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Fertility, pregnancy, and breastfeeding among younger breast cancer survivors

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Fertility, pregnancy, and breastfeeding among younger breast cancer survivors

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The dissertation of Jessica Lynn Rickard Gorman is approved, and it is acceptable quality and form for publication on microfilm:

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DEDICATION

To my husband, Alex, for his tremendous support. It is not possible to put my appreciation into words, but I know that I would not have been able to do this without him.

To my daughter, Abigail, for reminding me daily to appreciate every moment and to have fun.

To my mom and step-dad, Viki and Bill, for making learning and education a priority in my life.

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Research paper I has been accepted and published in ‘Journal of Cancer Survivorship’ on May 22 2009 (Epub ahead of print). The dissertation author is the primary investigator and the first author and Dr. Paula Usita, Dr. Lisa Madlensky, and Dr. John P. Pierce are coauthors of this manuscript.

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Research paper III has is currently being prepared for submission. The dissertation author is the primary investigator and the first author and Dr. Scott C. Roesch, Dr. Vanessa Malcarne, Dr. Lisa Madlensky, and Dr. John P. Pierce are co-authors of this manuscript.

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ABSTRACT OF THE DISSERTATION

Fertility, pregnancy, and breastfeeding among younger breast cancer survivors.

by

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Doctor of Philosophy in Public Health (Health Behavior)

University of California, San Diego, 2009

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This dissertation's three research papers examine issues relevant to younger breast cancer survivors and their health care providers. Research Paper I is an exploratory, qualitative study to investigate breast cancer survivors' experiences with breastfeeding (N=11). Research Paper II is a nested case-control study to evaluate physical and mental health differences among women who had a child after breast cancer compared to those who did not (N=81). Research Paper III is a cohort study evaluating the association between long-term depressive symptoms and post-diagnosis reproductive concerns (N=131). All three studies include participants diagnosed with early stage breast cancer at age 40 or younger who participated in the Women's Healthy Eating and Living (WHEL) study (N=3088), a multiyear randomized trial of a dietary intervention.

Research Paper I includes a purposeful sample of 11 survivors who had a child after treatment ended. We conducted open-ended semi-structured interviews and used cross-case inductive analysis to identify themes. Ten of 11 participants initiated breastfeeding. The main themes were: 1) Cautiously hopeful, 2) Exhausting to rely on one breast, 3) Motivated despite challenges, 4) Support and lack of support, and 5) Encouraging to others. Participants were motivated to breastfeed but faced significant challenges, largely due to a reliance on one lactating breast.

Research Paper II is a nested case-control study involving 81 WHEL participants, 27 cases who had a child after cancer and 54 controls who did not (matched on age and stage at diagnosis). This study explores a selection bias indicating that cancer survivors who become pregnant are a self-selected healthier group. After controlling for covariates in a multilevel model, physical health was not different between groups but mental health was marginally higher among cases, meeting a level of clinical significance.

Research Paper III is a cohort study involving 131 WHEL participants who participated in a continuation survivorship study. This study investigates whether recalled concerns about reproduction after breast cancer treatment are associated with long-term depressive symptoms, monitored at up to 6 time-points. Multi-level modeling identified higher reproductive concerns as an independent predictor of consistent depressive symptoms after controlling for both social support and physical health.

General Introduction:

Research Paper I, II and III (references included)

Breast cancer is the most frequently diagnosed cancer in women and is the number one cause of cancer death among women aged 20-39 [1]. In the United States, a quarter of breast cancer cases are diagnosed in premenopausal women [2]. About 5% of cases are diagnosed in women younger than 40 [3]. The 5-year survival rate for women diagnosed at 40 and younger is 82%, slightly lower than the 89% survival rate for women diagnosed at 40-74 years of age [4]. There are an estimated 250,000 women under the age of 40 currently living with breast cancer [5].

Because of their stage in life, younger women diagnosed with breast cancer are more likely to have survival concerns related to fertility, pregnancy and breastfeeding. Breast cancer does not appear to interfere with women's motivations toward having a child [6], though treatment may result in reproductive difficulties [7-10]. While the risk of chemotherapy-induced amenorrhea depends on chemotherapeutic agent and dose, it is lower among breast cancer patients diagnosed at age 40 or younger (occurring 13-62% of the time) [10]. However, even women who resume menstruation may face difficulties with fertility due to ovarian damage and menopause at an earlier age [9, 10]. Infertility alone is an emotionally challenging problem and may be even more challenging for cancer survivors [11]. In addition to biological reasons, a cancer diagnosis may also influence childbearing decisions in other ways. Women are typically advised to wait 2-3 years after treatment ends before conceiving, which may preclude pregnancy for women who feel that it will be too late in life to have a child. Decisions about having a child as a cancer survivor may also involve feelings of guilt and anxiety due to uncertainty about the future [12, 13]. Some women experience fear of recurrence and worry about transmitting genetic risk for cancer to their children [13-15].

The majority of research on pregnancy among breast cancer survivors has focused on survival. Current research does not indicate that there is an adverse affect of pregnancy on survival; in fact, it may be protective [16-20]. While findings do not indicate that women should avoid pregnancy after breast cancer, the strength of evidence is limited by selection and recall biases [21-23]. Key among these is the “healthy mother” bias, which suggests that breast cancer survivors who go on to have full term pregnancies are a self-selected healthier group based on their prognosis [20]. Researchers have not been able to evaluate this bias due to limitations in available data, such as cancer registry data. In addition, subsequent pregnancies may not be tracked or reported [21, 24].

Younger survivors also have greater psychosocial needs as compared to older survivors, particularly with respect to dealing with the physical impact of treatment and associated gynecological and reproductive consequences [25]. The need for support related to fertility and early menopause has been identified as very important to younger women [25-28]. Younger women are also at greater risk for short- and long-term depressive symptoms [19, 21, 22, 36, 55]. Depression and distress negatively impact on quality of life [12, 28], including family life [56-58], and may increase risk for progression of cancer and cancer mortality [25-27]. Psychological concerns can last for years after treatment and have a significant negative impact on quality of life [26, 29-32] .There is limited research on the psychosocial impact of difficulties with fertility after breast cancer. One cross-sectional study explored the association between reproductive concerns and long-term QOL (5-10 years after diagnosis) among younger female cancer survivors [33]. After controlling for disease and psychosocial variables, greater reproductive concerns were associated with lower long-term QOL (p<.001). Studies have not explored how reproductive concerns may be associated with depressive symptoms.

For those survivors who do have a child, there is very limited information on breastfeeding after breast cancer. While there is evidence that breastfeeding is protective against incident breast cancer [34, 35], there are no epidemiological data regarding breastfeeding after breast cancer. The relationship between prior duration of breastfeeding and risk of second primary cancer is not significant [36]. Breastfeeding after breast cancer treatment may be possible, although some surgeries and treatments can eliminate or reduce the chances of lactation [37-39]. Studies have found that lactation after radiation therapy occurs between about 10 and 50 percent of the time [38-40]. One qualitative study found that women wanted to breastfeed but had fear and anxiety about the potential difficulty of detecting a recurrence [12]. There is no evidence that breastfeeding after breast cancer is either harmful or beneficial with regard to breast cancer risk. The benefits of breastfeeding to the newborn and mother are well-established [41] and existing research suggests that breast cancer survivors who wish to breastfeed should be encouraged and supported in their efforts [42-45].

The three research papers presented were designed to: I) explore breast cancer survivors’ experiences with breastfeeding, II) evaluate physical and psychosocial correlates of pregnancy after breast cancer, and III) assess how survivors’ reproductive concerns may be associated with long-term depressive symptoms. For Research Paper I, we collected new qualitative data. The data for Research Paper II came from younger participants in the Women’s Healthy Eating and Living (WHEL) study and the data for Research Paper III came from both existing

WHEL data and new data from younger participants in a continuation survivorship study. Further qualitative and quantitative exploration of these issues may help researchers interpret existing research findings and plan future studies.

The WHEL study is a multi-site randomized controlled trial to evaluate the effectiveness of a high-vegetable, low-fat diet to reduce recurrence of breast cancer and early death. The study enrolled 3,088 women diagnosed between the ages of 18 and 70 who had completed initial treatment for early stage breast cancer. According to the accepted staging principles at the time of enrollment [41], approximately 40% of WHEL participants were diagnosed with Stage I (≤1cm), 55% with Stage II, and 5% with Stage IIIA breast cancer within the previous four years. The WHEL study enrolled participants between 1995 and 2000. The average age at study entry was 53.3 years and 376 (12.2%) of participants were 40 or younger at diagnosis. Over 85% of the study population was Caucasian. Participants were recruited from seven clinical sites in California, Arizona, Oregon and Texas. Exclusion criteria included pregnancy at the time of enrollment, evidence of recurrent disease, previous diagnosis of invasive breast carcinoma, receiving estrogen replacement therapy, and other primary or recurrent invasive cancer within the last 10 years. Other inclusion and exclusion criteria for WHEL are extensive and described elsewhere [46].

Younger, premenopausal women who are diagnosed with breast cancer have different concerns, particularly with respect to their long-term reproductive health and well-being, and research addressing these issues is scarce. There is limited research on fertility, pregnancy and breastfeeding to inform and guide younger breast cancer survivors and their health care providers on these important issues. It does not appear that pregnancy after breast cancer poses a risk to survival, although potential biases have lead to some uncertainty about these findings. It is also unknown whether difficulties with reproduction associated with cancer treatment have an impact on long-term psychosocial health. Finally, survivors' experiences with breastfeeding, including potential challenges and unique needs, have not been documented. The three research papers presented provide both qualitative and quantitative data to build on existing research in these areas.

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Research Paper I (references included)

A qualitative investigation of breast cancer survivors’ experiences with breastfeeding.

ABSTRACT

Introduction

This is an exploratory, qualitative investigation of breast cancer survivors' experiences with breastfeeding. Previous studies have focused on the physiology of lactation after surgery and treatment, but have not explored factors influencing breastfeeding decisions and behavior.

Methods

We used purposeful sampling to identify 11 breast cancer survivors who had a child after their diagnosis and treatment. Participants were recruited from among those in the Women's Healthy Eating and Living (WHEL) study and a Young Survival Coalition (YSC) affiliate. We conducted semi-structured, open-ended telephone interviews lasting 45-75 minutes. We used social cognitive theory (SCT) to structure questions regarding influences on breastfeeding behavior. We transcribed interviews and used cross-case, inductive analysis to identify themes.

Results

Ten of 11 participants initiated breastfeeding. The following main themes emerged: 1) Cautiously hopeful, 2) Exhausting to rely on one breast, 3) Motivated despite challenges, 4) Support and lack of support, and 5) Encouraging to others.

Discussion/Conclusions

Study participants were highly motivated to breastfeed but faced considerable challenges. Participants described problems that are not unique to women with breast cancer, but experienced these to a much greater degree because they relied mostly or entirely on one lactating breast. This study revealed a need for improved access to

information and support and greater sensitivity to the obstacles faced by breast cancer survivors.

Implications for cancer survivors

Results of this qualitative analysis indicate that interventions to support the efforts of breast cancer survivors who are interested in breastfeeding are warranted. Additional research would aid in the development of such interventions.

INTRODUCTION

Personal, cultural, social and environmental factors influence women's decisions regarding initiation and duration of breastfeeding [1]. Women previously treated for breast cancer face a unique set of physical and emotional factors that might impact their decisions and ability to breastfeed. Breastfeeding after breast cancer treatment might be possible, although some surgeries and treatments can eliminate or reduce the chances of lactation [2-5]. Breastfeeding can be fraught with anxiety and breast cancer survivors, like many other women, need information and support to help them succeed [6, 7].

Even though breastfeeding might be possible for many breast cancer survivors, lactation can be restricted. Several studies have reported on the ability to lactate after breast cancer surgery and treatment [3, 4, 8-10]. Surgical characteristics, such as proximity of the incision to the areola and nipple, and dose and type of radiotherapy might affect lactation [5]. In an early study of breastfeeding behavior among breast cancer survivors, 1 of 11 patients successfully breastfed from the treated breast after surgery and radiotherapy and most women successfully breastfed from the untreated breast [3]. In another, 34% of women who had a child after radiation therapy lactated and about a quarter successfully breastfed from the treated breast [4]. In a more recent retrospective study of 21 patients where 22 breasts were analyzed, lactation occurred in about half of breasts, did not occur in about 40% and was unknown in the remainder [8].

Beyond the physiological ability to lactate, research on breast cancer survivors' experiences with breastfeeding is sparse. In one qualitative study, young breast cancer survivors wanted to breastfeed, but had anxiety and concerns about doing so [7]. In particular, participants were worried about the potential difficulty of detecting breast cancer recurrence [7]. Other researchers have also noted this [11, 12]. Other influences included social expectations about breastfeeding, convenience, desire to experience breastfeeding, and benefits for the infant. Social expectations about breastfeeding might also lead women to feel conflicted if they are unable or choose not to breastfeed [7].

There is evidence that breastfeeding is protective against incident breast cancer [13-15]. However, there are no epidemiological data regarding breastfeeding after breast cancer. The relationship between prior duration of breastfeeding and risk of second primary cancer is not significant [16]. Although there is no evidence that breastfeeding after breast cancer is either harmful or beneficial with regard to breast cancer risk, the benefits of breastfeeding to the newborn and mother are well-established [17]. Current research suggests that breast cancer survivors who wish to breastfeed should be encouraged and supported in their efforts [6, 18-20].

There are an estimated 250,000 women under the age of 40 currently living with breast cancer [21]. Women in this younger group are more likely than older survivors to be interested in having children and possibly breastfeeding [22]. Previous studies suggest that lactation after breast cancer treatment is possible but do not explore the factors influencing breastfeeding decisions and behavior. Given the established benefits of breastfeeding for all women, it is important to learn more about the factors that support breastfeeding as well as potential challenges faced by breast cancer survivors. This information will benefit practitioners as well as researchers interested in developing interventions to support the efforts of women who wish to breastfeed after breast cancer.

