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Association between Cardiovascular Disease and Cognitive Dysfunction in Breast Cancer Survivors

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Abstract

Background: Breast cancer survivors (BCS) may have a greater risk for cardiovascular disease [congestive heart failure (CHF) and hypertension (HTN)], which in turn, can affect cognitive dysfunction, a frequent, bothersome, and potentially debilitating symptom.

Objective: The purpose of this study was to examine the relationship of cardiovascular disease on cognitive function in BCS.

Methods: Baseline data from a double-blind RCT for cognitive training of BCS were examined. Early stage BCS (Stage I-IIIA) who were ≥21 years of age, completed adjuvant therapy (≥ 6 months), and reported cognitive concerns completed questionnaires and a brief neuropsychological assessment, including tests of memory, attention and working memory, speed of processing, and verbal fluency. Descriptive statistics, Pearson's correlation coefficient and separate linear regression models for each cognitive domain were conducted.

Results: 47 BCS, who were on average 57.3 (SD=8.1) years old, 58% White and had some college education (75%), completed the study. 44.7% of the BCS had cardiovascular disease (CHF or HTN). In linear regression models, cardiovascular disease was significantly related to immediate and delayed memory and attention and working memory ($p<0.01–0.05$).

Conclusions: BCS who have cardiovascular disease may also be at a greater risk for cognitive dysfunction post-treatment. Results from this study inform both clinical practice and future research, specifically by examining the intersect between cancer, cardiovascular disease (cardiotoxicity), and cognition.

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Conflict of interest:
The authors have no conflicts of interest to disclose.

Implications for Practice: Nurses should be aware that BCS with co-occurring cardiovascular disease are at higher risk for cognitive dysfunction, and work within the multidisciplinary team to optimize BCS health and function.

Keywords

cognitive dysfunction; breast cancer survivor; cardiovascular disease; symptoms; neuropsychological assessment

Background

Breast cancer is one of the most prevalent cancers in women, with estimates that up to 13% of all women will incur breast cancer at some point in their lifetime.[1] Advances in treatment modalities have resulted in breast cancer survivors (BCS) living longer. In fact, there are up to 3.8 million BCS living in the United States today.[1] BCS may enter treatment with other comorbid conditions, such as cardiovascular disease or incur cardiovascular disease due to the effects of cancer treatments.[2]

Breast cancer and cardiovascular disease have many common underlying risk factors, including age and lifestyle behaviors (e.g., diet, obesity, tobacco use and sedentary lifestyle).[3] Thus, it is not uncommon for BCS to enter treatment with co-occurring cardiovascular disease.[4] In addition, many treatments for breast cancer are cardiotoxic. Cardiotoxicities, including treatment-related diagnoses of congestive heart failure (CHF) and hypertension (HTN), are often reported in BCS.[2, 5] In fact, studies have shown that up to 25% of BCS have some level of cardiotoxicity post-treatment.[5] Chemotherapy treatment regimens, especially those regimens that include anthracycline-based chemotherapy (e.g., doxorubicin)[6] or alkylating agents (e.g., cyclophosphamide)[7] have been associated with long-term cardiovascular disease (CHF or HTN). Radiation therapy has also been associated with a variety of cardiotoxic effects, often presenting years after the completion of treatment.[8] In addition, aromatase inhibitors routinely used for estrogen-positive cancers for up to 10 years have been associated with HTN and cardiovascular disease.[9] Thus, while women are living longer after breast cancer diagnosis, they may also be dealing with cardiovascular disease and other associated symptoms.[4]

One such untoward symptom often reported by BCS is cognitive dysfunction.[10, 11] Breast cancer and cardiovascular disease are both known independent risk factors for cognitive dysfunction.[12–15] In BCS, researchers have documented the incidence of post-treatment cognitive dysfunction ranging from 15–25% on neuropsychological exam[10, 16], although percentages as high as 75% have been reported.[17] Specifically, studies have shown that BCS perform poorer on objective neuropsychological tests, especially tests of memory, attention and working memory, speed of processing, verbal fluency and executive function[18, 19] and many experience this cognitive dysfunction long into survivorship.[16, 20] Similar findings of poor performance on neuropsychological tests have been reported in women with cardiovascular disease.[21, 22] Cognitive dysfunction, in turn, has negative ramifications on work ability, employment, social, psychological, and physical well-being of BCS.[23–26] However, despite its prevalence and negative impact, little is known about the association of

cardiovascular disease, either as a comorbid condition pre-treatment or as a result of cancer treatment (cardiotoxicity) on cognitive function in BCS. Thus, more work is needed to fully understand the relationship of cardiovascular disease on cognitive function in BCS.

