surface.

We used an in-depth, semi-structured two-part interview guide (Appendix 1). The interview was conducted over two sessions for most of the participants, but three women requested to complete the entire interview in one session since it was more convenient for them. The first part of the interview lasted on average 35 minutes (Range: 18-66 minutes) and the second part lasted on average 57 minutes (Range: 33-99 minutes). The first part of the interview included 24 questions and covered topics such as reproductive history, breast cancer diagnosis and treatment story, and reproductive/sexual health experiences around the time of diagnosis. The second part of the interview included 19 questions and inquired more about experiences that occurred around the time of their breast cancer diagnosis and treatment, including reproductive health information received or desired, met and unmet reproductive health needs or concerns, reproductive or fertility issues, and life experiences that may have affected their health. All questions were open-ended. Many of them included probes to ensure

all desired information was captured and to explore participants' responses more deeply. The questions were asked in sequence; however, those that did not apply to the participant were skipped (e.g., questions regarding breastfeeding children post-diagnosis when woman delivered all children prior to diagnosis). Each interview session was audio recorded and professionally transcribed. The PI took notes during each interview session in order to track key information that helped guide the interview discussion.

Analysis Approach

In order to ground the findings in the data, the PI utilized ResearchTalk's *Sort and Sift, Think and Shift*© method (28), a multidimensional qualitative analysis approach. The *Sort and Sift* toolbox includes a variety of methods that assist with familiarizing yourself with the data, as well as analyzing the data. These methods include writing memos, monitoring topics in your data, inventorying quotations, and diagraming quotations and topics. This is an iterative process of diving in and familiarizing yourself with the data and stepping back to reflect on what you learned, so that you can access how to move forward with analyzing your data. The main emphasis is on comparing the experiences of different participants and analyzing each participant's transcript in order to learn about the lived experience of each individual as it relates to your research topic. This allows for the monitoring of topics vertically by participant and horizontally across participants.

This analysis approach along with member checking with the community advisory committee and interview participants allowed for the identification of the most salient themes that emerged from the data. Prior to reviewing the data, the PI composed a memo to reflect on the interviews with breast cancer survivors and capture what was known so far based on these interviews. This memo captured initial lessons learned from the interviews before she was influenced by a deeper read of the transcripts. Second, she reviewed each transcript, identified pulse quotations (i.e., quotations that highlighted the women's key life experiences and

reflections), and wrote a brief memo for each pulse quotation about why it was chosen. Third, after the review of a transcript and identification of pulse quotations, the PI wrote a memo about that transcript that addressed two questions: 1) What did we learn from this data collection episode?; and 2) Why is this data collection episode important to this study? Under the first question, she composed complete statements that captured the main topics discussed in the transcript and placed exemplary quotations under each statement. Under the second question, she wrote a brief memo to describe what was important about the topics discussed in the transcript and how the topics addressed the study's research question. Fourth, she grouped the statements from each transcript memo into key topics. Fifth, the PI further explored these grouped key topics and associated quotations to develop a uniting theme. Lastly, using matrices she explored the grouped key topics to compare the reproductive needs and concerns between women who did/desired and did not have a child after their breast cancer diagnosis and women of color and white women.

Since the goal of this research was to learn about the multiple realities and complexities of the reproductive health experiences of premenopausal breast cancer survivors, the *Sort and Sift, Think and Shift*© Method was appropriate to use since it allowed for the analysis approach to be grounded in the interview participants' commentary and experiences, while also accounting for and compartmentalizing our own biases and preconceived notions. The PI used ATLAS.ti version 7, a qualitative data software package, to manage and organize the data.

Once we established the key themes, the community advisory committee and the interview participants were invited to separate group sessions to discuss the preliminary findings. The first group session was with the community advisory committee and was an opportunity for the PI to garner their feedback on the themes that emerged from the data. From this discussion, we determined the most relevant themes to explore further, specifically the themes that addressed the original intent of the study. The second group session was held in-person with the interview participants, in which four of the 17 attended. During the discussion,

the participants' provided their feedback on the emergent themes confirmed by the community advisory committee and exemplary quotes, as well as share any additional insights. This discussion was audio-recorded in order to capture all participants' comments, but not for analysis purposes. The PI used the feedback from the community advisory committee and the participants to determine which themes resonated most with the community and to enhance the wording and presentation of the themes and participants' quotes.

Findings

Details regarding the characteristics of the 17 study participants with a breast cancer history are provided in Table 3.1. The mean age at first breast cancer diagnosis was 38.6 years and the mean age at the time of the interview was 45.8 years. This group of women was highly educated; all of them had at least some college education. At the time of the interview, a majority of them were married or engaged (n=13), had two or more children (n=11), and never smoked (n=14). Twelve of the women gave birth to all of their children prior to their breast cancer diagnosis. Yet, one had all of her births occur after her diagnosis, two had births before and after their diagnoses, and two did not have any children. Ten of the women identified as white, non-Hispanic and seven of the women identified as women of color (e.g., black/non-Hispanic, Asian, Latina). In regards to breast cancer stage, 14 had invasive (stage 1-3) breast cancer. Most of the women had a lumpectomy (n=12), received chemotherapy (n=11), did not receive breast reconstruction (n=12), and received adjuvant endocrine therapy (n=14). Two of the 17 women experienced a breast cancer recurrence, including one woman that was diagnosed three times over a 12-year period with the second diagnosis occurring during a pregnancy. Additionally, one woman was diagnosed with melanoma a week after her breast cancer diagnosis and was treated for both at the same time.

Five overarching themes emerged from the data that shed light on the spectrum of met and unmet reproductive needs identified by women with a breast cancer history (Table 3.2).

The five themes are: 1) women received limited reproductive health information from their cancer care providers; 2) medical providers often told the women that they would not be able to have children after cancer treatment and did not give an honest depiction of the feasibility of conceiving post-treatment; 3) having a family history of breast cancer influenced women's and their family members' decision-making about their cancer treatment and lifestyle choices; 4) most women who received breast reconstruction struggled with adjusting to their altered physical appearance, which affected their body image; and 5) the menopause symptoms caused by chemotherapy, adjuvant endocrine therapy, and hysterectomies led to sexual health issues that affected the women's intimacy with their partners and quality of life. Despite the many commonalities in these women's experiences, there were differences between women who did/desired and did not have a child after their breast cancer diagnosis, as well as between women of color and white women. The concordances and discordances in the reproductive health needs of women with a breast cancer history are described below and selected quotes are exhibited in Table 3.2.

Theme 1: Received Limited Reproductive Health Information

Concordances. The extent of the reproductive health information that a majority of the women received from their cancer care providers was limited in nature and did not comprehensively address their concerns. Most women learned from their providers that chemotherapy and adjuvant endocrine therapy treatment might impair their fertility or cause the early onset of menopause. Providers urged women with hormone receptor-positive tumors to not become pregnant in order to decrease the risk of cancer recurrence and to not take hormone-based contraception. Although the women learned about what not to do, they did not receive sufficient advice about how to manage menopause symptoms or prevent pregnancy. Furthermore, women felt that if they were of advanced maternal age or expressed that they did

not want to have any more children, their cancer care providers assumed they were not concerned with reproductive health issues and therefore provided limited education in this area.

Pregnancy prevention during breast cancer treatment was a particularly challenging issue for women who used hormone-based contraception methods (e.g., intrauterine devices, birth control pills) prior to their breast cancer diagnosis. Their providers advised them against becoming pregnant at all or at least not during treatment, including during adjuvant endocrine therapy. Yet, many of the women did not receive recommendations on which contraception methods to utilize and there seemed to be an underlining assumption that their only option was condoms. When asked if her cancer care providers recommended she use contraception, a survivor of color (Age 45 at diagnosis; no children) responded, *"No, the only thing he said was just don't get pregnant right now."* When asked what type of conception she uses, she said, *"None really."* This response was concerning especially since this woman was actively going through treatment and other women had similar responses when asked about their contraception usage during and after their breast cancer treatment. In fact, only one white survivor (Age 40 at diagnosis; 2 children pre-diagnosis) shared that her provider suggested her husband receive a vasectomy. This was a suitable option for this woman since she had reached her ideal family size and it was a highly reliable solution to preventing pregnancy during her treatment and beyond. Yet, it is alarming that more women did not receive adequate counseling on their contraception options, especially since the potential fetal health complications and increased risk of cancer recurrence associated with pregnancy during or within a short interval after cancer treatment completion.

As reproductive health-related issues arose during their breast cancer journeys, the women felt their cancer care providers provided limited information and did not address their array of concerns. They relied on their obstetricians/gynecologists (OB/GYNs), support groups, Dr. Susan Love's Breast Book (29), and the Internet to fill the gaps in their breast cancer-related reproductive health education. The women felt that their OB/GYNs specialized in reproductive

health and were better equipped to address their specific concerns that ranged from vaginal dryness to the pros and cons of hysterectomies. In addition to discussing their concerns with their providers, these women valued conversations they had with other breast cancer survivors since they directly experienced and understood their challenges. A white survivor (Age 40 at diagnosis; 2 children pre-diagnosis) shared that her favorite resource was her support group:

> *"I guess because you're talking to people that have actually gone through it. Talking to a male doctor about hot flashes, it's not really – he's like, 'Oh, yeah, it could happen 10 to 20 times a day.' And I thought, 'Oh, yeah, 'cause that's no big deal.' Easy for him to say, 'cause he'll never experience anything like that. I find it more comforting to talk to other women that have been through it."*

She felt that she was able to relate to other survivors since they shared a common experience and that male providers were limited in their ability to convey the magnitude of menopausal symptoms since they would never experience them. A survivor of color (Age 37 at diagnosis; 2 children post-diagnosis) did not remember receiving much reproductive health information from her cancer care providers. However, after being introduced to Dr. Love's book, it became her go-to resource:

> *"Yeah. I think Dr. Love's book was great. And I think talking to people – I have just found out by accident I have neighbors who had breast cancers. She's much older… But I remember… she's the one who told me about the book… I thought [Dr. Love's book] was very comprehensive."*

Other women displayed the same resourcefulness and sought out information to address their reproductive health concerns via their OB/GYNs, other breast cancer survivors, and books on breast cancer.

Even though many women received advice to not conduct searches on the Internet, some women felt that the Internet was a more readily available resource than their cancer care providers. A white survivor (Age 33 at diagnosis; 1 child pre- and 1 post-diagnosis) explained:

> *"People run to the internet. They rely on the Internet so much. You can hand someone a piece of paper, but it's going to get stuffed in the bottom of their purse, depending on how busy they are, or at the foot of their car, or maybe even end up in the trash as they walk out the door. The person themselves, if they're really interested in it, is going to research it themselves."*

She remarks on the inevitably of women utilizing the Internet as a resource and how easy it is to misplace a brochure that a provider may give you. Another white survivor (Age 39 at diagnosis; 1 child pre-diagnosis) discussed her disagreement with discouraging breast cancer patients from using the Internet. She exclaimed:

> *"There wasn't just a ton of resources around …reproductive health in general, either on the fertility side or the sexual functioning side. …So, I did a lot of my own research. And one of the things that I think has been so weird to me, …all the women are in the support groups, telling each other to stay off the Internet. I'm like, 'Why are we telling each other to stay off the Internet?' Like that's where all the great information is. Yes, there's crap out there, but if you're a reasonably intelligent adult, you can filter through what's crap, what is one person's experience versus what is more valuable information I think. Anyway, so that drives me a little crazy about the culture of breast cancer; we're not supposed to be on the Internet. But going on the Internet helped me get a more balanced picture from different resources of what I might be looking at. …More of the spectrum of that experience rather than, 'Here's all the awful things that are probably gonna happen to you, so get ready.'"*

She sheds light on how breast cancer patients are receiving limited reproductive health information from their providers, so the Internet is the obvious resource to access in order to address their concerns.

