TRAJECTORIES OF EMOTIONAL AND FUNCTIONAL WELL-BEING IN BREAST CANCER SURVIVORS

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ABSTRACT

Yumeng Ren: Trajectories of Emotional and Functional Well-being in Breast Cancer Survivors
(Under the direction of Marc Emerson)

Background: Emotional and functional well-being are important components of mental health. Long-term and trajectories of emotional and functional well-being among breast cancer (BC) survivors have been understudied in previous research. Limited work on the impact of demographic and clinical characteristics on emotional and functional well-being change results in a lack of guidance to support BC survivors' unmet emotional and functional needs.

Methods: This project had two aims 1) to characterize long-term emotional and functional well-being overall and in association with demographic characteristics and clinical correlates; and 2) to describe trajectories of emotional and functional well-being in breast cancer survivors and explore disparities by age, race, and other characteristics. To achieve these two aims, we used data from the Carolina Breast Cancer Study Phase 3, a racially diverse population-based cohort, including 2,781 women diagnosed with invasive breast cancer between 2008 to 2013.

Results: For Aim 1, 37% of our participants had improved well-being, nearly 42% had no obvious change, and 21% had decreased well-being over time since diagnosis. More advanced cancer stage and older age at diagnosis were moderately associated with well-being decrease at 84 months relative to baseline, whereas Black race and no receipt of chemotherapy were moderately associated with well-being decrease at 25 months and 84 months post diagnosis. Breast cancer recurrence was strongly associated with well-being decrease at both

follow-up survey timepoints. In Aim 2, five trajectory groups were identified for emotional and functional well-being, separately. Two had consistently high/medium well-being levels during the follow-up (i.e., “good well-being” trajectories), whereas the other three had moderate/low levels, with one staying stable, one having a substantial decrease by 25 months, and another with an extremely low baseline level and only having a small increment (i.e., “poor well-being” trajectories). Younger women, Black women, women with BC recurrence, and women with lower socioeconomic status, advanced cancer stage, and more aggressive treatment modality were more likely to fall into “poor well-being” trajectories.

Conclusions: Trajectories of emotional and functional well-being are associated with important demographic and clinical features.

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TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

AIC	Akaike's information criterion
ASCO	American Society of Clinical Oncology
BC	breast cancer
BCS	breast conservation surgery
BIC	Bayesian information criterion
CBCS	Carolina Breast Cancer Study
CI	confidence interval
COPD	chronic obstructive pulmonary disease
DAG	directed acyclic graph
EWB	emotional well-being
FACT-B	Functional Assessment of Cancer Therapy - Breast
FACT-G	Functional Assessment of Cancer Therapy - General
FWB	functional well-being
GED	General Educational Diploma
HADS	Hospital Anxiety and Depression Scale
HR	hazard ratio
HRQoL	health-related quality of life
HS	high school
LCGA	latent class growth analysis
MICE	multiple imputation by chained equations
MID	minimally important difference
NC	North Carolina

OR	odds ratio
QoL	quality of life
RFD	relative frequency difference
RR	rate ratio
SES	socioeconomic status
std	standard deviation
USD	United States Dollar
vs.	versus
WB	well-being
WHO	World Health Organization

LIST OF SYMBOLS

β	beta coefficient
ε	epsilon, a disturbance term in the latent class growth analysis model

CHAPTER 1: BACKGROUND

1.1 Emotional and Functional Decline among Breast Cancer Survivors

The number of breast cancer (BC) survivors has been increasing in recent decades.[1] For all stages combined, the 5-year relative survival rate of female BC diagnosed during 2010 through 2016 was 90% in the United States.[1,2] At this time there are more than 3.8 million women living in the U.S. with a history of invasive BC.[3] A diagnosis of BC is often overwhelmingly distressing.[4] Based on the World Health Organization's (WHO's) definition, "Mental health is a state of well-being in which an individual can realize his or her own abilities, interact positively with others, cope with the stressors of life and study, work productively and fruitfully, and contribute to his or her family and community."[5] Emotional well-being includes happiness, interest in life, and satisfaction, whereas functional well-being represents the ability to perform usual tasks of daily living. Therefore, emotional and functional well-being is an important component of mental health.[6] Research has highlighted a burden of emotional and functional decline (e.g., symptoms of depression, anxiety) among BC survivors.[4,7-9] It is reported that among BC survivors ≥ 1 year after diagnosis, the prevalence of post-treatment anxiety symptoms varied from 18% to 33%, and of depressive symptoms from 9% to 66%.[8] Patients with BC face extensive uncertainty about the outcome of treatment, survival, potential recurrence, and the impact of treatment on their life.[10-13] These all may contribute to elevated anxiety levels.[14] The prevalence of depression is the third highest among patients with BC only after pancreatic and head and neck cancer,[15] and one study found that approximately 20% of women with BC had depressive symptoms persisting 2 years post-diagnosis.[16] Underscoring the

importance of well-being, one systematic review found that BC survivors had a 37% to 60% higher risk of suicide compared to women with no prior cancer.[9]

Emotional and functional decline is often overlooked and under-treated, despite their high prevalence.[17-19] In one study among low-income women with breast or gynecological cancer (N= 472) who received care in a public hospital in the U.S., 24% met criteria for a major depressive disorder. Of this group, only 12% of women received antidepressant medication and only 5% reported seeing a counselor or participating in a support group.[20] The treatment gap might be attributed to objective factors as well as subjective factors. The former includes the lack of availability or accessibility of specialized services, services not tailored to the specific population in need, physicians not familiar with the symptoms of emotional and functional decline in cancer patients. Subjective factors are of diverse nature, such as patients not willing to disclose their emotional and functional symptoms.[21,22] However, an important gap is adequate understanding of the key emotional and functional well-being gaps among breast cancer survivors, overall and according to key demographic variables. Filling this gap will provide evidence-based information for cancer care providers to modify the objective factors mentioned above.

1.2 Impact of Severe Emotional and Functional Decline in Breast Cancer Survivors

Emotional and functional decline can have a detrimental impact on the overall quality of life in BC survivors.[23-28] Emotional and functional decline may compound and thus affect interpersonal relationships, occupational performance, stress and perception of physical symptoms.[26,29-31] One study conducted among a group of stage I-III breast cancer survivors (disease free for at least 5 years) found that higher scores on depression and elevated age-adjusted anxiety were related to lower quality of life functioning.[24] Similarly, findings from another study showed that among 240 breast cancer survivors who participated in clinical trials

of paclitaxel between 1994 and 2001 at the University of Texas MD Anderson Cancer Center, 16.2% of them could be categorized as being depressed, and depression was inversely associated with the health-related quality of life (HRQoL) subscale scores for global health, functionality, and financial difficulties owing to disease or treatment.[27] Furthermore, in a longitudinal study conducted among 691 breast cancer patients aged ≥ 65 years, better emotional and functional support assessed 3 months post surgery appeared to predict more favorable self-perceived health 15 months after surgery.[28]

Some evidence showed that emotional and functional decline impairs cognitive focus, energy and motivation, and therefore could also affect patients' adherence to treatment.[32,33] One meta-analysis found that in a general medical setting, compared with non-depressed patients, depressed patients had 3 times the odds of being noncompliant with medical treatment recommendations.[32] Specifically for breast cancer, one systematic review suggested that depression is associated with decreased acceptance of and compliance with adjuvant therapy in women with breast cancer.[33]

In addition, cancer survivors experiencing emotional and functional decline seem to encounter more perceived barriers to cancer care.[20,34] One study concentrating on young adult cancer survivors reported that barriers to engaging in survivorship care included depression and anxiety, and many participants were not willing to continue medical care to avoid anxiety-provoking information regarding their health.[34] Specifically, one study found that compared to non-depressed women with breast or gynecologic cancer, depressed patients reported significantly more barriers to cancer care, including lack of understanding of treatment recommendations (odds ratio [OR]=2.17, 95% confidence interval [CI]: 1.32, 3.56), and worries about treatment side effects (OR=1.98, 95% CI: 1.20, 3.26).[20]

Furthermore, there are arguments supporting the assertion that emotional and functional decline could be a prognostic factor for BC mortality. For instance, problems such as major depression could predict late-stage BC because depression patients with a breast lump will delay seeking for medical consultation,[35] and these problems further reduce compliance with BC treatment.[28,32,33] In addition, some studies suggest a link between well-being and mortality of BC survivors.[36-38] There is evidence supporting postoperative depressive disorder as a prognostic factor of BC (rate ratio [RR] for all-cause mortality=1.73 among early-stage BC survivors with postoperative depressive disorder versus those with no postoperative depressive disorder, 95% CI: 1.30, 2.28).[37] One prospective study among 578 women with early-stage BC found that high depression scores were significantly associated with lower chance of 5-year overall survival (hazard ratio [HR]=3.59, 95% CI: 1.39, 9.24), but the effect on the event-free survival was not significant.[38]

1.3 Risk Factors of Emotional and Functional Decline among Breast Cancer Population

Some individual characteristics that vary by demographics and individual circumstances may be important in determining the emotional and functional well-being of cancer populations. Risk factors in breast cancer population appear to be similar to those for the general female population, such as socioeconomic status (e.g., lack of social support, being unemployed or unable to work).[39] As for other composites such as education and marital status, they seemed to not be correlated with depression and anxiety.[20,40,41] Other than that, age was found to be correlated with well-being decline with younger women more likely to report depression or anxiety.[20,40]

On the other hand, individual characteristics alone are not sufficient to explain emotional and functional decline. Disease and treatment-related factors are also critical.[35] Clinical

correlates, such as BC adjuvant chemotherapy, surgery type, and BC recurrence might be associated with emotional and functional decline.[42-46] Some studies report that BC patients who received adjuvant chemotherapy had higher levels of depression compared to patients not treated with adjuvant chemotherapy, while the levels of anxiety were comparable between the two groups.[45,46] Evidence suggests that women who had breast conservation surgery (BCS) experienced significantly greater levels of psychological distress from 40 months after surgery onward than did women who received a mastectomy.[43] One possible explanation proposed by those researchers was that women who received a mastectomy usually had more advanced disease and worse prognosis, thus, they might have improved emotional and functional well-being over time as they become more confident in remaining disease free; whereas women who had BCS still have an intact breast, therefore, they might have increased anxiety about disease recurrence. One cross-sectional study showed that among 55 women with recurrent BC, more than 40% showed either major depressive disorder or adjustment disorder with depressive mood, anxious mood or both,[44] which might be due to the fact that first BC recurrence is an extreme difficult time and can often provoke psychological distress.[47,48] Similarly, a cohort study revealed that 45% of those with BC recurrence experienced depression, anxiety, or both within three months of the diagnosis,[42] which highlights the adverse effect of this event on women's emotional and functional well-being. To our knowledge, the impact of BC clinical correlates on long-term (>2 years post BC diagnosis) emotional and functional well-being has been understudied. Filling this gap could contribute to providing targeted preventive support to BC survivors with specific clinical features in their BC care continuum.

1.4 Trajectories of Emotional and Functional Well-Being and Individual and Clinical Characteristics

While some studies have evaluated long-term well-being in survivors, it is also important to consider the specific temporal patterns of change in well-being at multiple time points in the years following diagnosis. Breast cancer survivorship experience is dynamic, changing over time, with particular moments of stressful transitions, such as the transition from active treatment to long-term follow-up.[49] According to Bonanno, there are four distinct patterns of adjustment to traumatic life events, including no signs of distress (resilience), recovery, delayed distress, and a stable high level of distress (Figure 1.1).[50] Resilient individuals often have the ability to maintain relatively stable, healthy levels of psychological and physical functioning; recovering individuals initially have psychological symptoms and then gradually return to pre-event status after a period of time; individuals who have the delayed trajectory seem to recover quickly but then experience expected health problems; while individuals of the chronic type are not usually able to recover from the distress they encounter.[50]

More complex well-being trajectories have also been proposed. One study of breast cancer survivors focused on depressive symptoms and identified six groups of BC survivors exhibiting different patterns (trajectories) over 24 months since diagnosis (i.e., “consistently very low”, “consistently low”, “consistently borderline”, “initially high then declined”, “increased”, and “chronically high”).[16] The study reported that approximately 20% of the participants had levels of depressive symptoms indicative of clinical depression that maintained even 2 years post-diagnosis, which indicated that they had been in need of preventive care. Almost 30% of the participants lived with borderline levels of depressive symptoms, suggesting that they might need continued screening for depression.[16] Therefore, investigating the heterogeneity of change

in emotional and functional well-being among BC survivors is important for designing and carrying out interventions at appropriate time points in the cancer journey.

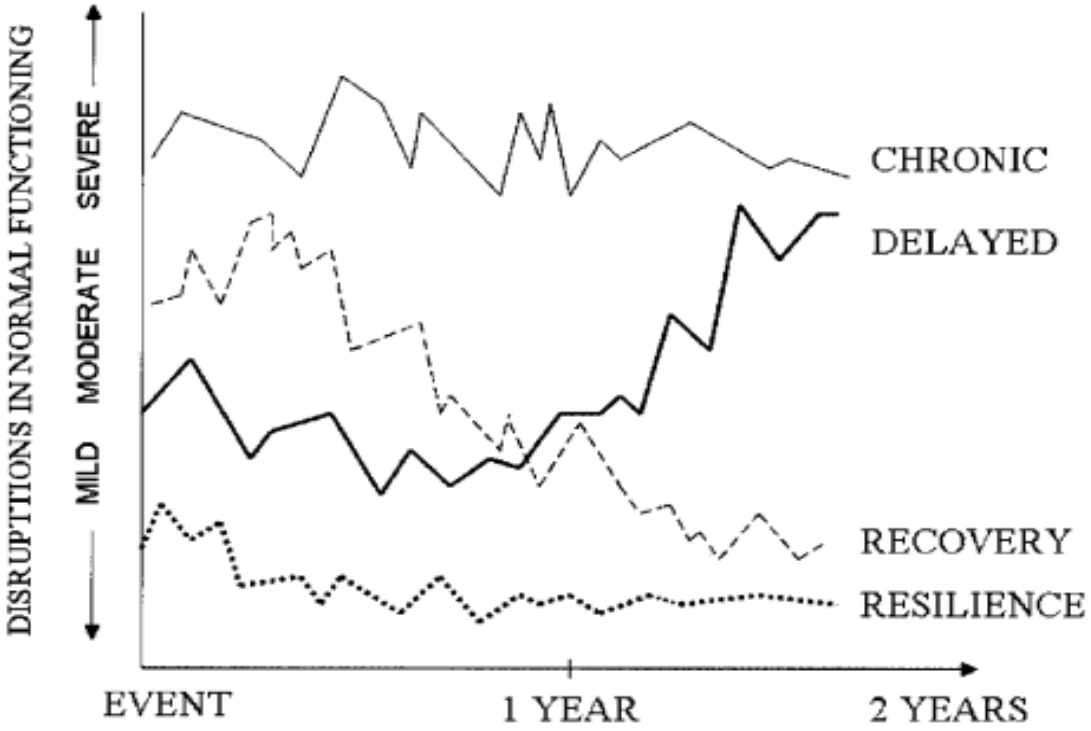


Figure 1. 1 Prototypical patterns of disruption in normal functioning across time following interpersonal loss or potentially traumatic events. Adapted from Bonanno, 2004[50]

When evaluating trajectories of emotional and functional well-being in BC survivors to identify possible subgroups in need of interventions, patient characteristics (e.g., age, race, socioeconomic status) and clinical characteristics (e.g., cancer stage at diagnosis, surgery type, adjuvant chemotherapy, recurrence status) should be considered.

It has been suggested that trajectories of emotional and functional well-being among BC survivors might depend on women's age, with several studies showing that younger (< 50 years in age) patients tend to struggle with emotional and social disturbances, whereas older patients experience more physical health concerns and poorer HRQoL.[51-54] There are two possible explanations for the results. Young patients are more likely to have higher levels of appraisal of

threat from BC, thus suffered from emotional and functional decline.[53] Another reason might be that young women with BC possess fewer coping strategies and resources necessary to manage a life-threatening disease.[54]

Other than age, race is also a critical factor for well-being trajectories. Black women have the lowest breast cancer survival rate of any racial/ethnic group in the U.S. and a mortality rate that is 40% higher than that of White women.[1,3] Emotional and functional impact of cancer in general was also significantly worse for Black women than for non-Hispanic white women,[55] with Black survivors having poorer quality of life (QoL) scores,[56] and increased levels of depressive symptoms along BC survivorship.[16] One possible explanation is that Black women are less likely to receive specialty psychological care compared to white women, even with adjusted demographic characteristics, insurance status, and psychiatric morbidity.[57] Emotional and functional decline has been associated with both higher all-cause mortality and breast cancer-specific mortality.[58-60] Therefore, studying potential differences in well-being trajectories by race might inform further research on the possible attribution of such trajectories to racial disparity in BC mortality.

It is not clear whether BC survivors' socioeconomic factors (e.g., education, marital status, household income, insurance) or clinical characteristics would affect group membership of trajectories of emotional and functional well-being. The majority of studies showed no association between marital status, education, or household income and the patterns of change in depressive symptoms or psychological distress,[16,29,61-64] but not all. One study found that higher education seemed to be associated with maintaining depressive symptoms at a lower level among women following BC surgery.[64] With respect to clinical factors, some evidence suggested that early cancer stage at diagnosis,[16] lumpectomy,[16,63] less rigorous chemotherapy,[16,63] not receiving

hormonal therapy[16] were significantly associated with maintaining lower levels of depressive symptoms or psychological distress over time, whereas other studies had null results for such hypothesized associations.[29,61,62,64]

Understanding trajectories of emotional and functional well-being could help BC survivors better cope beyond initial diagnosis and treatment. Most studies on emotional and functional well-being among BC patients used conventional methods (e.g., two-sample t-test, hierarchical regression) to analyze differences or changes in mean symptom scores according to predefined group status (e.g., age groups), and did not explore potential heterogeneity.[65-68] Examining mean differences alone may lead to erroneous conclusions regarding outliers or subgroups, and subgroups that have similar well-being trajectories can be hard to disentangle based on these standard analyses. Several previous studies have assessed the trajectory of depression, anxiety or psychological distress,[16,29,61-64,69-71] but studies examining the course of emotional and functional well-being in early breast cancer survivorship have mostly been relied on convenience samples drawn from a few treatment centers.[16,29,61,62,64,70] In addition, these studies either only included women recently diagnosed with BC,[16,61] or focused on BC patients just completing treatment.[29,62,64,70,71] Long-term (>2 years post BC diagnosis) well-being trajectories have seldom been investigated, with only one study having a time span of 4 years.[63] In addition, The work on potential heterogeneity in well-being trajectories by race, age and other individual and clinical characteristics has been limited, because most study populations were predominately white[16,29,63,64,70] and older women.[16,29,61-64,69,70]

1.5 The Functional Assessment of Cancer Therapy - Breast (FACT-B)

There are many instruments for assessing mental health and emotional and functional well-being. The Functional Assessment of Cancer Therapy - Breast (FACT-B) was designed to

measure five domains of HRQoL in breast cancer patients: physical, social, emotional, and functional well-being as well as a breast cancer subscale.[72] The FACT-B (version 4.0) has 37 items and consists of two parts: 27 core FACT-G (the Functional Assessment of Cancer Therapy - General) items and 10 items on the additional concerns specific to breast cancer. Each item is rated on a five-point rating scale ranging from 0 (not at all) to 4 (very much). Higher total scores indicate higher quality of life. It has been proved to demonstrate ease of administration, brevity, reliability (alpha coefficient for the internal consistency for the total score=0.90, and subscale alpha coefficients ranging from 0.63 to 0.86), validity (significantly correlated with another measure of QoL, the Functional Living Index - Cancer), and sensitivity to change in QoL overtime.[72]

The Hospital Anxiety and Depression Scale (HADS) is a popular instrument commonly used to assess mental health in a general medical population of patients.[73] It has been validated in different settings for patients with various medical conditions including breast cancer.[74] Most of the items from the FACT-B emotional and functional well-being domains can be mapped to items or the reverse of items from the HADS (as shown in Table 1.1 created by this dissertation), and the difference is that items from the FACT-B specifically target cancer patients and have taken into account how cancer diagnosis, treatment, and survivorship experience might influence patients' emotional and functional well-being. Evidence suggested that the emotional and functional well-being subscale scores were significantly negatively associated with the HADS scores (correlation coefficients ranging from -0.34 to -0.54 with $p<0.01$).[75] To be scientifically rigorous, results based on the FACT-B emotional and functional subscales will be interpreted in terms of well-being that approximates mental health levels, though there is considerable overlap between items from the FACT-B and the HADS.

Table 1. 1 Mapping items from FACT-B emotional and functional subscales to items from HADS

FACT-B		**HADS**
Emotional well-being subscale (6 questions in total; range: 0-24)	Item	Item
	1. I feel sad	(reverse) I feel cheerful
	2. I am satisfied with how I am coping with my illness	(reverse) I feel as if I am slowed down
	3. I am losing hope in the fight against my illness	NA
	4. I feel nervous	I feel tense or "wound up"
		I get sudden feeling of panic
		I get a sort of frightened feeling like "butterflies" in the stomach
	5. I worry about dying	I get a sort of frightened feeling as if something awful is about to happen
	6. I worry that my condition will get worse	Worrying thoughts go through my mind
Functional well-being subscale (7 questions in total; range: 0-28)	Item	
	1. I am able to work (include work at home)	NA
	2. My work (include work at home) is fulfilling	NA
	3. I am able to enjoy life	I look forward with enjoyment to things
		I can laugh and see the funny side of things
	4. I have accepted my illness	(reverse) I have lost interest in my appearance[a]
	5. I am sleeping well	I feel restless as if I have to be on the move
		I can sit at ease and feel relaxed
	6. I am enjoying the things I usually do for fun	I still enjoy the things I used to enjoy
		I can enjoy a good book or TV program
	7. I am content with the quality of my life right now	NA

[a.] For women with breast cancer, surgery (especially mastectomy) could be related to damaged body image. However, mapping for this item is less clear than others.

1.6 Significance and Study Rationale

Despite the need for screening of emotional and functional decline, only recently have related guidelines been created. In 2014, the American Society of Clinical Oncology (ASCO) published adapted guidelines for the screening, assessment, and treatment of anxiety and depressive symptoms in adults with cancer.[76,77] The guidelines recommend periodic emotional and functional screening using validated instruments across the continuum of cancer care. All patients should be screened at their initial visit, at appropriate intervals, and as clinically indicated, especially with changes in disease or treatment status (i.e., post-treatment, recurrence, progression, transition to palliative and end-of-life care) and other points of vulnerability (i.e., times of personal transition such as family crisis).[77] The guidelines also indicate that clinicians have a vital role in mitigating the negative emotional and behavioral sequelae. Targeted screening of vulnerable survivors and early intervention may prevent the onset and/or reduce the severity of emotional and functional decline in early survivorship.[8] Mental health support during survivorship care is also likely to help reduce the burden of emotional and functional decline.[9]

The Carolina Breast Cancer Study – Phase 3 (CBCS3) is unique in that it is a large population-based study of racially diverse women with breast cancer and contains longitudinal information on emotional and functional well-being. It is important to understand long term and trajectories of well-being in diverse populations because of their potential heterogeneity by age, race, and other important factors. While differentiated emotional and functional care is becoming the norm in specialized breast cancer clinics, only a fraction of the breast cancer survivors are followed-up based on routine clinical visits.[78] Health care professionals need evidence-based information on the optimal management strategies to fulfill BC survivors' unmet emotional and functional needs. By evaluating long-term emotional and functional well-being and identifying

well-being trajectories in breast cancer survivors, this dissertation has the potential of substantially enhancing our ability to provide more specific recommendations for survivorship care and improving BC survivors' well-being along their recovery (e.g., more frequent screening for the subgroup with a higher risk of maintaining "consistently low" well-being status). Furthermore, by assessing associations between individual and disease characteristics with well-being trajectories, this dissertation could inform clinical practice and decision-making regarding carrying out appropriate interventions to ameliorate the effects of BC diagnosis on BC survivors' well-being accounting for their age, race, and other factors.

REFERENCES

1. Siegel RL, Miller KD, Fuchs HE, Jemal A. Cancer statistics, 2021. *CA: a cancer journal for clinicians*. 2021;71(1):7-33.

2. Narod SA, Iqbal J, Miller AB. Why have breast cancer mortality rates declined? *Journal of Cancer Policy*. 2015;5:8-17.

3. Society A. Cancer treatment & survivorship facts & figures 2019–2021. American Cancer Society Atlanta; 2019.

4. Payne DK, Sullivan MD, Massie MJ. Women's psychological reactions to breast cancer. 1996:89-97.

5. Organization WH. *Promoting mental health: Concepts, emerging evidence, practice: Summary report*. World Health Organization; 2004.

6. Galderisi S, Heinz A, Kastrup M, Beezhold J, Sartorius N. Toward a new definition of mental health. *World psychiatry*. 2015;14(2):231.

7. Howard-Anderson J, Ganz PA, Bower JE, Stanton AL. Quality of life, fertility concerns, and behavioral health outcomes in younger breast cancer survivors: a systematic review. *Journal of the National Cancer Institute*. 2012;104(5):386-405.