METHODS

Study Design

We used an exploratory, qualitative research approach to investigate breast cancer survivors' experiences with breastfeeding. Qualitative research provides in-depth and contextual information that cannot be obtained from quantitative research alone [23]. This approach allowed us to explore the context and meaning of women's experiences and motivations around breastfeeding. The study protocol was approved by both the University of California San Diego and San Diego State University.

Sampling and eligibility criteria

Participants were recruited from the Women's Healthy Eating and Living (WHEL) study (N=3088). The WHEL study is a multi-site randomized controlled trial to evaluate the effectiveness of a high-vegetable, low-fat diet to reduce recurrence of breast cancer and early death. Participants included those diagnosed with Stage I, II or IIIA invasive breast cancer within the previous four years. Participants were enrolled between 1995 and 2000. The average age at study entry was 53.3 years and 376 (12.2%) of participants were 40 or younger at diagnosis. Over 85% of the study population was Caucasian. Approximately 45% of the sample was diagnosed with Stage II breast cancer, 40% with Stage I, and less than 15% with Stage IIIA disease. Women who were pregnant were excluded. Other inclusion and exclusion criteria for WHEL are extensive and described elsewhere [24]. From among all WHEL study participants, we identified 28 survivors who: 1) had a live birth after the time of their diagnosis and treatment and 2) agreed to be contacted in the future during their exit interview. All women were age 40 or younger at the time of diagnosis. To broaden the study population, we made an announcement through the local YSC affiliate. Five women agreed to participate and one of those had a child after breast cancer and provided information about breastfeeding.

We used purposeful sampling to identify breast cancer survivors who had a child after their diagnosis and treatment. Among WHEL participants, we aimed to include those who had a lumpectomy as well as those who had a mastectomy involving one breast. This strategy was chosen to identify a representative group of young breast cancer survivors who would be able to provide rich, in-depth information on the interview topics, including their unique experiences with breastfeeding. The final sample size was determined by informational considerations; the sampling ended when saturation had been reached and no new information was provided by participants [25]. The final sample included 11 participants. Table 1 outlines participant characteristics.

Interviewing and data collection

The interviewer first contacted potential WHEL study participants via telephone. We attempted to contact 15 participants who had a child after their cancer diagnosis and were able to reach 11 of those. Ten agreed and completed the interview and one declined. The interviewer described the study briefly and completed oral informed consent for those who were interested. The participant from the YSC contacted the study directly to participate. All participants completed one telephone interview between February and March, 2008. Interviews lasted 45 to 75 minutes. With participants' permission, we recorded the telephone interview.

We used a semi-structured interview guide, which included questions about fertility after breast cancer, experiences with pregnancy and postpartum, and experiences with breastfeeding, including facilitators and barriers. The interview guide was informed by existing research on factors influencing breastfeeding behavior, including sources of support [1]. We used social cognitive theory (SCT) to structure questions regarding individual- and environmental-level factors that might have influenced breastfeeding behavior. SCT provides a framework for understanding the reciprocal influence between individual factors (e.g. cognitive and physiological), environmental factors, and individual behavior [26, 27]. In particular, we focused on two environmental-level factors, health care providers and partner/spouse, and two individual-level factors, outcome expectations and outcome expectancies. Outcome expectancies refer to the values placed on a particular outcome, such as the value of breastfeeding. Individuals are expected to behave in a way that maximizes the valued outcome. Outcome expectations refer to the anticipated outcomes that guide a person’s behavior [26, 27]. Breastfeeding specific questions from the interview guide are outlined in Table II.

Analysis

We transcribed all interviews verbatim and used cross-case analysis to identify themes, combining answers from all participants and using these grouped answers to analyze responses [23]. First, we examined data by theme/topic following the interview guide to identify facilitators and challenges to breastfeeding. We then used inductive analysis to identify themes, sub-themes, and patterns in the data. Although SCT helped identify internal and external influences on breastfeeding behavior, we did not restrict our analysis to SCT constructs. We used the following steps for qualitative data analysis: 1) Reading and re-reading qualitative data to become familiar with the text and begin developing codes; 2) Coding data to begin developing themes and sub-themes; 3) Displaying details of categories and themes (e.g. identifying variations of each theme, noting differences between individuals and among sub-groups, exploring nuances in text); 4) Reducing data to essential points; and 5) Developing an overall interpretation based on this process [25]. This process was iterative and continued as we collected data. We imported the transcripts into the QSR NVivo 8 software package [28] to code, sort and analyze the data.

The PI conducted all interviews and was responsible for coding and identification of themes, using continuous coding as new data were collected in order to identify and resolve potential gaps in questions as well as potential biases. Through this process, several consistent themes emerged. In the final step, the PI re-read the interviews and evaluated the coding categories to ensure that the meaning and intent of the participant comments was captured accurately.

RESULTS

Study Participants

This study includes 11 younger breast cancer survivors who had at least one child after their breast cancer treatment and did not have a bilateral mastectomy. Participants were diagnosed at Stage I (27%) or Stage II (73%) breast cancer between the ages of 27 and 36 (average age 31.7 years). Prior to diagnosis, 4 participants (36%) had one or more child and 3 of those had breastfed. Participants became pregnant between less than one year and six years post-diagnosis. Compared to other WHEL participants, the 10 women who participated in this study were younger, more likely to be White, more likely to be college graduates or higher, more likely to have been Stage II and less likely to have been Stage I at diagnosis, more likely to have had a lumpectomy, and less likely to have ever used antiestrogens. Participants had a total of 19 children after breast cancer, with a range of one to three children each. One participant chose not to breastfeed and two were unable to breastfeed all of their children post-cancer; one had difficulty breastfeeding her twins and another was taking medication contraindicated during breastfeeding. Ten women did breastfeed a total of 15 children. These women were able to provide breast milk to their children for between six weeks and three and a half years, for an average of 8 months. The majority of participants supplemented with formula either immediately or after a short time, between one and four months after initiating breastfeeding. Participant characteristics are outlined in Table I.

Themes

The following themes were identified from the semi-structured interviews. They include both facilitators and challenges to breastfeeding. The main themes identified were: 1) Cautiously hopeful, 2) Exhausting to rely on one breast, 3) Motivated despite challenges, 4) Support and lack of support, and 5) Encouraging to others. Sub-themes are also discussed within each main theme.

Theme 1: Cautiously hopeful

The majority of participants expressed hope about their ability to breastfeed and reported uncertainty about what to expect. Despite their uncertainty, women were hopeful and planned to try to breastfeed and “see what happens”:

> I was just hoping to be able to do it. You know I wanted to try it…. It was I’m gonna try it and if I can do it I’m gonna do it for as long as I can do it and if I can’t then I’ll have to accept the fact that I can’t. (Mother of 2 after cancer, breastfed 4 months and 2 months)
>
> I was just hoping I could do it. I was just hoping my milk would come in. I was just praying that it would all work. (Mother of 1 after cancer, breastfed 14 months)
>
> I was just going to give my all and try. You know, as much as I could. (Mother of 1 after cancer, breastfed 6 months)

Subtheme 1a: Worried about nursing from one side

Women generally expected it to be different than the experience of most other women because they would have to rely mainly or entirely on one breast. All but one participant planned to try to breastfeed, and the majority of those who planned to try expressed concerns about whether or not they would have a sufficient milk supply:

> My biggest thing was I was super nervous about nursing, I wanted to be able to nurse and would I be able to nurse on one side? And would I have enough milk? (Mother of 1 after cancer, breastfed 14 months)

> My main concern was I wanted to breastfeed, and the one side, the right side where I had the breast cancer wouldn't produce milk like the other side. (Mother of 3 after cancer, breastfed 7 ½ months, 5 months and 4 months)

Subtheme 1b: Expected it to be like a mother with twins

Several participants were optimistic about breastfeeding and expected their experience to be similar to that of other women who had twins:

> I basically remember coming up with my own idea that if a woman with twins can nurse two babies with two boobs, basically, I could do it with one with one baby, so you know. So I just figured supply and demand, as long as he can be satisfied, I will nurse him. You know? Because I think it's good for them and good for us, no matter what. (Mother of 1 after cancer, breastfed 6 months)

> Well I think that for most women it would be like having twins. You know it's sort of supply and demand. So if you, if you know, even though it's only on one side you can still produce enough. Because they're just sucking on that one side, you're still going to produce. You can still make enough to provide for your child. (Mother of 1 after cancer, breastfed 14 months)

Subtheme 1c: Didn't stress about it

Although women were generally hopeful about breastfeeding, a few also reflected on the fact that they would not worry too much if they were unable to because, as breast cancer survivors, their situations were different than most other women:

> [Breastfeeding] is a natural thing you want to do it … it builds up their immunities and it's the perfect thing for babies to drink, but for women like us, who have gone through breast cancer treatment, if we're blessed and fortunate enough to be able to have children… [we] may not be able to breastfeed them….I guess it goes back to everything I've been through, I just don't stress about it. I can't change it, I have no control over it. So why am I gonna spend any time and energy worrying about it? I'm going to get them on formula and they're going to be fine. (Mother of 2 after cancer, breastfed 4 months and 2 months)

Theme 2: Exhausting to rely on one breast

Ten of the study participants breastfed their children and all of them discussed significant challenges to breastfeeding. Primary among these was not having a sufficient milk supply because they relied primarily on one breast. Those who had a mastectomy only had one breast to feed from and those who had a lumpectomy reported little or no milk from the side that had been operated on. Among those who had a lumpectomy, five of seven reported no milk production on the side that was operated on. The remaining two participants reported very little milk on one side.

> I only had one breast that lactated. The breast that was operated on didn't get the memo that we were pregnant. So I only had one breast that was utilized for breastfeeding. (Mother of 1 after cancer, breastfed 6 months)

> Depending on what [surgery] you've had, its really hard afterwards if you try and breastfeed…It was really hard. Doable, but you've got, it was just really hard because the one side produced milk and the other side didn't, so you're feeding just on one side. (Mother of 1 after cancer, breastfed 2 months)

Subtheme 2a: Huge commitment

All study participants who breastfed reported that it was physically and emotionally very difficult. The main challenges were related to the fact that women had to rely primarily or entirely on one breast. As a result, breastfeeding was a huge commitment that included needing to use a breast pump and supplement with formula for the majority of women.

> It’s hard, you have to pump, you have to do a lot… you have to be really committed to it. (Mother of 2 after cancer, breastfed 4 months and 2 months)
>
> You can’t just leave and go take off and go do something, because you have to always be attached to the baby and pumping is just horrible, you definitely feel like a cow. And I had to pump every three hours to keep up my supply. And that was horrendous and then you’re just, everything is about, in the beginning you know, first 6 months about feeding the baby, it's like you nurse every 3 hours and you pump every 3 hours and then give, I had to give him the supplement because I wasn’t making enough, so I’d pump and then give him that supplement. (Mother of 1 after cancer, breastfed 14 months)
>
> The hard part was, in addition to breast feeding both of them, I had to pump, so it was like having triplets. So I was constantly attached, which, so that was difficult. So, you know, early on, I breast fed them both, and pumped. As it, as they got bigger, I would bottle feed one, breast feed the other, and then pump. (Mother of 3 after cancer, including twins, breastfed 5 months and then 4 months with twins)

Subtheme 2b: Frustrated with milk supply

Several women expressed frustration with the experience of low milk supply, and this was the reason why many either began supplementing or transitioned entirely to formula:

> I thought it was going to be easier than it was. I had thought that side would produce more than it did. So it was kind of frustrating when it didn’t. (Mother of 3 after cancer, breastfed 7 ½ months, 5 months and 4 months)
>
> I only had my cancer was in my left breast and that breast did not produce any milk… So that one did not produce any milk and I got some out of my right breast so my daughter got, I was only able to breast feed her about 4 months. And then my supply just dwindled down… Even my breast that was making milk wasn’t making that much so we would only be able to do it for a few minutes, and then it was drained and so I was having to give her a bottle, you know, anyway. So actually after a, probably with my daughter about a month or so of actually putting her on the breast, I just started pumping… for me, I was so glad when my supply started going down. Because it was more work, than anything, you know it's so much easier to mix up a bottle and give them a bottle and you’re done. We probably would have been successful at it if my breast would have been enough

> nutrition for them. And had filled them up enough, but it wasn’t so. (Mother of 2 after cancer, breastfed 4 months and 2 months)

Subtheme 2c: Physically difficult

Women also reported many physical challenges from feeding from only one side, including pain and physical appearance:

> [Breastfeeding is] doable, but you’ve got, it was just really hard because the one side produced milk and the other side didn’t, so you’re feeding just on one side. So it kind of not only looks kind of awkward, but it’s really just hard physically, too, you know. (Mother of 1 after cancer, breastfed 2 months)

> I remember somebody saying, don’t you wish you were a cow? And I’m like, to have like however many? Like they have like six or seven, I’d be happy with two right now, okay? I’d just be really happy with two… this one nipple is killing me! …And then the hard thing is you’ve got one huge boob and one regular sized boob. And you look ridiculous! (Mother of 1 after cancer, breastfed 14 months)

> The experience was difficult at first because it was one side and I could not take a break for the other side. So I had…specifically I had a chapped nipple and a split nipple and it was painful and I actually nursed through it… (Mother of 1 after cancer, breastfed 3 ½ years)

Subtheme 2d: Took what I could get

Despite the many physical and emotional challenges that women faced, in the end, they reported that they were happy to have had the experience. Participants who were able to provide breast milk to their child(ren) to whatever degree they were able seemed satisfied:

> And I think under different circumstances I would have breastfed my kids longer, you know? And it would have been different but you know, you take it, I have been, and that’s all I can ask for. You know? If I can’t breastfeed them, well that’s okay. (Mother of 2 after cancer, breastfed 4 months and 2 months)

> There’s something very comforting and very soothing about sitting on a breast pump and having the milk being expressed, just knowing that, you know, even though he’s not latched on, I’m still doing what I need to do to, you know, supply for my son or my daughter. (Mother of 2

after cancer, breastfed 14 months and 0 months)