Discordances. The women interviewed shared similar experiences regarding the lack of comprehensive reproductive health information received. Yet, there were some discordance by post-diagnosis birth status and race in regards to proposed fertility preservation options, cancer treatment decision-making, sources of reproductive health information, and level of comfort discussing reproductive health issues with providers.

Women who desired to have children after completing cancer treatment, particularly women of color, were more proactive in choosing the least invasive treatment options in order to preserve their fertility options. One survivor of color (Age 37 at diagnosis; 2 children post-diagnosis) received a Lupron shot to suppress her ovaries during treatment and preserve the option for her to conceive post-treatment. Another survivor of color (Age 45 at diagnosis; no children) sought out treatment from a specific cancer center that offered her the least invasive treatment route, so that she could preserve her fertility after the first cancer center where she

was diagnosed was pushing a more aggressive treatment approach. When asked about what she had learned about the potential effect of cancer treatment on her reproductive health, a survivor of color (Age 40 at diagnosis; 2 adopted children pre-diagnosis) responded:

> *"Overall is that it could kill your fertility issues. There were things that you could do definitely to preserve your fertility, but it just seemed like it would take away from – at the time your main focus is just taking care of the cancer, and it seemed like preserving your fertility just took time away from that in my mind. That's why it kind of pushed it to the back burner."*

She had undergone multiple fertility treatments prior to being diagnosed and knew the time and effort that process takes. She was not willing to delay her cancer treatment in order to pursue fertility preservation options. Although some of the white survivors advocated for young breast cancer survivors choosing treatment options to preserve their fertility if they wanted to conceive later, none of these women personally chose less invasive treatment options with the intent of preserving their fertility.

White women mentioned more often that they attended cancer center-sponsored support groups and workshops that shared reproductive and sexual health information. They also expressed a different level of dissatisfaction with the reproductive information they received. A white survivor (Age 42 at diagnosis; 2 children pre-diagnosis) shared:

> *"It was only discussions at group about people that had concerns with intimacy or side effects of some of the drugs. Nothing specific was given to me. I just had exposure from the women around me, not from a doctor or a nurse."*

Another white survivor (Age 45 at diagnosis; 1 child pre-diagnosis) commented on the reproductive health education she received:

> *"I didn't really have any counseling. The oncologist spoke with me about it, my [obstetrician] has, and then after treatment we had at least one class and they have them on occasion, in the [cancer center workshop series] that kind of talked about maybe not necessarily reproductive, but your intimacy and sexual intercourse after the treatment and that kind of thing. Not necessarily your menopause or ability to have children or any of that, but more of the fun part of it."*

None of the survivors of color mentioned utilizing these cancer center-sponsored support groups and workshop series. The survivors of color were more involved in community-based

cancer support groups and one even established a local foundation for young breast cancer survivors. White survivors expressed how their cancer care providers did not seem comfortable discussing reproductive health topics and the information that was shared painted a disheartening perspective of their post-treatment sexual health outcomes. A white survivor (Age 39 at diagnosis; 1 child pre-diagnosis) in active treatment exclaimed:

> *"They gave me a book at the cancer center, which is a great book. It's all about treatment and side effects, and there was a section about reproductive health and sexuality. And it painted a very dark picture, honestly. It was like, 'Your libido is gonna go away. You're not gonna be interested. You're not gonna be capable.' I was like, 'This is awful.' There was a very negative perspective."*

When asked about her concerns regarding the effect of cancer treatment on her reproductive health, she shared:

> *"Yeah, that was one of my actually biggest concerns about the whole thing. ...my oncologist...he's great. He actually draws pictures and writes everything down so you have something to take away. It's really a wonderful approach. But he's listing side effects and he's like, 'Hair loss and nausea, but here's what we're gonna do.' And I had to actually ask, 'Is this gonna kick me into menopause?' ...just wasn't even brought up as a concern, like it was not as important. But I was super concerned about it. Anything that I've learned about what kind of impact is this going to have reproductively or sexually has just been independent study. ...And I just felt like there wasn't good information about that. It's hard to get the doctor to talk about it."*

Her comments suggest that cancer care providers are good at explaining the general side effects of cancer treatment, but are not well prepared to convey how treatments may affect women's reproductive and sexual health or how they can manage these side effects. Furthermore, she conducted her own research to address her reproductive and sexual health concerns since it was so difficult to discuss these concerns with her cancer care providers. Although survivors of color recognized the limitations of the reproductive health information they received, none of them expressed the level of discontent that the white survivors openly shared.

Theme 2: Desired Realistic Expectations of Conceiving Post-Treatment

Concordances. The breast cancer journey made several women reflect on childbearing. Women who had completed their families were thankful they had reached their

ideal family size prior to their breast cancer diagnosis. A survivor of color (Ages 29 & 37 at diagnosis; 4 children pre-diagnosis) reflected on what she would have done if she had not reached her ideal family size at the time of her diagnosis:

> *"Had I not had my tubes tied and had the kids, I definitely would've been concerned, and probably doing everything that I could to have kids, 'cause that's just something that was very important to me. Even, like, my girl did, I would've tried to freeze eggs, doing something. Even with my friend that was told she couldn't have [kids], that just would've have been enough for me – I would've just probably tried to do anything that I could. I read people all the time that's gone through cancer and still able to have children. ...I'm just thankful for the time that – you know, of course, I hate that I had to go through cancer, but thankful that I was able to complete my family, with my four, before I had to go through it. Especially since, you know, as soon as I did, the doctor said, 'I don't think you should have anymore.'"*

Having children was extremely important to her and she was grateful to give birth to all of her children because her doctor recommended that she not bear any more children after treatment. Similarly, when asked if the negative reproductive health effects of breast cancer treatment affected her family completion goals, a white survivor (Ages 28, 37, & 40 at diagnosis; 1 child pre-diagnosis and pregnant with 1 child at second diagnosis) responded:

> *"I don't know. I think I told you last time I may have had another child if I hadn't gotten cancer again. But like I said, I'm happy with what I have, and I feel blessed to be able to have them. So, I don't really know how to answer that question, 'cause it's possible that I would have had another child, but I try not to think about it too much. You know? And I just, like I say, I'm a glass-half-full kinda girl. So, I'm just as happy, and I feel blessed that I have what I have."*

Women who wanted to, but were not able to have children after their treatment made peace with their circumstances. A survivor of color (Age 40 at diagnosis; no children) articulated:

> *"My journey is an ongoing journey and I don't regret anything that I have been through my journey, even though it is to the point that I will never, ever be able to have children. I am okay with that; I came to an agreement and an understanding and it is okay, because I have other kids that I can love like my nieces and nephews and godchildren."*

Even when coming to terms with not being able to bear any more children after completing treatment, some women still felt remorseful of this situation. When asked if being diagnosed

with breast cancer influenced her ideal family goals, a white survivor (Age 40 at diagnosis; 2 children pre-diagnosis) exclaimed:

> *"It didn't, but I do remember it making me think I guess. I mean I thought I was done anyway, but you know what I mean? I don't know how to explain it, but at 40 people do have babies in their 40s. So, I mean yeah I guess I thought about it, but luckily I had my two boys, and they were what I wanted. Yeah it just made it more final I guess. It just made me think about the fact that that door was closed, whereas before it wasn't closed. I mean it was closed by me I guess mentally, but it wasn't totally closed. I mean you think about a lot of stuff when you're going through cancer. So it was just one of the things."*

Going through breast cancer made several of the women realize that their childbearing years had come to an end even though it was earlier than anticipated.

A few women remained hopeful that they would be able to conceive after treatment. One survivor of color (Age 45 at diagnosis; no children) and was still in active treatment said:

> *"Well, ideally I wanted to have two children, a boy and a girl, but I do come from a large family, so my thing was whatever I was blessed with, that's what I would do. But ideally, that was my desire and I still have not totally given up on that. Even though right now while I'm on the Zoladex and Anastrozole, the doctor says not to get pregnant because that could be potentially harmful for a fetus and with all of the other stuff that I'm taking, they don't know. So right now, I'm not actively trying to conceive, but that was one of the things early on that we had talked about that… I wanted to preserve that option because even though I recognize with my age that it presents some health risk for my age… And it has been posed to me to look into adoption, but I won't say it hasn't crossed my mind, but that's not my desire right now. I wanted to at least leave the possibility open to preserve that, so that's my right to choose whether or not to do that."*

Despite her age, she chose the least invasive treatment route, so the possibility of conceiving remained an option for her. Women who were years past treatment were still keeping their childbearing options open. A white survivor (Age 42 at diagnosis; 2 children pre-diagnosis) shared:

> *"My husband and I always said we would have two or three children and as far as we're concerned, we're pretty much done, but…there's always just that little bit that, I don't know for sure… Mentally, I think I'm done, but physically I think we're both still capable. Just emotionally, and professionally, and the ages of our kids and stuff, I think it's a done deal, but mentally, I think I'm at the normal stage for a woman my age that you go, 'Oh, I'm about to be done for good.'"*

Some women possessed a glimmer of hope that they would be able to have children after treatment, but the combined reality of their advancing age and the potential effect that cancer

treatment may have had on their reproductive health made them face the inevitability of their reproductive years coming to an end.

Discordances. The time of treatment is a crucial decision-making period, particularly for women that desired to conceive after the completion of their breast cancer treatment. Unfortunately, several women shared that they were not well supported by their providers (e.g., cancer care team, obstetricians/gynecologists [OB/GYNs]) in their goals to preserve their fertility or carry out a pregnancy. Among the women who desired to conceive or did bear children after treatment, there were distinct differences in how the survivors of color versus the white survivors discussed their challenges conceiving after treatment.