8. Maass SW, Roorda C, Berendsen AJ, Verhaak PF, de Bock GH. The prevalence of long-term symptoms of depression and anxiety after breast cancer treatment: a systematic review. *Maturitas*. 2015;82(1):100-108.

9. Carreira H, Williams R, Müller M, Harewood R, Stanway S, Bhaskaran K. Associations between breast cancer survivorship and adverse mental health outcomes: a systematic review. *JNCI: Journal of the National Cancer Institute*. 2018;110(12):1311-1327.

10. Liao M-N, Chen M-F, Chen S-C, Chen P-L. Uncertainty and anxiety during the diagnostic period for women with suspected breast cancer. *Cancer nursing*. 2008;31(4):274-283.

11. Barlow DH. Unraveling the mysteries of anxiety and its disorders from the perspective of emotion theory. *American psychologist*. 2000;55(11):1247.

12. Montgomery GH, David D, Goldfarb AB, et al. Sources of anticipatory distress among breast surgery patients. *Journal of behavioral medicine*. 2003;26(2):153-164.

13. Walker L, Heys SD, Walker M, et al. Psychological factors can predict the response to primary chemotherapy in patients with locally advanced breast cancer. *European Journal of Cancer*. 1999;35(13):1783-1788.

14. Ng CG, Mohamed S, Kaur K, et al. Perceived distress and its association with depression and anxiety in breast cancer patients. *PloS one*. 2017;12(3):e0172975.

15. Golden-Kreutz DM, Andersen BL. Depressive symptoms after breast cancer surgery: Relationships with global, cancer-related, and life event stress. *Psycho-Oncology: Journal of the Psychological, Social and Behavioral Dimensions of Cancer*. 2004;13(3):211-220.

16. Avis NE, Levine BJ, Case LD, Naftalis EZ, Van Zee KJ. Trajectories of depressive symptoms following breast cancer diagnosis. *Cancer Epidemiology, Biomarkers & Prevention*. 2015;24(11):1789-1795.

17. Fallowfield L, Ratcliffe D, Jenkins V, Saul J. Psychiatric morbidity and its recognition by doctors in patients with cancer. *British journal of cancer*. 2001;84(8):1011-1015.

18. Boyes AW, Girgis A, D'Este CA, Zucca AC, Lecathelinais C, Carey ML. Prevalence and predictors of the short-term trajectory of anxiety and depression in the first year after a cancer diagnosis: a population-based longitudinal study. *Journal of Clinical Oncology*. 2013;31(21):2724-2729.

19. von Heymann-Horan AB, Dalton SO, Dziekanska A, et al. Unmet needs of women with breast cancer during and after primary treatment: a prospective study in Denmark. *Acta Oncologica*. 2013;52(2):382-390.

20. Ell K, Sanchez K, Vourlekis B, et al. Depression, correlates of depression, and receipt of depression care among low-income women with breast or gynecological cancer. *Journal of clinical oncology: official journal of the American Society of Clinical Oncology*. 2005;23(13):3052.

21. Levav I. The treatment gap of depression in persons with cancer. *Asian Pac J Cancer Prev*. 2010;11:117-119.

22. Maguire G, Lee E, Bevington D, Küchemann C, Crabtree R, Cornell C. Psychiatric problems in the first year after mastectomy. *Br Med J*. 1978;1(6118):963-965.

23. Caplette-Gingras A, Savard J. Depression in women with metastatic breast cancer: a review of the literature. *Palliative & supportive care*. 2008;6(4):377-387.

24. Weitzner MA, Meyers CA, Stuebing KK, Saleeba AK. Relationship between quality of life and mood in long-term survivors of breast cancer treated with mastectomy. *Supportive Care in Cancer*. 1997;5(3):241-248.

25. Reich M, Lesur A, Perdrizet-Chevallier C. Depression, quality of life and breast cancer: a review of the literature. *Breast cancer research and treatment*. 2008;110(1):9-17.

26. YEN JY, KO CH, YEN CF, et al. Quality of life, depression, and stress in breast cancer women outpatients receiving active therapy in Taiwan. *Psychiatry and clinical Neurosciences*. 2006;60(2):147-153.

27. Reyes-Gibby CC, Anderson KO, Morrow PK, Shete S, Hassan S. Depressive symptoms and health-related quality of life in breast cancer survivors. *Journal of women's health*. 2012;21(3):311-318.

28. Ganz PA, Guadagnoli E, Landrum MB, Lash TL, Rakowski W, Silliman RA. Breast cancer in older women: quality of life and psychosocial adjustment in the 15 months after diagnosis. *Journal of Clinical Oncology*. 2003;21(21):4027-4033.

29. Deshields T, Tibbs T, Fan MY, Taylor M. Differences in patterns of depression after treatment for breast cancer. *Psycho-Oncology: Journal of the Psychological, Social and Behavioral Dimensions of Cancer*. 2006;15(5):398-406.

30. Aapro M, Cull A. Depression in breast cancer patients: the need for treatment. *Annals of Oncology*. 1999;10(6):627-636.

31. Badger TA, Braden CJ, Mishel MH, Longman A. Depression burden, psychological adjustment, and quality of life in women with breast cancer: patterns over time. *Research in nursing & health*. 2004;27(1):19-28.

32. DiMatteo MR, Lepper HS, Croghan TW. Depression is a risk factor for noncompliance with medical treatment: meta-analysis of the effects of anxiety and depression on patient adherence. *Archives of internal medicine*. 2000;160(14):2101-2107.

33. Fann JR, Thomas-Rich AM, Katon WJ, et al. Major depression after breast cancer: a review of epidemiology and treatment. *General hospital psychiatry*. 2008;30(2):112-126.

34. Berg CJ, Stratton E, Esiashvili N, Mertens A. Young adult cancer survivors' experience with cancer treatment and follow-up care and perceptions of barriers to engaging in recommended care. *Journal of Cancer Education*. 2016;31(3):430-442.

35. Desai MM, Bruce ML, Kasl SV. The effects of major depression and phobia on stage at diagnosis of breast cancer. *The International Journal of Psychiatry in Medicine*. 1999;29(1):29-45.

36. Giese-Davis J, Collie K, Rancourt KM, Neri E, Kraemer HC, Spiegel D. Decrease in depression symptoms is associated with longer survival in patients with metastatic breast cancer: a secondary analysis. *Journal of clinical oncology*. 2011;29(4):413.

37. Hjerl K, Andersen EW, Keiding N, Mouridsen HT, Mortensen PB, Jørgensen T. Depression as a prognostic factor for breast cancer mortality. *Psychosomatics*. 2003;44(1):24-30.

38. Watson M, Haviland J, Greer S, Davidson J, Bliss J. Influence of psychological response on survival in breast cancer: a population-based cohort study. *The Lancet*. 1999;354(9187):1331-1336.

39. Bailey EH, Pérez M, Aft RL, Liu Y, Schootman M, Jeffe DB. Impact of multiple caregiving roles on elevated depressed mood in early-stage breast cancer patients and same-age controls. *Breast cancer research and treatment*. 2010;121(3):709-718.

40. MacFarlane ME, Sony SD. Women, breast lump discovery, and associated stress. *Health Care for Women International*. 1992;13(1):23-32.

41. Maunsell E, Brisson J, Deschênes L. Psychological distress after initial treatment of breast cancer. Assessment of potential risk factors. *Cancer*. 1992;70(1):120-125.

42. Burgess C, Cornelius V, Love S, Graham J, Richards M, Ramirez A. Depression and anxiety in women with early breast cancer: five year observational cohort study. *Bmj*. 2005;330(7493):702.

43. Cohen L, Hack TF, Moor Cd, Katz J, Goss PE. The effects of type of surgery and time on psychological adjustment in women after breast cancer treatment. *Annals of surgical Oncology*. 2000;7(6):427-434.

44. Okamura H, Watanabe T, Narabayashi M, et al. Psychological distress following first recurrence of disease in patients with breast cancer: prevalence and risk factors. *Breast cancer research and treatment*. 2000;61(2):131-137.

45. Schagen SB, van Dam FS, Muller MJ, Boogerd W, Lindeboom J, Bruning PF. Cognitive deficits after postoperative adjuvant chemotherapy for breast carcinoma. *Cancer: Interdisciplinary International Journal of the American Cancer Society*. 1999;85(3):640-650.

46. van Dam FS, Boogerd W, Schagen SB, et al. Impairment of cognitive function in women receiving adjuvant treatment for high-risk breast cancer: high-dose versus standard-dose chemotherapy. *JNCI: Journal of the National Cancer Institute*. 1998;90(3):210-218.

47. Cella DF, Mahon SM, Donovan MI. Cancer recurrence as a traumatic event. *Behavioral medicine*. 1990;16(1):15-22.

48. Mahon SM, Cella DF, Donovan MI. Psychosocial adjustment to recurrent cancer. 1990:47-52; discussion 53.

49. Council NR. *From cancer patient to cancer survivor: lost in transition*. National Academies Press; 2005.

50. Bonanno GA. Loss, trauma, and human resilience: have we underestimated the human capacity to thrive after extremely aversive events? *American psychologist*. 2004;59(1):20.

51. Arndt V, Merx H, Stürmer T, Stegmaier C, Ziegler H, Brenner H. Age-specific detriments to quality of life among breast cancer patients one year after diagnosis. *European Journal of Cancer*. 2004;40(5):673-680.

52. Colby DA, Shifren K. Optimism, mental health, and quality of life: A study among breast cancer patients. *Psychology, health & medicine*. 2013;18(1):10-20.

53. Vinokur AD, Threatt BA, Vinokur-Kaplan D, Satariano WA. The process of recovery from breast cancer for younger and older patients. Changes during the first year. *Cancer*. 1990;65(5):1242-1254.

54. Wenzel LB, Fairclough DL, Brady MJ, et al. Age-related differences in the quality of life of breast carcinoma patients after treatment. *Cancer: Interdisciplinary International Journal of the American Cancer Society*. 1999;86(9):1768-1774.

55. Alcalá HE. Differential mental health impact of cancer across racial/ethnic groups: findings from a population-based study in California. *BMC public health*. 2014;14(1):1-9.

56. Matthews AK, Tejeda S, Johnson TP, Berbaum ML, Manfredi C. Correlates of quality of life among African American and white cancer survivors. *Cancer nursing*. 2012;35(5):355.

57. Alegria M, Canino G, Ríos R, et al. Mental health care for Latinos: Inequalities in use of specialty mental health services among Latinos, African Americans, and non-Latino Whites. *Psychiatric services*. 2002;53(12):1547-1555.

58. Ahlgrén-Rimpiläinen AJ, Arffman M, Suvisaari J, et al. Excess mortality from breast cancer in female breast cancer patients with severe mental illness. *Psychiatry Research*. 2020;286:112801.

59. Iglay K, Santorelli ML, Hirshfield KM, et al. Impact of preexisting mental illness on all-cause and breast cancer–specific mortality in elderly patients with breast cancer. *Journal of Clinical Oncology*. 2017;35(36):4012-4018.

60. Onitilo AA, Nietert PJ, Egede LE. Effect of depression on all-cause mortality in adults with cancer and differential effects by cancer site. *General hospital psychiatry*. 2006;28(5):396-402.

61. Henselmans I, Helgeson VS, Seltman H, de Vries J, Sanderman R, Ranchor AV. Identification and prediction of distress trajectories in the first year after a breast cancer diagnosis. *Health Psychology*. 2010;29(2):160.

62. Lam WW, Bonanno GA, Mancini AD, et al. Trajectories of psychological distress among Chinese women diagnosed with breast cancer. *Psycho-Oncology*. 2010;19(10):1044-1051.

63. Helgeson VS, Snyder P, Seltman H. Psychological and physical adjustment to breast cancer over 4 years: identifying distinct trajectories of change. *Health Psychology*. 2004;23(1):3.

64. Dunn LB, Cooper BA, Neuhaus J, et al. Identification of distinct depressive symptom trajectories in women following surgery for breast cancer. *Health psychology*. 2011;30(6):683.

65. Compas BE, Stoll MF, Thomsen AH, Oppedisano G, Epping-Jordan JE, Krag DN. Adjustment to breast cancer: age-related differences in coping and emotional distress. *Breast cancer research and treatment*. 1999;54(3):195-203.

66. Ganz PA, Kwan L, Stanton AL, Bower JE, Belin TR. Physical and psychosocial recovery in the year after primary treatment of breast cancer. *Journal of Clinical Oncology*. 2011;29(9):1101.

67. McCorry NK, Dempster M, Quinn J, et al. Illness perception clusters at diagnosis predict psychological distress among women with breast cancer at 6 months post diagnosis. *Psycho-Oncology*. 2013;22(3):692-698.

68. Wong-Kim EC, Bloom JR. Depression experienced by young women newly diagnosed with breast cancer. *Psycho-Oncology: Journal of the Psychological, Social and Behavioral Dimensions of Cancer*. 2005;14(7):564-573.

69. Crane TE, Badger TA, Sikorskii A, Segrin C, Hsu C-H, Rosenfeld AG. Trajectories of Depression and Anxiety in Latina Breast Cancer Survivors. 2019:

70. Stanton AL, Wiley JF, Krull JL, et al. Depressive episodes, symptoms, and trajectories in women recently diagnosed with breast cancer. *Breast cancer research and treatment*. 2015;154(1):105-115.

71. Lotfi-Jam K, Gough K, Schofield P, Aranda S, Jefford M. A longitudinal study of four unique trajectories of psychological distress in cancer survivors after completing potentially curative treatment. *Acta Oncologica*. 2019;58(5):782-789.

72. Brady MJ, Cella DF, Mo F, et al. Reliability and validity of the Functional Assessment of Cancer Therapy-Breast quality-of-life instrument. *Journal of clinical oncology*. 1997;15(3):974-986.

73. Stern AF. The hospital anxiety and depression scale. *Occupational medicine*. 2014;64(5):393-394.

74. Abu-Helalah M, Al-Hanaqta M, Alshraideh H, Abdulbaqi N, Hijazeen J. Quality of life and psychological well-being of breast cancer survivors in Jordan. *Asian Pacific Journal of Cancer Prevention*. 2014;15(14):5927-5936.

75. Patoo M, Allahyari AA, Moradi AR, Payandeh M. Persian version of functional assessment of Cancer therapy-breast (FACT-B) scale: confirmatory factor analysis and psychometric properties. *Asian Pacific Journal of Cancer Prevention*. 2015;16(9):3799-3803.

76. Andersen BL, DeRubeis RJ, Berman BS, et al. Screening, assessment, and care of anxiety and depressive symptoms in adults with cancer: an American Society of Clinical Oncology guideline adaptation. *Journal of Clinical Oncology*. 2014;32(15):1605.

77. Howell D, Keshavarz H, Esplen M, et al. Pan-Canadian practice guideline: screening, assessment and management of psychosocial distress, depression and anxiety in adults with cancer. *Canadian Partnership Against Cancer, Canadian Association of Psychosocial Oncology*. 2015;

78. Rojas MPM, Telaro E, Moschetti I, et al. Follow-up strategies for women treated for early breast cancer. *Cochrane Database of Systematic Reviews*. 2000;(4)

CHAPTER 2: SPECIFIC RESEARCH AIMS

Due to improved treatment and the high incidence of breast cancer (126 per 100,000 women in the US from 2013-2018), the number of breast cancer (BC) survivors is increasing.[1] BC diagnosis is associated with subsequent emotional and functional decline (e.g., symptoms of depression, anxiety).[2-4] However, emotional and functional decline in cancer patients is often overlooked and under-treated,[5-7] which could significantly impact daily functioning and treatment outcomes.[8-11] Few studies have evaluated long-term emotional and functional well-being in BC survivors.

While previous studies have demonstrated different patterns of psychosocial distress following BC diagnosis, crucial knowledge gaps remain. First, the majority of previous studies have study population consisting of predominately white[12-16] and older women,[12-19] which limits the ability to explore potential racial disparity in mental health trajectories. This is important to understand because emotional and functional impact of cancer in general was significantly worse for Black women[20]. Second, the longest follow-up of previous studies is 4 years post BC diagnosis.[14] BC recurrence could happen after 4 years following the initial diagnosis, especially for Black women,[21] which could influence emotional and functional adjustment during survivorship. Therefore, understanding long-term emotional and functional well-being is critical to designing preventive interventions and fulfilling the unmet emotional and functional needs.

The purpose of this dissertation is 1) to characterize long-term emotional and functional well-being overall and in association with demographic characteristics (i.e., age, race) and

clinical correlates (i.e., BC surgery type, chemotherapy, BC recurrence); and 2) to contribute to literature on descriptive epidemiology of trajectories of emotional and functional well-being in breast cancer survivors and explore possible disparities by age, race, and other characteristics. Two major aims will be addressed:

Aim 1a: To quantitatively characterize long-term emotional and functional well-being, and to compare with norm scores among a general U.S. adult population.

Aim 1b. To evaluate whether demographic characteristics (i.e., age, race) and clinical correlates (i.e., BC surgery type, chemotherapy, BC recurrence) influence long-term emotional and functional well-being.

Approach: Emotional and functional well-being was assessed by the Functional Assessment of Cancer Therapy - Breast (FACT-B) at baseline and at long-term time points. Mean and standard deviation will be calculated for the well-being score at each survey, and the score at each follow-up survey will be compared to baseline and the norm scores of mental health of a general U.S. adult population.[22] Changes in well-being from baseline to long-term time points will be estimated overall and in association with demographic and clinical characteristics.

Hypothesis: We hypothesize that relative to baseline, overall emotional and functional well-being among BC survivors is decreased at 25 months but recovers in the long run and approaches the U.S. norm levels; Black women, younger women, and women with BC recurrence, chemotherapy, and mastectomy have lower levels of well-being at follow-up surveys relative to the baseline.

Aim 2: To identify trajectories of emotional and functional well-being and assess associations with individual and clinical characteristics.

Approach: Based on participants' FACT-B scores, latent class growth analysis (LCGA), a person-centered approach, will be used to divide BC survivors into subgroups, such that individuals within a group (i.e., class) have similar patterns of change in emotional and functional well-being over time.[23] The frequency of these trajectory groups will be estimated overall, and in association with race, age, socioeconomic status (SES) composites (i.e., education, marital status, household income, insurance), and breast cancer-related clinical characteristics (i.e., cancer stage, surgery type, chemotherapy, recurrence status). Relative frequency differences will be used as the measure of association.

Hypothesis: We hypothesize that there are multiple distinct well-being trajectory groups (e.g., "consistently good", "consistently medium", "initially poor then improved", "chronically poor"). The frequency of "chronically poor" group will be higher among younger women, Black women, women with poorer SES status (e.g., less educated, not married, lower household income, no insurance), and women with poorer clinical characteristics (e.g., more advanced cancer stage, BC recurrence, receiving mastectomy, receiving chemotherapy).

Understanding how women's emotional and functional well-being relates to BC history will allow health care providers to better track and identify patients requiring referral and could help development of targeted emotional and functional support for survivors with specific demographic and clinical characteristics.

REFERENCES

1. Siegel RL, Miller KD, Fuchs HE, Jemal A. Cancer statistics, 2021. *CA: a cancer journal for clinicians*. 2021;71(1):7-33.

2. Linden W, Vodermaier A, MacKenzie R, Greig D. Anxiety and depression after cancer diagnosis: prevalence rates by cancer type, gender, and age. *Journal of affective disorders*. 2012;141(2-3):343-351.

3. Zabora J, BrintzenhofeSzoc K, Curbow B, Hooker C, Piantadosi S. The prevalence of psychological distress by cancer site. *Psycho-Oncology: Journal of the Psychological, Social and Behavioral Dimensions of Cancer*. 2001;10(1):19-28.

4. Massie MJ. Prevalence of depression in patients with cancer. *JNCI Monographs*. 2004;2004(32):57-71.

5. Fallowfield L, Ratcliffe D, Jenkins V, Saul J. Psychiatric morbidity and its recognition by doctors in patients with cancer. *British journal of cancer*. 2001;84(8):1011-1015.

6. Boyes AW, Girgis A, D'Este CA, Zucca AC, Lecathelinais C, Carey ML. Prevalence and predictors of the short-term trajectory of anxiety and depression in the first year after a cancer diagnosis: a population-based longitudinal study. *Journal of Clinical Oncology*. 2013;31(21):2724-2729.

7. von Heymann-Horan AB, Dalton SO, Dziekanska A, et al. Unmet needs of women with breast cancer during and after primary treatment: a prospective study in Denmark. *Acta Oncologica*. 2013;52(2):382-390.

8. Payne DK, Sullivan MD, Massie MJ. Women's psychological reactions to breast cancer. 1996:89-97.

9. Howard-Anderson J, Ganz PA, Bower JE, Stanton AL. Quality of life, fertility concerns, and behavioral health outcomes in younger breast cancer survivors: a systematic review. *Journal of the National Cancer Institute*. 2012;104(5):386-405.

10. Maass SW, Roorda C, Berendsen AJ, Verhaak PF, de Bock GH. The prevalence of long-term symptoms of depression and anxiety after breast cancer treatment: a systematic review. *Maturitas*. 2015;82(1):100-108.

11. Carreira H, Williams R, Müller M, Harewood R, Stanway S, Bhaskaran K. Associations between breast cancer survivorship and adverse mental health outcomes: a systematic review. *JNCI: Journal of the National Cancer Institute*. 2018;110(12):1311-1327.

12. Avis NE, Levine BJ, Case LD, Naftalis EZ, Van Zee KJ. Trajectories of depressive symptoms following breast cancer diagnosis. *Cancer Epidemiology, Biomarkers & Prevention*. 2015;24(11):1789-1795.

13. Deshields T, Tibbs T, Fan MY, Taylor M. Differences in patterns of depression after treatment for breast cancer. *Psycho-Oncology: Journal of the Psychological, Social and Behavioral Dimensions of Cancer*. 2006;15(5):398-406.

14. Helgeson VS, Snyder P, Seltman H. Psychological and physical adjustment to breast cancer over 4 years: identifying distinct trajectories of change. *Health Psychology*. 2004;23(1):3.

15. Dunn LB, Cooper BA, Neuhaus J, et al. Identification of distinct depressive symptom trajectories in women following surgery for breast cancer. *Health psychology*. 2011;30(6):683.

16. Stanton AL, Wiley JF, Krull JL, et al. Depressive episodes, symptoms, and trajectories in women recently diagnosed with breast cancer. *Breast cancer research and treatment*. 2015;154(1):105-115.

17. Henselmans I, Helgeson VS, Seltman H, de Vries J, Sanderman R, Ranchor AV. Identification and prediction of distress trajectories in the first year after a breast cancer diagnosis. *Health Psychology*. 2010;29(2):160.

18. Lam WW, Bonanno GA, Mancini AD, et al. Trajectories of psychological distress among Chinese women diagnosed with breast cancer. *Psycho-Oncology*. 2010;19(10):1044-1051.

19. Crane TE, Badger TA, Sikorskii A, Segrin C, Hsu C-H, Rosenfeld AG. Trajectories of Depression and Anxiety in Latina Breast Cancer Survivors. 2019:

20. Alcalá HE. Differential mental health impact of cancer across racial/ethnic groups: findings from a population-based study in California. *BMC public health*. 2014;14(1):1-9.

21. Benefield HC, Reeder-Hayes KE, Nichols HB, et al. Outcomes of hormone-receptor positive, HER2-negative breast cancers by race and tumor biological features. *JNCI Cancer Spectrum*. 2021;5(1):pkaa072.

22. Pearman T, Yanez B, Peipert J, Wortman K, Beaumont J, Cella D. Ambulatory cancer and US general population reference values and cutoff scores for the functional assessment of cancer therapy. *Cancer*. 2014;120(18):2902-2909.

23. Grimm KJ, Helm JL. Latent class analysis and growth mixture models. *The Encyclopedia of Adulthood and Aging*. 2015:1-7.

CHAPTER 3: RESEARCH STRATEGY

3.1 Study Design Overview

The proposed study will be a longitudinal study of long-term emotional and functional well-being and their trajectories among BC survivors from the third phase of the Carolina Breast Cancer Study (CBCS3). Repeated measures of emotional and functional well-being at baseline (approximately 5 months post diagnosis), 25 months, and 84 months post diagnosis (3 measurements in total) will be utilized to examine their association with demographic characteristics and clinical correlates (Aim 1), and to identify subgroups of women with similar well-being trajectories over time (Aim 2).

3.2 Study Design and Data Collection

3.2.1 Study Design

The proposed study will be a longitudinal study using data from the CBCS-III, which is a large population-based case-only study of racially diverse women with BC (50% Black women). Demographics (e.g., race and age) and HRQoL data were collected in-person by nurses within 9 months of BC diagnosis. Emotional and functional well-being was measured by the Functional Assessment of Cancer Therapy - Breast (FACT-B) at baseline (approximately 5 months post diagnosis), 25 months, and 84 months post diagnosis. Data on the first BC recurrence (classified as “Local”, “Regional”, or “Distant”), chemotherapy, and types of surgery were extracted from participants’ certified medical records. Pathology report data provided information regarding tumor stage and grade. Information over 84-month follow-up survey is being ascertained for this

proposed study. To our knowledge, no previous research has been conducted over such an extended period of follow-up. The longitudinal study design and repeated measurements of emotional and functional well-being offer us an opportunity to assess long-term well-being and identify unobserved subgroups of BC survivors with similar trajectories of well-being and examine potential differences by race, age, and other important characteristics.