To guide this work, we turned to the conceptual framework developed by Merriman and colleagues[27] entitled, "Proposed Mechanisms of Cancer and Cancer Treatment-related Cognitive Changes." This model depicts the important role of inter-individual factors including both cancer treatment (chemotherapy, radiation & hormonal therapy) and other clinical factors including comorbidities (e.g., cardiovascular disease) which may impact cognitive function to produce cognitive changes. Furthermore, this model identifies that these factors may be mediated by upregulation of inflammation, hormonal changes, and neurotransmitter dysregulation. In addition, the model identifies innate inter-individual differences (e.g., age, education, genetic factors) which may moderate these effects and resultant cognitive changes. In review of the literature, we identified age, education, and race as potential confounding innate inter-interindividual factors which may influence cognitive dysfunction.[28–31] Older age and lower educational level have been associated with poorer performance on neuropsychological tests in BCS.[28–29] Social determinants of health often play into poorer health outcomes in BCS.[30] Researchers have also shown that Black women experience poorer outcomes from both breast cancer and cardiovascular disease[30–31] and its role in the sequela of treatment-effects especially in cognitive dysfunction which can have significant social, physical, and financial impacts[23–26], need further exploration. Therefore, the purpose of this study was to examine the relationship of cardiovascular disease on cognitive function controlling for known confounding factors of age, education, and race in BCS.

Methods

Design

This study leveraged the baseline cross-sectional data from a double-blind randomized controlled trial for cognitive training in BCS. BCS enrolled in this study were 21 years of age and older, had been diagnosed with early-stage disease (Stage I-IIIA) and completed adjuvant therapy (≥ 6 months). Those enrolled reported cognitive concerns and were seeking non-pharmacological treatment.

Procedure and Data Collection

BCS were recruited using two methods including (1) directed and targeted mailings (cancer registry, Pink Ribbon Connection, etc.) and (2) direct referral from healthcare providers from an NCI-designated Cancer Center. Eligible and interested BCS were explained the study and consented by the project staff. A trained and blinded neuropsychological tester conducted the baseline neuropsychological assessment and administered the demographic and medical questionnaire within our neuropsychological lab. Participants received $20 and were compensated for parking for completing this baseline assessment to offset participant burden. The Cancer Center Scientific Review Committee and Institutional Review Board for the University approved the study.

BCS completed survey questionnaires that included a self-report of demographic (age, education, race, and marital status) and medical information (comorbidities). Cardiovascular disease in this study was defined as self-reported diagnoses of CHF and HTN.

The neuropsychological test battery included objective tests of memory and delayed memory, attention and working memory, speed of processing and verbal fluency/executive functioning. These tests are reliable and valid instruments which have been used previously with BCS.[32–35] **Memory and Delayed Memory** were derived by the Rivermead Behavioral Paragraph Recall Test which is a story recall test that was used to test verbal memory.[36] Participants listened to a short passage read aloud and were then asked to write down as much as they can remember both immediately and again 30 minutes later (delayed memory). **Attention & Working Memory** was derived from the Digit Span from the WAIS-III.[37] This test requires verbal repetition of ever longer digit strings forward and then backward. The total score is the number of strings correctly recalled, with higher scores indicating better performance. **Speed of processing** was measured by Symbol Digit Modalities Test Oral Response Version[38] which requires decoding a series of symbols by verbally stating the number that should be paired with each symbol by reference to a constantly available legend or key. The higher score reflects better processing speed. **Verbal Fluency/Executive Function** was measured by the Controlled Oral Word Association (COWA)[39] which requires the spontaneous production of words beginning with a given letter with the total number recorded, with higher scores indicating better performance.

Data Analysis

Descriptive statistics were conducted to describe the characteristics of the sample and values of for each cognitive measure was reported for all BCS and those with and without cardiovascular disease. In addition, to further describe the sample, t-tests were conducted to determine if there were differences between those BCS with and without cardiovascular disease on each cognitive measure. Initial bivariate correlations were conducted using Pearson's correlation coefficient or Spearman's correlation coefficient. Separate linear regression models assessed the association of cardiovascular disease (CHF and HTN) and cognitive function including each cognitive domain, controlling for known covariates including age, education, and race (proxy for social determinants). Data were analyzed using IBM SPSS version 26 software. Significance level was set at p-value=0.05.