The survivors of color discussed not receiving much guidance from their providers on how long they should wait after treatment before trying to conceive. One survivor of color (Age 37 at diagnosis; 2 children post-diagnosis) had it set in her mind that she would try to conceive six months after completing her treatment, even though it is typically recommended that women with breast cancer wait two to three years after diagnosis before becoming pregnant. Reflecting on how quickly she became pregnant with her first child post-treatment, she said:

> *"I was surprised, actually, how easy I conceived our daughter. 'Cause I was – I don't know, I just think that – You know, I wasn't very young; I was 38. I just thought it was gonna take – it's going to take a while. But I think – yeah, I think we – I got pregnant after a couple of months."*

She had stage 1 breast cancer and her oncologist did approve of her becoming pregnant. Her providers were more concerned about her age than her breast cancer status in regards to her pregnancy outcomes. A survivor of color (Age 40 at diagnosis; no children) was less lucky in being able to pursue her childbearing goals after treatment. Even though she had in situ breast cancer, her treatment included multiple biopsies, two lumpectomies, a mastectomy, and TRAM (i.e., stomach) flap breast reconstruction all in one year. The following year she was diagnosed with multiple uterine fibroids, which resulted in a hysterectomy. It was then she knew that her "*chances of giving birth [where] no more.*" Her dreams of having children abruptly came to an

end after reproductive and chronic health issues impaired her ability to conceive. She and other women discussed how they were not emotionally prepared for losing their capability of conceiving children after treatment. This reality was particularly challenging for women who did not have any children.

One white survivor (Age 33 at diagnosis; 1 child pre- and 1 post-diagnosis) experienced both the benefits of provider support and the challenges with provider discouragement in regards to becoming pregnant after treatment. She was the only woman to report that her oncologist fully educated her about her reproductive health and fertility options even though she told him that she was not planning on having any more children. Regarding the usefulness of the reproductive health information she received from her oncologist, she stated:

> *"I think it was great. I mean not useful because we weren't planning to have children, okay. So, I mean I don't want to say I used the information. But when I got pregnant, I was like, 'Oh my goodness, I remember what he said. This could be really bad.' And so I saw a specialist because of the cancer. I had the gestational diabetes. I was one of those people I was like, 'Okay, I remember the oncologist saying this could come out really bad,' and so me and my husband just talked about it. If something was wrong with the baby, what would we do, and that's 'cause we remembered everything he said."*

Although she believed that she did not need the fertility education at the time and most of the information she received focused on the potential negative outcomes, she found the information she received from her oncologist to be extremely useful once she unexpectedly became pregnant. What she learned from him prompted her to seek the proper care during her pregnancy and her oncologist was very supportive and happy for her and her husband once she became pregnant. However, once she was under the care of her OB/GYN specialists the provider support ceased. She stated:

> *"Because of my age, cancer, and then right away, like as soon as I found out I was pregnant I went to the doctor. They gave me that gestational diabetes test; I failed it right then and there… Like I was diabetic; it was terrible. The lady said to me…, 'The chances of this being successful for you and the baby are very small.' She was just like, 'By 32 weeks, I expect to have you induced, in the hospital, and having a premature baby. …You've just gone through cancer treatment, so your body has been chemo-infused. I don't know how strong your body overall, if it can even carry a baby that long.' And she's like, 'You already have gestational diabetes, which means the baby's probably going to be fairly large, and I don't think you're going to be able to carry.' And*

so I left that doctor's office just pure crying my eyes out. I went home, I told my husband…, 'I'm just not going to be able to carry this baby. She's going to die. She's going to come out sick.' And I made it 39 weeks. Absolutely healthy."

Her OB/GYN team was pessimistic about her potential pregnancy outcome and painted a discouraging picture of what to expect. She ultimately had an inconsequential pregnancy and delivery, but experienced great anguish from their predictions. She feels they should have provided her with the full spectrum of possibilities and not just the negative outcomes. She hoped these providers learned from her situation that it is possible for breast cancer survivors to have healthy babies. Once she had her child and went back to her cancer providers for check-ups, she felt her surgeon and radiation oncologist lacked the experience and bedside manner to deal with a lactating patient. She exclaimed:

"…the whole pregnancy, lactation, breast cancer thing, they had no experience with. 'We've not had lactation patients in here. This does not happen.' They weren't against it, but I just think it was so out of – they didn't know what to do. They were blushing. …Like the one doctor, the surgeon, didn't want to do the mammogram; he just did an ultrasound for the first year. …even though I'm still breastfeeding, he feels like it's further along, like it's not going to be as detrimental to the breast. He wouldn't even touch it. He was, 'It's working.' I mean he was like just, 'Cover up. Do you need more paper towels?' …and then when they palpate the breast, they don't know the difference between a lactating with all the milk ducts full, so to them, it does not feel like an okay breast. And that's because they're not used to feeling one that has got the full milk ducts in it. So, I mean the lack of experience on that, and everyone was like, 'I don't know what to do; I'm sorry.'"

Her cancer care providers' lack of comfort examining a lactating patient made for an awkward situation that negatively influenced her relationship (and potentially trust) with these providers.

Many women were able to make peace with not being able to conceive after treatment, especially if they were already approaching the end of their reproductive years at the time of diagnosis. Yet, women who desired to have children or were in their prime reproductive years needed support from their cancer care providers and OB/GYNs to successfully attempt and carry out their post-treatment pregnancies. Furthermore, they wished to have a more comprehensive and balanced depiction of their ability to successfully conceive after treatment. A focus on the potential negative outcomes did not provide a sense of encouragement or hope to

women who had already survived breast cancer, but still wanted to bear children. This attests to providers' lack of knowledge and experience with women who successfully conceive and deliver children after breast cancer treatment.

Theme 3: Family History of Breast Cancer Influenced Lifestyle Choices

Concordances. As expected, some women had strong family histories of breast cancer and others were the only person in their family to be diagnosed. When asked about her family history of breast cancer, a white survivor (Age 45 at diagnosis; 1 child pre-diagnosis) said, *"Zero. I am the history."* One survivor of color (Age 40 at diagnosis; 2 adopted children pre-diagnosis) was the only participant who had a positive *BRCA* gene mutation result and she did not have any blood relatives that had been diagnosed with breast cancer. Even though she had a life long struggle with infertility, she felt grateful that she did not have any biological children to pass on this gene mutation. However, among the women that did have a strong family history of breast cancer, there seemed to be a trend where the older generations were diagnosed at age 50 and above and the younger generations were being diagnosed at much younger ages. Despite these similar cancer history patterns, the survivors of color and white survivors responded in different ways to this knowledge about the lack or strong occurrence of breast cancer in their families.

Discordances. Knowing an immediate or distant family member that had breast cancer either encouraged women to take preventive measures or discouraged them out of fear of being diagnosed. One survivor of color (Age 40 at diagnosis; 2 adopted children pre-diagnosis) did not have a family history of breast cancer, but when she was sixteen her aunt by marriage was diagnosed and died of breast cancer at age 40. She was eager to start getting mammograms at age 40 and was diagnosed with breast cancer as a result of her first mammogram. This eagerness and awareness prompted by the death of a loved one resulted in her getting diagnosed early on in the development of her breast cancer. Having a breast cancer role model, such as a mother or aunt, made some women less distressed about treatment and more focused on

survivorship since they have seen someone live through breast cancer. A white survivor (Age 39 at diagnosis; 1 child pre-diagnosis) whose mother had breast cancer stated:

> *"And I think for me, I was not totally shocked to be diagnosed, 'cause my mother was diagnosed at a relatively young age, and I watched my mother go through treatment. So, I think I had sort of an innate sense that you can come through this and come out okay, 'cause she's now 60-whatever-she –is. You know? And she's happy, and she dates, and she has a – she's a registered dietitian, and… She's totally fine. So, I had a very clear role model of, 'You can come through this,' and it will be terrible' 'cause it was, 'and still have a great life on the other side of it.' So, I think I was more concerned about not, 'Am I gonna die,' but, 'What is the quality of life that I'm gonna experience, and what does that look like?' So, I wonder if that makes me a bit of an outlier. I didn't have the same sort of cancer terror that I think some people will have."*

Her mother showed her that living through cancer was possible, so she was able to see through to the other side of her journey and think about life after breast cancer. Her mother's breast cancer experience also influenced her treatment decisions. She was in the midst of chemotherapy treatment and was still determining which surgical route she would take. She explained why she was leaning towards undergoing the least invasive treatment option:

> *"I think I'm intimidated by the prospect of reconstruction for mastectomy. My mother actually had a mastectomy and then had it reconstructed and it was a long process. I'd rather they just do nothing. I'm like, 'What's the least invasive choice?' Another thing is, they can't uncut. If they do a lumpectomy and there's issues or something, you can always go back and have more taken off, but they can't really undo that, so less cutting it good I think."*

She approached her treatment with a sense of awareness of how each decision she made would affect her quality of life.

Survivors of color described being motivated to get mammograms since they knew someone who had breast cancer and they prepared their daughters to do the same. A survivor of color (Ages 29 & 37 at diagnosis; 4 children pre-diagnosis), who established a breast cancer foundation for young survivors, described how she would take her daughters to breast cancer events with her. She wanted them to see what she went through and be well informed once it was time for them to begin getting mammograms. Some white survivors shared that their strong family histories of breast cancer caused their daughters and nieces to live in fear of being diagnosed with breast cancer themselves. One white survivor (Age 42 at diagnosis; 2 children

pre-diagnosis) shared that one of her daughters was hypersensitive to being diagnosed with breast cancer since in addition to her mother being diagnosed with breast cancer, her father's mother and sister both died from it. Her daughter sought out genetic testing and did not have the *BRCA* gene mutation, but she remained terrified that she would be diagnosed as well. Another white survivor (Age 42 at diagnosis; 2 children pre-diagnosis) had nieces in their twenties who were making lifestyle decisions based on their strong family history of breast cancer, which included their maternal great grandmother, maternal grandmother, paternal great-great aunt, maternal great aunt, and maternal aunt (the interviewee). She explained how her nieces responded differently than her and her sisters to their family breast cancer history by sharing:

> *"I've got a few nieces that have told me that [they are] exercising and running half marathons and doing things that me and my sisters, none of us are exercise anything… I feel like I'm active, but I don't do structured exercise. And my sisters are the same way, but some of our nieces are not doing that at all. They're Fitbit wearers… and part of the reason they do that is because they're worried. And one of my mother's sisters is more healthy, health driven, more nutrition conscious. And she's never had a breast cancer diagnosis… So, I think whether conscious or subconsciously, the younger girls are watching it and going, 'Oh, Aunt [A] never had anything, and she's the more health conscious overall.' And so, I think they've taken that to heart. So, they have made some lifestyle decisions. …like it's hardwired in [them], 'What can we do to make ourselves healthier by what we eat?'…And I think it is partially because of the cancer stuff in our family."*

While the younger generation in her family was very health conscious in an effort to prevent breast cancer, her generation was less apt to engage in breast cancer prevention activities. Her nieces also sought counsel from her about whether they should delay graduate school to have a family or stop taking birth control to reduce their risk of breast cancer. The assumed high risk of breast cancer was affecting all areas of her nieces' lives and this greatly concerned her because she did not want them to live in fear of this disease or let it unnecessarily dictate their lives. This sense of fear of the inevitable was very apparent in the stories shared by some white survivors, but not in those of the survivors of color.