3.2.2 Study Population

The Carolina Breast Cancer Study (CBCS) is a population-based study designed to identify causes of breast cancer among female residents of North Carolina by taking into account both genetic and environmental contributions to the disease.[1] The third phase of CBCS (CBCS3) is a prospective, population-based case-only study based in 44 counties in eastern and central North Carolina.[2] This study was initiated to comprehensively evaluate the survivorship following invasive breast cancer diagnosis.[2] Eligibility for study participation was limited to those individuals who were female, English-speaking, newly diagnosed with invasive breast cancer, and aged 20 to 74 years. Younger (<50 years in age) and Black cases were oversampled by randomized recruitment from the following strata: (i) Black women <50 years old, (ii) Black women ≥50 years old, (iii) non-Black women <50 years old, and (iv) non-Black women ≥50 years old, with sampling fractions of 100%, 60%, 40%, and 15%, respectively.[2] Therefore these underrepresented subpopulations would represent approximately 50% of the study population. To achieve representativeness, CBCS enrolled women in rural and urban areas, women with private, public or no insurance, and women of varying household incomes.[2] Through rapid case ascertainment and within two months of diagnosis, a total of 2,998 incident, invasive, pathologically confirmed BC cases were identified between May 1, 2008 and October 21, 2013 from the North Carolina Central Cancer Registry.[2]

Study participants were interviewed in-person by trained nurses about information on sociodemographics, lifestyle factors, and HRQoL (including emotional and functional well-being) within 9 months of BC diagnosis and at a median of 5.2 months post diagnosis.[3] At the initial interview, participants consented for researchers to abstract their medical records by chart review to collect information on BC treatment, types of surgery, BC recurrence, and comorbidities.[4] Tumor characteristics (e.g., stage, grade) were ascertained from pathology laboratory reports.[5] By design, participants completed follow-up questionnaires for HRQoL via mail at a median of 25 months, and 84 months post diagnosis. Study retention rates were 85.4% and 62.5% of eligible women completing the follow-up surveys at 25 months and 84 months, respectively (as shown in Table 3.1).

Table 3. 1 Survey retention rates by race in the third phase of the Carolina Breast Cancer Study (CBCS3)

	Complete: Black participants	Retention rate: Black participants	Complete: non-Black* participants	Retention rate: non-Black participants	Completed total	Retention rate of total participants
Baseline	1495	-	1503	-	2998	100%
25 months post diagnosis	1229	82.2%	1332	88.6%	2561	85.4%
84 months post diagnosis	865	57.9%	1010	67.2%	1875	62.5%

*Participants were asked to self-identify themselves as “White”, “African American/Black”, “American Indian, Eskimo”, “Asian or Pacific Islander”, or “Other”. In this table, “White”, “American Indian, Eskimo”, “Asian or Pacific Islander” and “Other” are collapsed into one race category as “non-Black”, because approximately 50% of the population was Black and 50% was non-Black.

Inclusion and exclusion criteria:

i. For this specific study, we will only include survivors diagnosed with stage I-III BC, because treatment and prognosis are very different for women with stage I-III BC vs. those with stage IV BC.[6]

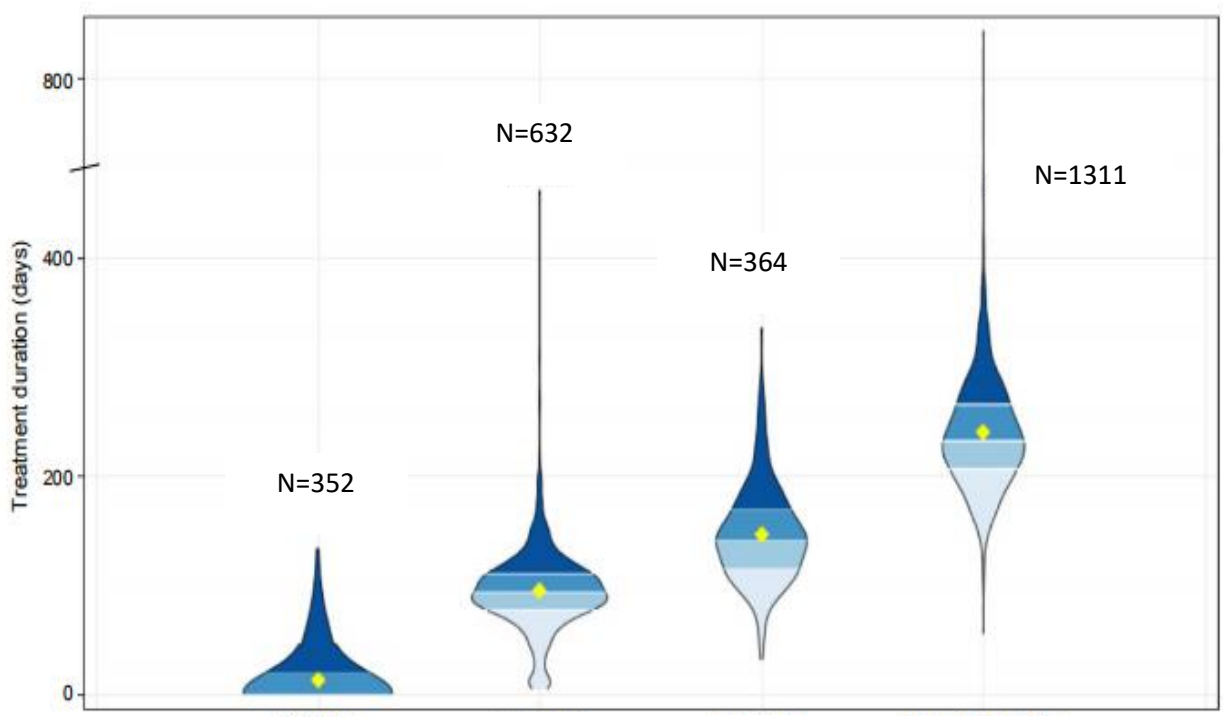
ii. Subjects who did not have their first course surgery will be excluded, because one of the exposures of interest is breast cancer surgery type.

iii. Subjects who had their first course chemotherapy but did not finish it by the 25-month follow-up survey will be excluded. Subjects with prolonged treatment (defined as treatment duration in the 4th quartile of the distribution shown in Figure 3.1) should be considered as outliers,[7] because they could produce skewed well-being trajectories due to potentially extra burden reflected by their long treatment duration. Participants had no first course chemotherapy/radiation therapy will remain in the study.

iv. Women identifying themselves as "American Indian, Eskimo", "Asian or Pacific Islander", "Other races", or "Hispanic" will be excluded due to their small representation (3%).[3] Because Black breast cancer survivors were underrepresented in previous studies, this dissertation aims to better understand Black participants' well-being experience. Although this study planned to be inclusive of other races than Black and white, and Black participants could be compared to non-Black counterparts, we have to exclude women of races other than Black or white as well as Hispanic women, because the proportion of other races and Hispanic women is so small (less than 3% of the total population) that it makes the non-Black population consisting mostly of white women. That means comparisons between Black and non-Black participants will be essentially comparisons between Black and white

women. Additionally, women of other races or Hispanic women were not oversampled as Black women, therefore they might not be representative of the true subpopulations.

v. Women who did not complete the FACT-B at baseline will be excluded.



	Surgery only	Surgery & radiation	Surgery & chemotherapy	Surgery, radiation, & chemotherapy
25th %ile	0	77	115	206
Median	0	94	141	233
Mean	13.7	94.9	146.3	239.8
75th %ile	20	111	169	266

Figure 3. 1 Distribution of the treatment duration by treatment group. Adapted from Reeder-Hayes, 2019[7]

After the study criteria, there will be 2,767 participants included in this specific study. Compared to white women, Black women were more likely to have higher BMI, lower household income, public health insurance, and more advanced breast cancer; Older women were more likely to have public health insurance, less advanced breast cancer stage, and breast conservation surgery, but less likely to have chemotherapy (as shown in Table 3.2).

Table 3. 2 Baseline characteristics of women in the Carolina Breast Cancer Study 3 (2008-2013)

Characteristics	All cases N=2,781 Unweighted %	Race and age, y: White <50 N=667 Unweighted %	White ≥50 N=713 Unweighted %	Black <50 N=699 Unweighted %	Black ≥50 N=702 Unweighted %
Married (Yes)	56.42	75.1	67.5	43.8	40.0
Education					
<HS	7.6	2.4	6.3	6.4	15.1
HS graduate/GED[a]	52.8	38.8	55.0	57.1	59.4
College+	39.6	58.8	38.7	36.5	25.5
Household income ($USD)					
<$15K	15.9	4.8	8.8	22.0	27.6
$15K-$50K	38.0	26.1	33.9	44.3	47.6
≥$50K	46.1	69.2	57.3	33.8	24.9
Insurance type					
Public only	20.1	7.8	12.6	28.3	31.3
Private only	59.1	86.1	51.8	58.4	41.6
Other	15.0	1.8	33.2	4.0	19.9
None	5.7	4.4	2.4	9.0	7.1
Cancer stage					
I	42.6	40.9	56.8	27.2	45.2
II	42.3	44.5	32.1	52.2	40.7
III	15.1	14.5	11.1	20.6	14.1
Surgery type					
Mastectomy	45.6	58.5	37.9	49.1	37.8
Breast conservation surgery	54.4	41.5	62.1	50.9	62.3
Chemotherapy (Yes)	64.2	70.0	46.7	81.3	59.4
Recurrence (Yes)	14.7	12.0	11.2	20.7	14.8
Comorbid factors					
Diabetes	14.9	3.0	13.5	8.9	33.5
COPD[b]	2.6	1.5	4.5	1.1	3.1
Heart disease	5.2	1.1	8.6	2.3	8.7
Hypertension	44.3	15.6	46.0	38.8	75.5

[a.] GED = General Education Diploma.

[b.] COPD = chronic obstructive pulmonary disease.

The CBCS3 is uniquely poised to answer questions about long-term emotional and functional well-being and distinct well-being trajectories in BC survivors. Multiple assessments of emotional and functional well-being allow us to capture different patterns of change in well-being over time among BC survivors. Additionally, CBCS3 is racially diverse, offering advantages over other cohorts, which were predominantly white women. This feature provides

the opportunity of addressing potential racial disparity of well-being trajectories among BC survivors.

3.2.3 Outcome Assessment and Construction

Because both aims will use emotional and functional well-being at multiple time points and the primary difference is in analytical methods, outcome assessment will be described at once for both aims. Study participants were interviewed in-person by trained nurses on HRQoL (including physical, emotional, functional and social well-being) within 9 months of BC diagnosis and at a median of 5.2 months post diagnosis (referred to as the baseline survey).[3] By design, HRQoL was repeatedly assessed at baseline and in follow-up surveys by mail at a median of 25 months and 84 months post diagnosis by the FACT-B questionnaire, a 44-item BC-specific instrument that has been psychometrically validated and shown to be sensitive to changes over time in women with BC.[8] Emotional and functional well-being was assessed by the emotional and the functional well-being subscales of the FACT-B. The emotional well-being section mainly consists of statements related to coping with BC (e.g., “I feel sad”, “I worry about dying”), and the functional well-being section includes statements on whether BC affects normal life and work (e.g., “I am able to enjoy life”, “I am sleeping well”). Participants were asked to indicate how true each statement has been for them during the past 7 days. An item score ranges from 0-4 as “Not at all”, “A little bit”, “Somewhat”, “Quite a bit”, and “Very much”. Subscale scores will be derived and added as the total score. The higher the score, the better the well-being.

Table 3.3 shows that questions from the emotional and functional well-being subscales are phrased either positively or negatively. Directionality is considered and accounted for by the algorithm of calculating the subscale scores. Reversals will be performed as indicated, and

individual item scores will be summed to obtain an overall score. The sum will be multiplied by the number of items in the subscale and then divided by the number of items answered, which produces the subscale score. The total score will be derived by adding the two subscale scores, ranging from 0-52. Same procedures will be repeated for all three measurements of emotional and functional well-being (baseline, 25 months, and 84 months post diagnosis).

Table 3. 3 Items for the FACT-B emotional and functional subscales

Description	**Operationalization**	
Emotional well-being subscale (6 questions in total, 6 of which are related to mental health; range: 0-24)	Item	Reverse item?
	1. I feel sad	✓
	2. I am satisfied with how I am coping with my illness	
	3. I am losing hope in the fight against my illness	✓
	4. I feel nervous	✓
	5. I worry about dying	✓
	6. I worry that my condition will get worse	✓
Functional well-being subscale (7 questions in total, 5 of which are related to mental health; range: 0-28)	Item	Reverse item?
	1. I am able to work (include work at home)	
	2. My work (include work at home) is fulfilling	
	3. I am able to enjoy life	
	4. I have accepted my illness	
	5. I am sleeping well	
	6. I am enjoying the things I usually do for fun	
	7. I am content with the quality of my life right now	

Long-term emotional and functional well-being is typically considered as well-being over 2 years after BC diagnosis. This cutoff was chosen because most initial emotional and functional decline (e.g., symptoms of depression, anxiety) episodes were resolved at around four months, with a further fall-off after two years.[9] Long-term emotional and functional well-being in this specific study will be represented by well-being assessed 84 months post diagnosis. A conceptual diagram is presented in Figure 3.2.

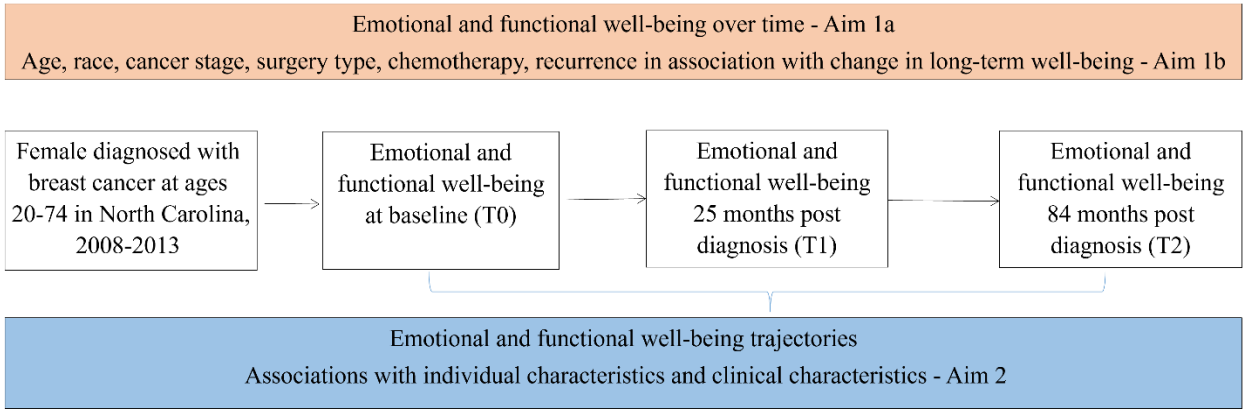


Figure 3. 2 Conceptual diagram

3.2.4 Exposure Assessment and Construction

Information on individual characteristics was collected in-person by nurses at baseline. Patients were asked to self-identify themselves as “White”, “Black/African American”, “American Indian”, “Asian or Pacific Islander”, or “Other”. A binary variable will be created for race as “White” and “Black”, and participants self-identified as “American Indian, Eskimo”, “Asian or Pacific Islander” and “Other” will be excluded due to small representation (3%).[3] A binary variable will be created for age at diagnosis as <50, or ≥ 50 years, in which participants aged under 50 years represented younger women. Patients were asked: “What is the highest level of school that you completed?” A binary variable will be created for education, in which “0-8

years" and "9-12 years, but not a high school graduate" will be combined as "<High school (HS)", "High school graduate (or GED)", and "Technical or business school", and "some college" will be combine as "HS and post HS", "College graduate" and "Post-graduate or professional degree" will be combined as "College+". Patients were asked to identify themselves as "Never married or lived as married", "Married, or living as married", "Widowed", or "Separated, divorced, or no longer living as married". A binary variable will be created for marital status, in which all categories except "Married, or living as married" will be combined as "Not married". Patients were asked about their total family income range before taxes during the previous year. According to this, household income will be categorized into "USD<$15K" (including "Less than $5,000", "$5,000 to $10,000", and "$10,000 to $15,000"), "$15K to $50K" (including "$15,000 to $20,000", "$20,000 to $30,000", and "$30,000 to $50,000"), and ">$50K" (including "$50,000 to $100,000", and "More than $100,000"). Participants' insurance type will be "Private" (including "Private health insurance purchased on your own or by your husband or partner", and "Private health insurance from your employer or workplace or that of your husband or partner"), "Public" (including "Medicaid" and "Medicare"), "Other" (except "Private" and "Public"), and "None".

Table 3. 4 Operationalization for exposure variables

Variable	Source	Operationalization
Race	Baseline questionnaire	Black, White
Age at diagnosis	Baseline questionnaire	<50, ≥50 years
Education	Baseline questionnaire	<HS, HS and post HS, College+
Marital status	Baseline questionnaire	Married, Not married
Household income	Baseline questionnaire	USD<$15K, $15K-$50K, >$50K
Insurance	Baseline questionnaire	Private, Public, Other, None
Cancer stage	Pathology report	I, II, III
Surgery type	Medical record	Breast conservation surgery, Mastectomy
Chemotherapy	Medical record	Yes, No
Recurrence	Medical record	Yes, No

Pathology report data provided information regarding tumor stage (I-III). Patients with stage IV BC will be excluded from this study. At the initial interview, participants consented for researchers to abstract their medical records by chart review.[4] Patients' surgery type will be categorized as "Breast conservation surgery (BCS)" and "Mastectomy". Binary variables (Yes or No) will be created for chemotherapy. Updated information on BC recurrence was extracted from participants' certified medical records at multiple time points.[10] A binary variable ("Ever had subsequent recurrent breast cancer", Yes or No) will be created for BC recurrence based on information of the first subsequent recurrence type ("Local", "Regional", "Distant").

A variable for treatment duration will be considered for surgery and chemotherapy in potential sensitivity analysis, because the time of treatment completion in addition to treatment type might influence long-term well-being as well as well-being trajectories. Similarly, the

distribution of time to first recurrence will be investigated. If most of first recurrences happen before the 25-month survey, the variable for recurrence will be remained as binary (Yes/No); if first recurrences are common after the 25-month survey, a categorical variable incorporating time to recurrence will be considered (e.g., recurrence 24 months, 60 months, or 72 months post diagnosis) in sensitivity analyses.

3.2.5 Covariate Assessment and Construction

Aim 1a is a descriptive analysis and does not include modeling process, so there are no additional covariates for them. Information on comorbid conditions (e.g., diabetes, chronic obstructive pulmonary disease [COPD], heart disease, hypertension) at baseline will be collected from medical records, because only baseline comorbidities occurred before surgery type and chemotherapy were determined or recurrence happened, thus are able to behave as confounders. Statistical models for clinical characteristics in Aim 1b will condition on demographic characteristics (i.e., age, race), cancer stage, and comorbid conditions, which were identified as confounders a priori with the use of a directed acyclic graph (DAG, as shown in Figure 3.3). For Aim 2, relative frequency differences (RFDs) for age and race will be adjusted for each other, and RFDs for other factors of interest will be adjusted for both race and age.

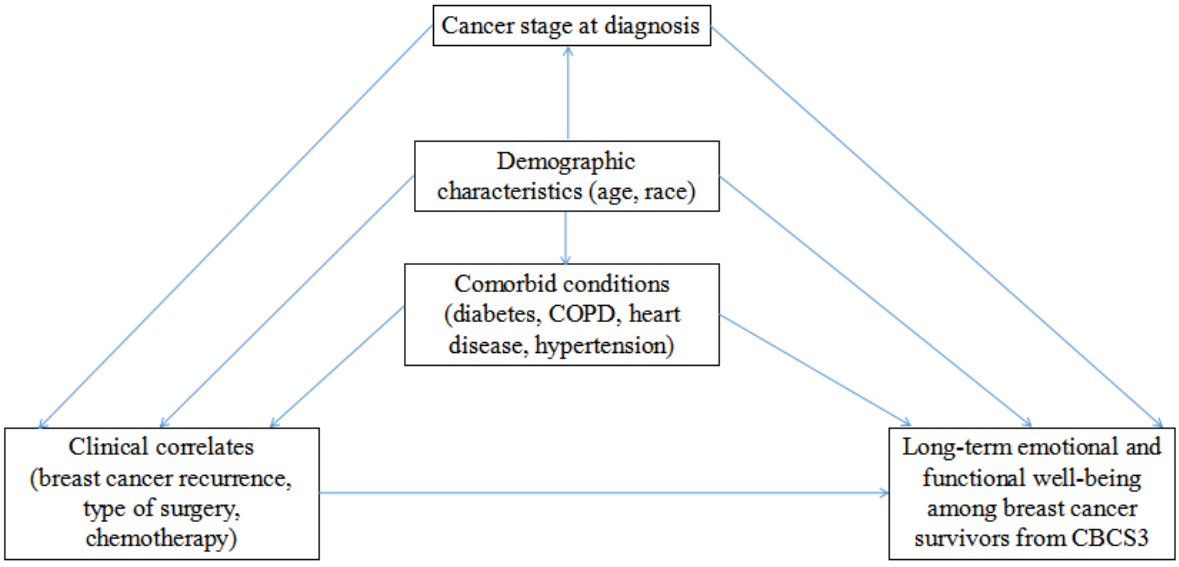


Figure 3. 3 Directed acyclic graph for the association between clinical correlates (i.e., breast cancer recurrence, type of surgery, chemotherapy) and long-term emotional and functional well-being (25- and 84-months post diagnosis) changes

3.3 Statistical Analysis

The primary objective of the proposed study is to characterize long-term emotional and functional well-being and assess its relationship with demographic characteristics and clinical correlates (Aim 1), and to investigate different patterns of change in emotional and functional well-being among BC survivors (Aim 2). There are four principle analyses to accomplish these aims: (A) description of change in emotional and functional well-being from baseline to long-term time points, (B) estimation of associations between demographic and clinical features and change in emotional and functional well-being, (C) identification of well-being trajectories among the BC survivor population, and (D) description of trajectories distribution within groups of race, age, SES composites, and other important disease and treatment characteristics.

3.3.1 Aim 1: Multinomial Logit Model

As the baseline assessment could potentially be conducted soon after the diagnosis - a time at which participants are expected to be quite distressed, and at a level of distress that is not expected to maintain so high, participants with longer survey time (e.g., 9 months post diagnosis) might have better well-being compared to those with shorter survey time (e.g., 1 month post diagnosis). Therefore, a basic descriptive analysis will be performed to investigate the baseline well-being scores distribution against the baseline survey time. If well-being scores are not evenly distributed, survey time since diagnosis will be adjusted for baseline well-being.

Both weighted and unweighted mean and standard deviation will be calculated for the total scores of the emotional and functional well-being subscales at each survey, and the subscale scores at each follow-up survey will be compared to baseline and the norm scores among a general U.S. adult population, where the mean scores are 19.9 and 18.5 for emotional well-being and functional well-being, respectively.[11] The purpose of comparing to a general population is to understand the level of emotional and functional well-being among breast cancer survivors in North Carolina relative to the level among a country-wise population and provide a context of CBCS3's uniqueness. We anticipate that well-being will be different for these two populations. Changes in emotional and functional well-being from baseline to 25 months and 84 months post diagnosis will be estimated in association with demographic (i.e., age, race) and clinical characteristics (i.e., cancer stage, BC surgery type, chemotherapy, recurrence).

Cutoffs of score change (e.g., increase >4, no obvious change, decrease >4, relative to baseline) will be explored and determined by reviewing relevant literature. Multinomial logit models will be used to estimate odds ratios (ORs) and 95% confidence intervals (95% CIs)[12] for associations between age, race and change in well-being scores, as well as for associations of BC

stage, surgery type, chemotherapy, recurrence, adjusting for age, race, cancer stage, and comorbidity conditions.

3.3.2 Aim 2: Latent Class Growth Analysis

Based on FACT-B scores of BC survivors, latent class growth analysis (LCGA) will be used to classify women into distinctive trajectories of emotional and functional well-being, so that there is homogeneity within a trajectory group in scores over time and heterogeneity between groups.[13] LCGA has been increasingly recognized for its usefulness for identifying homogeneous subpopulations within the larger heterogeneous population and for the identification of meaningful groups or classes of individuals.[14] This innovative approach goes beyond conventional analyses that examine only mean levels of emotional and functional well-being in predetermined strata (e.g., age groups or strata defined by cutoff points of instrument scores) and presents a more detailed portrait of women displaying different patterns of change in well-being over time.[15]

The group-based SAS PROC TRAJ procedure for LCGA will identify distinct subgroups of women who had similar trajectories in their total scores of the emotional and the functional well-being subscales from the FACT-B. LCGA will define the well-being trajectories based on the patterns of change over time and assigns posterior probabilities, which are estimates of a specific individual's probabilities of belonging to each of the model's trajectory groups. Women will be assigned to the group for which they have the maximum posterior probability.