Theme 3: Motivated despite challenges

Study participants overwhelmingly reported a strong desire to attempt to breastfeed their children. One woman reported going to great lengths to be able to breastfeed her child in the hospital: “I bugged the heck out of them in the hospital, let me nurse him while he’s in intensive care…they wouldn’t let me nurse him, until they finally did let me, but I had to beg and plead.” (Mother of 1 after cancer, breastfed 6 months)

Subtheme 3a: Baby’s nutrition and bonding were important

Study participants were highly motivated by the benefits of breast milk for the baby’s health. All of the women who reported breastfeeding stated that their decision was influenced by the benefits of breast milk for their child’s health. As one participant said, “It’s the healthiest thing for a baby…its designed specifically for the baby. That’s why its there.” (Mother of 1 after cancer, breastfed 3 ½ years)

The majority of women also commented on the importance of bonding with their child:

> Oh it's just that bonding with your child, you know? They’re right there you know, you are their sustenance, you’re giving them the food that they need to live. It's just that whole cliché with, you know just that special, close bonding time. That skin on skin time. I mean it was wonderful, it was wonderful.(Mother of 2 after cancer, breastfed 4 months and 2 months)
>
> It's just so beautiful I don’t know, it's so like bonding with your baby. Not that you’re not close when you’re bottle-feeding but it's just amazing that your body can do it. And I don’t know it's just really beautiful, I was really happy. (Mother of 1 after cancer, breastfed 14 months)

Subtheme 3b: Personal benefits

Additionally, several mothers discussed their beliefs that breastfeeding might be beneficial to their own health, possibly reducing their risk of breast cancer recurrence: “I’ve always heard that breastfeeding, well this is prior to cancer though, but I always heard breastfeeding was good. You know, you’re at a higher risk for breast cancer if you haven’t breastfed.” (Mother of 3 after cancer, breastfed 5 months and 4 months with twins)

A couple of participants also reported that they were motivated by the cost of formula and by the convenience of breastfeeding: “Have you seen how much formula is?...Cost, cost was I think the main thing.” (Mother of 2 after cancer, breastfed 4 months and 2 months)

Subtheme 3c: Influence of past experience

Another important motivating factor was having a previous positive experience with breastfeeding. One participant discussed how her earlier experiences with breastfeeding helped her to overcome the significant challenges she faced with post-cancer breastfeeding:

> It gave me a better perspective on women that have challenges with breastfeeding because my first two were like it was so easy and it was, I just fell right into it… it really took some perseverance for this one, the third one…And I’m glad that I had had the experience with the other two that I knew that it could eventually work so I didn’t give up easily. Oh yes, absolutely I would have given up, absolutely if I did not have that good…those two good experiences. (Mother of 1 after cancer, breastfed 3 ½ years)

One participant who had not breastfed her previous child chose not to breastfeed: “[I didn’t breastfeed] because I never breastfed my first child. My mom didn’t breastfeed, my sisters didn’t, you know so I just thought oh I’m not going to breastfeed. So no big reason why I didn’t, I just didn’t.” (Mother of 1 after cancer, breastfed 0 months) All other participants had either breastfed their previous children or had their first child after breast cancer.

Theme 4: Support and lack of support

Participants reported seeking information and support from a range of sources, including their physicians, lactation consultants, female family members/friends, and spouses/partners. However, several women reported that they did not seek support for breastfeeding and a few reported feeling unsupported by social norms and expectations surrounding breastfeeding.

Theme 4a: Support from multiple sources

The majority of women reported asking a physician about whether or not they would be able to breastfeed. Women reported talking to their obstetrician, general practitioner, oncologist, or radiation oncologist. Most of those reported that their physicians were very supportive: ”They were all for it…whatever my body produced was gonna be okay so…they were more than happy to, you know, support me in it and actually strongly encouraged that I do [breastfeed].” (Mother of 2 after cancer, breastfed 4 months and 2 months). Physicians generally advised a “wait and see” approach to breastfeeding because of the likelihood of a lower milk supply. Those who were encouraged to breastfeed by their physicians did initiate breastfeeding. One participant who didn’t plan on breastfeeding reported that her doctor supported her inclination not to breastfeed in order to better screen for recurrence: “And you know so I talked to my doctors, I said should I or should I not [breastfeed], and they said you know, let’s not. We can keep a better eye on your, on you that way, your healthy breast.” (Mother of 1 after cancer, breastfed 0 months)

Several women discussed the value of the practical support and information they received from lactation consultants, including those within hospitals and breastfeeding support groups:

> I really relied more on the maternity nurses in the hospital to get us going, and then at the lactation clinic, was phenomenal. I just highly

> recommend using the lactation clinic….But in general I definitely, the group was really helpful in helping me figure out ways to increase my supply and you know, I don't know, I wouldn't know the right time to pump, and when not to, you know? All that crazy stuff. When you produce the most… But, you know, I think every mom, if it's not working, it's my fault, what am I doing wrong, it's only me, nobody else has this problem, and that's why the lactation clinic's a great benefit because, you know, it is a process. (Mother of 1 after cancer, breastfed 6 months)

Many women also discussed the importance of the support they received from friends and family members, particularly their spouses/partners:

> You know everyone was supporting… my son's father was very supportive of me breast-feeding, and you know he would do whatever he could you know? So I would pump, and then he would give him the bottle from what I pumped, you know? To try to give me a break and, you know, everyone was really supportive. (Mother of 1 after cancer, breastfed 14 months)

Subtheme 4b: Negative impact of social expectations

Although the majority of participants reported feeling supported in their decisions about breastfeeding, a couple of women reported feeling unsupported because of others' expectations about the importance of breastfeeding. A couple of participants discussed feeling guilty for being unable to or choosing not to breastfeed because these cultural and social pressures. One participant expressed her frustration this way: "…you get some looks from some people if you don't breastfeed." (Mother of 1 after cancer, breastfed 0 months) Another participant described a negative experience with a lactation consultant who expected her to breastfeed regardless of the challenges she was facing:

> I felt more pressure to breastfeed, because she made it seem like there was no other option. And it kind of made you feel like, you know, you're a bad mother if you don't breastfeed. So I felt less supported, and more pressure to do it, and more like a failure if I couldn't. And she didn't care whether I had one breast or two. She thought it was, other women do it, you should be able to do it. (Mother of 3 after cancer, breastfed 5 months and 4 months with twins)

Theme 5: Encouraging to others

Among those participants who breastfed, the vast majority reported an overall positive experience and would encourage other survivors not to let breast cancer interfere with their desire to breastfeed. However, participants also advised others to be prepared for the possibility of an insufficient milk supply, resulting in the need to use a breast pump and supplement with formula. Overall, study participants felt that breastfeeding was a personal decision and a huge commitment, but that, for them, the benefits were substantial enough to justify the effort:

> It was a great experience, and I think breast feeding is a blessing to the child and the mother, and economically. So I would encourage moms to do that if they can do it. (Mother of 1 after cancer, breastfed 6 months)

> Just that you, you know, you probably won't produce enough milk on one side because of the radiation and milk glands and stuff that they cut out with surgery. So you're probably going to have to supplement with some type of formula. And just, it's hard because you feel like it's taking something away from you, and that, you get mad at the breast cancer, at least I did, for that. But you know, don't give up. Breast feed on one side. I fed three kids on one side, and you know, don't let it interfere with your bonding with your baby. (Mother of 3 after cancer, breastfed 7 ½ months, 5 months and 4 months)

> I mean it is a huge commitment… I think people think it's going to be really easy. Maybe for some people it is but, you know, so if they decide to do it, you know, definitely go to a, if you're having difficulty go to a breast feeding support group, and just get through the first 3 months, after that it's easier. (Mother of 1 after cancer, breastfed 14 months)

Subtheme 5a: It might not work out

Although women had positive experiences overall, they also talked about the importance of being aware that it might not be possible for some survivors to breastfeed. Participants also discussed the importance of being prepared for the possibility of it not working out as they had planned:

> I would say it's something that is definitely worth giving it a try, but also have a back up plan like, you know, introduce a bottle with breast milk so that they're used to a bottle if you need to. (Mother of 1 after cancer, breastfed 2 months)

> Oh, well, I mean I, I would just say if you've had radiation…there's a good chance you won't be able to breast feed. And you just have to be open to the fact that that's okay. That's just it, that's the way it is, and not stress about it, not get freaked out about it. (Mother of 2 after cancer, breastfed 4 months and 2 months)

IMPLICATIONS FOR RESEARCH AND PRACTICE

We have identified several key themes describing breast cancer survivors' experiences with breastfeeding. Our findings can be used to identify new research questions and to assist in the development of interventions aimed at supporting successful breastfeeding among this population. The majority of breast cancer survivors interviewed chose to initiate breastfeeding and participants were generally optimistic and motivated to breastfeed. Although those who breastfed experienced many hurdles, they were generally positive about their experiences and encouraged other breast cancer survivors who might be interested in breastfeeding not to let breast cancer stop them from trying. While participants in this study experienced many of the same barriers to breastfeeding as women without breast cancer, conversations highlighted a need for greater sensitivity to the challenges and pressures they may face. Milk supply was a major issue for most participants. Additional research to measure milk supply along with women's perceptions of their milk supply, and possible methods to increase milk supply would provide valuable information to aid in the development of interventions to support initiation and maintenance of breastfeeding. Based on the themes identified in this study, potential interventions include: professional assistance with breastfeeding initiation and building milk supply; opportunities to discuss specific concerns and needs about breastfeeding during prenatal visits; and improved postpartum support, such as through professional lactation consultants or other survivors who have breastfed.

Despite their enthusiasm, participants discussed several significant breastfeeding challenges. Difficulties related to having only one lactating breast, including lower milk supply, physical pain and exhaustion, posed significant obstacles for this group of breast cancer survivors. Literature on the experiences of breastfeeding women in general outlines similar challenges. Common reasons given for ending breastfeeding include sore nipples, inadequate milk supply, infant having difficulties, and perceptions that the infant was not satisfied [29]. The perception of insufficient milk supply is a common reason for the decision to wean, even in the general population, although it is unlikely that there is a physiological cause for this for the vast majority of women. [1, 30]. Although this study did not measure physical milk supply, participants did report on their perceptions of milk supply. Only two of seven participants, less than 30%, who received a lumpectomy reported having any milk available on the side that had been operated on. Even for those most committed to breastfeeding, participants reported that lower milk supply typically resulted in a need to use a breast pump and to supplement with formula. Although the problems encountered by breast cancer survivors mirror those of women without breast cancer in many ways, the availability of milk from only one breast appears to have amplified these.

Anxiety about breastfeeding was something that many women reported experiencing during pregnancy, generally stemming from concerns about having a sufficient milk supply. Connell et al [7] also reported that decisions about breastfeeding were difficult for many women. However, these authors reported that women’s anxiety was largely related to fear of recurrence. Participants in this study discussed fear of recurrence in relation to pregnancy, but only one participant identified this fear as a factor in her decision about breastfeeding. Several participants in this study reported that they spoke to a healthcare provider, typically an oncologist or obstetrician, about whether it would be possible and safe for them to breastfeed. Overall, women reported that their physicians encouraged them to breastfeed, but they did not provide additional education or support for breastfeeding. Some women looked to other sources for information; a few participants mentioned looking online, one went to a breastfeeding class, and others looked at breastfeeding books. Participants reported that information specific to breast cancer survivors was unavailable. Appointments such as prenatal visits would provide a valuable opportunity for providers to discuss the specific concerns and needs of breast cancer survivors who are interested in breastfeeding. This would also be an ideal time to connect women with support services that they might need postpartum, such as lactation consultation and breastfeeding support groups.

As is true for breastfeeding women in general [1], our interviews revealed that support was integral to breastfeeding success. A few women discussed the importance of the extensive support they received from their spouses/partners. Several also reported seeking outside help from lactation consultants from within hospitals, breastfeeding support groups, and private consultations. Spouses generally provided emotional support whereas lactation consultants provided education and practical assistance with breastfeeding techniques. However, participants reported that breastfeeding support for breast cancer survivors was lacking. In addition, the majority of participants did not seek outside help and about half did not report that their spouses/partners were a source of support. These results reveal an important area for improvement in providing postpartum support to breast cancer survivors. Potential interventions include professional support through lactation consultants trained to meet the unique challenges of breast cancer survivors, encouragement of spousal/partner support, and peer support from other breast cancer survivors who have breastfed.

Participants in this study were overwhelmingly motivated to try to breastfeed. Participants' outcome expectancies (value placed on breastfeeding) and expectations (anticipated outcomes of breastfeeding) were supportive of initiating breastfeeding. All participants who breast fed reflected on the value of bonding with their child through breastfeeding. Participants were also encouraged by the nutrition that breast milk would provide for their infants. Women also generally reported that they expected to be able to breastfeed successfully, with several women comparing their situation to a mother with twins who could breastfeed two infants. While participants did not expect breastfeeding to be easy, the experience, including physical and emotional challenges, was even more difficult than expected for most. Those that successfully initiated breastfeeding overwhelmingly reported that the experience was exhausting. Three participants appeared better able to cope with the challenges because of their previous breastfeeding experience. Participants identified low milk supply as the primary cause of their exhaustion, which resulted in the need to use a breast pump, supplement with formula and, in many cases, to end breastfeeding earlier than planned. Not only was it physically exhausting to breastfeed, but women also commented on the emotional challenges, particularly the guilt associated with having to supplement with formula or end breastfeeding. Others have also discussed the sense of guilt that arises from social pressure to breastfeed and the added stress that women experience as a result [7]. Breastfeeding is a struggle for many women and even more so for breast cancer survivors who typically have only one lactating breast. Conversations with women in this study highlighted a need for increased support across a range of experiences, including breastfeeding in combination with formula supplementation and the decision to end breastfeeding. These findings also illustrate the importance healthcare providers' sensitivity to the heightened challenges faced by breast cancer survivors wishing to breastfeed.