Theme 4: Struggled with Adjusting to Altered Physical Appearance

Concordances. There was a general consensus among the women's stories that breast reconstruction did not meet their expectations and they struggled with adjusting to their altered physical appearance. Many of the women felt that the implants could never be satisfactory replacements for the breast(s) they lost. A white survivor (Age 42 at diagnosis; 2 children pre-diagnosis) reflected on her breast reconstruction process and stated:

> *"I think just the scars and the implant process. It doesn't feel – you don't feel like yourself there after the implants. You know. And especially during the expander part, it feels very foreign and they're very hard. And every time you breathe, it's a reminder that there's something fake going like this every time you breathe. And then they put the implants in, and it's much better, but it still doesn't feel like you used to."*

The implants served as constant reminders of their breast cancer experience and what was lost in the process. After undergoing breast reconstruction and living with the results, some women regretted getting implants. A survivor of color (Age 34 at diagnosis; 1 child pre-diagnosis) shared her regrets about getting breast reconstruction:

> *"Sometimes I say if I could go back and change some things about my journey, that may have been one of the things that I would've done, is just kind of let it be. Um-mm. you know, because there's so many prosthesis and apparatuses and you know. Just like you can't look at me today and tell, I don't think anybody would've been able to look at me and tell otherwise either."*

With the variety of prosthesis and apparatus options, some women felt that breast reconstruction was not always necessary. Yet, the widespread dissatisfaction with breast reconstruction was centered in the women not being well prepared about what to expect from their new implants. It seems they wanted and needed clear expectations to be set by their cancer care providers about the breast reconstruction process. One white survivor (Age 42 at diagnosis; 2 children pre-diagnosis) even sought out this information from her providers and obtained a series of pictures of the breast reconstruction process (from post-operation through the healing process) that a breast cancer patient created and published. However, information of this caliber is not widely available to women and some complained that even the information on the Internet was tilted towards negative experiences of breast reconstruction.

Despite having regrets about undergoing breast reconstruction, some women came to terms with their altered physical appearance. When asked about her satisfaction with her breast reconstruction results, a white survivor (Age 42 at diagnosis; 2 children pre-diagnosis) exclaimed, *"Well, I'm happy enough. I came to the point where I thought my life, my boobs, and my life was so much more important than the other."* In the grand scheme of their breast cancer journeys, the fact that they lived through it was most important. Yet, breast surgery and reconstruction had a profound effect on these women's self-image and there were racial discordances in how women coped with the realities of their altered bodies.

Discordances. Although both survivors of color and white survivors expressed dissatisfaction with their breast reconstruction, there are differences in how they coped with their new bodies. Both survivors of color and white survivors received follow-up surgeries to repair issues with their breast implants. Yet, only one white survivor (Age 42 at diagnosis; 2 children pre-diagnosis) went through multiple surgeries to achieve her ideal symmetrical breasts. She was ultimately satisfied with her implants because she was able to regain breast sensation. The plastic surgeon set low expectations for regaining breast sensation, so when it did return this made her more satisfied with her breast reconstruction results. A survivor of color (Age 40 at diagnosis; 2 adopted children pre-diagnosis) who completed follow-up surgeries to fix issues with her implants drew the line with getting additional surgeries when her plastic surgeon suggested coming back for nipples:

> *"After the last reconstruction, my doctor was like you know…you can come back and we can do nipples and blah, blah, blah. I was like I do not care about nipples. Do not talk to me about nipples; I will not be coming back for nipples. [Laughs] And so you know of course it doesn't look normal, but even with nipples it wouldn't look normal to me because it's so manmade you know."*

Several women shared that they did not get nipples for similar reasons. They did not want to endure the additional procedure that ultimately would not improve the appearance of their breast implants. Some women struggled with their altered physical appearance. Survivors of color complained the most about scarring and residual pain from stomach or back flaps used to

construct their new breasts. In fact, survivors of color were the only ones to share that it was difficult for them to look at their undressed bodies in the mirror. A survivor of color (Age 34 at diagnosis; 1 child pre-diagnosis) shared:

> *"Nothing is ever like what God gave you. Today I can say that I'm good and I'm happy with it, but initially, I mean it takes some getting used to. Initially I would go in the bathroom and put the towel over the mirror into my shower and this is how I would do. Today I can say I'm good with them, I'm good without them."*

She and other survivors struggled with body image issues due to the appearance of their breast implants. Even though many of them reached a point of acceptance of their new physical appearance, it was evident that the implants could never replace the breasts they lost.

Most of the women who had a mastectomy also received breast reconstruction. However, only a couple of white survivors shared that they did not undergo breast reconstruction. When asked why she decided not to have breast reconstruction after her unilateral mastectomy, a white survivor (Age 40 at diagnosis; 2 children pre-diagnosis) stated:

> *"I don't want any more major surgeries that I don't have to have. I keep thinking someday there's going to be an easier better solution as things progress. Somebody the other day mentioned the 3D printing, you know how they're printing like ears, and whatever, and they're like why couldn't they do that. That's what I'm going to wait for. You know somebody is going to print a breast. Yeah I'm in no hurry."*

After the completion of cancer treatment, undergoing an additional surgery deterred some women from enduring breast reconstruction. Some of the women that did not receive breast reconstruction wore prostheses and others chose not to. They seemed to be more comfortable with their altered physical appearance and like many of the women that received breast reconstruction or not, they realized their breasts did not define their womanhood.

Theme 5: Menopause Symptoms Led to Sexual Health and Quality of Life Issues

Concordances. A majority of the women experienced menopause symptoms induced by chemotherapy, adjuvant endocrine therapy, or post-cancer hysterectomies that affected their sexual health and quality of life. The women discussed typical menopause symptoms, such as

hot flashes, vaginal dryness, low libido, and weight gain, while others suffered from less common side effects from chemotherapy and adjuvant endocrine therapy, such as neuropathy, vision impairment, and tear duct damage. Some women welcomed the early onset of menopause and found ways to successfully manage the side effects. A survivor of color (Age 45 at diagnosis; 1 child pre-diagnosis) shared how she managed her menopause symptoms:

> *"And you know people say it – women say you go through changes. Yes, I had the hot flashes. They weren't fun, but you learn to deal with them. I found out exercising helped some. And doing certain types of exercise, like yoga or breathing exercises – but it's just – you just have to be proactive and find these things and ask questions. And eating. You have to make sure you're eating – eating right."*

Finding ways to manage symptoms made it easier for some women to embrace menopause. However, women with partners, especially those who had hormone receptor-positive tumors, found it challenging to find solutions for low libido and vaginal dryness. Many of the over-the-counter and prescription products available to combat vaginal dryness contain estrogen, which women with hormone receptor-positive tumors are discouraged from using. Furthermore, they found it difficult to engage their providers in discussions about their sexual health and intimacy issues. Even when they were able to have conversations with their providers, they did not receive adequate information to fully address their concerns. When asked what reproductive health information she wished she had received prior to beginning treatment, a survivor of color (Age 40 at diagnosis; 2 adopted children pre-diagnosis) responded:

> *"I guess more so on the effects of treatment on your actual sexuality and desires and what to do. They kept telling me, 'Well, there are things we can do. There are things we can do.' But I don't feel like I ever got much information on what those things were after the fact. I have since gotten one – or tried one thing and it hasn't worked very well for me, so I just wish that all that had been given."*

She and other survivors desired solutions to address their sexual health issues and they did not receive adequate medical counseling or support in this area. Many of the women feared the challenges ahead with maintaining intimacy with their partners long-term since they experienced physical and emotional discomfort when engaging in sexual activity. A white

survivor (Ages 28, 37, & 40 at diagnosis; 1 child pre-diagnosis and pregnant with 1 child at second diagnosis) shared:

> *"So, I've had some problems with the dryness and, I guess, the lack of estrogen in my body – it's a problem. You know? So, I do not have sex as much as I used to. But I still do… Thankfully, my fiancé's very understanding about the whole thing."*

Fortunately, many of the women had supportive partners that understood the toll that cancer treatment had taken on their bodies and how the nature of their sexual activity may be limited or changed due to the effects of menopause symptoms.

Discordances. Although both survivors of color and white survivors experienced challenges managing the side effects of chemotherapy and adjuvant endocrine therapy, there were differences in their main complaints. Survivors of color described their issues with excessive weight gain once they began adjuvant endocrine therapy and started experiencing menopause symptoms. One survivor of color (Ages 29 & 37 at diagnosis; 4 children pre-diagnosis) stopped taking a medication for menopause symptoms because she felt it was causing her weight gain. She utilized non-pharmaceutical methods to manage her symptoms. After her providers told her that there was nothing that could be done about her excess weight, another survivor of color (Age 40 at diagnosis; no children) accepted her 30-pound weight gain as a side effect of adjuvant endocrine therapy treatment and remained hopeful she would shed the extra weight once she stopped adjuvant endocrine therapy in the coming year. While some survivors of color battled weight gain, a few white survivors discussed the unexpected side effects of adjuvant endocrine therapy. Two white survivors participated in clinical trials where they consumed double doses of adjuvant endocrine therapy, such as Tamoxifen, for short bouts of time. Both women reported developing a serious health issue that they felt resulted from this intensified adjuvant endocrine therapy. These health issues included benign uterine/ovary growths and long-term tear duct impairment. Other white survivors experienced neuropathy and vision impairment that may have been induced by chemotherapy and adjuvant endocrine therapy. Beyond the sexual health-related issues that women experienced as a result of the early

onset of menopause, they also developed other long-term health challenges caused by their cancer treatment that affected their quality of life.

Recommended Services and Resources for Premenopausal Breast Cancer Patients

In addition to exploring their breast cancer experiences and reproductive needs, we asked the women what types of information should young breast cancer patients receive about reproductive health and how should this information be delivered. The women shared an array of interesting ideas that honed in on the need to develop and provide premenopausal breast cancer survivors with reproductive and sexual health information that addressed their specific needs and concerns.

The types of information that the women felt were necessary to deliver to young breast cancer patients included: 1) options and risks related to conceiving after treatment, including the cost of fertility preservation; 2) picture diary of the breast reconstruction process from mastectomy surgery through the post-reconstruction healing phase; 3) comprehensive information about the potential side effects of cancer treatments and medications; and 4) potential effect of cancer treatment on reproductive health and pregnancy outcomes. Furthermore, women with strong family histories of breast cancer felt medical providers should be more forthcoming about the increased risk of breast cancer associated with birth control use, so young women can make informed decisions about their contraception use. In addition to more comprehensive reproductive health information, the women wanted providers to raise breast cancer patients' awareness about the ability for them to conceive after treatment and genuinely support their patients' decisions to pursue pregnancy. They wanted to know the risks associated with bearing children after completing their treatment, but they also desired to be given the full spectrum of options for conceiving children and the possible pregnancy and birth outcomes (i.e., not just the potential negative outcomes).