Trajectories of the total scores will be modeled as a function of survey time (in month) since diagnosis. The total scores of the emotional and the functional subscales at each survey will be the dependent variable, and survey time (in month) since diagnosis will be the independent variable modeled in a linear term plus a quadratic term.[16] Models will be tested examining one to

seven trajectory group(s). A combination of a statistical criterion (the Bayesian information criterion [BIC], and Akaike's information criterion [AIC]; higher BIC and AIC indicate better model fit) and subjective judgment (distinctiveness of trajectories) will be used to select the optimal number of groups. The model function can be written as:

$(y_{it}^{*}) = \beta_0^j + \beta_1^j X_{it} + \beta_2^j X_{it}^2 + \varepsilon_{it}$, where

(y_{it}^{*}) is a latent variable that represents the predicted score on a given dependent variable Y (which will be individual scores of the emotional and the functional well-being subscales at each survey)

j is a given trajectory

t is a specific time point

i is a specific participant

X_{it}, and X_{it}^2 represent the independent variable (i.e., survey time since diagnosis) entered in a linear or squared term, respectively

β_0^j, β_1^j, and β_2^j are the parameters defining the intercept and slopes (i.e., linear, quadratic) of the trajectory for a specific subgroup (j)

ε_{it} is a disturbance term which is assumed to be normally distributed with a mean of zero and a constant standard deviation.

The frequency of these well-being trajectory groups will be calculated within predefined groups of race, age, SES composites (i.e., education, marital status, household income, insurance), and disease and treatment characteristics (i.e., cancer stage, surgery type, chemotherapy, recurrence status). Relative frequency differences will be used to assess the

associations between group membership and the individual and cancer-related variables previously described.

3.4 Discussion

3.4.1 Potential limitations

Limitations of this work include temporal variability in timing of data collection and lack of data on history of mental health problems. The three measurements of emotional and functional well-being of our study were not equidistant on the time scale. There were 59 months between the 25-month survey and the 84-month survey. There might be fluctuation in well-being during this period of time, which might not be fully captured and depicted by only two measurements. Additionally, medically-confirmed baseline psychiatric comorbidities could provide insight into women comprising different well-being trajectories. However, such data was not available in our study.

3.4.2 Strengths of study

This study represents the first large, racially diverse longitudinal study of long term and trajectories of emotional and functional well-being in breast cancer survivors. Compared to previous studies which have between 84 and 653 participants,[13,17-21] the significantly larger population (n~2800) substantially increases the power to detect well-being trajectories. The unique study population also provides the opportunity to address potential race and age disparities in well-being trajectories among BC survivors. The longitudinal study design with repeated measurements of well-being allows us to characterize long-term emotional and functional well-being as well as to depict different patterns of change in well-being along the cancer journey. Furthermore, a novel statistical modeling technique, latent class growth analysis,

will be used to classify women into similar trajectories of emotional and functional well-being. It provides an advantage over other approaches that use predefined groups and has the ability of fully capturing information about unobserved heterogeneity to identify trajectories by assigning posterior probabilities of subgroup membership.[15]

REFERENCES

1. Newman B, Moorman PG, Millikan R, et al. The Carolina Breast Cancer Study: integrating population-based epidemiology and molecular biology. *Breast cancer research and treatment*. 1995;35(1):51-60.

2. McGee SA, Durham DD, Tse C-K, Millikan RC. Determinants of breast cancer treatment delay differ for African American and White women. *Cancer epidemiology, biomarkers & prevention*. 2013;22(7):1227-1238.

3. Pinheiro LC, Tan X, Olshan AF, et al. Examining health-related quality of life patterns in women with breast cancer. *Quality of Life Research*. 2017;26(7):1733-1743.

4. Hair BY, Hayes S, Tse CK, Bell MB, Olshan AF. Racial differences in physical activity among breast cancer survivors: implications for breast cancer care. *Cancer*. 2014;120(14):2174-2182.

5. Allott EH, Cohen SM, Geradts J, et al. Performance of Three-Biomarker Immunohistochemistry for Intrinsic Breast Cancer Subtyping in the AMBER ConsortiumAccuracy of Protein and RNA-Based Breast Cancer Subtyping. *Cancer Epidemiology, Biomarkers & Prevention*. 2016;25(3):470-478.

6. Wheeler SB, Reeder-Hayes KE, Carey LA. Disparities in breast cancer treatment and outcomes: biological, social, and health system determinants and opportunities for research. *The oncologist*. 2013;18(9):986.

7. Reeder-Hayes KE, Mayer SE, Olshan AF, et al. Race and delays in breast cancer treatment across the care continuum in the Carolina Breast Cancer Study. *Cancer*. 2019;125(22):3985-3992.

8. Brady MJ, Cella DF, Mo F, et al. Reliability and validity of the Functional Assessment of Cancer Therapy-Breast quality-of-life instrument. *Journal of clinical oncology*. 1997;15(3):974-986.

9. Burgess C, Cornelius V, Love S, Graham J, Richards M, Ramirez A. Depression and anxiety in women with early breast cancer: five year observational cohort study. *Bmj*. 2005;330(7493):702.

10. Wheeler SB, Spencer J, Pinheiro LC, et al. Endocrine therapy nonadherence and discontinuation in black and white women. *JNCI: Journal of the National Cancer Institute*. 2019;111(5):498-508.

11. Pearman T, Yanez B, Peipert J, Wortman K, Beaumont J, Cella D. Ambulatory cancer and US general population reference values and cutoff scores for the functional assessment of cancer therapy. *Cancer*. 2014;120(18):2902-2909.

12. Ananth CV, Kleinbaum DG. Regression models for ordinal responses: a review of methods and applications. *International journal of epidemiology*. 1997;26(6):1323-1333.

13. Avis NE, Levine BJ, Case LD, Naftalis EZ, Van Zee KJ. Trajectories of depressive symptoms following breast cancer diagnosis. *Cancer Epidemiology, Biomarkers & Prevention*. 2015;24(11):1789-1795.

14. Jung T, Wickrama KA. An introduction to latent class growth analysis and growth mixture modeling. *Social and personality psychology compass*. 2008;2(1):302-317.

15. Nagin DS, Nagin D. *Group-based modeling of development*. Harvard University Press; 2005.

16. Andruff H, Carraro N, Thompson A, Gaudreau P, Louvet B. Latent class growth modelling: a tutorial. *Tutorials in quantitative methods for psychology*. 2009;5(1):11-24.

17. Deshields T, Tibbs T, Fan MY, Taylor M. Differences in patterns of depression after treatment for breast cancer. *Psycho-Oncology: Journal of the Psychological, Social and Behavioral Dimensions of Cancer*. 2006;15(5):398-406.

18. Henselmans I, Helgeson VS, Seltman H, de Vries J, Sanderman R, Ranchor AV. Identification and prediction of distress trajectories in the first year after a breast cancer diagnosis. *Health Psychology*. 2010;29(2):160.

19. Lam WW, Bonanno GA, Mancini AD, et al. Trajectories of psychological distress among Chinese women diagnosed with breast cancer. *Psycho-Oncology*. 2010;19(10):1044-1051.

20. Helgeson VS, Snyder P, Seltman H. Psychological and physical adjustment to breast cancer over 4 years: identifying distinct trajectories of change. *Health Psychology*. 2004;23(1):3.

21. Dunn LB, Cooper BA, Neuhaus J, et al. Identification of distinct depressive symptom trajectories in women following surgery for breast cancer. *Health psychology*. 2011;30(6):683.

CHAPTER 4: EMOTIONAL AND FUNCTIONAL WELL-BEING IN LONG-TERM BREAST CANCER SURVIVORSHIP

4.1 Overview

Background: Emotional and functional well-being are important components of mental health, as well as overall quality of life. This longitudinal study sought to evaluate emotional and functional well-being change in breast cancer survivors up to 84 months following diagnosis, including evaluation of factors associated with change.

Methods: We used data from the Carolina Breast Cancer Study Phase 3, including 2,781 women diagnosed with invasive breast cancer between 2008 to 2013. Participants' emotional and functional well-being were measured using the Functional Assessment of Cancer Therapy – Breast survey at approximately 5- (baseline), and two follow-up timepoints at 25- and 84-months post diagnosis. Multinomial logit models were used to estimate adjusted odds ratios (ORs) and 95% confidence intervals (CIs) for associations between demographic and clinical characteristics and well-being change at each survey timepoint relative to baseline.

Results: Overall, the total of emotional and functional well-being of breast cancer survivors improved over time since diagnosis, with the largest increases during the first 25 months. Younger white women had the greatest increases relative to baseline, whereas older (≥50 years) Black women experienced only slight increases. More advanced cancer stage (OR=1.40, 95% CI=1.02 to 1.93) and older age at diagnosis (OR=1.33, 95% CI=1.08 to 1.67) were associated with emotional and functional well-being decrease at 84 months relative to baseline, whereas Black race (OR=1.25 and 1.32, 95% CI= 1.01 to 1.54, and 1.07 to 1.63,

respectively) and no receipt of chemotherapy (OR=1.79 and 1.82, 95% CI=1.35 to 2.38, and 1.35 to 2.5, respectively) were associated with well-being decrease at both 25 months and 84 months . Breast cancer recurrence was strongly associated with well-being decrease at both follow-up survey timepoints with ORs of 4.7 and 4.3, respectively.

Conclusions: Findings highlight that well-being changes among breast cancer survivors vary by demographics and clinical features. These factors could be used to identify those women at greatest need of emotional and functional support.

4.2 Introduction

Due to improved treatment and the high incidence of breast cancer (127 per 100,000 women in the US from 2014-2019), the number of breast cancer (BC) survivors is increasing.[1,2] For all stages combined, the 5-year relative survival rate of female BC diagnosed during 2011 through 2017 was 90% in the United States.[1] At this time there are more than 3.8 million women living in the U.S. with a history of invasive BC.[3] Breast cancer survivors have a higher burden of impaired emotional and functional well-being (e.g., symptoms of depression, anxiety), relative to the general population.[4-6] Emotional well-being includes happiness, interest in life, and satisfaction, whereas functional well-being represents the ability to perform usual tasks of daily living. Both emotional and functional well-being are important components of mental health and therefore it is crucial to understand the factors linked with decreasing well-being in breast cancer survivors.[7] However, emotional and functional decline in cancer patients is often overlooked and under-treated,[8-10] which could significantly impact daily functioning and treatment outcomes.[11-14] Few studies have evaluated long-term (>2 years post BC diagnosis) emotional and functional well-being in breast cancer survivors. Understanding how emotional and functional well-being

change over time among breast cancer survivors and factors associated with change could facilitate targeted preventive support and fulfill the unmet emotional and functional needs.

Most studies that have examined well-being have used cross-sectional study designs and had wide ranges of survey time following BC diagnosis.[15-21] Among a limited number of longitudinal studies assessing changes in emotional and/or functional well-being in BC survivors, the study populations have predominantly included white participants and participants were followed for short time windows post diagnosis (<=5 years).[22-24] Larger, longitudinal studies are needed to advance understanding of long-term emotional and functional well-being change as well as the related factors in diverse populations.

To address this knowledge gap of how race, age, sociodemographic characteristics, and clinical features might influence long-term emotional and functional well-being among breast cancer survivors, we used data from the third phase of the Carolina Breast Cancer Study (CBCS3). CBCS3 is a population-based racially diverse cohort study of women that oversampled Black and younger (<50 years in age) women diagnosed with BC in North Carolina between 2008 and 2013. Participants were followed for emotional and functional well-being using the Functional Assessment of Cancer Therapy – Breast (FACT-B) at three time points after diagnosis (5-, 25-, and 84-months). Using data from the CBCS, we assessed participants' emotional and functional well-being level at each survey, overall and by individual demographic and clinical characteristics.

4.3 Methods

4.3.1 Study population

This study used data from the third phase of the CBCS, a population-based prospective cohort study.[25] From May 1, 2008, to October 21, 2013, 2,998 women aged 20-74 years with a first diagnosis of invasive breast cancer in 44 counties in North Carolina were identified by rapid case ascertainment from the North Carolina Central Cancer Registry and recruited within two months of diagnosis.[26] The CBCS3 oversampled younger (<50 years in age) and Black women so that they each represent approximately 50% of the study population.[25] This study was conducted following informed consent by all participants, under a protocol approved by the University of North Carolina School of Medicine Institutional Review Board. In this study, we interpret race as a social construct under a cells-to-society framework where molecular, tissue, individual, community-level, and structural factors act simultaneously to influence well-being change.[27]

Study participants were interviewed in-person by trained nurses within 9 months (median 5 months, range 2-9 months) of BC diagnosis.[28] Information on age at diagnosis, self-identified race/ethnicity, and demographic characteristics was collected at the 5-month survey, which is referred to as "baseline survey". Participants also consented at the initial interview for researchers to extract their medical records by chart review and to collect data on their baseline comorbidities, breast cancer (BC) treatment, type of surgery, and recurrence status.[26] Participants also completed two follow-up surveys at medians of 25 months (range 20-36 months) and 84 months (range 60-110 months) post diagnosis, which are referred to as "25-month survey" and "84-month survey", respectively. Tumor characteristics were ascertained from pathology reports.[29]

A total of 2,998 patients with breast cancer in the CBCS3 were screened for study eligibility. The current analysis excluded participants who were diagnosed with stage IV BC (n=109) or who had unknown cancer stage (n=3). Additional exclusions included women who did not have first course surgery within 18 months of diagnosis (n=13), women who had their first course chemotherapy and/or radiation therapy but finished after the 25-month survey (n=2), and women who self-identified themselves as Hispanic or "other race" due to their small representation (n=80). The study further excluded participants who did not finish the FACT-B at baseline (n=10). After applying the study criteria, the final study population consisted of 2,781 participants.

4.3.2 Outcome Ascertainment

The Functional Assessment of Cancer Therapy – Breast (FACT-B) was designed to measure five domains of health-related quality of life (HRQoL) in BC patients: physical, social, emotional and functional well-being as well as a breast cancer subscale.[30] Participants were asked to self-report their emotional and functional well-being status at baseline (mean of 5 months post-diagnosis), 25 months, and 84 months. The emotional well-being section mainly consists of statements related to coping with BC (e.g., "I feel sad", "I worry about dying"), and the functional well-being section includes statements on whether BC affects normal life and work (e.g., "I am able to enjoy life", "I am sleeping well"). The emotional and functional subscales have 13 items in total. Each item was rated on a five-point rating scale ranging from 0 (not at all) to 4 (very much). Because the overlap is considerable between items from the emotional and functional well-being and items from the Hospital Anxiety and Depression Scale, which is a commonly used instrument measuring mental health levels, the sum of the emotional and functional subscale scores represented a participant's well-being in this study and was used

to approximate patients' mental health status; higher total (emotional + functional) score indicated better well-being and mental health status.

4.3.3 Exposure Assessment

Information on demographics was collected in-person at baseline (mean of 5-months post-diagnosis), including age at diagnosis and self-identified race. Cancer stage was obtained from pathology laboratory reports. Data on type of surgery, receipt of chemotherapy, and recurrence status during the follow-up were extracted from patients' medical records.

4.3.4 Covariates

Covariates were identified based on *a priori* knowledge, including associations previously reported for CBCS3, and directed acyclic graphs (DAGs). Socioeconomic status composites (i.e., marital status, education level, household income, and insurance type) were collected from the baseline survey. Medical-record confirmed comorbid conditions (i.e., diabetes, chronic obstructive pulmonary disease, heart disease, and hypertension) were also obtained at baseline.

4.3.5 Statistical Analysis

Individual demographic and clinical features were evaluated in relation to well-being from the FACT-B based on survey completion status. All included participants completed the baseline survey, but 409 and 998 participants did not complete the 25-month FACT-B and the 84-month FACT-B, respectively. Women who did not finish the FACT-B at follow-up surveys differed from women who finished follow-up FACT-Bs (Table 4.1). Participants who did not complete the 25-month and/or the 84-month FACT-B were younger at diagnosis compared to those who completed the follow-up FACT-Bs. Among the participants who did not complete the

follow-up FACT-Bs, the percentage of women with the following characteristics was higher compared to those who completed the follow-up FACT-Bs: Black race, not married, a lower education level, a lower household income, public or no insurance, more advanced cancer stage, received mastectomy, received chemotherapy, baseline comorbid conditions, and had first breast cancer recurrence during the follow-up. The median time to first recurrence since diagnosis was also shorter among participants who recurred and did not complete the follow-up FACT-Bs.

These results indicated that participants who did not complete the follow-up FACT-Bs had lower socioeconomic status and were sicker at baseline than participants who completed the follow-up FACT-Bs. Therefore, we applied "multiple imputation by chained equations (MICE) to impute missing values for emotional and functional well-being scores. This method models each variable with missingness by conditioning on the others. The variable with the least missingness was imputed conditional on all variables with no missingness, and the variable with the second least missingness was then imputed conditional on the variables with no missing values and that first variable which had been imputed, and so on until there were no longer any missing values in the data.[31] To achieve a relative efficiency of 99%, we created 40 imputed complete data sets.[32] In the imputation model, we included age, race, cancer stage, type of BC surgery, chemotherapy, and recurrence status before each FACT-B completion, and we also included auxiliary variables such as marital status, education level, income, insurance type, as well as baseline comorbid conditions, time of survey completion, and previous well-being scores, which were related to the missingness.

Unimputed and imputed means were calculated for the total (emotional + functional) well-being as well as the individual emotional and functional well-being scores at each survey, and the scores at follow-up surveys were compared to baseline. As the CBCS3 oversampled

Black and young women so that these underrepresented subpopulations would represent approximately 50% of the study population, weighted mean scores at each survey timepoint were calculated by using the following strata: (i) Black women <50 years old, (ii) Black women ≥50 years old, (iii) non-Black women <50 years old, and (iv) non-Black women ≥50 years old, with sampling fractions of 100%, 60%, 40%, and 15%, respectively,[25] and were compared to the norm scores among a general U.S. adult population.[33] Total (emotional + functional), which approximated mental health level, as well as individual emotional and functional well-being scores at each survey were also investigated by participants' demographic and clinical characteristics.

Well-being change in total (emotional + functional) score at each follow-up survey relative to baseline was classified into 3 categories based on the minimally important difference: increase⩾ 4, decrease ⩾ 4, and no obvious change. Participants with score increase ⩾ 4 served as the reference group. Multinomial logit models were run separately on each imputed dataset to estimate the odds ratios (ORs) and 95% confidence intervals (95% CIs) for associations between exposure variables and total (emotional + functional) well-being score change at follow-up surveys relative to baseline. Coefficients and covariance matrices were combined across data sets by using SAS procedure PROC MIANALYZE. A minimally important difference of 4 points for changes in total (emotional + functional) score was interpreted as a meaningful difference in clinical and subjective anchors.[34-36] Changes in total (emotional + functional) well-being score at 25- and 84-months were assessed separately. To evaluate potential time-varying influences from recurrence, we conducted sensitivity analyses by restricting our analytic sample to women who never recurred and women who had recurrence but did not recur before baseline survey, as well as by incorporating time to recurrence since diagnosis when constructing the recurrence variable.

Additionally, we performed a sensitivity analysis to investigate factors associated with emotional and functional well-being change, separately.

All statistical tests were two-sided and considered statistically significant at $P<0.05$; statistical analyses were performed using SAS software (version 9.4; SAS Institute, Inc, Cary, NC).

4.4 Results

4.4.1 Well-being Scores over Time

To compare emotional and functional well-being status over time in the overall study population with general population levels, we weighted the study population to the North Carolina population distribution. Unweighted well-being scores tended to be lower for our population which skewed toward Black and younger participants (Figure 4.1 and Supplementary Table 4.1). Imputation shifted the means of well-being score lower, given that participants with no missing data had distinct demographic characteristics. Compared to the general U.S. norms, this population's emotional well-being began slightly lower than the norm at baseline and gradually approached to the norm at follow-up surveys (Figure 4.1a), whereas total (emotional + functional) well-being and functional well-being were at or above the general U.S. norms (Figures 4.1b and 4.1c). Generally, study participants' well-being improved over time with differences in patterns of the emotional and functional well-being domains. The mean emotional well-being score changed little between baseline and 25 months, with some increase observed after 25 months. On the other hand, the mean functional well-being increased substantially between baseline and 25 months and then became relatively stable after 25 months. Temporal patterns for total (emotional + functional) well-being were driven by the larger changes in functional well-being and so reflected the larger increase in the first 25 months.

We further assessed changes in well-being by race and age (Figure 4.2 and Supplementary Figure 4.1). As seen from Figure 4.2A, compared to older (≥50) patients, younger (<50) patients had bigger increases in well-being. Younger white women had the largest increase in their total well-being during the follow-up, in part because of their second lowest baseline well-being (Figure 4.2B), whereas older Black women only experienced a slight increase in well-being since diagnosis. However, Black women seemed to have a larger variation in their well-being score change compared to white women and lower baseline well-being in both age groups. Figure 4.2B also shows that the greater change in well-being score happened between baseline and 25 months. Although on average the well-being was improving for all four categories of age and race cross-classification, Black women never achieved the baseline well-being that white women had, and the well-being scores of younger patients during the follow-up were always below the baseline well-being score of older patients, except that the well-being score at 84 months for younger white women was slightly higher than the baseline score of older white women.

Integration of information from Figures 4.2A and 4.2B indicated that the importance of investigating both individual level and change of well-being to fully understand breast cancer survivor's experience. Thus, for clinical features, we also evaluated emotional, functional, and total (emotional + functional) well-being scores at each survey (Figure 4.3). In general, total (emotional + functional) score increased from baseline to 84 months regardless of chemotherapy status or surgery type. However, this was not the situation for Stage III and recurrent cases. Stage III BC cases had improved well-being at 25 months, but decreased by 84 months. This may be driven by recurrence in some cases, because well-being decreased at both 25 months and 84 months for patients with recurrence. For women who received chemotherapy, their well-being

status was always poorer compared with women who did not receive chemotherapy. Despite the bigger improvement during the follow-up, well-being score at the end for women with chemotherapy was still lower than the level that their counterparts had at baseline. Figure 4.3 also shows that patterns of change for total (emotional + functional) well-being were recapitulated for functional well-being. Again, the majority of the increase in well-being happened earlier for functional well-being, whereas emotional well-being increased more obviously between 25 months and 84 months, although still at a smaller magnitude than functional well-being. Stage III and recurrent cases stood out, with a consistent decline in emotional well-being from baseline to 84 months.

4.4.2 Associations with Well-being Change

Table 4.2 contains the odds ratios obtained from multinomial logit models for relationships of categorized well-being score change relative to baseline with demographic characteristics as well as clinical features. Factors associated with well-being decrease relative to baseline differed slightly between 25 months and 84 months. Black race (1.3-fold) and no chemotherapy (1.8-fold) were moderately and statistically significantly associated with well-being decrease at both 25- and 84-months relative to baseline (1.3- to 1.8-fold). BC recurrence before each corresponding follow-up survey was strongly significantly associated with well-being decrease at both survey timepoints relative to baseline (4.3- to 4.7-fold). Older age and more advanced cancer stage were associated with well-being decrease only at 84 months (1.3- to 1.4-fold). However, surgery type was not significantly associated with well-being change at either follow-up survey. A sensitivity analysis was conducted in which 14 participants who had recurrence before baseline survey were excluded from the models (Supplementary Table 4.2). The ORs from the sensitivity analysis were essentially the same and significance also remained

the same. Additionally, the ORs did not differ substantially from the sensitivity analysis for recurrence incorporating time of recurrence relative to survey completion date (Supplementary Table 4.3).

As a sensitivity analysis, we also assessed emotional and functional well-being according to demographics and clinical factors (Supplementary Table 4.4), and found that emotional well-being decrease at 25 months relative to baseline was only significantly associated with early (before 25-month survey) recurrence, whereas functional well-being decrease at 25 months relative to baseline was significantly associated with Black race, older age, no receipt of chemotherapy, and early breast cancer recurrence. For score change at 84 months relative to baseline, emotional well-being decrease was significantly associated with more advanced cancer stage and recurrence (prior to 84 months), whereas functional well-being decrease was significantly associated with Black race, older age, no receipt of chemotherapy, and breast cancer recurrence.

Table 4. 1 Characteristics of women in the Carolina Breast Cancer Study 3 (2008-2013), N=2,781[a]

Characteristics	Functional assessment of cancer therapy questionnaire completion status				
	Baseline completed N=2,781 %	25-month completed N=2,372 %	25-month not completed N=409 %	84-month completed N=1,783 %	84-month not completed N=998 %
Age, mean (std)	52.0 (11.1)	52.4 (11.0)	49.4 (11.2)	52.6 (10.7)	50.9 (11.6)
Race					
Black	50.4	48.6	60.6	47.1	56.3
White	49.6	51.4	39.4	52.9	43.7
Married (Yes)	56.4	57.9	47.9	58.8	52.1
Education					
<HS	7.6	7.3	9.3	7.2	8.3
HS graduate/GED	52.8	52.2	55.8	50.3	57.1
College+	39.6	40.4	35.0	42.5	34.6
Household income ($USD)					
<$15K	15.9	15.3	19.0	14.7	17.9
$15K-$50K	38.0	37.7	40.0	35.9	41.9
≥$50K	46.1	47.0	41.0	49.3	40.2
Insurance type					
Public only	20.1	18.9	27.4	17.3	25.2
Private only	59.1	60.0	54.3	62.0	54.1
Other	15.0	15.8	10.5	15.5	14.0
None	5.7	5.4	7.8	5.2	6.7
Cancer stage					
I	42.6	44.9	29.1	47.7	33.5
II	42.3	41.7	46.0	40.6	45.5
III	15.1	13.4	24.9	11.7	21.0
Surgery type					
Mastectomy	45.6	44.3	53.3	42.3	51.4
BCS[b]	54.4	55.7	46.7	57.7	48.6
Chemotherapy (Yes)[c]	64.2	63.1	70.7	61.8	68.5
Recurrence (Yes)[d]	14.3	10.9	26.3	6.6	24.9
Month of recurrence since diagnosis, median	27.8	36.4	16.8	49.7	21.8
Comorbid factors[e]					
Diabetes	14.9	14.5	16.6	13.2	17.7

COPD[f]	2.6	2.4	3.7	1.7	4.1
Heart disease	5.2	5.1	5.6	4.0	7.4
Hypertension	44.3	44.4	43.8	42.8	47.1

[a.] All percentages are unweighted.