This study resulted in detailed information about women's experiences with breastfeeding after breast cancer, but it also has some limitations. As with other qualitative research, findings are specific to this sample and cannot be generalized to the larger population. In addition, although we sought to interview women with a broad range of experiences and our sample included women from multiple geographic regions, participants in this study are not representative of all women with breast cancer. All but one had participated in the WHEL study, a long-term research study evaluating the relationship between dietary factors and breast cancer recurrence, and might have been more interested in health issues than the general population. All participants were White and the majority were college graduates or higher. In addition, participants were diagnosed with early stage breast cancer, which might have influenced their decisions about pregnancy and experiences with breastfeeding. Finally, our findings are largely representative of women without previous breastfeeding experience. Those participants who did have prior breastfeeding experience conveyed more confidence and persistence in their efforts.

Literature on the experiences and needs of breast cancer survivors who are interested in breastfeeding is extremely limited. Women who participated in this qualitative, exploratory study provided in-depth information about their experiences with breastfeeding after breast cancer, including their motivation, expectations, support they received, and challenges they faced. Ten of eleven breast cancer survivors in this study initiated breastfeeding. Participants were overwhelmingly motivated to breastfeed and expected to be able to breastfeed but faced considerable physical and emotional challenges. Participants described problems that are not unique to women with breast cancer, but they appear to have experienced these to an even greater degree. This study revealed a need for improved prenatal education and postpartum support to better prepare women for the challenges of breastfeeding and to provide them with resources to support their efforts. Results of this qualitative analysis indicate that interventions to support the efforts of breast cancer survivors who are interested in breastfeeding are warranted. Larger scale studies to learn more about perceived and actual milk supply and factors influencing the initiation and duration of breastfeeding among breast cancer survivors would aid in the development of such interventions.

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Table 1.1. Characteristics of study participants (N=11).

Characteristic	Breast cancer survivors
Age at diagnosis (years)	
30 or younger	5
31-34	4
35-40	2
Education	
Some college	4
College graduate or higher	7
Ethnicity	
White	11
Cancer stage at diagnosis	
Stage I	3
Stage II	8
Surgery	
Lumpectomy	7
Mastectomy	4
Treatment	
Adjuvant Chemotherapy	9
Radiation	8
Antiestrogen use	4

Table 1.2. Semi-structured interview guide on breastfeeding.

Breastfeeding prior to breast cancer

1. Were any of the children that you had before your breast cancer diagnosis breastfed or fed breast milk? If yes, how many?
2. How old was the (first/second/third…) child when he/she completely stopped breastfeeding or being fed breast milk?
3. How old was the (first/ second/third…) child when he/she was first fed anything besides breast milk?

Breastfeeding as a breast cancer survivor

1. What can you tell me about breastfeeding for women who are breast cancer survivors?
2. Did you talk to your doctor about the possibility of breastfeeding after breast cancer?
    Probes:
    What did your doctor tell you?
3. What were your expectations about breastfeeding?
4. Was breastfeeding a possibility for you?
    Probes:
    Did you try to breastfeed?
    What motivated you to try to breastfeed?
    Can you tell me about your experiences with breastfeeding?
    What was the best part?
    What was the most difficult part?
5. How old was your (first/second/third…) child [born after breast cancer] when he/she completely stopped breastfeeding or being fed breast milk?
6. How old was your (first/second/third…) child [born after breast cancer] when he/she was first fed anything besides breast milk?
7. Where did you go for information about breastfeeding?
8. Where did you go for support?
9. Did you feel supported in your decision about breastfeeding?
    Probes:
    What made you feel most supported?
    Least supported?
10. What would you say to other breast cancer survivors who are interested in breastfeeding?
    Probes:
    What advice would you give them?
11. Is there anything else you would like to tell me about your experiences that we haven't covered?

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Research Paper II (references included):

Physical and mental health correlates of pregnancy following breast cancer.

ABSTRACT

Introduction

The safety of pregnancy after breast cancer is an important issue for many younger breast cancer survivors and their health care providers. Current research does not indicate that pregnancy negatively affects survival, but the “healthy mother bias,” suggesting that survivors who go on to become pregnant are a self-selected healthier group based on their prognosis, has led to cautious interpretation of these findings. No studies have systematically evaluated the potential for this bias.

Methods

This nested case-control study includes 81 younger participants from the Women’s Healthy Eating and Living Study (WHEL) (N=3088). Our sample includes 27 cases who had children after breast cancer and 54 controls, matched on age and stage at diagnosis. We used hierarchical linear modeling to accommodate longitudinal data with individuals nested within matched sets (cases and controls). The primary aim was to evaluate the association between summary scores of health and childbearing after breast cancer. Covariates were added for adjustment and to improve model precision.

Results

Controlling for other variables in the model, physical health scores were not different between cases and controls (B=0.14, p=0.96). Mental health scores were marginally higher among cases (B=6.40, p=0.08), as compared to controls, a difference considered clinically significant.

Conclusion

This preliminary study did not find evidence of a healthy mother bias based on physical health. However, mental health was marginally better among those who had children, indicating that the role of mental health needs evaluation in future research. Larger studies are needed to verify these findings.

INTRODUCTION

A quarter of breast cancer cases in the United States are diagnosed in premenopausal women [1], about 5% of those in women younger than 40 [2]. It is estimated that about 250,000 women under the age of 40 are currently living with breast cancer [3].Younger women have a unique set of concerns when faced with this diagnosis, especially those who may want to have a child. While younger survivors are more likely to be interested in having children, they may worry about whether or not it is safe [4]. One concern is that hormonal changes during pregnancy could have an adverse affect on the course of breast cancer [5, 6]. The majority of research on pregnancy among breast cancer survivors has focused on its potential impact on mortality with most showing no harm and some suggesting it may be protective. [7-11]. Studies have failed to find significantly different outcomes for those who conceive after breast cancer compared to those who do not [10, 12]. A review of the data found no published studies reporting decreased survival associated with subsequent pregnancy [13]. On the contrary, there is evidence that women who become pregnant after breast cancer have a lower relative risk of death compared to those who do not [7, 9, 11, 12, 14]. Women are usually advised to wait at least two to three years before conceiving since this is when recurrence is most likely, particularly for those with ER negative receptor status. However there is minimal evidence that waiting is necessary [9, 15].

While pregnancy after breast cancer appears safe, several researchers have questioned the strength of available evidence. Limitations in current research include small sample sizes, reliance on limited data sources, such as cancer registry data, and selection and recall biases [13, 16, 17]. Key among these is the selection bias termed the “healthy mother bias,” which suggests that breast cancer survivors who go on to become pregnant are a self-selected, healthier group based on their prognosis [11]. Without additional information about the health of survivors who go on to have a child and those who don’t, researchers have been unable to verify this bias or control for potentially important health characteristics in their analyses. Subsequent pregnancies after breast cancer have also not consistently been tracked or reported [6, 13].

The limitations in current research leave younger survivors and their health care providers with insufficient information to make decisions and recommendations about pregnancy. The potential for the healthy mother bias has been described as a key limitation in current research exploring the effect of pregnancy on long-term survival [11]. Our aim was to begin exploring this bias by providing some descriptive, preliminary evidence about the health characteristics of younger survivors who go on to have successful pregnancies after breast cancer as compared to those who do not. This nested case-control study is an evaluation of physical and mental health characteristics among 27 younger breast cancer survivors who had a child after treatment compared to 54 controls (matched on age at diagnosis and cancer stage) who did not. The purpose of this study was to evaluate whether mean health scores were higher among those who had a child, as the healthy mother bias suggests.

PATIENTS AND METHODS

Overview of the WHEL Study

Participants for this study were identified from among participants in the Women’s Healthy Eating and Living (WHEL) study, a multi-site randomized controlled trial to evaluate the effectiveness of a high-vegetable, low-fat diet to reduce recurrence of breast cancer and early death. The WHEL study enrolled 3,088 women diagnosed between the ages of 18 and 70 who had completed initial treatment for early stage breast cancer. According to the accepted staging principles at the time of enrollment [18], approximately 40% of WHEL participants were diagnosed with Stage I (≤1cm), 55% with Stage II, and 5% with Stage IIIA breast cancer within the previous four years. Exclusion criteria included pregnancy at the time of enrollment. Other inclusion and exclusion criteria are extensive and described elsewhere [19].

The WHEL study's primary outcomes were breast cancer recurrence and death from any cause. Outcome assessments were based on self-report every six months and researchers reviewed medical records to provide verification. Participants were followed from the date of study entry until the date of last follow-up or death. Participants who had a recurrence were encouraged to stay in the study.

The WHEL study enrolled participants between 1995 and 2000. The average age at study entry was 53.3 years and 376 (12.2%) of participants were 40 or younger at diagnosis. Over 85% of study participants were White. The results of the study were published in 2007 [20]. Over the mean 7.3-year follow-up, 256 women in the intervention group (16.7%) and 262 in the comparison group (16.9%) experienced an invasive breast cancer event. There were 155 deaths in the intervention group (10.1%) compared to 160 deaths in the comparison group (10.3%). Forty five percent of participants were enrolled 2-4 years post-diagnosis, so WHEL recurrence rates are likely more reflective of later recurrence.

Nested Case-Control Study Inclusion and Exclusion Criteria

This nested case-control study includes 81 WHEL participants; 27 cases who reported having a child during their study participation and 54 matched controls that did not. All participants were diagnosed with Stage I or Stage II invasive breast cancer between the ages of 26 and 40. Cases included only those who became pregnant after their enrollment into the WHEL study, rather than between diagnosis and study entry, to ensure that baseline measures were taken prior to pregnancy. Cancer stage was an exact match and age at diagnosis was the closest match within four years. The mean age difference at diagnosis between cases and controls was just under 12 months and 75% of participants were matched within 18 months. The potential pool of matched controls included those who: 1) had not had a child since their breast cancer diagnosis, 2) had the potential to become pregnant at the time of study entry, 3) completed at least one survey evaluating physical and mental health, and 4) were 40 or younger at diagnosis. Exclusion criteria included: 1) age at menopause is less than/equal to age at diagnosis, 2) postmenopausal at baseline, 3) hysterectomy at baseline, and 4) bilateral oophorectomy at baseline. These criteria were chosen to identify a control group with the potential to become pregnant at study baseline. Recurrence and survival outcomes were not considered as part of the inclusion/exclusion or matching criteria.

Measures

The criterion variables in this analysis, physical health summary score (PHSS) and mental health summary score (MHSS), were taken from the RAND 36 item health survey (SF-36). The survey was administered at five time points over the course of the WHEL study: baseline, 12, 24 or 36 (split sample- 50% at each time point), 48, and 72 months. Questionnaires were administered at baseline and mailed prior to each clinic visit.

Responses from the SF-36 are categorized into four mental health (mental health index, vitality, role limitations due to emotional problems, and social functioning) and physical health (physical functioning, general health perceptions, bodily pain, and role limitations due to physical health problems) sub-scales. The mental and physical health dimensions are consolidated into two separate scores, the MHSS and PHSS. [21]. The SF-36 has been used extensively in other research involving women with breast cancer (alpha=0.75-0.91) [22-24]. Using WHEL study baseline data (N=2,999), coefficient alpha was good to excellent (0.93 SF-36, 0.93 PHSS, and 0.89 MHSS). Responses are scored 0-100, where higher scores equal improved health. A difference of 5 points is considered clinically meaningful [25].

Having a child after breast cancer was the primary predictor of physical and mental health scores. Births were identified through an extensive review of existing WHEL study data, including reported hospitalizations, reported number of children at baseline and exit interviews, and review of written participant notes throughout the study. Two researchers completed an independent review of the data to identify cases and came to a consensus.

Statistical Analyses

We first characterized the sample using descriptive statistics for the entire sample and stratified by case-control group (Table 1). We assessed possible baseline differences between groups using conditional logistic regression to control for matching. We identified potential covariates by evaluating differences in PHSS and MHSS across individual variable categories using bivariate analyses. We added potential covariates in the following order: demographics, lifestyle, reproductive history, and cancer characteristics and treatment. Covariates were added to the initial model based on preliminary analyses of an association with the criterion variable (p<.25). To control for demographic characteristics, race/ethnicity and marital status were retained in all models. Additional significant covariates (p<.10) were added for adjustment and improved precision. We then evaluated the residual distribution of each outcome. With PHSS as the criterion variable, it was necessary to remove four (of a possible 156 data points) extreme outliers to meet the normality assumption required for SAS Proc Mixed. For the MHSS analysis, two data points were removed.

The primary aim of this study was to assess whether or not there was a mean difference in PHSS or MHSS between women who had a child after breast cancer (cases) compared to a matched group who did not (controls). Hierarchical linear modeling (HLM) using SAS Proc Mixed was used to analyze a data structure of participants with repeated measures nested within groups of matched sets (cases and controls). The first analysis evaluated the association between PHSS (level-1 criterion variable) and childbearing after breast cancer (level-2 predictor variable). Model testing was conducted in 2 phases: 1) an unconditional, intercept-only model was developed to calculate the intra-class correlation (ICC) to identify the percent of variability in PHSS between individuals and across time periods and 2) a 3-level means-as-outcome model [26] was developed to accommodate longitudinal data with individuals nested within matched sets. Level-2 covariates were added to the initial model based on preliminary analyses of an association with the primary criterion variable (p<.25). Ages at diagnosis and cancer stage were matching criteria and were not included in the model. The primary criterion variable, demographic variables, and covariates that were significantly associated with the primary criterion variable ($p \leq .10$) were retained in the final model. We followed the same procedure with MHSS as the criterion variable. Due to small sample size, we did not evaluate random effects.

For cases, we used only data collected prior to the probable time of pregnancy based on when the child was born. For controls, we censored available data so that each matched control had data only up to the last point of data collection for the matched case. Among the 54 controls, 33 had 1 data point, 6 had 2 data points, 11 had 3 data points, 3 had 4 data points, and 1 had 5 data point. Among the 27 cases, 13 had 1 data point, 2 had 2 data points, 5 had 3 data points, 6 had 4 data points and 1 had 5 data points. HLM accounts for correlations of observations within subjects and within matched sets, accommodates missing data, and allows inclusion of data from all available measurement periods.