Along with advocating for typical avenues for educating patients, the women shared some innovative approaches for reaching young breast cancer patients. They provided several recommendations for delivering reproductive health information. First, all young breast cancer patients should receive one-on-one counseling with a navigator, peer mentor, or psychologist, so they receive the individualized emotional or reproductive health support they need. Second, down time during appointments could be an opportune time to deliver reproductive health counseling and printed information (e.g., waiting room, while receiving chemotherapy). Third, the cancer care providers could review key talking points or questions regarding reproductive health with patients (e.g., Are you experiencing any menopause symptoms that are causing discomfort? If so, what are your concerns?), rather than asking more open-ended questions (e.g., Do you have any questions or concerns?). Fourth, cancer centers should offer workshops, support groups, and other resources that are exclusively for young patients, who are at a different stage of life and have different needs than older patients. Fifth, cancer centers should create a breast cancer information binder cover and materials that are more gender neutral since not all women connect to the pink-centric theme often associated with breast cancer paraphernalia. Lastly, cancer centers should centralize and widely distribute information on workshops and resources, so this information reaches all patients. Overall, the women felt that reproductive health information should be reiterated at various time points throughout breast cancer patients' care. They wanted the cancer center-based support to extend beyond the treatment period and be readily available to them during the survivorship period since they still manage the effects of cancer treatment on their health and quality of life for months to years after completing treatment.

Discussion

In an effort to learn more about the reproductive and sexual health needs of women with a breast cancer history, we interviewed women diagnosed at or before the age of 45 who did and

did not have children. Through an examination of their expressed reproductive and sexual health needs and concerns around the time of their breast cancer diagnosis, we learned about the post-diagnosis birth status and racial concordances and discordances in these women's experiences, as well as their recommendations for improving reproductive and sexual health counseling for young breast cancer patients. We learned several things about women with a breast cancer history. First, they are not receiving sufficient breast cancer treatment-related reproductive health information from their cancer care providers and are relying on the Internet, their OB/GYNs, and support groups to address their concerns since they found it difficult to discuss their reproductive and sexual health concerns with their male oncologists, in particular. Second, they desire realistic expectations about their ability to conceive after treatment and for providers to support their decisions to become pregnant if they are healthy and able. Third, breast cancer survivors and their younger family members are making treatment and lifestyle decisions based on their family history of breast cancer. Fourth, some women have regrets about undergoing breast reconstruction and struggle with accepting their new bodies, but some have come to terms that their life is more important than their physical appearance. Lastly, they learned to manage some treatment induced menopause symptoms, but are not receiving sufficient support in resolving their sexual health issues that have resulted from the early onset of menopause.

Many of the women's stories mirrored each other and attested to the spectrum of reproductive and sexual health needs and concerns that women with a breast cancer history have during the treatment phase and into survivorship. Nonetheless, there were some discordances between women who did/desired and did not have a child after their breast cancer diagnosis, as well as between survivors of color and white survivors. Women who had or still wanted children after completing treatment advocated for less invasive treatment options in order to preserve their fertility and leave the option open for them to attempt to conceive after treatment. Compared to women who had completed their families prior to their diagnosis, the

women who wanted to conceive after treatment were more likely to receive information from their cancer care providers about fertility options, but this information mostly depicted the potential negative pregnancy and birth outcomes. However, the women who desired to have children were the most remorseful about being unable to start or complete their families after completing breast cancer treatment. Survivors of color were the only ones to report receiving ovary suppression shots to assist in the process of preserving their fertility during their breast cancer treatment. They also shared more about their struggles with body image disturbance and how they had to work on acceptance of their physical appearance after treatment. Unlike the white survivors, the survivors of colors discussed weight gain as a major adjuvant endocrine therapy or menopausal side effect. The white survivors felt the information they received painted a bleak picture of their reproductive and sexual health outcomes, which was discouraging. They were more likely to utilize cancer center-sponsored support groups and workshops, whereas the survivors of color were involved in community-based breast cancer support groups. White survivors that had mothers who were also breast cancer survivors felt less terrified about the breast cancer journey and were more concerned about how their treatment decisions would affect their quality of life long-term. Furthermore, they shared how younger generations in their families lived in fear of being diagnosed with breast cancer since their family history of it was so strong. Only white survivors shared that they did not get breast reconstruction, participated in adjuvant endocrine therapy clinical trials, and experienced non-reproductive health-related side effects of chemotherapy and adjuvant endocrine therapy that affected their quality of life (e.g., neuropathy, vision impairment, tear duct damage). The experiences shared by these women with a breast cancer history were more similar than different, yet it is important to acknowledge how various sub-sets of women may have reproductive and sexual health needs and concerns that diverge from what is considered the norm.

The literature examining the reproductive and sexual health needs of women with a

breast cancer history in the United Studies is limited, but has garnered more attention over the past few years. Researchers have used validated survey instruments, focus groups, and in-depth interviews to determine what are the reproductive and sexual health needs of women with a breast cancer history. Among the studies that have utilized qualitative research methods to learn about these issues from the perspective of breast cancer survivors there is a general consensus that premenopausal women are dissatisfied with the lack of information they are receiving about breast cancer treatment-related reproductive, fertility, and sexual health issues (30–34), which aligns with the findings of this study. One study that explored how young breast cancer survivors' values about conceiving after treatment influenced their treatment decisions compared the experiences of sub-groups of survivors (e.g., women who did versus did not have children after treatment), but they did not find any significant differences and only presented the joint findings.(32) A majority of the women in these studies (81-100%) were white breast cancer survivors (30–33), except for one study that included only black women.(34) The racially homogenous populations recruited for these studies did not allow for racial differences in experiences to be examined. Lewis and colleagues (34) found that black women seemed to report more severe issues with their intimate relationships, distress with their fertility, and more often lacked information on sexual dysfunction after breast cancer compared to white women in other studies. In contrast to Gorman et al.'s (32) finding that their participants (85% white) chose more aggressive treatment approaches since they were motivated by survival and preventing recurrence, our study found that women who desired to conceive after treatment were more likely to choose the least invasive treatment route, especially the survivors of color. Our findings mostly align with the previous literature and reinforce that young women with a breast cancer history are concerned about sexual dysfunction and body image (30); found it difficult to discuss reproductive and sexual health issues with their providers (17); felt that their cancer care providers were dismissive of or not knowledgeable about how to address their reproductive and sexual health concerns (31,33); and had to conduct their own research and

speak with other breast cancer survivors to learn more about breast cancer treatment-related reproductive health issues (32).

The strengths of this study are grounded in the use of the *Sort and Sift, Think and Shift*© method, diversity of participants, and engagement of breast cancer survivors and advocates throughout the study. The method used to review and analyze the interview data allowed for the findings to be grounded in the true experiences of the women interviewed and not limited to our preconceived notions. This iterative review and analysis process of the interview data paved the way for sharing findings that truly reflect the participants' experiences. Additionally, we recruited a diverse group of women with a breast cancer history, so that comparisons could be made based on post-diagnosis birth status and race. Our engagement of breast cancer survivors and advocates in various aspects of the study, including the development of recruitment materials and the interview guide, as well as feedback on the themes and illustrative quotes prior to the dissemination of the findings, further strengthened our findings. Overall, we placed value in the experiences of women with a breast cancer history and attempted to incorporate their voices and insights in various aspects of the study's process in order to enhance the validity of our findings.

The main limitations of this work pertain to the recruitment sources and the generalizability of the findings. We recruited a majority of the women via cancer center-supported and community-based breast cancer support groups located in a major metropolitan area in North Carolina and most of these women received care from the same regional cancer center. The resources available at this one regional facility may vary from other cancer centers in North Carolina. This may explain some of the differences in participants' access to cancer center-sponsored workshops that covered reproductive and sexual health topics. The experiences of the women interviewed did partly depend on the providers and resources available to them at their given cancer centers. Recruiting women from a range of cancer centers in North Carolina may have increased the diversity of women we interviewed.

Furthermore, since this study is based in North Carolina and includes women with convenient access to a cancer center, this study may not be generalizable to women in other parts of the United States, especially women with less access to medical facilities. Future studies on this topic would benefit from recruiting from a range of cancer centers and within rural communities. Despite these limitations, this study provides a strong methodology that can be replicated and a basis for comparison with a more diverse recruitment sample.

It is apparent from this study's findings that women with a breast cancer history are in need of and desire more education and resources to address their reproductive and sexual health concerns. Young breast cancer survivors would greatly benefit from receiving reproductive health counseling and access to resources to address their concerns during the breast cancer treatment phase and beyond. Additional resources outside of the services currently offered by cancer care providers are needed. Offering regularly scheduled workshops in the cancer center that cover reproductive and sexual health topics, as well as having designated reproductive health specialists available may be useful resources and safe spaces for women, especially those who are not comfortable discussing such topics with their cancer care providers. Additionally, providing trustworthy websites that discuss and provide solutions for breast cancer patients' reproductive health concerns may be another welcomed resource. It may also be beneficial for cancer centers within larger healthcare systems to partner with their obstetrics and gynecology departments to develop useful approaches for jointly supporting breast cancer patients with reproductive health concerns or that desire to conceive after the completion of their treatment. Overall, the reproductive health needs and concerns of young breast cancer survivors deserve more attention as an important quality of life and survivorship issue.

TABLES

TABLE 3.1. CHARACTERISTICS OF 17 YOUNG WOMEN WITH A BREAST CANCER HISTORY AT TIME OF INTERVIEW

	N or Mean (SD)
Education	
Some or graduated college (13-16 years)	10
Professional/graduate degree (≥17 years)	7
Marital Status	
Married/Engaged	13
Divorced	3
Single/Never Married	1
Parity	
Nulliparous (0 births)	2
Primiparous (1 birth)	4
Multiparous (≥ 2 births)	11
Birth of Child(ren) Relative to Breast Cancer Diagnosis Date	
No births	2
Birth(s) occurred before diagnosis	12
Birth(s) occurred after diagnosis	1
Birth(s) occurred before and after diagnosis	2
Race/Ethnicity	
White, non-Hispanic	10
Black, non-Hispanic	5
Other	2
Smoking	
Never Smoked	14
Former Smoker	3
Stage[a]	
Stage 0 (In Situ)	2
Stage 1	4
Stage 2	7
Stage 3	3
Unsure	1
Hormone Receptor Status[a]	
ER+/PR+	9
ER+/PR-	4
ER-/PR-	1
ER-/PR-/HER2- (Triple Negative)	3
Treatment Type[a,b]	
Lumpectomy	12
Unilateral Mastectomy	3
Bilateral Mastectomy	4
Chemotherapy	11
Radiation	12
Breast Reconstruction	5
Adjuvant Endocrine Therapy	14
Breast Cancer Recurrence	
1 breast cancer diagnosis	15
2 or more breast cancer diagnoses	2
BRCA Mutation	
No	12
Yes	1
Variants of Unknown Significance	1
Not Tested	3
Time Since Diagnosis[a]	
< 1 year	2
1 ≤ years < 5	6
5 ≤ years < 10	4
≥ 10 years	5
Age at Diagnosis (in years)[a]	38.6 *(5.0)*
Range	28-45
Age at Time of Interview (in years)	45.8 *(7.2)*
Range	37-64

N=total number; SD= standard deviation
[a]Refers to participant's first breast cancer diagnosis
[b]This column does not add up to 100% since a participant may be included in >1 category based on their treatment regimen