[b.] Breast conservation surgery.

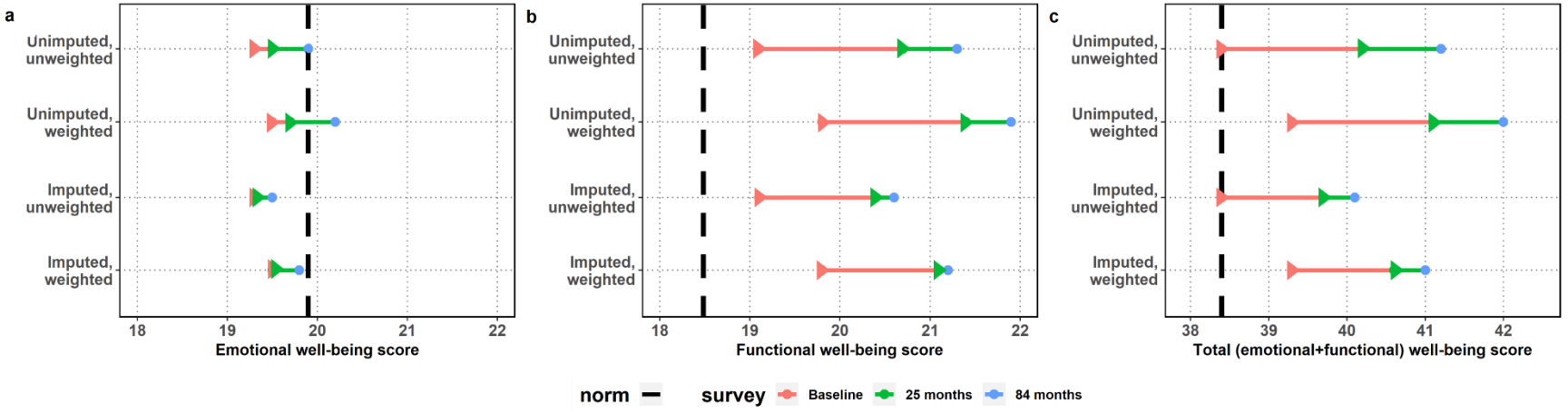
[c.] Only first course chemotherapy was included in the study.

[d.] First breast cancer recurrence was captured at any time between baseline and 84-month survey. 14 participants who recurred before baseline survey were excluded from subsequent analyses only for recurrence.

[e.] Comorbid factors were reported at baseline.

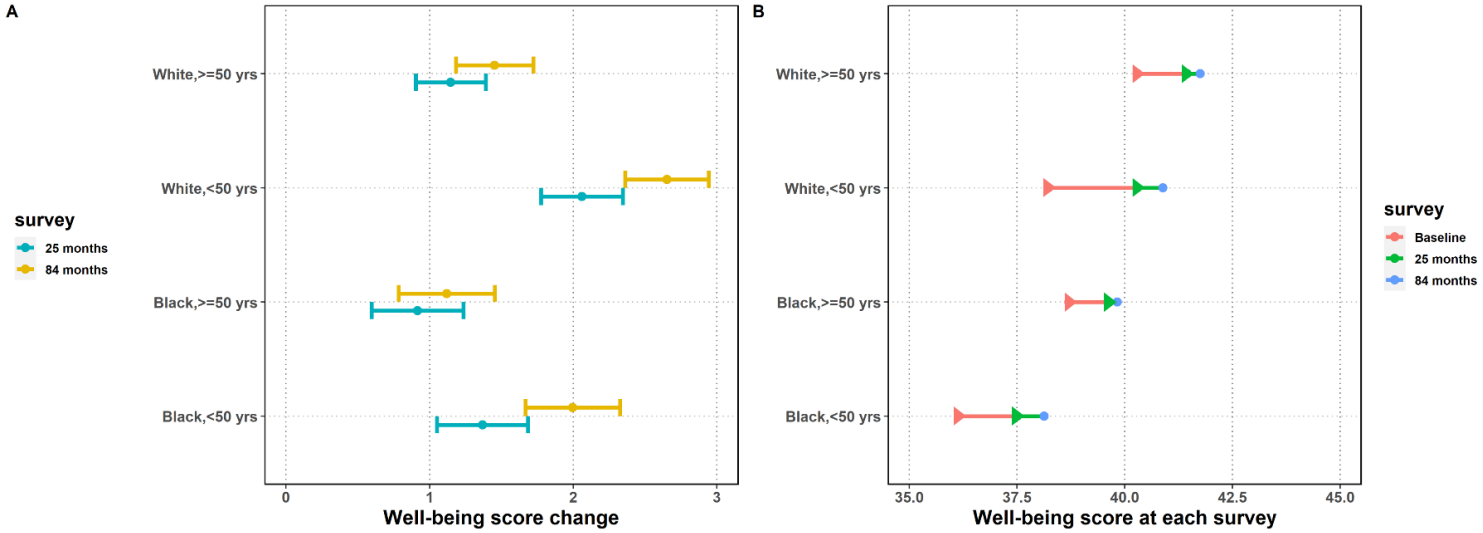
[f.] Chronic obstructive pulmonary disease.

Figure 4. 1 Well-being score by timepoint, with weighting and imputation, Carolina Breast Cancer Study 3 (2008–2013).[a] Arrows represent the direction of changes over time.



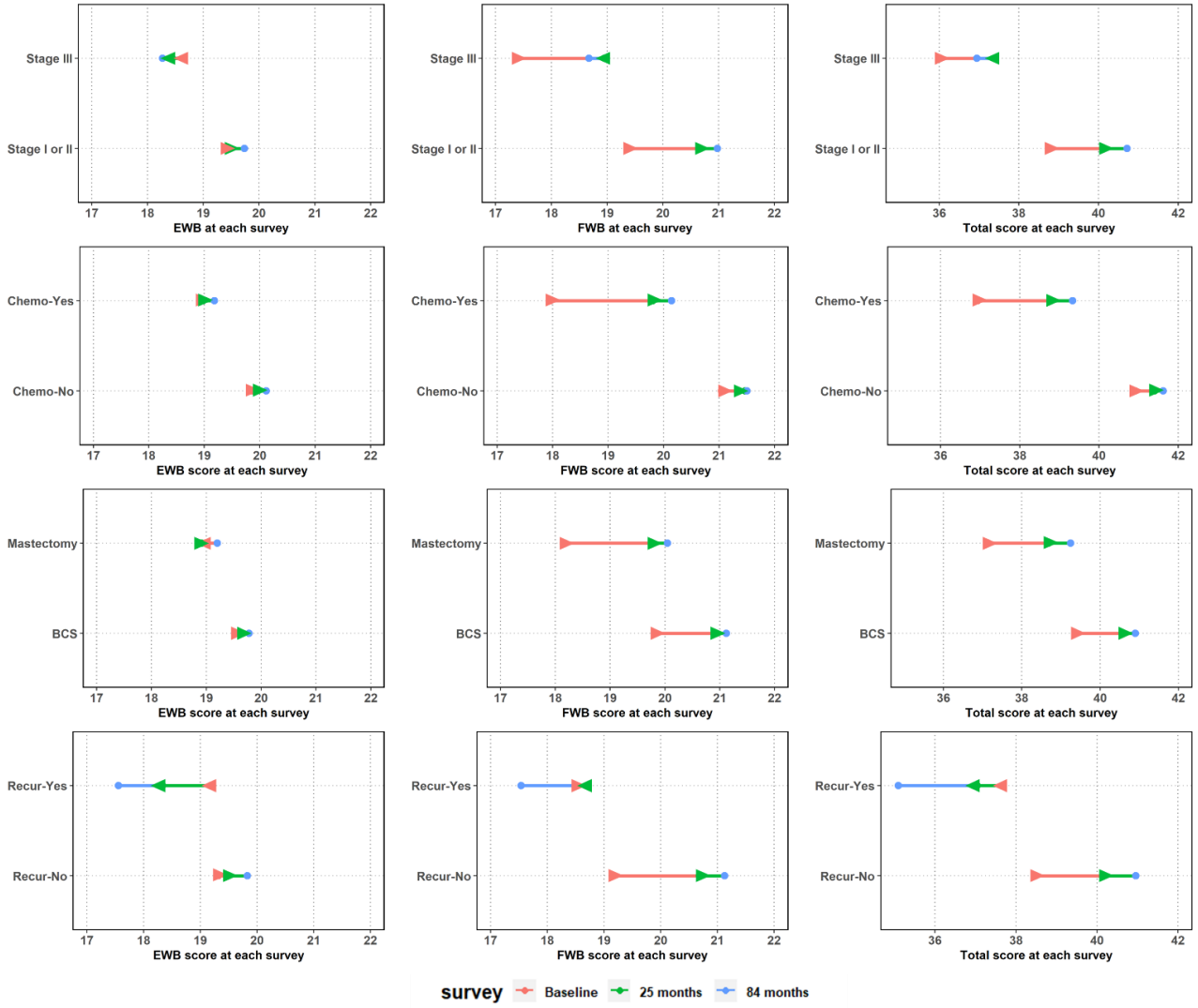
[a.] Dashed lines represent norm scores of a general U.S. adult population.

Figure 4. 2 Total well-being (emotional+functional) score (A) changes at follow-up surveys relative to baseline and (B) at each survey by race and age.[a] Arrows represent the direction of changes over time.



[a]. Figure 2A presents mean and standard error of change in well-being score at each follow-up survey relative to baseline; Figure 2B presents mean well-being score at each survey.

Figure 4. 3 Well-being score at each survey by clinical features in the Carolina Breast Cancer Study 3 (2008–2013).[a] Arrows represent the direction of changes over time.



[a] FWB – Functional well-being; EWB – Emotional well-being; BCS – Breast conservation surgery.

Table 4. 2 Odds ratios with 95% confidence intervals for demographic and clinical features in association with well-being score changes (minimally important difference=4), Carolina Breast Cancer Study 3 (2008–2013)[a], N=2,781

		Change at 25-month relative to baseline		Change at 84-month relative to baseline	
		Total participants (N in index group)	Odds ratio (95% CI)	Total participants (N in index group)	Odds ratio (95% CI)
Race					
Black (vs. white)	Increase ≥ 4	991 (500)	1.00	1,037 (513)	1.00
	No obvious change	1,217 (575)	0.84 (0.70, 1.00)	1,163 (548)	0.93 (0.76, 1.15)
	Decrease ≥ 4	573 (326)	1.25 (1.01, 1.54)	581 (340)	1.32 (1.07, 1.63)
Age at diagnosis					
Younger than 50 yrs (vs. older)	Increase ≥ 4	991 (523)	1.00	1,037 (555)	1.00
	No obvious change	1,217 (575)	0.76 (0.63, 0.92)	1,163 (551)	0.73 (0.60, 0.89)
	Decrease ≥ 4	573 (268)	0.82 (0.66, 1.02)	581 (260)	0.75 (0.60, 0.93)
Cancer stage					
III (vs. I & II)	Increase ≥ 4	991 (162)	1.00	1,037 (153)	1.00
	No obvious change	1,217 (156)	0.74 (0.56, 0.96)	1,163 (142)	0.82 (0.61, 1.12)
	Decrease ≥ 4	573 (101)	1.05 (0.78, 1.43)	581 (124)	1.40 (1.02, 1.93)
Surgery type					
Mastectomy (vs. BCS[b])	Increase ≥ 4	991 (474)	1.00	1,037 (510)	1.00
	No obvious change	1,217 (528)	0.90 (0.74, 1.09)	1,163 (492)	0.79 (0.65, 0.97)
	Decrease ≥ 4	573 (266)	0.96 (0.77, 1.21)	581 (266)	0.87 (0.67, 1.12)
Chemotherapy					
Yes	Increase ≥ 4	991 (728)	1.00	1,037 (742)	1.00
	No obvious change	1,217 (689)	0.52 (0.41, 0.66)	1,163 (681)	0.62 (0.49, 0.79)
	Decrease ≥ 4	573 (368)	0.56 (0.42, 0.74)	581 (362)	0.55 (0.40, 0.74)
Breast cancer recurrence[c]					
Yes	Increase ≥ 4	982 (19)	1.00	1,028 (54)	1.00
	No obvious change	1,216 (72)	1.99 (1.17, 3.40)	1,162 (147)	2.10 (1.44, 3.07)
	Decrease ≥ 4	569 (85)	4.65 (2.72, 7.95)	577 (161)	4.29 (2.81, 6.55)

[a.] Multinomial logistic regression was performed separately for each variable. Well-being scores were imputed for those who did not respond. Model for age was adjusted for race and survey times, model for race was adjusted for age and survey times, model for

cancer stage was adjusted for age, race, and survey times, models for breast cancer surgery type, chemotherapy, and breast cancer recurrence were adjusted for race, age, cancer stage, baseline comorbid conditions, and survey times.

[b.] Breast conservation surgery.

[c.] Breast cancer recurrence was defined separately based on time of recurrence relative to 25-month survey completion and relative to 84-month survey completion. If a participant had recurrence before completion of 25-month survey, her recurrence status should be "yes" in models for score change at 25-month, otherwise recurrence status should be "no". If a participant had recurrence before completion of 84-month survey, her recurrence status should be "yes" in models for score change at 84-month, otherwise recurrence status should be "no". 14 participants who recurred before baseline survey were excluded for analysis for recurrence in this table.

Supplementary Table 4. 1 Mean well-being scores at each survey timepoint, Carolina Breast Cancer Study 3 (2008-2013)

		General U.S. population	Baseline		25 months post-diagnosis		84 months post-diagnosis	
			N	Mean	N	Mean	N	Mean
Unweighted	EWB[a] before imputation[b]	19.9	2,781	19.3	2,376	19.5	1,786	19.9
	EWB after imputation	-	2,781	19.3	2,781	19.3	2,781	19.5
	FWB[c] before imputation	18.5	2,781	19.1	2,378	20.7	1,796	21.3
	FWB after imputation	-	2,781	19.1	2,781	20.4	2,781	20.6
	Total (EWB+FWB) before imputation	38.4	2,781	38.4	2,372	40.2	1,783	41.2
	Total (EWB+FWB) after imputation	-	2,781	38.4	2,781	39.7	2,781	40.1
Weighted[d]	EWB before imputation	19.9	2,781	19.5	2,376	19.7	1,786	20.2
	EWB after imputation	-	2,781	19.5	2,781	19.5	2,781	19.8
	FWB before imputation	18.5	2,781	19.8	2,378	21.4	1,796	21.9
	FWB after imputation	-	2,781	19.8	2,781	21.1	2,781	21.2
	Total (EWB+FWB) before imputation	38.4	2,781	39.3	2,372	41.1	1,783	42.0
	Total (EWB+FWB) after imputation	-	2,781	39.3	2,781	40.6	2,781	41.0

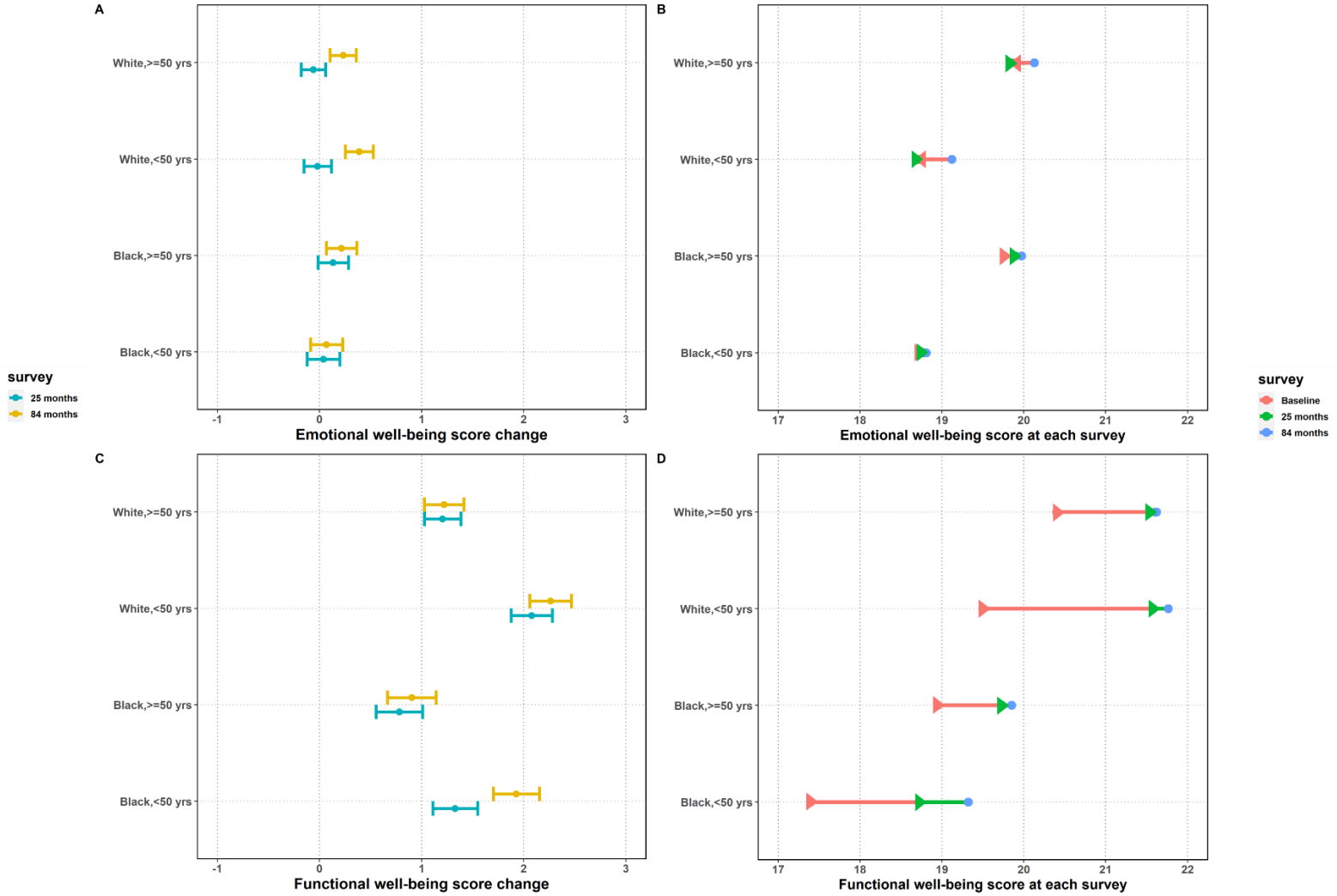
[a.] Emotional well-being.

[b.] Multiple imputation (n=40) was conducted to impute emotional and functional well-being scores for participants who did not respond follow-up FACT-B, based on information of age at diagnosis, race, marital status, education level, household income, insurance type, cancer stage, type of breast cancer surgery, chemotherapy, recurrence status before survey completion, baseline comorbid conditions (i.e., diabetes, chronic obstructive pulmonary disease, heart disease, hypertension), time of survey completion, and previous well-being scores.

[c.] Functional well-being.

[d.] Means of well-being scores were weighted by the inverse of the CBCS3 sampling probabilities – 100% young (age <50 years) Black women, 60 % old (age ≥ 50 years) Black women, 40% young non-Black women, and 15% old non-Black women.

Supplementary Figure 4. 1 Emotional and functional well-being score (A, C) changes at follow-up surveys relative to baseline and (B, D) at each survey by race and age.[a] Arrows represent the direction of changes over time.



[a]. Supplementary Figures 4.1A and 4.1C presents mean and standard error of change in well-being score at each follow-up survey relative to baseline; Figures 4.1B and 4.1D presents mean well-being score at each survey.

Supplementary Table 4. 2 Odds ratios with 95% confidence intervals for well-being score changes (minimally important difference=4) after imputation, with participants who recurred before baseline survey excluded, Carolina Breast Cancer Study 3 (2008–2013), N=2,767

		Change at 25-month relative to baseline	Change at 84-month relative to baseline
		Odds ratio (95% CI)	Odds ratio (95% CI)
Race			
Black (vs. white)	Increase ≥ 4	1.00	1.00
	No obvious change	0.84 (0.70, 1.00)	0.94 (0.76, 1.15)
	Decrease ≥ 4	1.25 (1.01, 1.54)	1.31 (1.06, 1.62)
Age at diagnosis			
Younger than 50 yrs	Increase ≥ 4	1.00	1.00
(vs. older)	No obvious change	0.77 (0.64, 0.92)	0.73 (0.60, 0.89)
	Decrease ≥ 4	0.82 (0.66, 1.01)	0.74 (0.60, 0.93)
Cancer stage			
III (vs. I & II)	Increase ≥ 4	1.00	1.00
	No obvious change	0.73 (0.56, 0.96)	0.82 (0.61, 1.12)
	Decrease ≥ 4	1.02 (0.76, 1.38)	1.37 (0.99, 1.88)
Breast cancer surgery type			
Mastectomy (vs. BCS)	Increase ≥ 4	1.00	1.00
	No obvious change	0.90 (0.75, 1.09)	0.79 (0.65, 0.97)
	Decrease ≥ 4	0.97 (0.77, 1.22)	0.87 (0.67, 1.13)
Chemotherapy			
Yes	Increase ≥ 4	1.00	1.00
	No obvious change	0.52 (0.41, 0.66)	0.62 (0.48, 0.78)
	Decrease ≥ 4	0.56 (0.42, 0.74)	0.54 (0.40, 0.73)

Supplementary Table 4. 3 Odds ratio with 95% confidence intervals for recurrence incorporating timeline in association with well-being score changes, Carolina Breast Cancer Study 3 (2008–2013)

		Change at 25-month relative to baseline	Change at 84-month relative to baseline
		Odds ratio (95% CI)	Odds ratio (95% CI)
Recurrence[a]			
Recurrence no earlier than 360 days before completion of 25-month survey (vs. no recurrence/recurrence after 25-month survey)	Increase ≥ 4	1.00	-
	No obvious change	2.04 (1.09, 3.82)	-
	Decrease ≥ 4	4.40 (2.39, 8.12)	-
Recurrence no earlier than 540 days before completion of 25-month survey (vs. no recurrence/recurrence after 25-month survey)	Increase ≥ 4	1.00	-
	No obvious change	1.96 (1.13, 3.41)	-
	Decrease ≥ 4	4.54 (2.65, 7.82)	-
Recurrence no earlier than 360 days before completion of 84-month survey (vs. no recurrence/recurrence after 84-month survey)	Increase ≥ 4	-	1.00
	No obvious change	-	1.65 (0.57, 4.78)
	Decrease ≥ 4	-	3.90 (1.38, 11.01)
Recurrence no earlier than 540 days before completion of 84-month survey (vs. no recurrence/recurrence after 84-month survey)	Increase ≥ 4	-	1.00
	No obvious change	-	1.65 (0.57, 4.78)
	Decrease ≥ 4	-	3.90 (1.38, 11.01)

[a.] Participants who recurred earlier than the cutoff-points of time relative to each follow-up survey were excluded from analyses respectively.