RESULTS

Sample Characteristics

The sample includes 81 participants, 27 cases and 54 controls matched on cancer stage and age at diagnosis (Table 1). Approximately the same percentage of cases and controls were in the WHEL intervention and control arms, with no significant differences in recurrence or survival rates between groups. Though cases and controls were matched on age within 4 years, controls were slightly older at study entry (34.4 years compared to 33.9 years for cases, $p=0.06$). Cases were also marginally significantly more educated ($p=0.06$) and likely to be White ($p=0.09$). There were no significant differences in lifestyle or health behaviors. More cases had no previous children, though this was not statistically significant. Almost twice as many women in the control group had a mastectomy compared to cases.

Physical Health Summary Score (PHSS)

Without controlling for other variables, the mean PHSS across cases (85.5, 95%CI 81.4- 89.6) and controls (81.3, 95%CI 78.2-84.3) were not significantly different (Table 2). The intercept-only model revealed an ICC of .48. Thus, 48% of the variance in PHSS was between-individuals, indicating that values were equally variable within persons across occasions and between persons. With only the primary level-2 predictor variable in the model, the regression coefficient relating childbearing to individual PHSS was positive and not statistically significant (B=4.61, p=0.15) (Table 3). Participant's PHSS was not significantly higher among those survivors who had children compared to those who did not. After adding demographic characteristics and significant covariates (p≤ 0.10) to the model, PHSS was not significantly higher in those who had a child after breast cancer (B=0.14, p=0.96) or those who were White (B=4.87, p=0.15). PHSS was significantly higher in those who were married (B=9.27, p=0.003) and those who were older at menarche (B=2.59, p=0.009). PHHS was significantly lower among those with higher BMI at baseline (B=-0.78, p=0.005) and those with a recurrence during the study (B=-6.23, p=0.04).

Mental Health Summary Score (MHSS)

The mean MHSS for cases (81.7, 95%CI 77.2-86.2) was significantly higher than for controls (72.5, 95%CI 68.9-76.1) prior to controlling for other variables (Table 2). Similarly to the PHSS model, the intercept only model for MHSS indicated that values were equally variable within persons across occasions and between persons (ICC= 0.49). With only the primary predictor variable in the model, the regression coefficient relating childbearing to individual MHSS was positive and statistically significant (B=7.79, p=0.04) (Table 4). After adding demographic characteristics and significant covariates ($p \leq 0.10$), MHSS was marginally significantly higher in those who had a child after breast cancer (B=6.40, p=0.08) and those who were married (B=7.14, p=0.08). MHSS did not vary by race/ethnicity (B=-4.36, p=0.33). MHSS was significantly lower among those with higher BMI (B=-0.82, p=0.02).

DISCUSSION

The healthy mother bias is a selection bias that may result when women who have better prognoses go on to have successful pregnancies. In an attempt to account for this possibility, survival analyses have controlled for age and cancer stage at diagnosis. However, this may inadequately address potential health differences between groups, including aspects of physical and mental health. Among WHEL study participants, for example, physical health summary scores significantly predict breast cancer recurrence [27]. We conducted this study to further explore the physical and mental health of younger breast cancer survivors who had successful pregnancies compared to a group who did not, matched on cancer stage and age at diagnosis. Multi-level analysis did not identify a difference in physical health scores between those who became pregnant and those who did not. This indicates the lack of a healthy mother bias based on physical health among our sample. However, we did find a marginal difference in mental health; those who went on to become pregnant appeared to have higher scores. While mental health has not been traditionally identified as a component of the healthy mother bias, it is possible that mental health is part of a “healthy mother” and needs to be considered.

Unlike previous studies, we compared cases and controls across several variables and included key covariates in a multi-level model. Results of conditional multivariate modeling showed that the PHSS between these groups were very similar

(Table 3). However, women who had children after breast cancer had marginally higher mental health scores prior to pregnancy than those who did not (Table 4). After controlling for other variables in the model, the MHSS of cases was about 6 points higher (B=6.40, p=0.08) than the scores of a control with an average value of ethnicity, marital status, and BMI (Table 4). While the conditional model did not find a statistically significant difference in MHSS, a difference of 5 points is considered clinically meaningful [25]. Though this study cannot determine causality, it is possible that those women with better mental health, including lower levels of stress and anxiety, improved social and emotional functioning, better support, and higher energy, were more likely to have successful pregnancies. Research on the link between psychosocial functioning and fertility is mixed [28-30], with some studies reporting an association between psychosocial variables and reproductive status [e.g. 31, 32] and other studies reporting no link [e.g. 33, 34]. It is also possible that those with improved mental health would be more likely to desire children based on factors such as an expectation of long-term survival, a strong family life, and the availability of a support system. Other researchers have found that some women who survive breast cancer experience an intensified desire for children in order to feel normal and have the positive experience of having a child. Women's negative motivations may also be strengthened by fears related to health and the long-term well being of themselves and their children [35-37]. Adverse treatment outcomes, such as premature menopause, infertility and fertility concerns, have also been associated with poorer QOL scores [38-40]. It is possible that those who had difficulties with fertility had lower scores, though we were unable to evaluate this in the current study due to lack of data on attempted pregnancy. Future studies evaluating pregnancy outcomes should include an assessment of pregnancy intentions and factors influencing those decisions to better understand the differences between women who have children after breast cancer and those who do not.

QOL, as measured by the SF-36, encompasses self-reported physical and psychosocial well-being within the context of one's experiences with disease, but it is not age, disease or treatment specific [41]. QOL scores among cancer survivors have not previously been explored as indicators of physical and mental health prior to pregnancy. One study explored QOL after pregnancy among a small group of younger breast cancer survivors, but found no significant differences between those who had children and those who did not [42]. The current study found relatively high mean scores in both the physical (81.3, 85.5) and mental health (72.5, 81.7) domains (Table 2), with controls having lower overall scores. In previous analyses with WHEL participants (N=2,582), QOL scores were generally high and comparable to the norms for women in the general population and others with breast cancer [25].

While there were no significant differences in demographics or lifestyle between cases and controls, cases were slightly younger, more educated and more likely to be White (Table 1). Health behavior choices that would likely influence overall health, such as diet and tobacco use, were similar between groups. Also, while the percentage of women with radiation and chemotherapy was similar across groups, a significantly larger portion of cases had a lumpectomy rather than a mastectomy. This cannot be explained by a difference in cancer stage, since this was a matching criterion. There are many potential reasons for this disparity, including medical history, physician recommendations, and personal choices. Further study is needed to identify factors that may influence cancer treatment and surgical choices among younger women.

This study is the first to systematically evaluate differences in physical and mental health among a group of young breast cancer survivors who had children after their diagnosis compared to those who did not. Typical of studies focused on pregnancy after breast cancer, the primary limitation of this study is small sample size, which restricted our ability to detect statistically significant differences between groups. Also, because of the small sample of young participants, we were not able to match on exact age and those in the case group are slightly, though not significantly, younger than controls. We had a smaller amount of data for our analyses because we restricted our dataset to pre-pregnancy time points for each matched set. However, the multilevel modeling technique allows for unbalanced data sets and missing data. Although extensive effort went into identifying cases, it is possible that some women were miscategorized. Finally, the WHEL study did not collect participant's full reproductive history, including attempted pregnancy or pregnancies that were terminated spontaneously or therapeutically. Therefore, we could not evaluate attempted pregnancy in our control group or control for reproductive history in our analyses. That issue is beyond the scope of this study, but is important for future investigation.

Younger women represent a minority of breast cancer cases, but the experience of having breast cancer does not appear to interfere with women's motivations toward childbirth [35] and many younger survivors are interested in having children [4, 43, 44]. Those who want to have children need to know the potential risks. Information to help younger breast cancer survivors make important reproductive decisions is sparse and patient-provider communication on these issues is limited [4, 45-47]. Current research does not indicate that women should avoid pregnancy after breast cancer. However, selection and recall biases, such as the healthy mother bias, have resulted in cautious interpretation of these findings. This is the first study to investigate this bias. While our small sample size restricted our ability to detect statistical significance, physical health scores were very similar between groups and we found no evidence of a healthy mother bias. However, mental health, while not traditionally discussed in the context of this bias, was marginally better among women who had children. Mental health is an important component of overall health and our findings indicate that its relationship to post-cancer pregnancy should be evaluated in future studies. Evaluation of the association between mental health, attempted pregnancy, and pregnancy outcomes would further clarify these findings.

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Table 2.1. Descriptive characteristics at baseline by case-control status (N=81).

	Cases (n=27)		Controls (n=54)		p-value [a]
	N (%)	Mean (SD)	N (%)	Mean (SD)	
WHEL study participation					0.75
Intervention	12 (44.4)		22 (40.7)		
Control	15 (55.6)		32 (59.3)		
Demographics					
Age at study entry (Mean, SD)		33.9 (3.8)		34.4 (3.2)	0.06
Age at diagnosis					1.00
30-34	20 (74.1)		40 (74.1)		
35-40	7 (25.9)		14 (25.9)		
Education level					0.06
Less than college grad	7 (25.9)		26 (48.1)		
College grad or higher	20 (74.1)		28 (51.9)		
Race/ethnicity					0.09
White, non-Hispanic	24 (88.9)		40 (74.1)		
Other	3 (11.1)		14 (25.9)		
Marital status					0.13
Married	23 (85.2)		38 (70.4)		
Single/ Other	4 (14.8)		16 (29.6)		
Health insurance					1.00
Private/ Military	27 (100)		52 (96.3)		
None/ Unknown	-----		2 (3.7)		
Lifestyle					
BMI (Mean, SD)		23.4 (3.8)		24.8 (5.9)	0.28
Dietary guidelines met [b]					0.87
Meets 0-1		19 (70.4)		37 (68.5)	
Meets 2-3		8 (29.6)		17 (31.5)	
Physical activity [c] (Mean, SD)		973.2 (896.0)		1030.8 (1110.3)	0.82
Smoking					0.21
Current	-----			-----	
Ever	10 (37.0)			12 (22.2)	
Never/Unknown	17 (63.0)			42 (77.8)	
Reproductive history					
No. live births at study entry					0.22
0	14 (51.9)		21 (38.9)		
1 or more	13 (48.1)		33 (61.1)		
No. pregnancies at study entry					0.57
0	10 (37.0)		17 (31.5)		
1 or more	17 (62.9)		37 (68.6)		

Table 2.1: Descriptive characteristics at baseline by case-control status, Continued.

	Cases (n=27)		Controls (n=54)		p-value [a]
	N (%)	Mean (SD)	N (%)	Mean (SD)	
Age at first live birth (Mean, SD)		28.6 (5.1)		26.5 (4.2)	0.08
Age at menarche (Mean, SD)		13.0 (1.6)		12.6 (1.2)	0.13
Cancer characteristics and treatment					
Mother with breast cancer	6 (22.2)		5 (9.3)		0.10
Cancer stage at diagnosis					1.00
Stage I	6 (22.2)		12 (22.2)		
Stage II	21 (77.8)		42 (77.8)		
Receptor status					0.48
ER+/PR+ and ER+/PR-	20 (80.0)		36 (69.2)		
ER-/ PR-	5 (20.0)		16 (30.8)		
Radiation	19 (70.4)		29 (53.7)		0.14
Chemotherapy	25 (92.6)		52 (96.3)		0.49
Lumpectomy	19 (70.4)		21 (38.9)		0.01
Mastectomy	8 (29.6)		33 (61.1)		0.01
Antiestrogen use					0.32
Never used at baseline	18 (69.2)		30 (56.6)		
Previous/current use	8 (30.8)		23 (43.4)		
Any recurrence	8 (29.6)		15 (27.8)		0.86
Survival	24(88.9)		47 (87.0)		0.80

[a] Conditional logistic regression, adjusted for matching

[b] Based on National Cancer Institute daily dietary recommendations. 1 point for each recommendation met: ≤30% energy from fat, ≥20g fiber, ≥ 5 servings fruit/vegetables

[c] Metabolic equivalents per week

Table 2.2. Mean physical health summary score (n=152) and mental health summary score (n=154) across observations.

Physical health summary score [a]

Case			Control		
Mean	SE	95% CI	Mean	SE	95% CI
85.49	2.08	81.38-89.60	81.27	1.53	78.24-84.30

Mental health summary score [a]

Case			Control		
Mean	SE	95% CI	Mean	SE	95% CI
81.70	2.29	77.19-86.22	72.46	1.83	68.85-76.07

[a] Scores range from 0-100, where higher scores equal improved health

Table 2.3. Results of fitting models to physical health summary score data (n=152).

Variable	**Unconditional Model** Estimate (SE)	p-value	**Conditional Univariate Model** Estimate (SE)	p-value	**Conditional Multivariate Model [a]** Estimate (SE)	p-value
Intercept	82.83 (1.52)	<0.001	81.19 (1.88)	<0.001	82.58 (1.67)	<0.001
Case/Control			4.61 (3.14)	0.15	0.14 (2.74)	0.96
Ethnicity (Ref= Non-White)					4.87 (3.38)	0.15
Marital status (Ref= Not married)					9.27 (3.03)	<0.01
BMI					-0.78 (0.27)	<0.01
Age menarche					2.59 (0.98)	<0.01
Recurrence (Ref= No recurrence)					-6.23 (3.01)	0.04

[a] All level-2 covariates are centered on the sample mean except case/control status. The intercept represents a control with an average value of ethnicity, marital status, BMI, age at menarche, recurrence.

Table 2.4. Results of fitting models to mental health summary score data (n=154).