TABLE 3.2. FIVE OVERARCHING THEMES AND SELECTED ILLUSTRATIVE QUOTES REGARDING THE REPRODUCTIVE AND SEXUAL HEALTH NEEDS IDENTIFIED BY WOMEN WITH A BREAST CANCER HISTORY

1: Received Limited Reproductive Health Information
"No, the only thing he said was just don't get pregnant right now."
"There wasn't just a ton of resources around reproductive or – reproductive health in general, either on the fertility side or the sexual functioning side. It was just not there. So, I did a lot of my own research… But going on the Internet helped me get a more balanced picture from different resources of what I might be looking at. But you – yes, chemopause is a thing that happens. Maybe that will happen, maybe it won't. There's really no way to predict. You know? More of the spectrum of that experience rather than, 'Here's all the awful things that are probably gonna happen to you, so get ready.'"
"It was only discussions at group about people that had concerns with intimacy or side effects of some of the drugs. Nothing specific was given to me. I just had exposure from the women around me, not from a doctor or a nurse."
"…my oncologist…he's great. He actually draws pictures and writes everything down so you have something to take away. It's really a wonderful approach. But he's listing side effects and he's like, 'Hair loss and nausea, but here's what we're gonna do.' And I had to actually ask, 'Is this gonna kick me into menopause?' …just wasn't even brought up as a concern, like it was not as important. But I was super concerned about it. Anything that I've learned about what kind of impact is this going to have reproductively or sexually has just been independent study. …And I just felt like there wasn't good information about that. It's hard to get the doctor to talk about it."
2: Desired Realistic Expectations of Conceiving Post-Treatment
"I wanted to preserve that option because even though I recognize with my age that it presents some health risk for my age… And it has been posed to me to look into adoption, but I won't say it hasn't crossed my mind, but that's not my desire right now. I wanted to at least leave the possibility open to preserve that, so that's my right to choose whether or not to do that."
"I was surprised, actually, how easy I conceived our daughter. 'Cause I was – I don't know, I just think that – You know, I wasn't very young; I was 38. I just thought it was gonna take – it's going to take a while. But I think – yeah, I think we – I got pregnant after a couple of months."
"Because of my age, cancer, and then right away, like as soon as I found out I was pregnant I went to the doctor… The lady said to me…, 'The chances of this being successful for you and the baby are very small.' She was just like, 'By 32 weeks, I expect to have you induced, in the hospital, and having a premature baby.' …And so I left that doctor's office just pure crying my eyes out. I went home, I told my husband…, 'I'm just not going to be able to carry this baby. She's going to die. She's going to come out sick.' And I made it 39 weeks. Absolutely healthy."
3: Family History of Breast Cancer Influenced Lifestyle Choices
"And I think for me, I was not totally shocked to be diagnosed, 'cause my mother was diagnosed at a relatively young age, and I watched my mother go through treatment. So, I think I had sort of an innate sense that you can come through this and come out okay, 'cause she's now 60-whatever-she – is. You know? And she's happy, and she dates, and she has a – she's a registered dietitian, and… She's totally fine. So, I had a very clear role model of, 'You can come through this,' and it will be terrible' 'cause it was, 'and still have a great life on the other side of it.' So, I think I was more concerned about not, 'Am I gonna die,' but, 'What is the quality of life that I'm gonna experience, and what does that look like?' So, I wonder if that makes me a bit of an outlier. I didn't have the same sort of cancer terror that I think some people will have."
"I've got a few nieces that have told me that [they are] exercising and running half marathons and doing things that me and my sisters, none of us are exercise anything… I feel like I'm active, but I

don't do structured exercise. And my sisters are the same way, but some of our nieces are not doing that at all. They're Fitbit wearers… and part of the reason they do that is because they're worried. …So, they have made some lifestyle decisions. …like it's hardwired in [them], 'What can we do to make ourselves healthier by what we eat?'…And I think it is partially because of the cancer stuff in our family."

4: Struggled with Adapting to Altered Physical Appearance

"I think just the scars and the implant process. It doesn't feel – you don't feel like yourself there after the implants. You know. And especially during the expander part, it feels very foreign and they're very hard. And every time you breathe, it's a reminder that there's something fake going like this every time you breathe. And then they put the implants in, and it's much better, but it still doesn't feel like you used to."

"Sometimes I say if I could go back and change some things about my journey, that may have been one of the things that I would've done, is just kind of let it be. Um-mm. you know, because there's so many prosthesis and apparatuses and you know. Just like you can't look at me today and tell, I don't think anybody would've been able to look at me and tell otherwise either."

"Nothing is ever like what God gave you. Today I can say that I'm good and I'm happy with it, but initially, I mean it takes some getting used to. Initially I would go in the bathroom and put the towel over the mirror into my shower and this is how I would do. Today I can say I'm good with them, I'm good without them."

5: Menopause Symptoms Led to Sexual Health and Quality of Life Issues

"I guess more so on the effects of treatment on your actual sexuality and desires and what to do. They kept telling me, 'Well, there are things we can do. There are things we can do.' But I don't feel like I ever got much information on what those things were after the fact. I have since gotten one – or tried one thing and it hasn't worked very well for me, so I just wish that all that had been given."

"So, I've had some problems with the dryness and, I guess, the lack of estrogen in my body – it's a problem. You know? So, I do not have sex as much as I used to. But I still do… Thankfully, my fiancé's very understanding about the whole thing."

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CHAPTER 4: CONCLUSIONS

Overview of Findings

This mixed methods analysis provided additional insights on the risk of adverse birth outcomes and reproductive health concerns of premenopausal breast cancer survivors in the United States. The quantitative findings exhibited that premenopausal breast cancer survivors have a higher prevalence of preterm birth and low birthweight, especially if they received chemotherapy treatment or conceived less than two years after their diagnosis date. Furthermore, there seems to be a significant interaction between breast cancer and race/ethnicity in terms of the prevalence of preterm birth, but this interaction is not significant for low birthweight. The qualitative findings demonstrated that women with a breast cancer history are in need of reproductive and sexual health resources to address their spectrum of concerns. Their cancer care providers are not providing sufficient reproductive health counseling prior to treatment and during their breast cancer journeys, so women have been utilizing books and support groups, as well as consulting their gynecologists to address their concerns. Although many of the women shared similar stories, there were differences in experiences according to post-diagnosis birth status and race. These discordances included the findings that women wanting to conceive post-treatment were more likely to seek less invasive treatment options, survivors of color shared more about their challenges with body image disturbance and weight gain, and white survivors were more likely to use cancer center-sponsored support groups and workshops.

Overall, the quantitative findings demonstrated women with a breast cancer history have an increased preterm birth and low birthweight risk. The qualitative findings complement the quantitative findings by showing the importance of providing young breast cancer patients with

reproductive health counseling, so they are aware of the adverse pregnancy outcome risks associated with their course of cancer treatment. The importance of reproductive health education for breast cancer providers and their patients resonated with the findings from both aims of this study. Yet, these findings should be interpreted with caution since cancer treatment and the population demographics of North Carolina have changed over the 20-year period of this study. From 1990 to 2009, chemotherapy and adjuvant endocrine therapy have significantly advanced, more women are delaying childbearing and having their first birth in their thirties and even forties, and more women are not married at the time they give birth. Since the quantitative study factored in cancer treatment and maternal characteristics in its analyses, such as chemotherapy, maternal age, and marriage the findings reported may be influenced by a cohort effect. This means findings from women in the first decade of this study could have different results from those in the second decade. Nonetheless, the use of methods triangulation in this study provided a more complex and holistic look into the reproductive health outcomes and needs of women with a premenopausal breast cancer history.

Concordance between the Findings, Guiding Frameworks, and Conceptual Model

The healthy mother effect bias theory (1–3), Lu's and Halfon's (4) life-course health development model, as well the biological effect of chemotherapy on reproductive function are the frameworks that guided this study. From these guiding theories, a conceptual model was developed to depict how cumulative life exposures (i.e., risk and protective factors) may influence the reproductive health trajectories of premenopausal breast cancer survivors, as well as the assumed discordance in the trajectories of black and white women. The findings from this study confirmed some aspects of the conceptual model and provided a different perspective on how cumulative exposures may contribute differently to the risk of adverse birth outcomes among black premenopausal breast cancer survivors compared to their white counterparts.

Healthy mother effect bias and the biological effect of chemotherapy on reproductive function were evident in the quantitative and qualitative findings. The quantitative findings showed that having a breast cancer history does increase a woman's risk of experiencing an adverse birth outcome, but receiving chemotherapy and having a child within two years of being diagnosed amplified this risk. Breast cancer patients who do not undergo chemotherapy are more likely to have in situ breast cancer or stage 1 breast cancer tumors that are hormone receptor-negative or less than one centimeter in size.(5) Not receiving chemotherapy may indicate that the patient has a less invasive form of breast cancer and it also means the patient was not exposed to the known toxic effects of this treatment on reproductive function.(6–9) Furthermore, women that postponed pregnancy for at least two years after their diagnosis date, had more favorable birth outcomes. Therefore, women that do not undergo chemotherapy or wait more than two year post-diagnosis may be more "healthy" and able to conceive post-treatment.

Healthy mother effect bias was present in the qualitative findings, but in a different way than the quantitative findings. Three of the women with a premenopausal breast cancer history that were interviewed had children after their breast cancer diagnosis. All of these women had triple negative breast cancer and received chemotherapy, but did not receive endocrine therapy. Since they did not have to take endocrine therapy for five to ten years after their treatment regimen was completed, they were able to become pregnant naturally and delivered healthy infants despite having received chemotherapy treatment. These women with a breast cancer history were able to successfully conceive and they may have been "healthy" enough to do so because they did not have to go through endocrine therapy, which may have caused age-related decline in fertility.(6) They were able to optimize their remaining reproductive years and premenopausal status to conceive post-treatment and reach their ideal family size goals. The findings from this mixed methods study suggest that less aggressive treatment regimens and

postponing pregnancy for at least two years may decrease young breast cancer survivors' risk of adverse birth outcomes.

The original depiction of the biological effect of chemotherapy on reproductive function in this study's conceptual model has shifted as a result of the findings. At the onset of this study, it was believed that the reproductive function and potential of black women with a breast cancer history would decrease at a higher rate than their white counterparts at the point chemotherapy is received. The quantitative study revealed that although both black and white breast cancer survivors had a higher prevalence of preterm birth and low birthweight compared to the general population and their racial counterparts without a breast cancer history, the white breast cancer survivors exhibited higher preterm birth prevalence ratios than the black breast cancer survivors in the stratified (Table 2.4) and joint effects (Table 2.5) models. Due to black breast cancer survivors' lifetime cumulative exposure to potentially more risk factors than protective factors and baseline risk for preterm birth and low birthweight, this risk was not exacerbated by the additional assault of breast cancer treatment on their reproductive function. Their risk of adverse birth outcomes was essentially unchanged by being diagnosed with breast cancer. For example, in the joint effects models (Table 2.5), compared to white women in the general population, the black women in the general population exhibited a 45% increase in preterm birth risk and black breast cancer survivors had a 90% increase in risk, yet the 95% confidence intervals for these groups' prevalence ratios overlapped greatly (e.g., 1.44-1.47 and 1.45-2.50, respectively). This indicates that these two point estimates are more similar than different; therefore, there may not a significant difference in preterm birth risk between black survivors and their racial counterparts in the general population. Breast cancer treatment did appear to greatly affect the reproductive function of white breast cancer survivors. Although it was assumed that white survivors have more cumulative exposures to protective factors than risk factors over their lifetimes, their risk of preterm birth appeared to be higher than what was indicated for black survivors. White breast cancer survivors had more than two times the

preterm risk of white women without a breast cancer history, whereas black breast survivors had a 90% increase in risk compared to the same population.