Supplementary Table 4. 4 Odds ratios with 95% confidence intervals for relationships of demographic and clinical features with emotional and functional well-being score changes (minimally important difference=2) after imputation, Carolina Breast Cancer Study 3 (2008–2013)[a], N=2,781

		Change at 25-month relative to baseline		Change at 84-month relative to baseline	
		EWB[b], odds ratio (95% CI)	FWB[c], odds ratio (95% CI)	EWB, odds ratio (95% CI)	FWB, odds ratio (95% CI)
Race					
Black (vs. white)	Increase ≥ 2	1.00	1.00	1.00	1.00
	No obvious change	0.93 (0.77, 1.12)	0.87 (0.72, 1.05)	1.00 (0.82, 1.22)	0.91 (0.74, 1.12)
	Decrease ≥ 2	0.89 (0.73, 1.10)	1.43 (1.17, 1.74)	1.22 (0.98, 1.52)	1.33 (1.09, 1.62)
Age at diagnosis					
Younger than 50 yrs (vs. older)	Increase ≥ 2	1.00	1.00	1.00	1.00
	No obvious change	0.86 (0.71, 1.03)	0.68 (0.56, 0.82)	0.83 (0.68, 1.01)	0.69 (0.55, 0.87)
	Decrease ≥ 2	0.99 (0.80, 1.21)	0.74 (0.60, 0.90)	1.03 (0.83, 1.27)	0.68 (0.55, 0.84)
Cancer stage					
III (vs. I & II)	Increase ≥ 2	1.00	1.00	1.00	1.00
	No obvious change	0.77 (0.58, 1.01)	0.79 (0.59, 1.06)	0.89 (0.66, 1.20)	0.80 (0.57, 1.13)
	Decrease ≥ 2	1.14 (0.86, 1.51)	1.01 (0.76, 1.33)	1.42 (1.05, 1.91)	1.17 (0.87, 1.57)
Breast cancer surgery type					
Mastectomy (vs. BCS)	Increase ≥ 2	1.00	1.00	1.00	1.00
	No obvious change	0.98 (0.80, 1.20)	0.97 (0.80, 1.19)	0.99 (0.80, 1.22)	0.80 (0.63, 1.01)
	Decrease ≥ 2	1.08 (0.86, 1.34)	0.90 (0.73, 1.11)	0.99 (0.78, 1.25)	0.88 (0.70, 1.11)
Chemotherapy					
Yes	Increase ≥ 2	1.00	1.00	1.00	1.00
	No obvious change	0.86 (0.67, 1.09)	0.52 (0.41, 0.66)	0.83 (0.65, 1.07)	0.59 (0.45, 0.77)
	Decrease ≥ 2	0.84 (0.64, 1.10)	0.57 (0.44, 0.73)	0.88 (0.65, 1.18)	0.52 (0.40, 0.68)
Breast cancer recurrence[d]					
Yes	Increase ≥ 2	1.00	1.00	1.00	1.00
	No obvious change	1.98 (1.10, 3.56)	1.80 (1.06, 3.08)	1.61 (1.09, 2.36)	1.94 (1.35, 2.77)
	Decrease ≥ 2	4.13 (2.35, 7.27)	2.90 (1.76, 4.78)	3.58 (2.41, 5.33)	3.12 (2.11, 4.64)

[a.] Multinomial logistic regression was performed separately for each variable. Model for age was adjusted for race and survey times, model for race was adjusted for age and survey times, model for cancer stage was adjusted for age, race, and survey times, models for breast cancer surgery type, chemotherapy, and breast cancer recurrence were adjusted for race, age, cancer stage, baseline comorbid conditions, and survey times.

[b.] Emotional well-being.

[c.] Functional well-being.

[d.] Breast cancer recurrence was defined separately based on time of recurrence relative to 25-month survey completion and relative to 84-month survey completion. If a participant had recurrence before completion of 25-month survey, her recurrence status should be "yes" in models for score change at 25-month, otherwise recurrence status should be "no". If a participant had recurrence before completion of 84-month survey, her recurrence status should be "yes" in models for score change at 84-month, otherwise recurrence status should be "no". 14 participants who recurred before baseline survey were excluded for analysis for recurrence in this table.

4.5 Discussion

The objective of this study was to evaluate the long-term (84 months post BC diagnosis) emotional and functional well-being in women from a large population-based racially diverse BC cohort and to determine demographic and clinical characteristics associated with well-being change relative to baseline/time of diagnosis. Overall, the emotional and functional well-being among BC survivors improved during the 84-month follow-up compared to baseline levels. Few prior studies have specifically evaluated long-term well-being change by race, and we found that Black participants had somewhat greater variance (i.e., larger standard error of the mean) in well-being change. We considered well-being change during two windows – short term (25 months) and long term (84 months) and found that factors associated with well-being decrease relative to baseline differed slightly between these windows. Specifically, at 25 months, older age and more advanced cancer stage were statistically significantly associated with well-being decrease relative to baseline, with an emphasis on functional well-being changes. Black race, no receipt of chemotherapy, and BC recurrence were statistically significantly associated with well-being decrease at both 25 months and 84 months relative to baseline. Changes in emotional well-being were generally smaller than those for functional well-being.

A variety of assessment tools have been used to evaluate mental health status among breast cancer survivors. The Hospital Anxiety and Depression Scale (HADS) is a popular instrument commonly used to assess anxiety and depression for patients with various medical conditions including breast cancer.[37,38] Although it was not designed to track mental health status, most of the items from the FACT-B emotional and functional well-being domains can be mapped to items or the reverse of items from the HADS, and the difference is that items from the FACT-B specifically target BC patients and have taken into account how BC diagnosis,

treatment, and survivorship experience might influence patients' emotional and functional well-being. Evidence suggested that the emotional and functional well-being subscale scores were significantly negatively associated with the HADS scores (correlation coefficients ranging from -0.34 to -0.54 with $p<0.01$).[39] Given the considerable overlap between items from the FACT-B emotional and functional subscales and the HADS, it is reasonable to use the total of emotional and functional well-being as an approximation of mental health of BC survivors.

Previous literature mostly focused on the overall HRQoL rather than specific domains such as emotional and functional well-being.[12,28,40] Only a few studies have investigated emotional well-being among breast cancer survivors, and most have found that younger women reported lower emotional well-being compared to older women.[18-21] Consistent with these findings, our study showed that younger women had lower emotional well-being at both baseline and follow-up surveys. Some previous studies suggest racial/ethnic variation in well-being among BC survivors, with lower acculturated Latina women reporting lower functional well-being,[15] and African American women reporting better emotional well-being compared with white women,[15,16] whereas our study revealed that Black participants had consistent lower emotional well-being scores. The inconsistency might be resulted from the fact that the Janz et al. study has a larger proportion of older BC patients (76%),[15] and the Rao et al. study included colon, head/neck, and lung cancers as well.[16] To our knowledge, there have not been studies evaluating the total of emotional and functional well-being, but consistent with one previous study assessing longitudinal emotional well-being,[22] we did not find differences in emotional well-being change during the follow-up by age at diagnosis, race, BC surgery type, or chemotherapy.

Contrary to our hypotheses that younger women and women who received chemotherapy might be more likely to experience decreased well-being relative to baseline, we found that older age and no receipt of chemotherapy were associated with decrease in well-being at follow-up surveys relative to baseline. However, we observed that compared to older women, younger women had a larger increase in their well-being but also had much lower well-being levels at baseline. Similarly for women who received chemotherapy, they experienced more obvious improvement in well-being but their well-being level at the end of the follow-up did not approach the baseline level of their counterparts. Baseline levels are critical to the interpretation of these results. Results showed that type of surgery was not significantly associated with either short-term or long-term well-being changes. One previous study on early trajectories (i.e., 3 months and 6 months after surgery) of psychosocial well-being in BC patients undergoing lumpectomy versus mastectomy found that women with lumpectomy had better psychosocial well-being status at follow-up surveys compared to the baseline level, whereas women with mastectomy experienced consistent decline in psychosocial well-being during the 6 months after surgery; and significant larger proportions of lumpectomy patients returned to their baseline psychosocial well-being compared with mastectomy patients.[41] The timing of our HRQoL data collection may have masked these early effects on well-being. In our study population, the surgery initiation occurred on average at 1.7 months post diagnosis, prior to our baseline HRQoL assessment (approximately 5 months, ranging from 2-9 months post diagnosis), which means the influence from type of surgery on early well-being change might not be captured. On the other hand, our result is consistent with a previous study showing that BC relapse was associated with poorer emotional well-being at a follow-up survey, although that study only followed participants for 12 months post diagnosis.[24]

Our study has several key strengths including the racially diverse population-based cohort of the CBCS3, which oversampled young and Black women with breast cancer. Additionally, our cohort has a long-term follow-up (i.e., up to 84 months post BC diagnosis), with in-depth data from questionnaires and medical records. As the FACT-B has been proved to demonstrate reliability, validity, and sensitivity to change in well-being overtime among populations consisting of both Black and white breast cancer patients,[30] utilizing these self-reported data yielded accurate description of well-being experiences post BC diagnosis. Finally, our population size after imputation was substantial to explore multiple patterns of change (i.e., increase/decrease or no obvious change over time) in well-being during BC survivorship.

We used a measurement that has not been studied previously – total scores of emotional and functional well-being to approximate mental health levels in our study population more closely, and score changes were more obvious when assessing the total versus the individual emotional and functional scores. This is a novel approach, but also has not been previously well studied and validated as a way of assessing mental health. However, our analysis using the sum score did demonstrate that change in total scores was dominated by change in functional well-being. Future research could evaluate these subscales separately and even consider other domains including the physical and social well-being as well as the breast cancer specific subscales. Another possible limitation of our work was that imputation was performed without history of medically confirmed mental health problems, because the items in the emotional and functional subscales are highly correlated with mental health status,[39] and missingness may also vary according to this status. Furthermore, we analyzed group-level (e.g. race and age groups) changes in mean scores and did not explore heterogeneity in BC survivors' lived experiences. Group analyses can mask important individual differences.[42] Future studies are needed to

identify distinct trajectories which reflect well-being adjustment patterns among women with BC.

In summary, our study assessed long-term well-being change among BC survivors and we found well-being change varies by demographics and clinical features. By evaluating factors associated with well-being decrease during follow-up relative to baseline, our findings, if replicated, has the potential to inform emotional and functional support early in the BC care continuum. Continued research on determinants of emotional and functional well-being is critical for developing targeted strategies. Older women, Black women, women with late-stage BC, and women with BC recurrence, are at particular risk for well-being decreases and may benefit from targeted interventions to improve emotional and functional well-being during survivorship.

REFERENCES

1. Siegel RL, Miller KD, Fuchs HE, Jemal A. Cancer statistics, 2021. *CA: a cancer journal for clinicians*. 2021;71(1):7-33.

2. Narod SA, Iqbal J, Miller AB. Why have breast cancer mortality rates declined? *Journal of Cancer Policy*. 2015;5:8-17.

3. Society A. Cancer treatment & survivorship facts & figures 2019–2021. American Cancer Society Atlanta; 2019.

4. Linden W, Vodermaier A, MacKenzie R, Greig D. Anxiety and depression after cancer diagnosis: prevalence rates by cancer type, gender, and age. *Journal of affective disorders*. 2012;141(2-3):343-351.

5. Zabora J, BrintzenhofeSzoc K, Curbow B, Hooker C, Piantadosi S. The prevalence of psychological distress by cancer site. *Psycho-Oncology: Journal of the Psychological, Social and Behavioral Dimensions of Cancer*. 2001;10(1):19-28.

6. Massie MJ. Prevalence of depression in patients with cancer. *JNCI Monographs*. 2004;2004(32):57-71.

7. Galderisi S, Heinz A, Kastrup M, Beezhold J, Sartorius N. Toward a new definition of mental health. *World psychiatry*. 2015;14(2):231.

8. Fallowfield L, Ratcliffe D, Jenkins V, Saul J. Psychiatric morbidity and its recognition by doctors in patients with cancer. *British journal of cancer*. 2001;84(8):1011-1015.

9. Boyes AW, Girgis A, D'Este CA, Zucca AC, Lecathelinais C, Carey ML. Prevalence and predictors of the short-term trajectory of anxiety and depression in the first year after a cancer diagnosis: a population-based longitudinal study. *Journal of Clinical Oncology*. 2013;31(21):2724-2729.

10. von Heymann-Horan AB, Dalton SO, Dziekanska A, et al. Unmet needs of women with breast cancer during and after primary treatment: a prospective study in Denmark. *Acta Oncologica*. 2013;52(2):382-390.

11. Payne DK, Sullivan MD, Massie MJ. Women's psychological reactions to breast cancer. 1996:89-97.

12. Howard-Anderson J, Ganz PA, Bower JE, Stanton AL. Quality of life, fertility concerns, and behavioral health outcomes in younger breast cancer survivors: a systematic review. *Journal of the National Cancer Institute*. 2012;104(5):386-405.

13. Maass SW, Roorda C, Berendsen AJ, Verhaak PF, de Bock GH. The prevalence of long-term symptoms of depression and anxiety after breast cancer treatment: a systematic review. *Maturitas*. 2015;82(1):100-108.

14. Carreira H, Williams R, Müller M, Harewood R, Stanway S, Bhaskaran K. Associations between breast cancer survivorship and adverse mental health outcomes: a systematic review. *JNCI: Journal of the National Cancer Institute*. 2018;110(12):1311-1327.

15. Janz NK, Mujahid MS, Hawley ST, et al. Racial/ethnic differences in quality of life after diagnosis of breast cancer. *Journal of Cancer Survivorship*. 2009;3(4):212-222.

16. Rao D, Debb S, Blitz D, Choi SW, Cella D. Racial/ethnic differences in the health-related quality of life of cancer patients. *Journal of pain and symptom management*. 2008;36(5):488-496.

17. Ashing-Giwa KT, Lim J-W. Examining emotional outcomes among a multiethnic cohort of breast cancer survivors. 2011:

18. Giedzinska AS, Meyerowitz BE, Ganz PA, Rowland JH. Health-related quality of life in a multiethnic sample of breast cancer survivors. *Annals of behavioral medicine*. 2004;28(1):39-51.

19. Ganz PA, Greendale GA, Petersen L, Kahn B, Bower JE. Breast cancer in younger women: reproductive and late health effects of treatment. *Journal of Clinical Oncology*. 2003;21(22):4184-4193.

20. Ganz PA, Guadagnoli E, Landrum MB, Lash TL, Rakowski W, Silliman RA. Breast cancer in older women: quality of life and psychosocial adjustment in the 15 months after diagnosis. *Journal of Clinical Oncology*. 2003;21(21):4027-4033.

21. Hack TF, Degner LF, Watson P, Sinha L. Do patients benefit from participating in medical decision making? Longitudinal follow-up of women with breast cancer. *Psycho-Oncology: Journal of the Psychological, Social and Behavioral Dimensions of Cancer*. 2006;15(1):9-19.

22. Janz NK, Friese CR, Li Y, Graff JJ, Hamilton AS, Hawley ST. Emotional well-being years post-treatment for breast cancer: prospective, multi-ethnic, and population-based analysis. *Journal of Cancer Survivorship*. 2014;8(1):131-142.

23. Clough-Gorr KM, Ganz PA, Silliman RA. Older breast cancer survivors: factors associated with change in emotional well-being. *Journal of clinical oncology*. 2007;25(11):1334-1340.

24. Rottmann N, Dalton SO, Christensen J, Frederiksen K, Johansen C. Self-efficacy, adjustment style and well-being in breast cancer patients: a longitudinal study. *Quality of Life Research*. 2010;19(6):827-836.

25. McGee SA, Durham DD, Tse C-K, Millikan RC. Determinants of breast cancer treatment delay differ for African American and White women. *Cancer Epidemiology and Prevention Biomarkers*. 2013;22(7):1227-1238.

26. Hair BY, Hayes S, Tse CK, Bell MB, Olshan AF. Racial differences in physical activity among breast cancer survivors: implications for breast cancer care. *Cancer*. 2014;120(14):2174-2182.

27. Warnecke RB, Oh A, Breen N, et al. Approaching health disparities from a population perspective: the National Institutes of Health Centers for Population Health and Health Disparities. *American journal of public health*. 2008;98(9):1608-1615.

28. Pinheiro LC, Tan X, Olshan AF, et al. Examining health-related quality of life patterns in women with breast cancer. *Quality of Life Research*. 2017;26(7):1733-1743.

29. Allott EH, Cohen SM, Geradts J, et al. Performance of Three-Biomarker Immunohistochemistry for Intrinsic Breast Cancer Subtyping in the AMBER ConsortiumAccuracy of Protein and RNA-Based Breast Cancer Subtyping. *Cancer Epidemiology, Biomarkers & Prevention*. 2016;25(3):470-478.

30. Brady MJ, Cella DF, Mo F, et al. Reliability and validity of the Functional Assessment of Cancer Therapy-Breast quality-of-life instrument. *Journal of clinical oncology*. 1997;15(3):974-986.

31. Stuart EA, Azur M, Frangakis C, Leaf P. Multiple imputation with large data sets: a case study of the Children's Mental Health Initiative. *American journal of epidemiology*. 2009;169(9):1133-1139.

32. Rubin DB. *Multiple imputation for nonresponse in surveys*. vol 81. John Wiley & Sons; 2004.

33. Pearman T, Yanez B, Peipert J, Wortman K, Beaumont J, Cella D. Ambulatory cancer and US general population reference values and cutoff scores for the functional assessment of cancer therapy. *Cancer*. 2014;120(18):2902-2909.

34. Cella D, Eton DT, Lai J-S, Peterman AH, Merkel DE. Combining anchor and distribution-based methods to derive minimal clinically important differences on the Functional Assessment of Cancer Therapy (FACT) anemia and fatigue scales. *Journal of pain and symptom management*. 2002;24(6):547-561.

35. Webster K, Cella D, Yost K. The F unctional A ssessment of C hronic I llness T herapy (FACIT) Measurement System: properties, applications, and interpretation. *Health and quality of life outcomes*. 2003;1(1):1-7.

36. Yost KJ, Eton DT. Combining distribution-and anchor-based approaches to determine minimally important differences: the FACIT experience. *Evaluation & the health professions*. 2005;28(2):172-191.

37. Stern AF. The hospital anxiety and depression scale. *Occupational medicine*. 2014;64(5):393-394.

38. Abu-Helalah M, Al-Hanaqta M, Alshraideh H, Abdulbaqi N, Hijazeen J. Quality of life and psychological well-being of breast cancer survivors in Jordan. *Asian Pacific Journal of Cancer Prevention*. 2014;15(14):5927-5936.

39. Patoo M, Allahyari AA, Moradi AR, Payandeh M. Persian version of functional assessment of Cancer therapy-breast (FACT-B) scale: confirmatory factor analysis and psychometric properties. *Asian Pacific Journal of Cancer Prevention*. 2015;16(9):3799-3803.

40. Cella D, Hahn EA, Dineen K. Meaningful change in cancer-specific quality of life scores: differences between improvement and worsening. *Quality of Life Research*. 2002;11(3):207-221.

41. Huynh V, Colborn K, Smith S, et al. Early trajectories of patient reported outcomes in breast cancer patients undergoing lumpectomy versus mastectomy. *Annals of Surgical Oncology*. 2021;28(10):5677-5685.

42. Andruff H, Carraro N, Thompson A, Gaudreau P, Louvet B. Latent class growth modelling: a tutorial. *Tutorials in quantitative methods for psychology*. 2009;5(1):11-24.

CHAPTER 5: PATTERNS OF CHANGE IN EMOTIONAL AND FUNCTIONAL WELL-BEING FOLLOWING BREAST CANCER DIAGNOSIS

5.1 Overview

Background: While some studies have evaluated long-term emotional and functional well-being (WB) change in breast cancer (BC) survivors, it is also important to consider the specific temporal patterns of change in WB at multiple time points in the years following diagnosis.

Methods: We used data from the Carolina Breast Cancer Study Phase 3 and included 2,767 women diagnosed with invasive BC between 2008 to 2013. Participants' emotional and functional WB were measured using the Functional Assessment of Cancer Therapy – Breast at approximately 5- (baseline), 25- and 84-months post diagnosis. Latent class growth analysis was used to identify WB trajectories. Relative frequency differences (RFDs) were calculated for associations between WB trajectory membership and demographic as well as clinical characteristics.

Results: We identified five trajectory groups for both emotional and functional WB. Two had consistently high/medium well-being levels during the follow-up (i.e., "good well-being" trajectories). The other three had moderate/low levels, with one staying stable, one having a substantial decrease by 25 months, and another with an extremely low baseline level and only a small increment during the follow-up (i.e., "poor well-being" trajectories). The vast majority (~70%) of our participants were classified into "good well-being" trajectories of WB. A small percentage of women (~10%) fell into trajectory groups with very low WB levels at the end of

follow-up. Overall, younger women (RFD ranging from 2.2% - 6.1%), Black women (RFD ranging from 1.3% - 7.6%), and women with BC recurrence (RFD ranging from 2.1% - 8.6%) were more likely to fall into "poor well-being" trajectories of both emotional and functional well-being. After restricting the analytic sample to women who never had recurrence, women with lower socioeconomic status, more advanced cancer stage, and more aggressive treatment modality were statistically significantly more likely to fall into "poor well-being" trajectories.

Conclusions: Findings suggest that the majority of women had a "good well-being" pattern, and demographics and clinical features may identify women at risk of experiencing poor WB trajectories. Women with these characteristics may benefit from targeted support.

5.2 Introduction

A diagnosis of breast cancer (BC) is often overwhelmingly distressing.[1] Emotional and functional decline is common among breast cancer survivors,[1-4] which could further have a detrimental impact on quality of life.[5] There are several mechanisms by which breast cancer can influence emotional well-being (EWB) and functional well-being (FWB). Treatment for BC has side effects such as nausea and vomiting from chemotherapy as well as impairment of upper limb function and body image from mastectomy, which have been linked to long-term difficulty in emotional and functional adjustment.[6-8] However, the impact of breast cancer may also depend on whether it is a first diagnosis or recurrence, with a recurrence being more distressing and difficult to cope with.[9,10] Understanding the association between clinical correlates and emotional and functional well-being could facilitate targeted preventive support for breast cancer survivors.

Beyond simply describing the incidence of emotional and functional decline at a fixed point in time, it is important to consider temporal patterns, or trajectories, of emotional and functional well-being in survivors. Based on a previous study,[11] there are four patterns of

adjustment to traumatic life events: resilience, recovery to normal after high levels of distress, persistent distress, and delayed distress. Because cancer recovery and adaption are a dynamic process, identifying different patterns of change in EWB and FWB among breast cancer survivors is important in carrying out preventive intervention at appropriate time points in the cancer journey, especially for transitions from diagnosis to active treatment completion further to long-term follow-up. However, few studies have assessed temporal patterns and those that have are not often inclusive of diverse women.[12-19]

The third phase of the Carolina Breast Cancer Study (CBCS3) is a population-based racially diverse cohort study of women that oversampled Black and younger (<50 years in age) women diagnosed with BC in North Carolina between 2008 and 2013. Participants were followed for EWB and FWB using the Functional Assessment of Cancer Therapy – Breast (FACT-B) at three time points after diagnosis (5-, 25-, and 84-months). In the previous chapter, we found that FWB scores have a larger impact on the total of the EWB and FWB scores. Therefore, we decided to evaluate EWB and FWB individually in this study. Using data from the CBCS, we identified distinct trajectories of EWB and FWB, and assessed the relationships of trajectory membership with demographic and clinical characteristics.

5.3 Methods

5.3.1 Study population

The CBCS3 is a prospective, population-based cohort study of women with invasive BC based in 44 counties in eastern and central North Carolina.[20] Eligible participants were female, English-speaking, newly diagnosed with invasive BC, and aged 20 to 74 years. Younger (<50 years in age) and Black women with BC were oversampled to each represent approximately 50% of the study population. Through rapid case ascertainment, a total of 2,998 incident, invasive,

pathologically confirmed BC cases were identified from the North Carolina Central Cancer Registry between May 1, 2008 and October 21, 2013 and recruited within two months of diagnosis. This study was conducted following informed consent by all participants, under a protocol approved by the University of North Carolina School of Medicine Institutional Review Board. In this study, we interpret race as a social construct under a cells-to-society framework where molecular, tissue, individual, community-level, and structural factors act simultaneously to potentially influence patterns of change in EWB and FWB.[21]

Study participants were interviewed in-person by trained nurses within 9 months (median 5 months, range 2-9 months) of BC diagnosis.[22] Information on age at diagnosis, self-identified race/ethnicity, and other demographic characteristics was collected at the 5-month survey, which is referred to as "baseline survey". Participants also consented at the initial interview for researchers to extract their medical records by chart review and to collect data on their breast cancer (BC) treatment, type of surgery, and recurrence status.[23] Participants also completed two follow-up surveys at medians of 25 months (range 20-36 months) and 84 months (range 60-110 months) post diagnosis, which are referred to as "25-month survey" and "84-month survey", respectively. Tumor characteristics were ascertained from pathology reports.[24]

A total of 2,998 patients with breast cancer in the CBCS3 were screened for study eligibility. The current analysis excluded participants who were diagnosed with stage IV BC or who had unknown cancer stage (n=109 and n=3, respectively). Additional exclusions included women who did not have first course surgery within 18 months of diagnosis (n=13), women who had their first course chemotherapy and/or radiation therapy but finished after the 25-month survey (n=2), women who self-identified themselves as Hispanic or "other race" due to their small representation (n=80; 3%), and women who did not finish the FACT-B at baseline (n=10).

The study further excluded 14 women who had BC recurrence before the baseline survey. After applying the study criteria, the final study population consisted of 2,767 participants.

5.3.2 Outcome Ascertainment

The FACT-B was used to measure the health-related quality of life (HRQoL) among BC survivors. It contains five domains: physical, social, emotional, and functional well-being as well as a breast cancer subscale. Participants were asked to self-report their EWB and FWB status at baseline (median of 5 months post-diagnosis), 25 months, and 84 months. The EWB section mainly consists of statements related to coping with BC (e.g., "I feel sad", "I worry about dying"), and the FWB section includes statements on whether BC affects normal life and work (e.g., "I am able to enjoy life", "I am sleeping well"). The emotional and functional subscales have 13 items in total. Each item was rated on a five-point rating scale ranging from 0 (not at all) to 4 (very much). Score ranges from 0 – 24 and 0 – 28 points for EWB and FWB, respectively.