Variable	**Unconditional Model** Estimate (SE)	p-value	**Conditional Univariate Model** Estimate (SE)	p-value	**Conditional Multivariate Model** [a] Estimate (SE)	p-value
Intercept	75.31 (1.84)	<0.001	72.58 (2.23)	<0.001	73.17 (2.14)	<0.001
Case/Control			7.79 (3.74)	0.04	6.40 (3.67)	0.08
Ethnicity (Ref= Non-White)					-4.36 (4.48)	0.33
Marital status (Ref= Not married)					7.14 (4.02)	0.08
BMI					-0.82 (0.35)	0.02

[a] All level-2 covariates are centered on the sample mean except case/control status. The intercept represents a control with an average value of ethnicity, marital status and BMI.

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Research Paper III (references included)

Depressive symptoms among younger breast cancer survivors:

The importance of reproductive concerns.

ABSTRACT

Purpose

Breast cancer diagnosis and treatment can have a negative impact on fertility in premenopausal women and can change reproductive planning. This study investigates whether concerns about reproduction after breast cancer treatment were a significant contributor to long-term depressive symptoms.

Patients and Methods

At the completion of the Women's Healthy Eating and Living (WHEL) randomized trial, 63% of the eligible 2364 participants were re-enrolled in a survivorship study. This included 131 women diagnosed with early-stage breast cancer at age 40 or younger. Depressive symptoms were monitored at 5 time-points throughout the WHEL study's 7.3 years of follow-up as well as in the survivorship study. Recall of reproductive concerns after treatment was collected in the survivorship study, approximately 10 years post-diagnosis. Multi-level modeling was used to evaluate whether mean long-term depressive symptoms differed as a function of reproductive concerns and significant covariates.

Results

Multi-level modeling identified higher reproductive concerns as an independent predictor of consistent depressive symptoms after controlling for both social support and physical health (B= 0.02, SE= 0.01, p=0.04). In bivariate analyses, being nulliparous at diagnosis and reporting treatment-related ovarian damage were both strongly associated with higher reproductive concerns and with depressive symptoms.

Conclusion

Reported reproductive concerns after breast cancer treatment were a significant contributor to consistent depressive symptoms. Younger survivors would benefit from additional information and support related to reproductive issues.

INTRODUCTION

In the United States, a quarter of breast cancer cases are diagnosed in premenopausal women [1] and about 5% of cases are diagnosed in women younger than 40 [2]. Advances in early detection and treatment have resulted in greater long-term survival among younger women. The 5-year survival rate for women diagnosed at 40 or younger is 82%, slightly lower than the 89% survival rate for women diagnosed at 40-74 years of age [3]. While adjuvant therapy has resulted in improved survival, it may also lead to amenorrhea, earlier than expected menopause, and difficulties with fertility [4-7].

Because they are at a different life stage, younger women diagnosed with breast cancer have different survival concerns than their older counterparts. These include anxiety about their ability to have children, apprehension about raising children as a cancer survivor, premature menopause and associated loss of fertility, early ovarian decline and related symptoms, and concern about how pregnancy may affect their risk of recurrence [8-11]. Younger survivors also appear to have greater psychosocial needs as compared to older survivors, particularly with respect to dealing with the physical impact of treatment and associated gynecological and reproductive consequences [12]. The need for support related to fertility and early menopause has been identified as very important to younger women [8, 12-14]. Psychological concerns can last for years after treatment and have a significant negative impact on quality of life [13, 15-18].

Young women newly diagnosed with breast cancer are also more likely to experience anxiety and distress and to need greater social support [8, 19-22]. Studies have found that the association between age and symptoms diminishes several months after diagnosis, indicating that young women adapt well over time [23, 24]. However, a study involving early stage breast cancer survivors found that young age was a risk factor for depression and anxiety 2-5 years after diagnosis [22]. In addition, clinically important depression and anxiety were higher in the first year after diagnosis (50%) than five years later (15%) [22]. Although study results are inconclusive, depression may be an important psychosocial risk factor for progression of cancer and cancer mortality [25-27]. While women may not be diagnosed with major depression, depressive symptoms can significantly lower quality of life and prevent women from returning to their previous level of functioning [12, 28].

Following a biopsychosocial model [29, 30], researchers have incorporated biological, psychological and social variables in predicting levels of distress and depression among breast cancer survivors [19, 22, 31, 32]. This systems approach provides a framework for understanding how varying factors may contribute to depressive symptoms among young breast cancer survivors. Studies involving breast cancer patients have found a range of risk factors for depressive symptoms, including cancer treatment characteristics [33-36], health behaviors [37], physical functioning [33, 36], and psychosocial functioning [19, 22, 31]. There is a strong association between prevalence of depression and physical health symptoms of pain and fatigue [33, 38, 39]. Lack of social support and an intimate confiding relationship are also significantly associated with depression and anxiety [22, 40-42]. Among younger women recently diagnosed with breast cancer, those with higher physical health symptoms of pain and lower emotional support are at greater risk of experiencing depressive symptoms [19]. Psychological distress can continue for years after diagnosis and treatment, but five years after diagnosis, psychosocial characteristics, rather than disease or treatment characteristics, appear to be important predictors of depression [22].

While researchers have identified a need for support related to reproduction and fertility among younger cancer survivors, it is not clear if these issues are associated with depressive symptoms. In this study, we take advantage of a large cohort of breast cancer survivors who participated in a randomized trial. The trial included premenopausal women and measured depression at multiple time points over the first 10 years after diagnosis [43]. Participants were re-enrolled into the survivorship study, where those diagnosed at age 40 or younger were surveyed on their recall of reproductive concerns. The primary aim of this study is to assess whether level of reproductive concerns after treatment is associated with long-term depressive symptoms among breast cancer survivors diagnosed at age 40 or younger.

PARTICIPANTS AND METHODS

Participants

Women's Healthy Eating and Living (WHEL) Study

Participants in the current study previously participated in the Women's Healthy Eating and Living (WHEL) study, a multi-site randomized controlled trial to evaluate the effectiveness of a high-vegetable, low-fat diet to reduce recurrence of breast cancer and early death. Participants included those diagnosed with Stage I (≥1cm), IIA or B, and IIIA or C invasive breast cancer within the previous four years, using the AJCC VI classification system.[44] . Approximately 39% of the sample was diagnosed with Stage I breast cancer, 45% with Stage II, and 16% with Stage III disease. Participants diagnosed between 1991 and 2000 were enrolled between

1995 and 2000. The average age at study entry was 53.3 years and 376 (12.2%) of participants were 40 or younger at diagnosis. Minimal information about reproductive history was assessed at the time of study entry. Women who were pregnant at enrollment were excluded. Other inclusion and exclusion criteria for WHEL are extensive and described elsewhere [43].

WHEL Survivorship Study

After the WHEL study concluded, researchers re-enrolled surviving volunteers into a continuation study focused on predictors of longer term survivorship. All data were collected during an annual telephone interview and included questions about additional breast cancer events, other health conditions, and a 24-hour dietary recall. Of the original 3088 women, 2364 were eligible for the survivorship study (582 breast cancer recurrences, 68 non-breast cancer deaths, 24 lost to follow up and 50 withdrew from study). The present study considered only the 1495 participants who had enrolled by April 1 2009 (63% of eligible). This included 131 women who were diagnosed with breast cancer at age 40 or younger and these are the subject of this study.

Measurement

Depressive symptoms

The WHEL study used the 8-item Center for Epidemiologic Studies Depression Scale screening form (CES-Dsf) to measure depressive symptoms [45]. This self-report scale was measured at baseline, 1 year, 2 or 3 years (split sample-50% at each time point), 4 years and 6 years in the WHEL study as well as in the first year of enrollment of the survivorship cohort. The instrument was developed originally to identify people who may have a mood disorder [45]. The raw score is log transformed and a higher score indicates a higher level of depressive symptoms. The score indicates a spectrum of depressive symptoms, rather than a dichotomous indicator of depression. Good reliability of the scale with WHEL participants has been reported (alpha=0.73) [31]. The measure has also recently been used to assess depression in studies of hormone replacement therapy and quality of life [46].

Reproductive concerns

The Reproductive Concerns Scale (RCS) is a 14 item-scale developed to assess concerns among cancer survivors who may have experienced loss or impairment of their reproductive ability due to cancer and/or cancer treatment [47]. The RCS assesses: Loss of control over reproductive future, discontent with number of children, inability to talk openly about fertility, illness affected ability to have children, sadness about inability to have children, frustration that ability to have children was affected, anger that ability to have children was affected, mourning over the loss of ability to have children, concerns related to having children, guilt about reproductive problems, lower satisfaction w/life because of this problem, feeling like less of a woman, blaming self for reproductive problems, and blaming others for reproductive problems. A total RCS score is produced by summing responses to the 14 items, with a range of 0-56. A higher score indicates reproductive concerns. In a sample of younger cancer survivors, the scale had an internal consistency of 0.91 (N=231)[47]. In our study, internal consistency was 0.81 (N=131).

Potential covariates

Potential covariates were identified based on a review of the literature and, following the broad approach of the biopsychosocial model [30], include cancer-related characteristics, health behavior/physical health, and psychosocial characteristics. Based on hypotheses about the potential significance of reproductive history, we also included several of these characteristics.

Demographics and Cancer Characteristics and Treatment

Prior to entry into the WHEL study, participants provided demographic information and details of their cancer diagnosis, which were verified by a medical record review by two oncologists [43]. A reproductive history and cancer history in the family were also collected at baseline.

Lifestyle Variables

At each major study time-point, participants were weighed and completed a lifestyles questionnaire that included smoking history, a validated 9-item Physical activity (PA) questionnaire, and a set of 4 24 hour dietary recalls[43]. Body Mass Index (BMI) was calculated as weight divided by height squared (kg/ m^2). Physical activity reports were converted to metabolic equivalents (METs) per week. Low PA is less than 300 METs per week, medium PA is between 300 and 999.9 METs per week and high PA is 1000 METs per week or greater [48]. In this study, we scored participants by their level of adherence to each of the published national dietary guidelines (i.e. 1 point each for $\leq$ 30% energy from fat, $\geq$ 20 grams of fiber, and $\geq$ 5 servings of fruit/vegetables for a score that ranged from 0 to 3).

Psychosocial and physical health characteristics

The Medical Outcomes Study Social Support measure includes nine items covering emotional and informational support, affection, tangible support and positive interaction (range 0-45, α=.93) [49]. Life events were assessed using nine items from the Alameda County Study (range 0-9), including stressful life events such as deaths and financial problems [50]. We did not include the RAND-36 mental health summary score because there is a strong inverse correlation between this and CES-Dsf score [31].

The physical health summary score (PHSS) is a sub-scale of the RAND-36 Item Health Survey (RAND-36). This self-report measure is composed of 4 subscales: physical functioning, general health perceptions, bodily pain, and role limitations due to physical health problems (range 0-100, $\alpha=0.93$ with WHEL data) [51]. This is a continuous variable and responses are scored 0-100, where higher scores equal improved health.

Reproductive characteristics

The WHEL study collected self-report data about previous pregnancies, live births, menopausal status, hysterectomy and oophorectomy at the time of study entry. During the survivorship study, interviewers asked participants about live births both before and after their cancer diagnosis, whether they wanted to have (more) children before and after cancer, pregnancy attempt/avoidance after treatment, whether they based cancer treatment decisions on the desire to preserve their fertility, whether they were told their ovaries were damaged after treatment, and their experience with irregular periods either during or after treatment.

Statistical Analysis

Univariate analysis of the reproductive concerns scale scores revealed a significantly skewed distribution toward lower scores, including a score of zero. We log-transformed this score so that the data approximated a normal distribution. After characterizing the sample using descriptive statistics, we compared the mean and standard deviation of CES-Dsf scores across reproductive characteristics. We calculated the bivariate association between CES-Dsf scores across all study points and all potential covariates (correlations for continuous variables and ANOVA for categorical variables).

We developed an intercept-only (unconditional) model to calculate the intraclass correlation coefficient (ICC), which identifies the percent of variability in the scores between individuals (level-2) and across time periods (level-1). We then developed an unconditional growth model to evaluate the association between depressive symptoms and time and a conditional growth model with reproductive concerns as the primary predictor. We evaluated the slope to determine whether scores of depressive symptoms reflected an increase, decrease, or stable pattern. After determining that depressive symptoms did not change over time in the unconditional or conditional models, we proceeded with developing a model to predict mean depressive symptoms [52]. We first developed a conditional model to evaluate whether level of depressive symptoms was predicted by level of reproductive concerns (level-2 predictor). We added potential covariates in the following order: demographics, cancer characteristics and treatment, health behavior/physical health, reproductive characteristics, WHEL study participation, and psychosocial characteristics. Continuous level-2 covariates were grand mean centered to provide an average score across participants. We used a step-up approach to model building. Level-2 covariates were added to the initial model based on preliminary analyses of an association with the criterion variable ($p<.25$). The primary predictor variable and covariates that were significantly associated with the criterion variable ($p\leq.05$) were retained in the final model. We evaluated potential interactions between RCS and covariates in the final model and also assessed how much the variance component for each model was reduced as covariates were added to develop the final model. In exploratory analyses, we developed a conditional model with having children (ever and after diagnosis) as the primary predictor. Finally, we explored the construct measured by the RCS by conducting chi-square tests to evaluate whether several reproductive characteristics were associated with high vs. low RCS scores (Table 3).

RESULTS

Participant Characteristics

We compared the 131 participants in the survivorship study with the remainder of the original WHEL sample of women diagnosed at 40 years or younger (Table 1). There was little difference in enrollment across socio-demographic characteristics with the exception of race/ethnicity where participation was higher in non-Hispanic White compared to other populations ($p \leq 0.05$). The average age at diagnosis for young survivorship participants was 36.7 years, with a quarter diagnosed at younger than 35 years of age. Average time between cancer diagnosis and WHEL study entry was about 1.5 years. Most participants were married (76%), White (88%) and had a college degree or higher (62%). Eighty seven percent of participants were diagnosed at stage I, IIA or IIB, the vast majority received chemotherapy (89%), and most had estrogen receptor positive status (70%). Baseline scores of depressive symptoms were similar across groups. Among young survivorship participants, depressive symptoms were moderate (CES-Dsf=0.06, SD=0.13) and 18% met a clinically elevated level.