Since nationwide black women have higher rates of preterm birth than white women (10), at the onset of this study it was assumed that black survivors would also have a higher prevalence of preterm birth compared to white survivors, yet this was not the case. To highlight these new insights on the biological effect of chemotherapy on reproductive function, the conceptual model was updated to exhibit that black survivors who receive chemotherapy do not experience the severity of effect on their reproductive potential as predicted and white survivors who undergo chemotherapy actually experience a greater detriment to their reproductive potential than black survivors (Figure 4.1). Yet, the disparity in reproductive potential between black and white breast cancer survivors continues to exist. The gap may not be as wide as predicted, but these results attest to the need for all premenopausal breast cancer survivors to receive reproductive health counseling prior to, during, and after the completion of treatment.

Practice and Research Implications

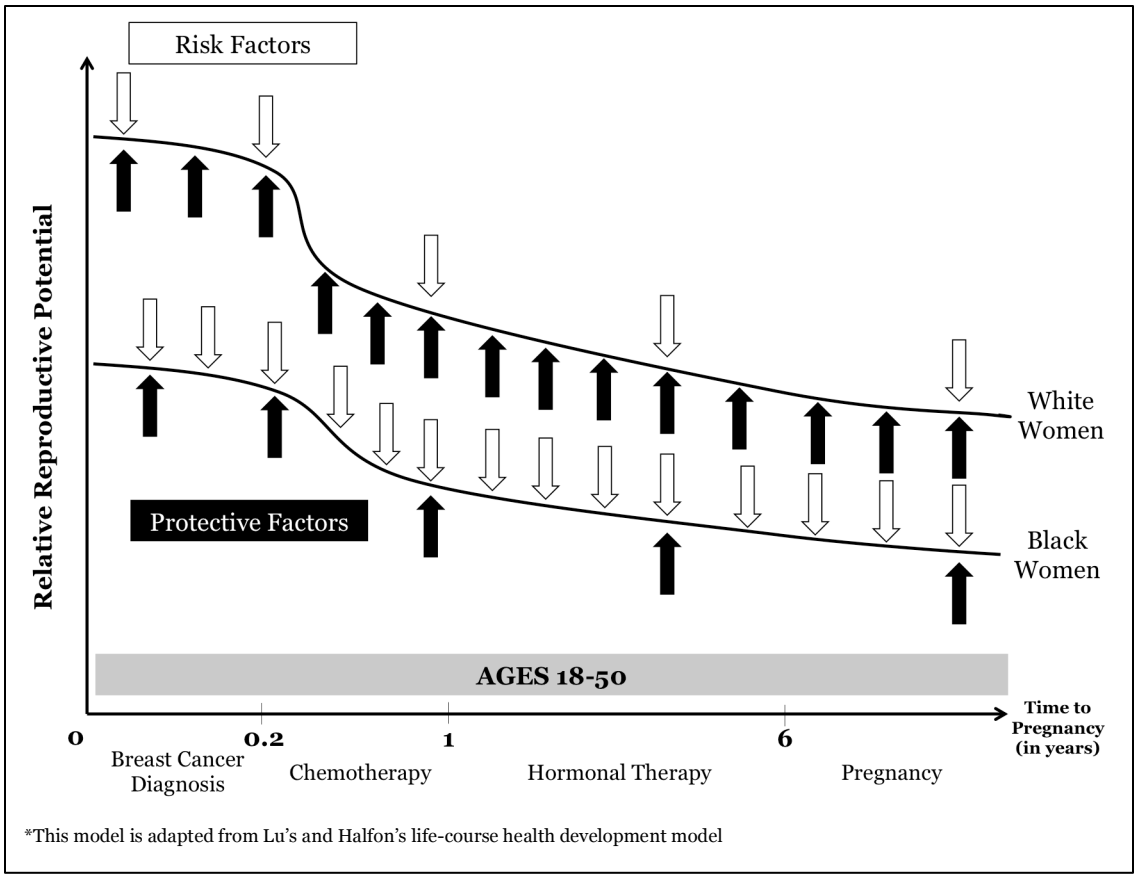
A breast cancer diagnosis and its treatment have long-term implications on the health and quality of life of women. Understanding the effects of breast cancer diagnosis and treatment on future reproductive and sexual health outcomes is an important concern for premenopausal women diagnosed with breast cancer. Women with a breast cancer history may benefit from targeted preconception health services and reproductive health counseling prior to and after cancer treatment. Cancer care providers should be equipped to educate breast cancer patients about the potential harmful effects of cancer treatment and the range of potential pregnancy and birth outcomes. Yet, if they are not able to provide this education, they should be able to refer their patients to a knowledgeable and easily accessible resource. Nonetheless, additional resources outside of the services currently offered by cancer care providers are needed. Offering regularly scheduled workshops that cover reproductive and sexual health

topics, as well as having designated reproductive health specialists available in the cancer center may be useful resources and safe spaces for women, especially those who are not comfortable discussing such topics with their cancer care providers. It may also be beneficial for cancer centers within larger healthcare systems to partner with their obstetrics and gynecology departments to develop useful methods for jointly supporting breast cancer patients with reproductive health concerns or that desire to conceive after the completion of their treatment. Overall, the reproductive health needs and concerns of young breast cancer survivors deserve more attention as an important quality of life and survivorship issue.

Mixed methods studies may be a beneficial avenue for further exploring the birth outcomes and reproductive needs of premenopausal breast cancer survivors. Longitudinal studies that follow premenopausal breast cancer patients from diagnosis through treatment completion to a post-treatment pregnancy or birth would provide additional insight into the reproductive health issues that these women endure and their range of pregnancy outcomes. A qualitative research component should be conducted concurrently with a longitudinal quantitative study. The qualitative study has the ability to reveal a deeper understanding of premenopausal breast cancer survivors' decision-making process regarding their treatment regimen as it relates to their post-treatment childbearing goals and the influence their cancer care providers may have on their treatment choices. They can also shed light on how their reproductive health, sexual health, and pregnancy outcomes influence their quality of life as breast cancer survivors. The triangulation of these two methods may provide a more comprehensive view of the reproductive health experiences and needs of young breast cancer survivors than a quantitative or qualitative study alone.

FIGURES

Figure 4.1. Revised conceptual model of how risk factors and protective factors differentially influence the reproductive potential of black and white women with a premenopausal breast cancer history



*This model is adapted from Lu's and Halfon's life-course health development model

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APPENDIX 1: BORN STUDY IN-DEPTH INTERVIEW GUIDE

1ST INTERVIEW

*Thank you **(participant #_____)** for agreeing to participate in this interview today the **(day_____)** of **(month_____) (year_____)**. During this first interview, I am going to ask you questions about your reproductive history, breast cancer diagnosis and treatment, and overall experience through the treatment process, as well as your reproductive health experiences around the time you were diagnosed with breast cancer. As I've shared with you before when we went through the consent form, I will be asking questions that may be sensitive topics for you. If you are not comfortable answering a question, please let me know and we can skip it. Do you have any questions before I begin? **(PAUSE; ADDRESS ANY QUESTIONS)** Okay, let's begin!*

I'm going to start off by asking you some questions about your reproductive history. Some of these questions may be sensitive, so please feel free to let me know if you want to skip a question. That's perfectly okay.

SECTION 1: REPRODUCTIVE HISTORY

(1.1) How many times have you been pregnant? ***(If 0, then SKIP to Section 2)*** _____

(1.2) How many times have you given birth? _____

(1.3) How many living children do you have? _____

		CHILD #1	CHILD #2	CHILD #3	CHILD #4	CHILD #5
(1.4)	What is child _'s birthdate? *(mm/dd/yyyy)*					
(1.5)	What was his/hers birthweight? *(grams or lbs/oz)*					
(1.6)	How many weeks pregnant were you when you had child _?					
(1.7)	Did child _ have any congenital abnormalities?					
(1.8)	Did you have any complications that developed during this pregnancy? (e.g., preeclampsia, gestational diabetes, high blood pressure, preterm contractions, placenta previa)					
(1.9)	Did you breastfeed child _? If so, for how long? What are some notable challenges or successes you had when breastfeeding?					

In this next set of questions, I'm going to ask you questions about your breast cancer journey, including your diagnosis and treatment.

SECTION 2: BREAST CANCER DIAGNOSIS and TREATMENT	
(2.1)	Please share with me your breast cancer diagnosis story. ▪ How old were you when you were diagnosed with breast cancer? ▪ What stage of breast cancer did you have at the time you were diagnosed?
(2.2)	For your first breast cancer diagnosis, do you know the details of the type of breast cancer you had? If so, what are the markers or sub-types of breast cancer that you had? **<u>LIST OF EXAMPLES</u>** ▪ *MARKERS: ER, PR, and HER2 +/-* ▪ *PATHOLOGY SUB-TYPES: Luminal A/B, triple-negative, basal-like tumors, HER2 type, normal breast like* ▪ *HISTOLOGY: in-situ (ductal or lobular), invasive*
(2.3)	Have you ever been tested for the BRCA 1 or 2 gene mutation? ▪ Do you have either of these gene mutations? If so, which one?
(2.4)	What is your family history with breast cancer? ▪ Which members of your family have been diagnosed with breast cancer? ▪ Was your family member(s) under the age of 50 OR 50 years old or older at the time s/he was diagnosed with breast cancer?
(2.5)	Tell me about what type(s) of breast cancer treatment you received. ▪ What type of surgery did you receive (e.g., lumpectomy, partial or total mastectomy)? ▪ If you had chemotherapy, how many sessions did you receive? For how long? ▪ If you had radiation, how many sessions did you receive? For how long? ▪ If you had hormonal therapy, what type did you receive? For how long? o *Drug (Brand Name): Tamoxifen (Nolvadex)*, Goserelin (Zoladex)*, Leuprolide (Lupron)*, Anastrozole (Arimidex), Letrozole (Femara), Exemestane (Aromasin)* o ** = Used in pre-menopausal women*
(2.6)	What was your experience with breast reconstruction?
(2.7)	Have you been diagnosed with any other cancers before? If so, which types of cancer? When were you diagnosed with these cancers (e.g., month/year, age)? ▪ Have you had any recurrences of breast cancer? If so, which types of cancer? When did these cancer reoccurrences take place?