Results

A total of 47 BCS, who were on average 57.3 (SD=8.1) years old, 57.8% White and had some college education (74.5%), were included in this study. Table 1 displays the characteristics of the sample. Cardiovascular disease was reported by almost half of the BCS (n=21, 44.7%) in the study. Table 2 displays the mean and standard deviation for all of the cognitive performance measures for all BCS and also compares those with and without cardiovascular disease. As depicted, there is a significant difference between those with and without cardiovascular disease on tests of immediate memory (p=.003), delayed memory (p=.020), and attention, concentration & working memory (p=.016) with those without cardiovascular disease performing better on these tests There were no significant differences

between cardiovascular disease groups for speed of processing (p=.190) or verbal fluency/executive function (p=0.607).

In bivariate correlations, cardiovascular disease was significantly associated with learning and immediate memory, delayed memory and attention and working memory, but not speed of processing, verbal fluency, or subjective cognitive function. In addition, age, education, and race were significantly related to most of the cognitive outcome measures (specific neuropsychological test performance) (p≤0.05–0.001), supporting their inclusion in the regression analyses.

The overall models including age, education, race, and cardiovascular disease were significant for immediate memory, delayed memory, and attention and working memory (p<0.01–0.05); however, speed of processing and verbal fluency/executive functioning were not significant. Table 3 displays the significant models, F-statistic, beta weights, r^2 and significance level for each of the significant models. In addition, in the following section we will outline each of these significant models and predictor variables.

Immediate Memory - Age, education, race, and cardiovascular disease were related to immediate memory [F(4,40)= 5.53, adjusted r^2=.25; p<0.01], explaining 28% of the variance of immediate memory. White race (β= −1.09, p≤0.05) and not having cardiovascular disease (β= 2.31, p≤0.05) related to better immediate memory performance. **Delayed Memory** - The model including age, education, race, and cardiovascular disease were significant related to delayed memory [F(4,40)= 4.05, adjusted r^2=.17; p<0.05]. This model explained 17% of the variance of delayed memory; however, none of the variables independently were significantly related with delayed memory. Those with more education, White race and not having cardiovascular disease were trending toward significance to better delayed memory (p=0.07–0.09). **Attention and Working Memory** - Having cardiovascular disease was significantly related to attention and working memory [F(4,40)= 2.19, adjusted r^2=.10; p<0.05]. The model explained 10% of the variance of attention and working memory, with cardiovascular disease (β=3.273, p=0.01) related to attention and working memory. Those BCS without cardiovascular disease had demonstrated better attention and working memory on neuropsychological exam.

Discussion

This study is important as it is one of the few studies designed to look at the relationships between cardiovascular disease and cognitive function in BCS. Although the field of cardio-oncology has been receiving more attention, few studies have examined the intersection between breast cancer and cardiovascular disease or cardiotoxicity.[4] In addition, to our knowledge none have fully examined the additive effects of breast cancer and cardiovascular disease on cognitive dysfunction, a common, bothersome, and potentially debilitating symptom.

In this cohort of female BCS almost half (45%) reported some form of cardiovascular disease (CHF and/or HTN). This finding is consistent with previous research which has demonstrated that women in general[12] and BCS specifically incur higher rates of

cardiovascular disease.[6] This intersection between cardiovascular disease and breast cancer may be attributed to their many common predisposing risk factors (e.g., age, diet, obesity, tobacco use and sedentary lifestyle).[4] Additionally, cancer treatment regimens may place BCS at greater risk for cardiovascular disease[6, 8, 9]; however, discussion of cardiovascular disease prevention and modification of risk factors in BCS is limited.[40]

Another main finding from this work is that cardiovascular disease was found to be associated with tests of cognitive performance in BCS. Specifically, the presence of cardiovascular disease was associated with poorer cognitive performance on tests of immediate memory and attention and working memory. These findings suggest that BCS who have cardiovascular disease are potentially at greater risk for cognitive dysfunction. Researchers have noted that patients with cardiovascular disease commonly incur problems with attention, memory, and working memory.[41,42] Multiple meta-analyses have also identified deficits in attention, working memory, and short- and long-term memory in BCS.[18, 19] However, studies have not fully examined the additive and potentially compounding effects of cardiovascular disease and breast cancer diagnosis and treatment on cognitive function. This finding is significant, especially given the fact that improvements in early detection are leading to women being diagnosed earlier and living longer post-treatment. Treatment regimens, although improved, may have serious late and long-term consequences such as cognitive dysfunction, that in turn, can have a detrimental impact on social interactions,[23, 24] work productivity[24, 45] and quality of life.[43]