5.3.3 Exposure Assessment

Information on demographics and socioeconomic status measures was collected in-person at baseline (median of 5 months post-diagnosis), including age at diagnosis, self-identified race, marital status, education level, household income, and insurance type. Cancer stage was obtained from pathology laboratory reports. Data on type of surgery, receipt of chemotherapy, and recurrence status during the follow-up were extracted from patients' medical records.

5.3.4 Statistical Analysis

As described previously, recurrence was strongly associated with EWB and FWB change at subsequent survey timepoints relative to baseline. Individual and clinical features were

evaluated based on recurrence status during follow-up. Because distributions of demographic and clinical characteristics were different between participants who completed the follow-up FACT-B versus participants who did not, multiple imputation was used to impute missing values for EWB and FWB scores for women who did not finish the 25- and/or 84-month FACT-B. The imputation method has been described in the previous chapter. Briefly, we applied a method called "multiple imputation by chained equations (MICE)", which models each variable with missingness by conditioning on the others. To achieve a relative efficiency of 99%, we created 40 imputed complete data sets.[25] Mean scores of the EWB and FWB were obtained separately by averaging respective subscale scores from the 40 imputed data sets. Change in EWB and FWB scores over the 84-month follow-up were also investigated by recurrence status.

The group-based SAS latent class growth analysis (LCGA) procedure PROC TRAJ identified distinct subgroups of women who followed similar trajectories over time in their EWB and FWB scores, so that there is homogeneity within a trajectory group in scores over time and heterogeneity between groups.[12] When applying this method, psychometric scale data often require censored normal distribution and assumes that missing data are missing completely at random.[12] We did not test this assumption because there was no missing data in our study after imputation.

All trajectories were modeled as functions of time since diagnosis. The scores of the emotional and the functional subscales at each survey were the dependent variables, and survey time (in month) since diagnosis was the independent variable with a form of a linear term as well as a quadratic term.[26] Models were tested that contained from one to seven trajectory group(s). We examined Akaike's information criterion (AIC) and Bayesian Information Criterion (BIC), goodness-of-fit measures to identify more parsimonious models, where larger AIC and BIC, for

which both values obtained from PROC TRAJ in SAS are negative, indicate a better model fit. Additionally, we used subjective judgement (i.e., distinctiveness of trajectories) to select the optimal number of trajectory groups. The LCGA assigns posterior probabilities, which are estimates of a specific individual's probabilities of belonging to each of the model's trajectory groups. Women will be assigned to the group for which they have the maximum posterior probability. For graphs displaying EWB and FWB trajectories, both the observed mean well-being scores over time were shown for women assigned to a specific trajectory group as well as the predicted trajectory plot line based on the linear and quadratic terms in the model. Cross tabulation was used to investigate group membership of EWB compared to group membership of FWB.

After participants were assigned to trajectory groups, associations between age, race, BC recurrence and group membership were assessed using relative frequency differences (RFDs), interpreted as the percentage difference between index and referent groups, and 95% confidence intervals (95% CI). RFD for age was adjusted for race, RFD for race was adjusted for age, and RFD for recurrence status was adjusted for age and race. We also calculated RFD for the association between clinical features and group membership after restricting our analytic sample to women who did not have BC recurrence during the follow-up. RFDs for clinical features were adjusted for age and race.

All statistical tests were two-sided and considered statistically significant at $P<0.05$; statistical analyses were performed using SAS software (version 9.4; SAS Institute, Inc, Cary, NC).

5.4 Results

5.4.1 Well-being Score Change

To understand the overall EWB and FWB score change at the end of the 84-month follow-up, we calculated the mean and standard deviation by participant characteristics and recurrence status (Table 5.1). A total of 362 participants had their first BC recurrence during the follow-up, with a larger proportion of recurrence among younger and Black women. Women with recurrence experienced decreases in both EWB and FWB, with greater decreases in EWB scores. In contrast, 2,405 participants were free from BC recurrence by the end of follow-up, and these women experienced increases in both EWB and FWB, with larger increases in FWB scores. Among participants who had BC recurrence, younger women, Black women, women who were not married, had lower education, had lower household income, had public or no insurance, and women who had more advanced BC stage, had mastectomy, received chemotherapy, had larger decrease in well-being scores compared to women without a recurrence. Among participants who never had BC recurrence, women who were not married, had lower education, had lower household income, had public or no insurance, and women who had more advanced BC stage, had smaller increase in well-being scores compared with women who had a recurrence.

5.4.2 Description of Well-being Trajectories

We examined the AIC and the BIC to select the optimal number (among two to seven) for trajectory groups of EWB and FWB. Although the largest AIC and BIC (i.e., the smallest in absolute value of the negative AICs and BICs) of any of the models was associated with the seven-trajectory model, the change in information from five to six/seven was not substantial, whereas the change in AIC (2-trajectory: -20969.61 and -24361.96; 3-trajectory: -20706.67 and -

24073.26; 4-trajectory: -20602.07 and -24001.79; 5-trajectory: -20528.02 and -23929.22 for EWB and FWB, respectively) and BIC (2-trajectory: -20993.32 and -24385.66; 3-trajectory: -20742.23 and -24108.82; 4-trajectory: -20649.47 and -24049.19; 5-trajectory: -20587.27 and -23988.48 for EWB and FWB, respectively) for all previous models was comparatively large. Additionally, the five-trajectory model allowed for better discrimination of the different groups who had a major early decrement in well-being scores compared with the discrimination allowed by the four-trajectory model. Therefore, five-trajectory models were determined to be the best fit for our data, even though two of the groups, composed of women with a sudden drop and women with increases from extremely low scores, respectively, were made up of only around 10% (n=277) of the entire sample.

As seen in Figure 5.1a for the EWB trajectories and Figure 5.1b for the FWB trajectories, approximately 10% of our participants fell into groups 1 and 3 (n=243 and 279 for EWB and FWB, respectively). Both groups had low levels of EWB at baseline, with one group having a large decrease during the first 25 months and another having a small increase from an extremely low baseline level. The only difference was the timing of the rise, which is slightly earlier for EWB vs. FWB. These two groups were considered as "early decrease" and "very low baseline", respectively. Women in group 2 (23.2%, n=642 for EWB; 20.8%, n=576 for FWB) showed a consistent moderately-low level in EWB during the entire follow-up, and this group was considered as "stable low". A large proportion of the participants (57.1%, n=1,578 for EWB; 41.3%, n=1143 for FWB) fell into group 4, which remained stable at a medium level, and this group was named "stable medium". Group 5 (11.0%, n=304 for EWB; 27.8%, n=769 for FWB) showed consistently high well-being scores (around 23 for EWB and 25 for FWB) over time, and

this group was considered as “stable high”. Groups 4 and 5 were “good well-being” groups, whereas groups 1, 2, and 3 were “poor well-being” groups.

We performed a cross classification to investigate participants’ membership of the EWB and FWB trajectories (Table 5.2). Women in the “stable high”, “stable medium”, and “stable low” groups of EWB were more likely to fall into the “stable high”, “stable medium”, and “stable low” groups of FWB, respectively. Among participants who were in “early decrease” or “very low baseline” EWB trajectories, the vast majority either belonged to “stable low” or “very low baseline” FWB trajectories. Interestingly, half of women with “early decrease” FWB trajectory fell into the “stable medium” EWB trajectory.

5.4.3 Associations with Trajectory Group Membership

Tables 5.3.1 and 5.3.2 present percentages of each trajectory group within levels of age, race, and recurrence status, along with corresponding RFDs and 95% CIs. There were significant differences across these characteristics in many of the trajectory groups, with clear general profiles emerging. After adjustment for race, younger (<50) participants were more likely to fall into the “stable low”, “early decrease”, and “very low baseline” trajectories of EWB (RFD ranging from 2.2% - 6.1%) with a monotonic pattern. Older participants ($\geq$ 50) were more likely to fall into the “stable high” EWB and FWB trajectory (RFD=5.4% and 6.9%, respectively). However, Black women lacked the similar linear pattern of age, compared to white women, with the percentages adjusted for age among Black women were significantly higher for the “very low baseline” and “stable high” EWB trajectories (RFD=1.9% and 6.1%, respectively) and the “stable low”, “early decrease”, and “very low baseline” FWB trajectories (RFD=7.6%, 1.3%, and 6.5%, respectively). In contrast, the percentage of the “stable high” FWB trajectory was significantly higher among white women (RFD=11.6%). Women who had BC recurrence during

the follow-up were significantly more likely to fall into the “stable low” and “early decrease” EWB and FWB trajectories (RFD, adjusted for race and age, ranging from 2.1% - 8.6%). In contrast, women who never had BC recurrence by the end of the 84 months were significantly more likely to fall into the “stable high” EWB and FWB trajectory (RFD=5.9% and 8.4%, respectively).

Because the “early decrease” and “very low baseline” groups of EWB and FWB were so small, and recurrence status seemed to have a large influence on participants’ trajectory membership, we restricted our subsequent analyses to women who never had recurrence during the follow-up to evaluate relationships of trajectory membership with socioeconomic status composites and clinical features. As seen in Figure 5.2, after adjustment for race and age, participants who were not married, had lower household income, and had no private insurance were significantly more likely to fall into the “poor well-being” groups, with the largest RFD belonging to the “stable low” trajectory. On the other hand, these participants were significantly less likely to fall into the “stable high” group. Women with lower education were more likely to belong to the “poor well-being” FWB groups as well as the “early decrease” and “very low baseline” EWB groups. Additionally, these socioeconomic status measures seemed to have a larger impact on FWB versus EWB trajectories.

Figure 5.3 displays the RFDs and 95% CIs for clinical features. After adjustment for race and age, cancer stage, surgery type, or chemotherapy did not predict the “early decrease” and “very low baseline” EWB trajectories or the “early decrease” FWB trajectory. However, participants who had more advanced cancer stage, treated by mastectomy, and received chemotherapy, were more likely to fall into the “stable low” EWB trajectory as well as the “stable low” and “very low baseline” FWB trajectories. And these participants were less likely to

belong to the “stable high” trajectory. Interestingly, clinical features seemed to have smaller influences on the well-being trajectory membership compared to socioeconomic status measures.

Table 5. 1 Change in emotional and functional well-being scores (mean and standard deviation) at 84 months relative to baseline by participant characteristics

Characteristics	Recurrence during follow-up					
	Yes, N=362			No, N=2,405		
	Number of participants	Change in EWB[a] Mean (std)	Change in FWB[b] Mean (std)	Number of participants	Change in EWB Mean (std)	Change in FWB Mean (std)
Age, years						
<50	198	-1.9 (3.9)	-0.7 (4.9)	1,155	0.6 (3.8)	2.6 (5.6)
≥50	164	-1.3 (3.6)	-1.3 (5.5)	1,250	0.4 (3.7)	1.4 (5.7)
Race						
Black	220	-1.7 (4.0)	-1.5 (5.1)	1,170	0.5 (3.9)	2.0 (6.2)
White	142	-1.5 (3.4)	-0.1 (5.2)	1,235	0.5 (3.5)	1.9 (5.2)
Married						
Yes	192	-1.4 (3.6)	-0.8 (5.3)	1,367	0.7 (3.4)	2.2 (5.3)
No	170	-1.9 (3.9)	-1.2 (5.0)	1,038	0.3 (4.1)	1.7 (6.1)
Education						
<HS	35	-2.6 (3.2)	-1.5 (5.2)	175	0 (3.7)	0.3 (7.1)
HS graduate/GED	192	-1.6 (3.8)	-1.5 (5.5)	1,267	0.4 (3.8)	1.9 (5.8)
College+	135	-1.4 (3.8)	-0.1 (4.4)	963	0.7 (3.6)	2.3 (5.1)
Household income ($USD)						
<$15K	71	-1.7 (4.4)	-1.8 (5.5)	384	0.3 (4.3)	1.0 (6.7)
$15K-$50K	146	-1.8 (3.6)	-1.0 (5.3)	895	0.5 (3.8)	1.9 (5.8)
≥$50K	145	-1.4 (3.6)	-0.5 (4.8)	1,126	0.6 (3.4)	2.3 (5.2)
Insurance type						
Public only	103	-1.7 (4.4)	-2.0 (5.1)	451	0.3 (4.4)	1.3 (6.4)
Private only	194	-1.3 (3.5)	-0.3 (5.3)	1,444	0.7 (3.5)	2.5 (5.3)
Other	46	-2.3 (3.5)	-1.1 (5.1)	371	0 (3.6)	0.4 (5.5)
None	19	-2.6 (3.3)	-1.6 (3.1)	139	0.7 (4.0)	2.4 (6.5)
Cancer stage						
I	65	-1.3 (4.2)	-1.3 (6.9)	1,119	0.5 (3.5)	1.3 (5.4)
II	184	-1.5 (3.6)	-0.9 (4.4)	992	0.6 (3.9)	2.7 (5.8)
III	113	-2.0 (3.9)	-0.8 (5.2)	294	0.3 (3.9)	2.3 (5.9)
Surgery type						
Mastectomy	197	-1.9 (3.9)	-0.8 (5.1)	1,060	0.6 (3.8)	2.4 (5.8)
BCS[c]	165	-1.3 (3.6)	-1.2 (5.3)	1,345	0.4 (3.6)	1.6 (5.6)
Chemotherapy						
Yes	290	-1.8 (3.7)	-0.7 (4.9)	1,482	0.6 (3.9)	2.8 (5.8)
No	72	-1.0 (3.8)	-2.1 (6.0)	923	0.3 (3.4)	0.6 (5.2)

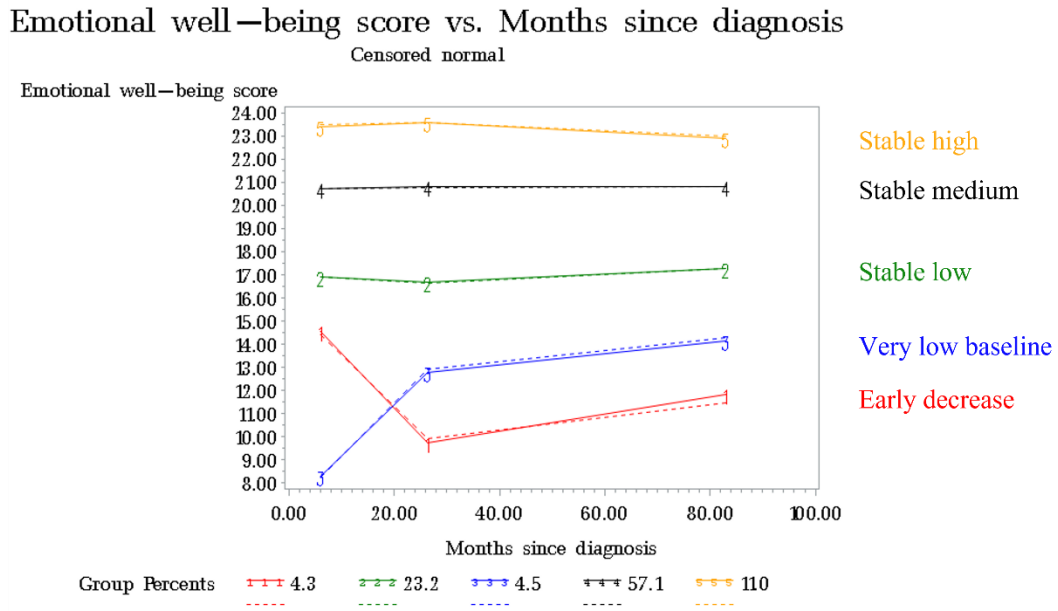
[a.] Emotional well-being.

[b.] Functional well-being.

[c.] Breast conservation surgery.

Figure 5. 1 Predicted (dashed lines) and observed (solid lines) (a) emotional and (b) functional well-being scores for each trajectory by months since diagnosis, Carolina Breast Cancer Study 3 (2008-2013). %, percentage of participants in each latent growth class.

a.



b.

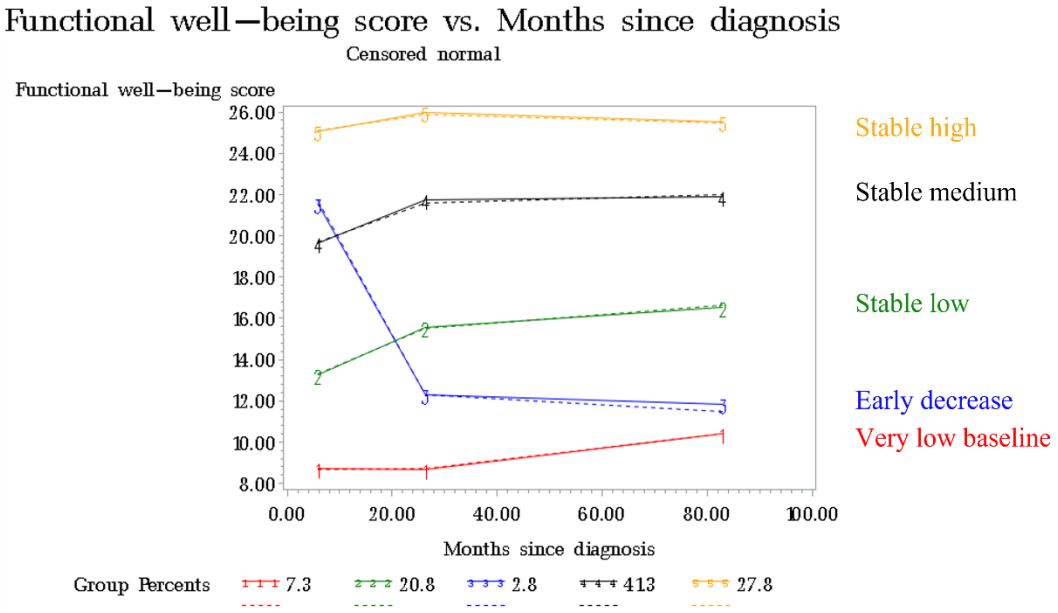


Table 5. 2 Cross-classification of trajectory membership for emotional and functional well-being (n;%), Carolina Breast Cancer Study 3 (2008-2013)

Class for emotional well-being	Class for functional well-being				
	Stable high	Stable medium	Stable low	Early decrease	Very low baseline
Stable high	186 (68.6)	75 (27.7)	9 (3.3)	0 (0)	1 (0.4)
Stable medium	532 (32.2)	847 (51.3)	214 (13.0)	31 (1.9)	28 (1.7)
Stable low	25 (4.1)	245 (39.7)	245 (39.7)	21 (3.4)	81 (13.1)
Early decrease	3 (2.8)	14 (13.2)	39 (36.8)	9 (8.5)	41 (38.7)
Very low baseline	4 (3.3)	15 (12.4)	59 (48.8)	1 (0.8)	42 (34.7)

Table 5.3. 1 Emotional well-being latent growth class membership (n;%) by age, race, and recurrence status, Carolina Breast Cancer Study 3[a]

	Stable high	Stable medium (reference)	Stable low	Early decrease	Very low baseline
Age, yrs					
≥50 (reference)	175 (12.4)	881 (62.3)	273 (19.3)	39 (2.8)	46 (3.3)
<50	96 (7.1)	771 (57.0)	344 (25.4)	67 (5.0)	75 (5.5)
RFD, % (95% CI)	-5.4 (-7.6 to -3.2)	0.0	+6.1 (3.0 to 9.2)	+2.2 (0.8 to 3.6)	+2.3 (0.7 to 3.8)
Race					
White (reference)	93 (6.8)	871 (63.3)	316 (23.0)	50 (3.63)	47 (3.4)
Black	178 (12.8)	781 (56.2)	301 (21.7)	56 (4.0)	74 (5.3)
RFD, % (95% CI)	+6.1 (3.9 to 8.3)	0.0	-1.4 (-4.5 to 1.7)	+0.4 (-1.1 to 1.8)	+1.9 (0.4 to 3.4)
Recurrence					
No (reference)	253 (10.5)	1456 (60.5)	513 (21.3)	83 (3.5)	100 (4.2)
Yes	18 (5.0)	196 (54.1)	104 (28.7)	23 (6.4)	21 (5.8)
Yes vs. No RFD, % (95% CI)	-5.9 (-8.5 to -3.4)	0.0	+7.3 (2.3 to 12.3)	+2.7 (0.1 to 5.4)	+1.3 (-1.2 to 3.9)

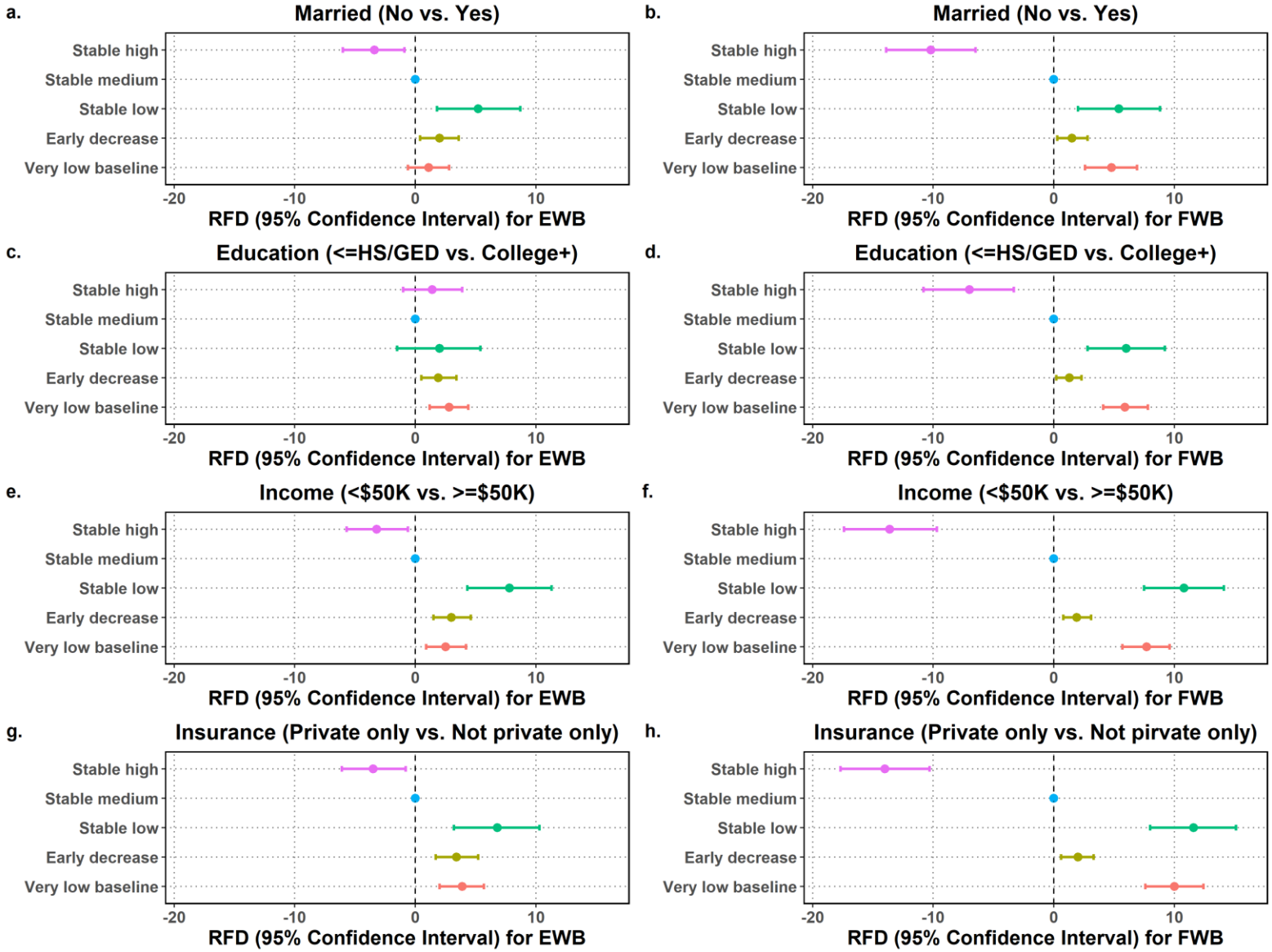
[a.] RFD = relative frequency difference. RFD for age adjusted for race, RFD for race adjusted for age, RFD for recurrence status adjusted for race and age.