Now, I'm going to ask you some questions about your reproductive health experiences around the time you were diagnosed with breast cancer.

SECTION 3: REPRODUCTIVE HEALTH CONCERNS around BREAST CANCER PERIOD	
(3.1)	What was your ideal family size prior to being diagnosed with breast cancer? ▪ Had you completed your family at the time you were diagnosed? ▪ If not, how many more children did you want?
(3.2)	What was your relationship status at the time of your breast cancer diagnosis? ▪ Were you single, in a relationship, or married?
(3.3)	When you were diagnosed with breast cancer, did you have any concerns about how the treatments may impact your reproductive health, such as the onset of menopause, fertility capability, sexual activity, reproductive outcomes, etc.? ▪ If YES: What were your concerns? o How were these concerns raised with your doctors, if at all? o If you did, how did your doctors react to your concerns? o How helpful were your doctors with addressing your concerns, or not? ▪ If NO: Why didn't you have any concerns?
(3.4)	Did being diagnosed with breast cancer influence your ideal family size goals? Will you please tell me more about that?
(3.5)	If you had children after your diagnosis, did being a breast cancer survivor influence your ability or desire to breastfeed your child(ren)? ▪ If YES: How did you cope with that?
(3.6)	Have you had any previous surgeries on your uterus, fallopian tubes, or ovaries? ▪ If so, why did you have this surgery? ▪ Did this surgery take place before of after your breast cancer treatment?

I just have two more general questions to ask you and then we'll be done for today.

SECTION A: MISCELLANEOUS QUESTIONS	
(A.1)	Is there any additional information that I did not cover that you would like to share with me?
(A.2)	Do you have any questions for me?

Thank you for meeting with me today! I really appreciate you participating in this interview and for thoughtfully responding to all of my questions. Your responses will truly help me learn more about the experiences of young breast cancer survivors. Here's $25 cash as a token of my appreciation for you spending time with me today.

I'd like to schedule a time to conduct the second interview with you. When's a good day and time for us to meet up again?

(2nd Interview Date/Time _____)

I'll give you a call and send you an email at least 2 days before the next interview. If you have any questions in the meantime, feel free email or call me at the contact information listed on the consent form. Thank you again for everything!

2nd INTERVIEW

*Thank you **(participant #_____)** for agreeing to meet with me for a second time and participating in this interview today the **(day_____)** of **(month_____) (year_____)**. During this second interview, I am going to ask about reproductive health information you may or may not have received, any reproductive or fertility issues that occurred during or after your breast cancer treatment, and life experiences that may have impacted your health.*

*As I shared with you during the last interview, I will be asking questions that may be sensitive topics for you. If you are not comfortable answering a question, please let me know and we can skip it. Do you have any questions before I begin? **(PAUSE; ADDRESS ANY QUESTIONS)** Okay, let's begin!*

Now, I'm going to ask you about the information you may have received about your reproductive health around the time of your breast cancer diagnosis and treatment.

SECTION 4: REPRODUCTIVE HEALTH INFO RECEIVED	
(4.1)	What types of information did you receive on the impact of cancer treatment on your reproductive health? **(If the answer is NONE, then SKIP to question 5.1)** ▪ Who gave you this information? ▪ At what point during your care was this information given to you (e.g., prior to, during, or after treatment completed)? ▪ Did you ask for this info, was it just given to you, or did you find it on your own? ▪ How useful was the information you received? ▪ What kind of reproductive health or fertility counseling did you receive?
(4.2)	Out of all the resources you received to address your questions and concerns, which was your favorite resource?
(4.3)	What is your opinion of the information you received about the impact of cancer treatment on your reproductive health? ▪ Did you receive enough information to address your concerns?
(4.4)	From the information you received, what did you learn about the potential impact of cancer treatment on your reproductive health? ▪ How did this information influence your decisions about your family completion goals?
(4.5)	What reproductive health information do you wish you had received before you began treatment?

Now, I'm going to ask you some more sensitive questions about your reproductive health. Please let me know if there is a question that you don't want to answer and we can definitely skip it.

SECTION 5: REPRODUCTIVE/FERTILITY ISSUES	
(5.1)	What types of menstrual cycle related issues have you experienced over your lifetime (e.g., irregular menses, absence of menses, onset of menopause)? ▪ If so, at what age did this take place? ▪ How long did this issue last? ▪ How was your menstrual cycle different after you received and completed your breast cancer treatment compared to before you were diagnosed with cancer? ▪ Did you ever regain your menses while you were still being treated?
(5.2)	After you completed your treatment, what were your plans for starting/completing your family? ▪ Why did or didn't you want to have children after completing your treatment? ▪ What type(s) of contraception did you use? **(If the answer was they DID NOT want any children, then SKIP to Section 6)**
(5.3)	What was your experience with trying to conceive children after completing your treatment? ▪ Were there any setbacks or difficulties you experienced with getting pregnant?
(5.4)	Did you have any fertility treatments prior to beginning your breast cancer treatment? ▪ If so, what type? ▪ What information were you provided about these methods from your cancer care team? ▪ What information did you discover on your own?
(5.5)	Did you utilize any assisted reproductive technologies (ARTs) to help you become pregnant after you completed your treatment? ▪ If so, what type? ▪ Did you become pregnant after using the ARTs? ▪ What information were you provided about these methods from your cancer care team? ▪ What information did you discover on your own?

This next section of questions will allow me to learn more about how historical and social factors may have impacted your health. This will include questions about your cancer care team and race. If you feel uncomfortable with responding to any of the questions, please let me know and we can skip those questions.

SECTION 6: SOCIAL DETERMINANTS OF HEALTH	
(6.1)	How was your overall experience with receiving care at your cancer center? ▪ Did you have any barriers or challenges to receiving care? ▪ Do you feel you were treated differently than other patients during your care? ▪ If so, why do you have the sense that your experience was different than other patients?
(6.2)	I'm going to ask you a few questions about the race/ethnicity and gender of the members of your cancer care team. Some patients like to receive care from doctors that look like them, so I want to learn more about how this may have impacted your care experience, if at all. What race and gender is your surgeon? How about your medical oncologist? How about your radiation oncologist? ▪ How did the race or gender of your cancer care team members positively or negatively impact your care experience, if at all?
(6.3)	What types of challenges did you face while going through your cancer journey? ▪ Were there any challenges at home? ▪ Were there any challenges at work? ▪ Were there any challenges in your community (e.g., church, neighborhood, social network, etc.)? ▪ Were there any challenges at your cancer center or hospital?
(6.4)	What types of challenges did you face while trying to become pregnant after your breast cancer treatment? ▪ Were there any challenges at home? ▪ Were there any challenges at work? ▪ Were there any challenges in your community (e.g., church, neighborhood, social network, etc.)? ▪ Were there any challenges at your cancer center or hospital?
(6.5)	How can cancer centers and the medical system help young breast cancer survivors overcome barriers to becoming pregnant after treatment?

I just have four more general questions to ask you and then we'll be done for today.

SECTION B: MISCELLANEOUS QUESTIONS	
(B.1)	How should information regarding the impact of breast cancer treatment on reproductive health during and after treatment be delivered to young breast cancer survivors'? ▪ *EXAMPLES of methods for delivering information: brochures, Internet links, videos, 1-on-1 counseling (with doctor, nurse, navigator, health educator), group counseling*
(B.2)	What types of information should young breast cancer survivors receive about their reproductive health during and after treatment?
(B.3)	Is there any additional information that I did not cover that you would like to share with me?
(B.4)	Do you have any questions for me?

Thank you for meeting with me today! I really appreciate you participating in this interview and for thoughtfully responding to all of my questions. Your responses will truly help me learn more about the reproductive health experiences of young breast cancer survivors. Here's $35 cash as a token of my appreciation for you spending time with me today.

After I finish conducting interviews and analyze all of the transcriptions of these interviews, I plan to organize a session where I will invite all of the women I interviewed and I will share my findings to receive additional feedback and insights. Are you interested in me contacting you about this session? **(□ YES □ NO)** Is it best to email or call you? **(□ EMAIL □ CALL)**

Thank you again for everything!

APPENDIX 2: CHARACTERISTICS OF LIVE BIRTHS ACCORDING TO MOTHER'S RACE/ETHNICITY, NORTH CAROLINA 1990-2009

	White, Non-Hispanic (N=1,383,302)		Black, Non-Hispanic (N=528,967)	
Breast Cancer History	N	%	N	%
No	1,382,978	*99.98*	528,779	*99.96*
Yes	324	*0.02*	188	*0.04*
Preterm Birth	0	*0.0*	0	*0.0*
Term (≥37 weeks gestation)	1,251,260	*90.5*	452,620	*85.6*
Preterm (<37 weeks gestation)	130,808	*9.5*	75,326	*14.2*
Missing	1,234	*0.1*	1,021	*0.2*
Low Birthweight				
Healthy weight (≥2,500 grams)	1,285,994	*93.0*	457,767	*86.5*
Low birthweight (<2,500 grams)	97,308	*7.0*	71,200	*13.5*
Missing	0	*0.0*	0	*0.0*
Education				
Less than high school (≤11 years)	168,189	*12.2*	98,010	*18.5*
High school diploma (12 years)	431,416	*31.2*	231,676	*43.8*
Some or graduated college (13-16 years)	636,465	*46.0*	178,660	*33.8*
Professional/graduate degree (≥17 years)	145,160	*10.5*	19,591	*3.7*
Missing	2,072	*0.2*	1,030	*0.2*
Marital Status				
Married	1,134,949	*82.1*	186,223	*35.2*
Not married	248,036	*17.9*	342,631	*64.8*
Missing	317	*0.02*	113	*0.02*
Parity				
Primiparous (1 birth)	599,342	*43.3*	188,072	*35.6*
Multiparous (≥ 2 births)	783,960	*56.7*	340,895	*64.5*
Missing	0	*0.0*	0	*0.0*
Smoking				
Non-Smoker	1,143,297	*82.7*	462,827	*87.5*
Smoker	232,823	*16.8*	63,260	*12.0*
Missing	7,182	*0.5*	2,880	*0.5*
Maternal Age at Infant Delivery (in years)				
Mean *(Standard Deviation)*	27.7 *(5.6)*		25.5 *(5.6)*	
Range	18.0-50.0		18.0-50.0	
Age at Breast Cancer Diagnosis (in years)				
Mean *(Standard Deviation)*	31.7 *(4.6)*		31.9 *(4.9)*	
Range	20.3-44.3		18.7-42.7	
Chemotherapy[a]				
Didn't receive chemotherapy	165	*50.9*	94	*50.0*
Received chemotherapy	159	*49.1*	94	*50.0*
Missing	0	*0.0*	0	*0.0*
Length of Time between Diagnosis & Infant Delivery[a]				
< 2 years	125	*38.6*	70	*37.2*
2 ≤ years < 5	124	*38.3*	73	*38.8*
≥ 5 years	75	*23.1*	45	*23.9*
Missing	0	*0.0*	0	*0.0*

N=total number; %=percentage

[a] Includes only women with a breast cancer history (n=512)