In an effort to understand who may be at greatest risk for cognitive dysfunction among BCS with and without cardiovascular disease, we also examined innate interindividual factors that may influence cognitive function. Significant relationships were noted between education and race with only one cognitive performance test. Specifically, we noted higher educational level was associated with better test performance on immediate memory. This finding is consistent with previous literature that has found educational level influences cognitive test performance in BCS.[44,45] Interestingly, race (social construct) was significant only in association with one cognitive domain, such that white BCS generally had better performance on a test of immediate memory. This finding underscores the need to fully examine the relationship of social determinants of health with breast cancer and cardiovascular disease, as well as with late and long-term effects of treatment, such as cognitive dysfunction.[44] Black women with cardiovascular disease and Black women with breast cancer have overall poorer health outcomes.[30,31] Race, in these previous studies, has often been used as an indicator of racism and the social inequity inherent in the provision of healthcare. As highlighted in the American Cancer Society’s Blueprint on social determinants to advance cancer health equity in the United States, more research is needed to fully understand the structural inequity and social factors influencing health disparities in our country.[30] Additionally, greater exploration is required to identify any potential biases that may exist with cognitive performance testing.[46] Finally, contrary to previous research, age was not significantly related to cognitive performance in this study.[45,47] The age range in this study, however, was fairly homogenous and more work is needed to include older BCS, as they are at the greatest risk for cognitive dysfunction post-breast cancer treatment.[48]

Implications for Practice and Future Research

Traditional survivorship care has generally focused on tertiary prevention, and more work is needed to address the broader long-term health implications of cancer and cancer treatment.[49] More emphasis must be placed on cardiovascular health and early identification of cognitive dysfunction in all BCS, but especially in those with cardiovascular disease. Interventions designed to address cardiovascular health (e.g., exercise or physical activity) may also have benefits for cognitive functioning in BCS.[50] In fact, Myers and colleagues' integrative review, which included 26 exercise studies, noted the majority of studies found some positive cognitive outcomes. While these authors note that more research is needed regarding the specific type, intensity, and duration, exercise may be an important intervention to address cognitive function in BCS.[50]

It is also important to note that special care may be required for the late and long-term effects of breast cancer and cancer treatment, including cardiotoxicity. In fact, the onset of heart failure from time of exposure of cardiotoxic treatments can be up to 10 years post-treatment.[49] Therefore, more research is needed in primary and secondary prevention of cardiotoxicity in BCS.[51] Efforts are needed to identify and validate prognostic and predictive biomarkers which signify increased susceptibility to cardiotoxicity and incorporate these evidenced-based predictors in a risk prevention.[49] Furthermore, McCabe and colleagues suggest a risk-based model that incorporates a personalized plan of screening, surveillance, and prevention are essential to improve the quality of cancer care.[52] Ultimately, clinicians need to incorporate evidence-based risk assessments in the cancer survivorship care plan with the goal for both preventing and/or treating cardiotoxicity and its sequela including cognitive dysfunction.

These findings emphasize the need for early identification of cardiovascular disease which can contribute to cognitive dysfunction in breast cancer patients. Over the past decade, the number of cardio-oncology programs has increased, but few have focused on early detection and prevention of cardiovascular disease in breast cancer patients. Thus, it is critical to include evidence-based cardiovascular risk assessment in cancer survivorship programs to reduce cardiovascular disease and cognitive dysfunction in breast cancer patients. Also, further research is needed to identify contributing factors for cognitive dysfunction.[10] This understanding will provide the foundation for developing personalized cancer survivorship programs that may help prevent adverse outcomes from cancer. In addition, comprehensive longitudinal research studies are needed to fully understand the trajectory of cardiovascular disease, either as comorbid and pre-adjuvant therapy or as a result of cancer treatment (cardiotoxicity) and its impact on cognitive functioning in a larger cohort of BCS. This observational work is necessary for designing evidence-based treatment interventions for BCS.