Table 5.3. 2 Functional well-being latent growth class membership (n;%) by age, race, and recurrence status, Carolina Breast Cancer Study 3[a]

	Stable high	Stable medium (reference)	Stable low	Early decrease	Very low baseline
Age, yrs					
≥50 (reference)	432 (30.6)	576 (40.7)	283 (20.0)	34 (2.4)	89 (6.3)
<50	318 (23.5)	620 (45.8)	283 (20.9)	28 (2.1)	104 (7.7)
RFD, % (95% CI)	-6.9 (-10.2 to -3.6)	0.0	+0.8 (-2.2 to 3.8)	-0.4 (-1.5 to 0.8)	+1.3 (-0.6 to 3.2)
Race					
White (reference)	454 (33.0)	621 (45.1)	229 (16.6)	22 (1.6)	51 (3.7)
Black	296 (21.3)	575 (41.4)	337 (24.2)	40 (2.9)	142 (10.2)
RFD, % (95% CI)	-11.6 (-14.9 to -8.3)	0.0	+7.6 (4.6 to 10.6)	+1.3 (0.2 to 2.4)	+6.5 (4.6 to 8.4)
Recurrence					
No (reference)	684 (28.4)	1057 (44.0)	462 (19.2)	47 (2.0)	155 (6.4)
Yes	66 (18.2)	139 (38.4)	104 (28.7)	15 (4.1)	38 (10.5)
Yes vs. No RFD, % (95% CI)	-8.4 (-12.7 to -4.0)	0.0	+8.6 (3.7 to 13.5)	+2.1 (0 to 4.2)	+3.1 (-0.2 to 6.4)

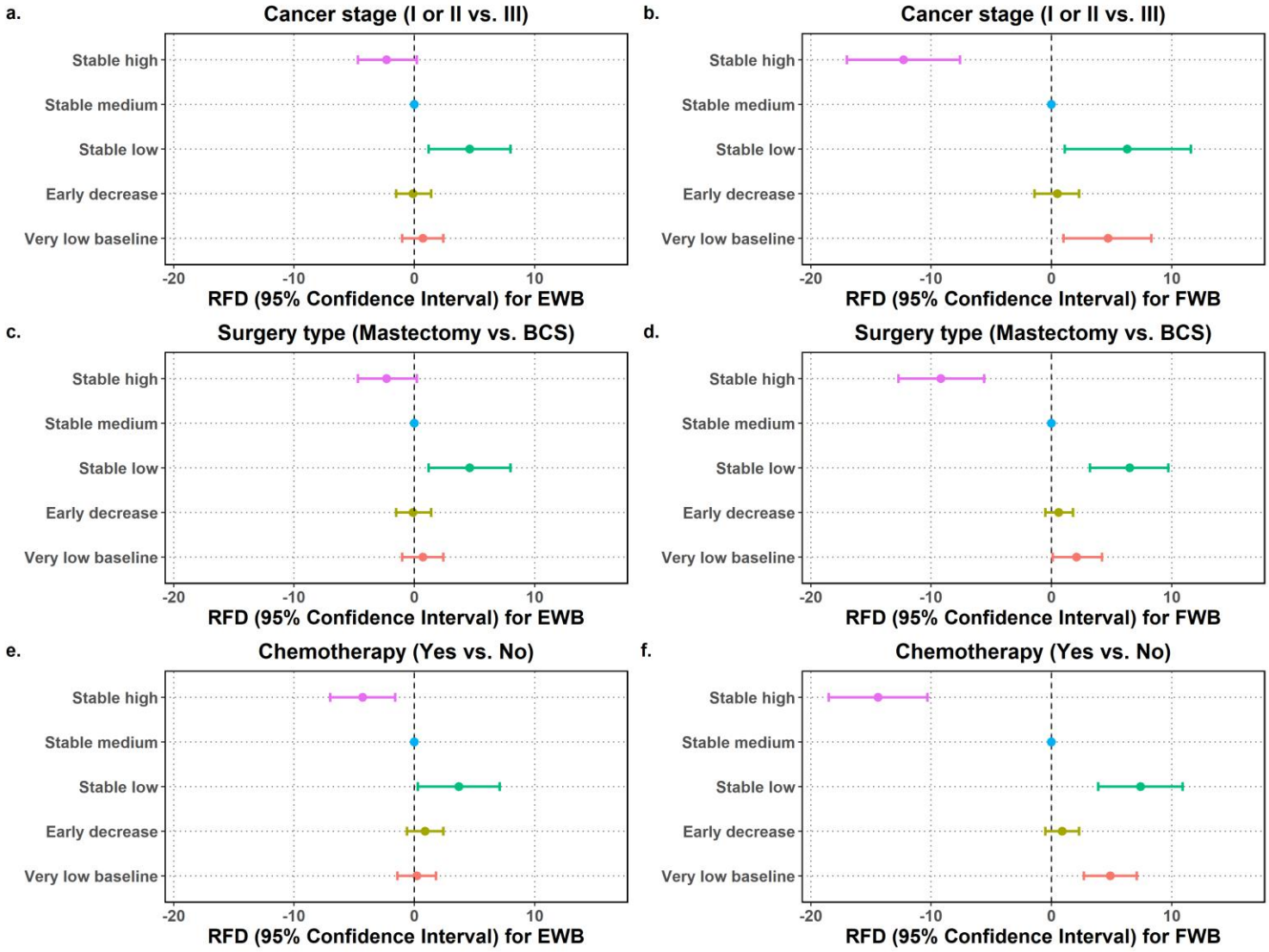
[a.] RFD = relative frequency difference. RFD for age adjusted for race, RFD for race adjusted for age, RFD for recurrence status adjusted for race and age.

Figure 5. 2 Relative frequency difference by demographic characteristics after excluding participants with breast cancer recurrence, Carolina Breast Cancer Study 3[a]



[a.] RFD = relative frequency difference, adjusted for race and age.

Figure 5. 3 Relative frequency difference by clinical features after excluding participants with breast cancer recurrence, Carolina Breast Cancer Study 3[a]



[a.] RFD = relative frequency difference, adjusted for race and age

5.5 Discussion

In this diverse, population-based cohort of 2,767 breast cancer patients, multiple distinct patterns of EWB and FWB emerged. Although almost 70% of the participants fell into the "good well-being" groups, a considerable number of women (~30%) still struggled with their emotional and functional adjustment after BC diagnosis. Generally, younger women, Black women, women with BC recurrence, more advanced cancer stage, receipt of chemotherapy, receipt of mastectomy, and lower socioeconomic status, were more likely to fall into the "poor well-being" groups. To our knowledge, no previous study has used the LCGA method in a BC cohort to describe and characterize EWB and FWB patterns.

Most of previous literature focused on either the overall HRQoL or specific mental health disorders after breast cancer diagnosis. One study identified six groups of BC survivors exhibiting different mental health patterns over 24 months since diagnosis.[12] Although that study used a different instrument which measured depressive symptoms and only followed their participants for 24 months post diagnosis, our study showed similar findings that there were five trajectories for both EWB and FWB, including "stable high", "stable medium", "stable low", "early decrease", and "very low baseline". And we observed similarities of change in the same window. In both studies, major changes of mental health happened within the first 25 months post diagnosis, implying a critical time window when women with BC are suspectable to changes and appropriate interventions should be carried out to avoid emotional or functional decrement. Women with low levels of EWB or FWB at the initial assessment post BC diagnosis might need more frequent evaluations in their following cancer care, because they tend to either maintain the baseline level or even have a further decrease and are at risk for longer-term poor well-being status.

It has been suggested that psychological adjustment among BC survivors might depend on women's age, with several studies showing that younger women tend to struggle with emotional disturbances, whereas older patients experience more physical health concerns.[27-30] Consistent with previous findings, our study found significant associations between younger age (<50 years) and membership of "poor well-being" groups.

Race/ethnicity is also a critical factor for well-being trajectories. Compared with non-Hispanic white women, Black women have increased levels of depressive symptoms along BC survivorship.[12] Our study also showed that Black women were more likely to belong to the "poor well-being" groups. However, we interpreted results for age and race under a cells-to-society framework, which means that disparities in well-being trajectory membership by age or race do not simply suggest underlying genetic variation, but should be explained under context individual, community, and treatment factors. For example, younger BC patients possess fewer coping strategies and resources necessary to manage a life-threatening disease.[30] Similarly, Black women with BC are less likely to receive specialty psychological care compared to their white counterparts, even with adjusted demographics, insurance status, and psychiatric morbidity.[31]

The majority of previous studies showed no association between marital status, education, or household income and patterns of change in depressive symptoms or psychological distress.[12-17] However, our study found that women with lower socioeconomic status (i.e., being not married, lower education level, lower household income, no private insurance) were more likely to fall into the "poor well-being" groups. The inconsistency may have resulted from relatively small sample sizes (n<1,000) and short follow up (<=4 y) in previous studies.

With respect to clinical factors, our results are consistent with previous research findings that women with less advanced cancer stage, breast conservation surgery (versus mastectomy),

and no chemotherapy were more likely to maintain higher levels of EWB and FWB over time.[12,16] It is important to note that BC patients with these associated features (e.g., lower socioeconomic status, more aggressive treatment) seemed to be more vulnerable to significant decrement in well-being because of their larger proportions in the "stable low" group, which implies that these women would benefit most from targeted intervention to prevent well-being decrease during their cancer continuum.

Our study has several key strengths. First, the CBCS3 is a racially diverse population-based study, which oversampled young and Black women with breast cancer. Second, our cohort had a long-term follow-up (i.e., up to 84 months post BC diagnosis), with in-depth data from questionnaires and medical records. By utilizing self-reported data obtained from the FACT-B, we were able to accurately describe and characterize BC survivors' lived experiences. Third, our population size after imputation was substantial to identify distinct patterns in well-being change during BC survivorship. Finally, a novel statistical modeling technique, latent class growth analysis, was used to classify women into similar trajectories of EWB and FWB. This method provides an advantage over traditional approaches that use predefined groups and also give us the ability to capture information about unobserved heterogeneity in terms of well-being change.

There are also limitations for our study. Although we have three measurements of well-being post diagnosis, they were not equidistant on the time scale. More specific data on how well-being changed between 25 months and 84 months was unavailable. There might be fluctuation in well-being status during this period of time, which might not be fully captured and depicted by only measurements at two time points. Future studies could collect well-being data on a more regular basis (e.g., every two years) to identify potentially more complicated patterns. Additionally, because the proportion of women who had BC recurrence was relatively small, we

were only able to perform a restriction to women without recurrence when evaluating associations between well-being trajectories and socioeconomic status as well as clinical features, which may limit the generalizability of our findings. And we observed that the "early decrease" group membership was not clearly characterized by any features except recurrence status. Predictors of well-being among those who experienced recurrence remain an area of uncertainty. Furthermore, baseline psychiatric comorbidities may provide additional insight into women comprising different trajectory groups. However, data on history of medical-record confirmed mental health problems was not available in our study.

In summary, our study demonstrated that most women were resilient to emotional and functional well-being change over the 84 months following BC diagnosis. By investigating factors associated with experiences of consistently low levels and decreases in EWB and/or FWB, this study has the potential to help identify women at increased risk of experiencing these less favorable well-being trajectories and implement targeted intervention to ameliorate the effects of BC diagnosis on patients' well-being.

REFERENCES

1. Payne DK, Sullivan MD, Massie MJ. Women's psychological reactions to breast cancer. 1996:89-97.

2. Howard-Anderson J, Ganz PA, Bower JE, Stanton AL. Quality of life, fertility concerns, and behavioral health outcomes in younger breast cancer survivors: a systematic review. *Journal of the National Cancer Institute*. 2012;104(5):386-405.

3. Maass SW, Roorda C, Berendsen AJ, Verhaak PF, de Bock GH. The prevalence of long-term symptoms of depression and anxiety after breast cancer treatment: a systematic review. *Maturitas*. 2015;82(1):100-108.

4. Carreira H, Williams R, Müller M, Harewood R, Stanway S, Bhaskaran K. Associations between breast cancer survivorship and adverse mental health outcomes: a systematic review. *JNCI: Journal of the National Cancer Institute*. 2018;110(12):1311-1327.

5. Weitzner MA, Meyers CA, Stuebing KK, Saleeba AK. Relationship between quality of life and mood in long-term survivors of breast cancer treated with mastectomy. *Supportive Care in Cancer*. 1997;5(3):241-248.

6. Figueiredo MI, Cullen J, Hwang Y-T, Rowland JH, Mandelblatt JS. Breast cancer treatment in older women: does getting what you want improve your long-term body image and mental health? *Journal of Clinical Oncology*. 2004;22(19):4002-4009.

7. Spiegel D, Nemeroff CB. Psychosocial aspects of breast cancer treatment. [New York] Grune & Stratton.; 1997:36-47.

8. Hidding JT, Beurskens CH, van der Wees PJ, van Laarhoven HW, Nijhuis-van der Sanden MW. Treatment related impairments in arm and shoulder in patients with breast cancer: a systematic review. *PloS one*. 2014;9(5):e96748.

9. Mahon SM, Cella DF, Donovan MI. Psychosocial adjustment to recurrent cancer. 1990:47-52; discussion 53.

10. Cella DF, Mahon SM, Donovan MI. Cancer recurrence as a traumatic event. *Behavioral medicine*. 1990;16(1):15-22.

11. Bonanno GA. Loss, trauma, and human resilience: have we underestimated the human capacity to thrive after extremely aversive events? *American psychologist*. 2004;59(1):20.

12. Avis NE, Levine BJ, Case LD, Naftalis EZ, Van Zee KJ. Trajectories of depressive symptoms following breast cancer diagnosis. *Cancer Epidemiology, Biomarkers & Prevention*. 2015;24(11):1789-1795.

13. Deshields T, Tibbs T, Fan MY, Taylor M. Differences in patterns of depression after treatment for breast cancer. *Psycho-Oncology: Journal of the Psychological, Social and Behavioral Dimensions of Cancer*. 2006;15(5):398-406.

14. Henselmans I, Helgeson VS, Seltman H, de Vries J, Sanderman R, Ranchor AV. Identification and prediction of distress trajectories in the first year after a breast cancer diagnosis. *Health Psychology*. 2010;29(2):160.

15. Lam WW, Bonanno GA, Mancini AD, et al. Trajectories of psychological distress among Chinese women diagnosed with breast cancer. *Psycho-Oncology*. 2010;19(10):1044-1051.

16. Helgeson VS, Snyder P, Seltman H. Psychological and physical adjustment to breast cancer over 4 years: identifying distinct trajectories of change. *Health Psychology*. 2004;23(1):3.

17. Dunn LB, Cooper BA, Neuhaus J, et al. Identification of distinct depressive symptom trajectories in women following surgery for breast cancer. *Health psychology*. 2011;30(6):683.

18. Stanton AL, Wiley JF, Krull JL, et al. Depressive episodes, symptoms, and trajectories in women recently diagnosed with breast cancer. *Breast cancer research and treatment*. 2015;154(1):105-115.

19. Crane TE, Badger TA, Sikorskii A, Segrin C, Hsu C-H, Rosenfeld AG. Trajectories of Depression and Anxiety in Latina Breast Cancer Survivors. 2019:

20. McGee SA, Durham DD, Tse C-K, Millikan RC. Determinants of breast cancer treatment delay differ for African American and White women. *Cancer epidemiology, biomarkers & prevention*. 2013;22(7):1227-1238.

21. Warnecke RB, Oh A, Breen N, et al. Approaching health disparities from a population perspective: the National Institutes of Health Centers for Population Health and Health Disparities. *American journal of public health*. 2008;98(9):1608-1615.

22. Pinheiro LC, Tan X, Olshan AF, et al. Examining health-related quality of life patterns in women with breast cancer. *Quality of Life Research*. 2017;26(7):1733-1743.

23. Hair BY, Hayes S, Tse CK, Bell MB, Olshan AF. Racial differences in physical activity among breast cancer survivors: implications for breast cancer care. *Cancer*. 2014;120(14):2174-2182.

24. Allott EH, Cohen SM, Geradts J, et al. Performance of Three-Biomarker Immunohistochemistry for Intrinsic Breast Cancer Subtyping in the AMBER ConsortiumAccuracy of Protein and RNA-Based Breast Cancer Subtyping. *Cancer Epidemiology, Biomarkers & Prevention*. 2016;25(3):470-478.

25. Rubin DB. *Multiple imputation for nonresponse in surveys*. vol 81. John Wiley & Sons; 2004.

26. Andruff H, Carraro N, Thompson A, Gaudreau P, Louvet B. Latent class growth modelling: a tutorial. *Tutorials in quantitative methods for psychology*. 2009;5(1):11-24.

27. Arndt V, Merx H, Stürmer T, Stegmaier C, Ziegler H, Brenner H. Age-specific detriments to quality of life among breast cancer patients one year after diagnosis. *European Journal of Cancer*. 2004;40(5):673-680.

28. Colby DA, Shifren K. Optimism, mental health, and quality of life: A study among breast cancer patients. *Psychology, health & medicine*. 2013;18(1):10-20.

29. Vinokur AD, Threatt BA, Vinokur-Kaplan D, Satariano WA. The process of recovery from breast cancer for younger and older patients. Changes during the first year. *Cancer*. 1990;65(5):1242-1254.

30. Wenzel LB, Fairclough DL, Brady MJ, et al. Age-related differences in the quality of life of breast carcinoma patients after treatment. *Cancer: Interdisciplinary International Journal of the American Cancer Society*. 1999;86(9):1768-1774.

31. Alegria M, Canino G, Ríos R, et al. Mental health care for Latinos: Inequalities in use of specialty mental health services among Latinos, African Americans, and non-Latino Whites. *Psychiatric services*. 2002;53(12):1547-1555.

CHAPTER 6: DISCUSSION

6.1 Summary of findings

Emotional and functional decline following breast cancer is associated with disrupted quality of life (QoL), treatment non-adherence, failure to engaging in survivorship care, and increased mortality,[1-7] yet long-term and trajectories of emotional and functional well-being remain underexplored, particularly in racially diverse population-based cohorts. The goals of this study were 1) to evaluate long-term emotional and functional well-being change and assess whether decrease in well-being is associated with demographic and clinical features, 2) to identify distinct trajectories of emotional and functional well-being and investigate differences in membership by demographic and clinical characteristics.

Table 6. 1 Comparisons of results from two aims[a]

Variable	Aim 1 Well-being decrease	Aim 1 Well-being low baseline	Aim 2 Poor well-being trajectories
Race (Black vs. white)	+	+	+
Age (younger vs. older)	-	+	+
Marital status (no vs. yes)	NA	NA	+
Education (<college vs. college+)	NA	NA	+
Income (<$50K vs. ≥$50K)	NA	NA	+
Insurance (private insurance vs. no private insurance)	NA	NA	+
Cancer stage (III vs. I or II)	+	+	+
Surgery type (Mastectomy vs. breast conservation surgery)	|	+	+
Chemotherapy (yes vs. no)	-	+	+
BC recurrence (yes vs. no)	+	+	+

[a.] "+" represents positive association, "-" represents negative association, and "|" represents no statistically significant association.

In Aim 1, we found that the overall well-being improved over time since BC diagnosis, with the largest increases at 25 months. Changes in well-being at follow-up survey timepoints varied by race and age, with younger white women having the greatest increases relative to baseline, whereas older Black women experiencing only slight increases. As seen in Table 6.1, results from the multinomial logit model with multivariate adjustment showed that more advanced cancer stage and older age at diagnosis were moderately associated with well-being decrease at 84 months relative to baseline, whereas Black race and no receipt of chemotherapy were moderately associated with well-being decrease at both follow-up survey timepoints. Breast cancer recurrence was strongly associated with well-being decrease at both 25 months and 84 months, respectively.

In Aim 2, we identified five distinct trajectory groups for both emotional and functional well-being. Although most of our participants were resilient to distress induced by BC diagnosis, a substantial proportion of women in our study experienced consistently low well-being levels and even worse, dramatic decreases. When we examined the associations between demographic and clinical characteristics, we found that Black women, younger women, women with lower socioeconomic status, women who had more advanced cancer stage, were treated by mastectomy, received chemotherapy, and had BC recurrence, were more likely to fall into "poor well-being" trajectories compared to their counterparts.

In summary, women with BC can experience different patterns of emotional and functional well-being change from one timepoint to another, and we discovered that there are also unobserved subgroups of BC patients with similar trajectories of well-being during their survivorship. Long-term and trajectories of emotional and functional well-being are associated with important demographic and clinical features, such as age, race, socioeconomic status,

treatment modalities. These findings underscore the importance of understanding emotional and functional adjustment after BC diagnosis, as targeted intervention could be developed and implemented after identifying women at higher risk of experiencing less favorable well-being changes.

6.2 Strengths

Our study is novel in its use of a large population-based study of racially diverse women with BC. The CBCS3 allows us to assess potential racial disparities in long-term emotional and functional well-being, whereas populations from previous studies are predominately white women. Our study applied a longitudinal study design and an advanced person-centered modelling technique, latent class growth analysis, which adds longitudinal evidence to previous research on cross-sectional quality of life patterns. Additionally, no previous studies have such a long follow-up in our study as 84 months post diagnosis. With the extended period of follow-up, we were able to describe BC survivors' emotional and functional well-being experiences more comprehensively.

6.3 Limitations

Our study should be interpreted with some limitations in mind. First, we used the sum scores of emotional and functional well-being to approximate mental health in our study population, which is not validated by previous studies. Ideally, a more direct instrument should be used to accurately assess important changes in mental health status following BC diagnosis. But on the other hand, given the strong correlation between the emotional well-being score and the functional well-being score (correlation coefficient=0.6) and the same algorithm of calculating the total HRQoL scores, the sum scores of emotional and functional well-being are

expected to be a valid measurement and might be the most optimal indicator of mental health levels in our study.

A second limitation is that although our study population is large, the small percentages of women in certain strata (e.g., women who had BC recurrence and fell into "poor well-being" trajectories) led to non-positivity, which prevented adjustment for all possible confounders of associations between trajectory membership and socioeconomic status composites as well as clinical features. We observed that women who had an early decrease in well-being could not be specifically characterized by their demographic or clinical features, and this pattern seemed only associated with recurrence status, meaning that future studies are needed with a larger size of BC patients who experience recurrence during the survivorship.

A third limitation of our study is lack of information on baseline psychiatric comorbidities. This information could improve the imputation of missing values of well-being scores, because existing mental health issues might influence psychosocial adjustment following BC diagnosis. Additionally, we could get a better understanding of the compositions of certain trajectory groups (e.g., "stable low") if histories of mental health problems are available.

6.4 Significance

Understanding how women live with BC is key to helping them cope beyond initial diagnosis and treatment. Knowledge on the long-term and trajectories of emotional and functional well-being will substantially enhance our ability to provide health care providers with more specific recommendations on survivorship care to improve BC patients' mental health along their recovery, and to offer targeted emotional and functional support to survivors with specific demographic and clinical characteristics. By achieving Aim 1, characterizing long-term emotional and functional well-being overall and in association with demographic and clinical

features, this study could be used to inform clinical practice and decision-making regarding offering appropriate support to BC survivors with different characteristics. By achieving Aim 2, identifying distinct well-being trajectories and addressing potential disparities by race, age and other important factors, this study provides a better understanding of different patterns of change in emotional and functional well-being during BC survivorship, and assist in designing and carrying out interventions at appropriate time points in the cancer continuum.

6.5 Future directions

In the Carolina Breast Cancer Study (CBCS), we have observed that adherence to treatment and treatment delay vary according to a range of demographic factors.[8] Understanding the role that emotional and functional well-being plays in such delay is an important question, as it may be possible to design interventions that facilitate timely identification of treatment delay.

Additionally, continued research on determinants of emotional and functional well-being trajectories is critical for developing targeted strategies. The next step is to investigate a broader range of potential associated factors, especially modifiable lifestyle factors such as physical activity. Social support and coping strategies are also worth exploring as they are related in predicting emotional well-being of women with breast cancer. These future studies are critical to tailoring interventions for efficient health care delivery.

Another important next step in understanding why women with breast cancer have distinct well-being trajectories is to evaluate their well-being more frequently in the long-term survivorship, and examine potential impacts from time-varying covariates such as transition from active treatment to surveillance, and changes in treatment regimens. Detailed treatment-related information is becoming increasingly important as the population of breast cancer grows.

REFERENCES

1. Bower JE. Behavioral symptoms in breast cancer patients and survivors: fatigue, insomnia, depression, and cognitive disturbance. *Journal of clinical oncology: official journal of the American Society of Clinical Oncology*. 2008;26(5):768.

2. DiMatteo MR, Lepper HS, Croghan TW. Depression is a risk factor for noncompliance with medical treatment: meta-analysis of the effects of anxiety and depression on patient adherence. *Archives of internal medicine*. 2000;160(14):2101-2107.

3. Fann JR, Thomas-Rich AM, Katon WJ, et al. Major depression after breast cancer: a review of epidemiology and treatment. *General hospital psychiatry*. 2008;30(2):112-126.

4. Berg CJ, Stratton E, Esiashvili N, Mertens A. Young adult cancer survivors' experience with cancer treatment and follow-up care and perceptions of barriers to engaging in recommended care. *Journal of Cancer Education*. 2016;31(3):430-442.

5. Hjerl K, Andersen EW, Keiding N, Mouridsen HT, Mortensen PB, Jørgensen T. Depression as a prognostic factor for breast cancer mortality. *Psychosomatics*. 2003;44(1):24-30.

6. Ell K, Sanchez K, Vourlekis B, et al. Depression, correlates of depression, and receipt of depression care among low-income women with breast or gynecological cancer. *Journal of clinical oncology: official journal of the American Society of Clinical Oncology*. 2005;23(13):3052.

7. Iglay K, Santorelli ML, Hirshfield KM, et al. Impact of preexisting mental illness on all-cause and breast cancer–specific mortality in elderly patients with breast cancer. *Journal of Clinical Oncology*. 2017;35(36):4012-4018.

8. Reeder-Hayes KE, Mayer SE, Olshan AF, et al. Race and delays in breast cancer treatment across the care continuum in the Carolina Breast Cancer Study. *Cancer*. 2019;125(22):3985-3992.