WHEL participants who had more serious disease (higher grade disease, chemotherapy treatment) were more likely to have an event and to be ineligible for the survivorship study. Both cancer stage and chemotherapy treatment were marginally significantly different ($p \leq 0.10$) between those enrolled in the survivorship study and those not enrolled.

Reproductive History and Depressive Symptoms

Sixty eight percent of this young survivor cohort had at least one live birth before their breast cancer diagnosis and 12% had at least one after their diagnosis. Participants had a median of 2 children at the time of the survivorship study. Almost half of participants reported possibly wanting children prior to their cancer diagnosis, but after diagnosis, the percentage dropped by almost half to 28%. A qualitative question about childbearing after cancer revealed a range of feelings, including: delaying pregnancy until after treatment ended, devastation and fear about not being able to have a child, resigning themselves to not having children, considering adoption, and being less likely to have children due to fear of recurrence, personal survival and possibly not being alive to raise children. More than half of participants reported that they either tried to become pregnant or did not avoid pregnancy after treatment. Only 12% reported that fertility preservation was a factor in their treatment decisions. Seventeen percent of participants were told by a physician that their treatment had resulted in ovarian damage and about three-quarters reported irregular periods either during or after their treatment. About 20% reported being postmenopausal at the time of WHEL study entry (Table 2).

Of the demographic characteristics, only marital status was significantly associated with depressive symptoms ($p<.001$), with those who were married having lower scores (data not shown). Three lifestyle variables (adherence to dietary recommendations, physical activity level and weight) were significantly associated with depressive symptoms ($p \leq 0.05$). There were few smokers in the study and a history of ever smoking was not associated (p=0.60). Later cancer stage at diagnosis (p=0.001) and ER positive receptor status (p<0.01) were significantly associated with higher depressive symptoms, but other cancer-related characteristics were not. WHEL study participation level and time between diagnosis and study entry were not significant. Higher social support and lower number of total life events were significantly associated with lower depressive symptoms (p<0.0001).

Higher levels on the reproductive concerns scale were associated with depressive symptoms (p=.0002) as were the following reproductive characteristics: not having children, being nulliparous at the time of diagnosis, not avoiding pregnancy after diagnosis, treatment-related ovarian damage, and menopausal status (all with p<0.01) (Table 2).

Reproductive Concerns Scale

In Table 3 we report associations between the reproductive concerns scale and other recalled reproductive characteristics and choices. Women in the high RCS group were more likely to report making treatment decisions based on fertility preservation and treatment-related ovarian damage. While those in the high RCS group were three times more likely to report that fertility was a factor in their treatment decisions, the proportion who mentioned this was only 16% in this high RCS group. A much larger proportion of those in the high RCS group had no children at the time of diagnosis (45% vs. 15%), wanted children before their diagnosis (66% vs. 26%), and wanted children after their diagnosis (37% vs. 15%). Finally about 18% of those in the high RCS group had a child after their diagnosis, compared to 4% of those in the low RCS group. Being diagnosed at younger than age 35 and reporting irregular periods during or after treatment were not significantly associated with level of reproductive concerns (Table 3).

Depressive Symptoms

Without controlling for other variables, mean CES-Dsf score for all participants across all time points was 0.06 (SE=0.01). The unconditional means model revealed that 41% of the variance in depressive symptoms scores was between-individuals. Initial analysis also indicated that depressive symptom scores were stable over time. Comparing the unconditional means model to the unconditional growth model, time did not explain a significant amount of variation in depressive symptoms ($p=0.19$). After adding the primary level-2 predictor to the model, the regression coefficient relating RCS to depressive symptoms was positive and statistically significant ($B=0.02$, $p=0.01$). There was not a significant interaction between time and RCS ($p=0.99$), so time was eliminated from the model and we continued developing a conditional means model. After adding significant covariates ($p\leq 0.10$) to the model, CES-Dsf was significantly higher in those with a higher RCS score ($B= 0.02$, $p=0.04$) and lower in those with higher scores of physical health ($B=-0.002$, $p<0.0001$) and those with higher scores of social support ($B=-0.01$, $p<0.0001$). There was not a significant interaction between RCS and social support. However, we identified a significant interaction between RCS and physical health, where physical health moderated the relationship between RCS and depressive symptoms. A closer investigation of the interaction revealed that the relationship between RCS and depression was minimally changed with the interaction term in the model, and the slopes of the RCS-depression association were very similar across physical health levels, indicating that there was not a clinically meaningful effect. Evaluation of random effects provided information about the proportion of reduction in error (PRE) [52]by adding each covariate to the final model: 5% of the explainable variation in individual depressive symptoms was explained by RCS, 40% by social support, and 12% by physical health (Table 4).

Before controlling for covariates, we found that women who did not have children had mean depressive symptoms scores 0.04 points greater than those with children (SE=.02, p=.01). However, this variable became insignificant after adding other variables to the model. There was no significant difference between women who had a child after breast cancer compared to those who did not (B=-.01, SE=0.03, p=0.80, without controlling for covariates).

DISCUSSION

With the rising number of reproductive age cancer survivors [53], researchers have recently begun to address important issues related to reproduction, infertility and psychosocial aspects of women's survivorship experiences. Almost 20% of participants in this study had clinically elevated levels of depressive symptoms at study entry [45]. CES-Dsf scores averaged 0.056 overall and did not change significantly over time. Higher levels of depressive symptoms were predicted by higher levels of reproductive concern. Depressive symptoms scores remained significantly higher even after controlling for social support and physical health. While we cannot determine causality, these finding indicate that younger breast cancer survivors who are concerned about reproduction have poorer long-term well-being.

In the first year after early-stage breast cancer diagnosis, the prevalence of depressive symptoms and/or anxiety is twice that of the general female population but this difference diminishes after the first year [22]. In the years following, personal and psychosocial characteristics, rather than disease or treatment characteristics, appear to be important predictors of clinically elevated depressive symptoms and anxiety [22, 31, 54]. Younger women diagnosed with breast cancer are at greater risk for short- and long-term depressive symptoms [19, 21, 22, 36, 55]. Depression and distress negatively impact on quality of life [12, 28], including family life [56-58], and may increase risk for progression of cancer and cancer mortality [25-27]. Symptoms of depression may be under-recognized, but are critical to address [59].

Following a systems perspective [30], we explored the association between depressive symptoms and a wide range of characteristics, including cancer characteristics, health behaviors, physical functioning and psychosocial functioning. Our findings indicate that younger breast cancer survivors with higher levels of reproductive concern, lower levels of social support and poorer physical functioning are at greater risk for elevated depressive symptoms. Identifying these risk factors is an important step toward addressing unmet psychosocial needs. Younger breast cancer survivors appear to have a greater need for social support, which is critical in maintaining long-term physical and mental well-being [20]. As in previous research, our findings indicate that social support is a significant predictor of depressive symptoms in younger breast cancer survivors [8, 19-22]. In the final multivariate model, social support described the greatest percentage of explainable variation in CES-Dsf scores (40%). The lack of an interaction between social support and RCS indicates that reproductive concern is uniquely associated with depression, regardless of support from a spouse or significant other. Our findings are also consistent with other research suggesting that younger breast cancer survivors need support related to reproductive issues [8, 12-14]. Interventions, such as peer-based support groups, focused on providing information and support related to fertility and reproduction would address both reproductive concerns and the need for social support. Another possible avenue to meet the needs of younger breast cancer survivors is through improved patient-provider communication. Research indicates that the informational needs of young women regarding fertility and menopause after breast cancer treatment are currently not being met [60]. In one study, only 57% of participants reported receiving information about infertility from their health care provider[10]. There may also be discordance between younger women's concerns about fertility issues and how this issue is addressed by their doctors [60, 61]. Some women feel that their concerns are not taken seriously by their health care providers [8].

We conducted an exploratory analysis of the association between depressive symptoms and having children. As in another study, multivariate analysis found no significant difference in depressive symptoms among those who had children compared to those who did not [19]. Level of depressive symptoms was also not significantly associated with having a child after breast cancer. Another small study found no significant differences in QOL or psychosocial characteristics among those who became pregnant after breast cancer compared with those who did not [62]. However, the authors reported that women who had children after breast cancer reported that their families provided the greatest satisfaction and were important to quality of life. Similarly, in preliminary qualitative interviews for this study, participants who had children before or after cancer overwhelmingly reported that their family life and children were the most satisfying and important aspects of their lives. Further studies with larger sample sizes are needed to adequately address these questions.

A significant strength of this study is the use of longitudinal depressive symptoms data collected at up to six time points over approximately 10 years of survivorship. Following the biopsychosocial model, we were also able to incorporate a broad range of potential covariates collected during the original WHEL study. However, our sample size required that we limit covariates included in the multilevel model to those of primary interest and important predictors of depression in previous studies. Also, the sample characteristics limit the findings of this study to long-term breast cancer survivors diagnosed at age 40 or younger. While not remaining significant in the final model, preliminary analyses indicated that it may be important to explore the association between depressive symptoms and other reproductive characteristics, such as having children before and after diagnosis, with larger sample sizes. Future studies with sufficient power could also explore a larger number of potentially important psychosocial variables associated with depression among younger cancer survivors. While sample size limited our power to detect significant effects, our statistical approach allowed us to include data across multiple time points, including participants with missing data. Because this measure of social support was taken at the time of WHEL study entry (≤ 4 years after diagnosis), we are unable to discuss how level of social support may have changed over time. Future studies evaluating level and type of social support and depression across multiple time points could provide important information to further address this issue.

Because the WHEL study collected limited data on reproductive history at baseline, we asked participants a series of questions about fertility and reproduction after breast cancer, including the RCS, during the follow-up survivorship study. Retrospective report of reproductive concerns introduces potential for biases based on recall and memory. Although we asked women to report on their feelings shortly after their breast cancer treatment ended, it is possible that women did not recall their feelings or that their answers were impacted by their experiences and changes in level of concern over time. Research suggests that women's feelings about fertility change over time [63] and concerns may increase as they move farther away from diagnosis [64]. Chi-square analysis (Table 3) provided additional details about the measurement of reproductive concerns in this study. To be valid, an assessment tool should show a relationship between reproductive concerns and several key variables.. We found the expected association across the key variables, including greater likelihood of being nulliparous at the time of diagnosis, wanting children before and after their diagnosis, reporting that fertility was a factor in their treatment decisions, and attempting pregnancy after diagnosis. However, the RCS scale may need to be refined, since there were several items on the scale that were not often reported.

Breast cancer treatment can increase the risk of early menopause and result in difficulties with fertility. This is a major issue affecting many young breast cancer survivors who have not finished growing their families. While research is still limited, it appears that infertility and concerns about reproductive issues after cancer treatment have a negative impact on quality of life [47, 65]. Participants in this study had moderate levels of depressive symptoms (CES-Dsf= 0.06, SD=0.01) that did not increase or decrease over time. Those who had greater reproductive concerns experienced higher levels of depressive symptoms over the long-term. While fertility may not be the primary concern at the time of diagnosis and treatment, it may become more important afterward [63, 64]. Further research is needed to determine how reproductive concerns change over time and whether there is a causal association between these concerns and overall well-being. Cancer survivors interested in having children would benefit from additional information and support [11, 66]. Health care providers can play an important role in filling the need for support and information after initial treatment ends and well into survivorship. Additional longitudinal studies would provide valuable information about how reproductive concerns change over time, the influence of experiences with infertility and pregnancy, and how these factors are related to survivors' overall well-being. This information is needed to identify groups at highest risk for depressive symptoms and to develop effective interventions to address their needs.

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Table 3.1. Comparison of sample characteristics and enrollment.

	No. (%) enrolled	No. (%) not enrolled
Total Enrollment (diagnosed ≤ 40 years)	131	245
Depressive Symptoms		
Clinically elevated depressive symptoms [1]	24 (18.3)	50 (20.4)
Demographic Characteristics		
Age at diagnosis		
Younger than 35	33 (25.2)	68 (27.8)
35 or older	98 (74.8)	177 (72.2)
Marital status		
Married	99 (75.6)	177 (72.2)
Single / Other	32 (24.4)	68 (27.8)
Race/ethnicity		
White	115 (87.8)	190 (77.6) *
Other	16 (12.2)	55 (22.4)
Education		
Some college or less	50 (38.2)	107 (43.7)
College graduate	81 (61.8)	138 (56.3)
Cancer and Treatment Characteristics		
Stage at diagnosis		
I	43 (32.8)	74 (30.2) †
IIA	54 (41.2)	76 (31.0)
IIB	17 (13.0)	36 (14.7)
IIIA	13 (9.9)	40 (16.4)
IIIC	4 (3.1)	19 (7.8)
Breast conserving surgery	55 (42.0)	99 (40.4)
Radiation	73 (55.7)	146 (59.6)
Chemotherapy	116 (88.6)	229 (93.5) †
Receptor status		
ER+/PR+ and ER+/PR-	92 (70.2)	168 (66.6)
ER-/ PR-	39 (29.8)	77 (31.4)

[1] CES-Dsf ≥ 0.06 at study entry

* Difference between groups based on X^2. p ≤0.05

† Difference between groups based on X^2. p ≤0.10

Table 3.2. Mean depressive symptoms across reproductive characteristics (N=131).