Strengths and Limitations of the Study

The study had a number of strengths and limitations. Strengths of this study included the use of neuropsychological tests, often considered the gold standard of cognitive assessment, to assess BCS abilities. Importantly, this study had a representative sample of women of color (42% Black) as most of this research has been done with predominately White

women. Although this study has many strengths, it was limited by its cross-sectional design and small sample size. Future studies need to explore and model the impact of breast cancer diagnosis, its treatment and the potential cardiotoxic effects of treatment on cognitive dysfunction over time. Understanding the temporal nature of cardiovascular disease as either pre-dating the breast cancer diagnosis or occurring as a side-effect of breast cancer treatment may also aid in identifying and improving prevention and treatment modalities. In addition, identifying a more inclusive approach to understanding the impact of social determinants of health is warranted to reduce disparities in cancer care.

Conclusion

BCS who have co-occurring cardiovascular disease may be at greater risk for cognitive dysfunction post-treatment. Based on these findings and others, clinical care needs to incorporate cardiovascular risk assessment and primary prevention strategies to reduce the occurrence of cardiovascular disease and/or identify it early to mitigate its effects which in turn, may reduce cognitive dysfunction in BCS. In addition, more research is warranted to examine the intersect between cancer, cardiotoxicity (cardiovascular disease), and cognitive function in BCS.

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Table 1.

Characteristics of the Sample (n=47)

Current Age, years	Mean ± SD	57.26 ± 8.05
	Median (Q1, Q3)	59 (52, 62)
Race	Black or more than one race	42.2%
	White	57.8%
Highest Education, years	Mean ± SD	15.66 ± 1.98
	Median (Q1, Q3)	16 (14, 17)
Marital Status	Single/divorced/widowed	38.3%
	Married/Partnered	61.7%
Stage of Breast Cancer	Stage I	29.8%
	Stage II	51.1%
	Stage III	14.9%
	Unsure	4.3%
Months since BCS Diagnosis	Mean ± SD	71.11±55.1
	Median (Q1, Q3)	51 (27, 93)
Surgery	Yes	91.5%
	No	8.5%
Radiation	Yes	80.9%
	No	19.1%
Tamoxifen Use	Never Used	42.2%
	Yes, Currently Using	15.6%
	Used in past, No current use	35.6%
	Unsure	6.7%
Aromatase Inhibitor Use	Never Used	31.8%
	Yes, Currently Using	29.5%
	Used in past, No current use	20.5%
	Unsure	18.2%

Table 2.

Descriptive Statistics of Cognitive Measures of All BCS and Those With and Without Cardiovascular Disease

Cognitive Domain (Measure)	All BCS		Cardiovascular Disease (n=21)		No Cardiovascular Disease (n=26)		t(45)	*p*
	M	SD	M	SD	M	SD		
Immediate Memory (RVMD)	9.36	2.69	7.17	2.62	9.75	2.94	3.15	.003[b]
Delayed Memory (RVMD-D)	9.09	3.04	6.67	2.85	8.75	3.00	2.42	.020[a]
Speed of Processing (Symbol Digit Modalities Test)	52.89	9.72	50.81	10.17	54.58	9.20	1.33	.190
Attention, Concentration & Working Memory (Digit Span)	17.47	4.18	15.86	3.80	18.77	4.10	2.51	.016[a]
Verbal Fluency - Executive Function (COWA)	44.32	9/94	43.48	9.23	45.00	10.60	0.52	.607

[a] p<.05;

[b] p<.01

Table 3.

Regression Models of Relationships of Age, Education, Race and Cardiovascular Disease on Cognitive Function in Breast Cancer Survivors

	Immediate Memory (ß, SE)	Delayed Memory (ß, SE)	Attention & Working Memory (ß, SE)
Variables			
Age	0.006, 0.500	−0.017, 0.055	0.054, 0.075
Education	0.425, 0.212	0.413[c], 0.233	0.169, 0.320
Race	−1.09[a], 0.482	−0.970[c], 0.529	−0.011, 0.727
Cardiovascular disease	2.31[b], 0.822	1.558[c], 0.903	3.273[a], 1.241
Model fits			
Adjusted R^2	.28	.15	.10
F	5.33	3.00	2.19
p of F	.002	.030	.047

[a] p < .05;

[b] p< .01;

[c] trend toward significance p=.07–.09