	No. (%)	Mean CES-Dsf (SD) [1]	p-value [2]
Reproductive Characteristics			
Reproductive concern after treatment [3]	-	-	0.0002
Total live births			
0	34 (26.0)	0.09 (0.19)	0.0007
1 or more	97 (74.0)	0.04 (0.12)	
Live births prior to breast cancer diagnosis			
0	42 (32.1)	0.08 (0.18)	0.004
1 or more	89 (67.9)	0.04 (0.12)	
Live births after breast cancer diagnosis			
0	116 (88.5)	0.06 (0.15)	0.79
1 or more	15 (11.5)	0.05 (0.12)	
Wanted (more) children prior to breast cancer			
Definitely / Maybe	63 (48.1)	0.06 (0.15)	0.29
No	68 (51.9)	0.05 (0.13)	
Wanted (more) children after breast cancer			
Definitely / Maybe	36 (27.5)	0.05 (0.14)	0.59
No	95 (75.5)	0.06 (0.14)	
Attempted pregnancy			
Attempted/ Did not avoid	69 (52.7)	0.07 (0.16)	0.004
Avoided	62 (47.3)	0.04 (0.11)	
Treatment decision-making			
Fertility a factor	15 (11.5)	0.08 (0.18)	0.13
Fertility not a factor	116 (88.5)	0.05 (0.14)	
Treatment related ovarian damage			
Reported	22 (16.8)	0.16 (0.24)	<0.0001
None reported	109 (83.2)	0.04 (0.10)	
Treatment-related amenorrhea			
Irregular periods during or after treatment	95 (72.5)	0.06 (0.15)	0.27
None	36 (27.5)	0.05 (0.10)	
Menopausal status reported at study entry			
Postmenopausal	26 (19.9)	0.13 (0.21)	<0.0001
Premenopausal	105 (80.2)	0.04 (0.11)	

[1] Unadjusted mean score for categorical variables.
[2] Based on correlation for continuous variables and ANOVA for categorical variables.
[3] Natural log plus one of reproductive concerns scale summary score.

Table 3.3. Characteristics associated with reproductive concerns scale (RCS) score[1].

Characteristic	High RCS score No. (%)	Low RCS score No. (%)	p-value [2]
Younger than 35 at time of diagnosis	19 (26.0)	14 (24.1)	0.80
Irregular periods during or after treatment	55 (75.3)	40 (69.0)	0.42
Treatment-related ovarian damage	17 (23.3)	5 (8.6)	0.03
Treatment decision based on fertility preservation	12 (16.4)	3 (5.2)	0.05
Did not prevent pregnancy after diagnosis	44 (60.3)	25 (43.1)	0.05
Wanted children after breast cancer diagnosis	27 (37.0)	9 (15.0)	0.01
Wanted children before breast cancer diagnosis	48 (65.8)	15 (25.9)	<0.0001
Nulliparous at time of diagnosis	33 (45.2)	9 (15.5)	0.0003
Child born after diagnosis	13(17.8)	2 (3.5)	0.01
No children	26 (35.6)	8 (13.8)	0.005

[1] Grand mean centered and log transformed RCS score, high score greater than 0.
[2] Based on X^2.

Table 3.4. Results of fitting models to depressive symptoms data (N=131).

Variable	**Unconditional Means Model** Estimate (SE)	p-value	**Conditional Univariate Model** Estimate (SE)	p-value	**Conditional Multivariate Model †** Estimate (SE)	p-value	**PRE ‡**
Intercept	0.056 (0.0093)	<0.0001	0.056 (0.0091)	<0.0001	0.057 (0.007)	<0.0001	
Reproductive concerns [1]			0.023 (0.0094)	0.016	0.015 (0.0074)	0.037	5%
Social support [2]					-0.0076 (0.0012)	<0.0001	40%
Physical health [3]					-0.0019 (0.00041)	<0.0001	12%

† Level-2 covariates are grand mean centered. The intercept represents a participant with an average value of reproductive concern, physical health and social support.
‡ Proportion of reduction in error [52].
[1] Natural log plus one of reproductive concerns scale summary score.
[2] Medical Outcomes Study Social Support measure. Includes nine items covering emotional and informational support, affection, tangible support and positive interaction.
[3] Physical health summary score from RAND-36 item health survey. Includes physical functioning, general health perceptions, bodily pain, and role limitations due to physical health problems.

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General Discussion:

Research Paper I, II and III (references included)

Participants in these three research studies represent an important and relatively understudied population of cancer survivors. Younger women diagnosed with breast cancer are at a different phase of life and have unique experiences, concerns, and needs. The three research papers presented focus on a specific set of issues related to fertility, reproduction and breastfeeding that are of concern to many younger survivors. The results of these papers build on existing research to explore the breastfeeding experiences of young breast cancer survivors, to investigate a potential selection bias in studies evaluating the safety of pregnancy after breast cancer, and to evaluate the association between symptoms of depression and reproductive concerns among long-term survivors. These issues are complex and deserve further attention, but our results help to provide direction for future research and the development of interventions designed to meet the needs of younger cancer survivors.

Research on breastfeeding after breast cancer is sparse. While several studies have reported on lactation after breast cancer surgery and treatment [1-5], researchers have only recently begun exploring the experiences and needs of breast cancer survivors who are interested in breastfeeding. One qualitative study involving young breast cancer survivors found that women wanted to breastfeed, but had anxiety and concerns about doing so, including fear of recurrence [6]. Given the established benefits of breastfeeding for all women [7], it is important to learn more about the factors that support breastfeeding as well as potential challenges faced by breast cancer survivors. Current research suggests that breast cancer survivors who wish to breastfeed should be encouraged and supported in their efforts [8-11].

In Research Paper I, we qualitatively explored the breastfeeding experiences of eleven younger breast cancer survivors who had one or more children after their treatment ended. Participants in this study were overwhelmingly motivated to breastfeed; ten initiated breastfeeding and continued for an average of 8 months (range 6 weeks to 2 ½ years).

Women discussed a number of benefits and barriers to breastfeeding. Participants described the experience as worthwhile, particularly the opportunity to bond with their child, but more difficult than anticipated. The vast majority supplemented with formula and ended breastfeeding earlier than they had hoped. Participants encouraged other survivors not to let breast cancer stop them from breastfeeding, but were also cautionary and advised women to have a back-up plan involving a breast pump and supplementing with formula.

Breastfeeding behavior is dictated by multiple influences [12] and breast cancer survivors have a greater degree of physical constraints and emotional challenges. Participants described pain and physical discomfort associated with breastfeeding and, while not exclusive to breast cancer survivors, their options for coping with this were limited by the fact that they primarily or solely relied on one lactating breast. Milk supply was also a major issue for most participants. The experience of mothers who successfully breastfeed twins suggests that breastfeeding one child with one breast would provide sufficient milk. However, women in this study overwhelmingly reported having an insufficient milk supply to breastfeed exclusively. In many cases, women discontinued breastfeeding earlier than they had planned. Discussions with participants also highlighted the negative impact of social expectations about breastfeeding, which can lead women to feel conflicted or guilty if they are unable or choose not the breastfeed [6].One participant discussed fear of recurrence associated with breastfeeding.

Women in general need support to breastfeed successfully [6, 9] and our findings suggest that cancer survivors need support specific to their circumstances. Results revealed a need for greater sensitivity to the challenges faced by breast cancer survivors, particularly from lactation professionals and health care providers. While results cannot be generalized to all women with breast cancer, study themes suggest several potential areas of intervention: professional assistance with breastfeeding initiation and building milk supply; opportunities to discuss specific concerns and needs about breastfeeding during prenatal visits; and improved postpartum support, such as through professional lactation consultants or other survivors who have breastfed.

Breast cancer survivors also need information and guidance from their health care providers when making decisions about pregnancy. Pregnancy is a major life decision and may be even more complicated for breast cancer survivors. Factors that could influence this decision include anxiety about raising a child as a cancer survivor and concern about how pregnancy may affect their risk of recurrence [13-16]. Researchers have begun to evaluate the safety of pregnancy after breast cancer and findings do not indicate that pregnancy has a negative impact on survival ([17-19]. On the contrary, it may be protective [17, 20-23]. However, researchers have also identified the potential for a selection bias, termed the “healthy mother” bias, which may result when women who have better prognoses go on to have successful pregnancies. In an attempt to account for this possibility, survival analyses have controlled for age and cancer stage at diagnosis. However, this may inadequately address potential health differences between groups, including aspects of physical and mental health.

In Research Paper II, we explored the potential for the “healthy mother” bias by comparing the physical and mental health of women who had children after breast cancer to a similar group of women who did not. This nested case-control study includes 81 participants from the Women’s Healthy Eating and Living Study (WHEL) (N=3088). All participants were diagnosed with Stage I or Stage II breast cancer and had an average age of 34 years at the time of diagnosis. Our sample includes 27 cases who had children after breast cancer and 54 controls, matched on age and cancer stage. We sought to identify a control group with the potential to become pregnant at the time of WHEL study entry. We did not find a significant difference in physical health scores or other indicators of physical health, such as health behaviors, between groups. Our findings do not indicate a healthy mother bias based on physical health differences. However, mean mental health scores were significantly higher for cases (81.7, 95%CI 77.2-86.2) than for controls (72.5, 95%CI 68.9-76.1). This association remained marginally significant in the final multilevel model (B=6.40, p=0.08). While not statistically significant, a difference of 5 points is considered clinically meaningful [24]. Our study design does not allow us to determine causality, but it is possible that those women with better mental health, including lower levels of stress and anxiety, improved social and emotional functioning, better support, and higher energy, were more likely to have successful pregnancies [e.g. 25, 26] . It is possible that those in the control group may have experienced difficulties with fertility and had lower scores of QOL [27-29], although we were unable to evaluate this in the current study due to lack of data on attempted pregnancy.

A strength of this analysis was the availability of a significant number of variables across a range of topics evaluated in the WHEL study. This is an improvement over most previous studies, which have had to rely on limited data from cancer registries and physician recall of pregnancy [19, 29-31]. Typical of studies focused on pregnancy after breast cancer, however, the primary limitation of this study is small sample size. This restricted our ability to detect statistically significant differences between groups and larger sample sizes are needed to verify our results.

Mental health is an important component of overall health. Our findings are preliminary, but suggest that studies evaluating the potential risk of pregnancy after breast cancer should include an assessment of mental health. This aspect of overall well-being may be associated with fertility, attempted pregnancy, desire for children, and/or pregnancy outcomes. Additional longitudinal research to clarify these issues would provide important information for health care providers counseling women who are thinking about becoming pregnant after breast cancer.

Pregnancy after breast cancer may be influenced by multiple factors, including potential fertility problems associated with cancer treatment [27, 32-34] and feelings about raising a child as a cancer survivor and uncertainty about the future [6, 35]. Researchers have found high psychosocial need in the areas of sexuality, fertility and reproduction among younger survivors [15, 36-38]. Evidence from previous studies indicates that younger cancer survivors have unmet needs regarding reproductive issues and results presented in Research Paper III are consistent with those findings.

Research Paper III includes 131 women who participated in the WHEL study and agreed to participate in a continuation survivorship study. Participants are long-term breast cancer survivors who have been involved in the WHEL study for approximately 10 years. We used multilevel analysis to investigate the association between mean scores of depressive symptoms (CES-Dsf) and reproductive concerns scale scores (RCS). We hypothesized that higher levels of depressive symptoms would be associated with higher levels of reproductive concerns. Following the biopsychosocial model, we evaluated the association between CES-Dsf scores and an extensive range of variables, including cancer characteristics, physical health/health behavior, and psychosocial characteristics. However, our sample size required that we limit the number of variables included in the final multilevel model.

CES-Dsf scores averaged 0.056 overall and did not change significantly over time. Higher levels of depressive symptoms were predicted by higher levels of reproductive concern. Depressive symptoms scores remained significantly higher even after controlling for social support and physical health (B= 0.02, SE= 0.01, p=0.04). While we cannot determine causality, these finding indicate that younger breast cancer survivors who are concerned about reproduction have poorer long-term well-being.

Study results are consistent with other research suggesting that the reproductive concerns of younger cancer survivors are important to address [13, 29, 36, 38, 42]. One other cross-sectional study evaluated reproductive concerns among younger cancer survivors using the RCS. This study found that a higher RCS score was associated with lower quality of life 5-10 years after diagnosis and treatment (p<0.001) [29]. Consistent with other research, our results also indicate that social support is an important contributor to well-being among younger breast cancer survivors [13, 41, 43, 44]. After controlling for other covariates, social support was a significant predictor of depressive symptoms (B=-0.01, SE=0.0001) and described the greatest percentage of explainable variation in CES-Dsf scores (40%). A limitation of both this study and the present study is that reproductive concerns and other covariates were assessed at one time point. Further research is needed to determine whether reproductive concerns change over time, their relationship to social support and other psychosocial characteristics, and whether there is a causal association between these concerns and overall well-being.

Younger survivors' needs for support and information specifically related to fertility and early menopause are currently not being met [13, 15, 36-38, 42]. The findings from this and other studies suggest that supportive interventions focused on reproductive issues would be beneficial for young breast cancer survivors. Preliminary research also indicates that women's feelings about fertility change over time [6] and concerns may increase as they move farther away from diagnosis [45]. Health care providers can play an important role in filling the need for support and information after initial treatment ends and well into survivorship. Longitudinal research to identify available sources of support and unmet needs, both shortly after diagnosis and over time, would help in the development of interventions to address these needs.

While about half of participants reported possibly wanting children prior to the time they were diagnosed, only 16 participants (12%) reported that fertility was a consideration in their cancer treatment decisions. This is significantly lower than the 29% reported by Partridge et al. [14], although the population surveyed in that study may have been more likely to be concerned about fertility. Additional research into whether women make treatment decisions based on fertility would provide important information to health care providers who are counseling women regarding treatment. Our results also suggest that women who have higher reproductive concerns may be especially important to identify at the time of diagnosis; 80% of those who reported that fertility was a factor in their treatment decisions were in the high RCS group. These women would likely benefit from health care provider support and information regarding their cancer treatment decisions and related reproductive concerns. Differential treatment choices based on a desire to preserve fertility may also impact on survival, thought his has not been evaluated.

Medical studies are underway to evaluate approaches to preserving fertility but it is also important to understand how concerns about reproduction impact the lives of survivors. Research in this area is still in the preliminary stage. Findings from this study indicate that higher levels of depressive symptoms during 10 years of survivorship are associated with higher post-treatment reproductive concerns. This suggests that reproductive concerns are important to address and may have a long-term impact on survivor’s well-being. The results of this and other studies suggest that younger breast cancer survivors would benefit from additional support and information regarding reproductive concerns. Health care providers in regular contact with breast cancer patients can play a critical role in addressing these concerns.

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