The Breast 44 (2019) 73–80

Contents lists available at ScienceDirect

The Breast

journal homepage: www.elsevier.com/brst

Original article

Cancer treatment effects on cognition and depression: The moderating role of physical activity

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ARTICLE INFO

Article history:
Received 19 October 2018
Received in revised form
8 January 2019
Accepted 14 January 2019
Available online 16 January 2019

Keywords:
Cognition
Depression
Physical activity
Breast cancer
Cancer treatment

ABSTRACT

Objectives: Breast cancer survivors report significant cognitive impairments post treatment, particularly following chemotherapy. Depression may also occur post treatment and may partially mediate the effects of cancer treatment on cognition. Additionally, physical activity has been shown to mitigate treatment effects on cognition and depression. This study examined the role of depression in mediating the effects of cancer treatment on cognitive function (perceived cognitive impairment, PCI; perceived cognitive ability, PCA) in breast cancer survivors and explored the role of physical activity in moderating these effects.

Materials and methods: 317 breast cancer survivors were recruited via Army of Women. Participants were 40–75 years old and had stage 0 (in situ) to IIIc breast cancer and were less than 10 years post treatment. Participants completed a demographic and treatment questionnaire, as well as the International Physical Activity Questionnaire, Functional Assessment of Cancer Therapy-Cognitive Function, and Center for Epidemiologic Studies Depression Scale.

Results: Depressive symptoms significantly contributed to cognitive function in all models. Moderate and vigorous levels of physical activity moderated breast cancer treatment effects on depression and cognition. Chemotherapy, tamoxifen, and anastrozole all demonstrated negative effects on cognition.

Conclusion: The results from this study support the importance of examining mediating factors in the effects of cancer treatment on cognition, particularly depression, following cancer treatment. Effects of treatment on cognition in breast cancer survivors are partially explained by changes in depressive symptoms, although chemotherapy may impact cognition independent of depression. Importantly, physical activity may reduce the risk of depression and cognitive impairment in breast cancer survivors.

1. Introduction

The prevalence of breast cancer survivors has increased substantially in recent years, in part due to earlier detection of cancer, better treatment outcomes, and the inclusion of multidisciplinary care teams in providing care [1]. Although these approaches may lengthen an individual's longevity, they are often associated with long-term impairment. Breast cancer survivors will often experience adverse effects such as depression and declines in cognitive function [2,3]. Acute cognitive declines, as measured via neuropsychological testing, occurs in 60% of breast cancer patients during treatment. An additional 29% of breast cancer patients show late (post-treatment) cognitive declines [4]. The incidence of depression in breast cancer survivors has also increased, with rates as high as 50% in some samples [5]. Depressive symptoms in breast cancer survivors are associated with reduced survival [6]. Given the high incidence of cognitive and depressive symptoms in breast cancer survivors, understanding which factors may mitigate them is an important area for further research.

Colloquially, terms such as 'chemofog' or 'chemobrain' have been used to describe the subsequent effects of systemic treatment in reference to cognitive impairment [1]. Chemotherapy has been

Abbreviations: PCI, perceived cognitive impairment; PCA, perceived cognitive ability; MPA, moderate physical activity; VPA, vigorous physical activity.

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https://doi.org/10.1016/j.breast.2019.01.004
0960-9776/

shown to be associated with cognitive decline [7]. This cognitive dysfunction has been demonstrated both acutely and long-term in cancer patients [8]. Recently, the use of aromatase inhibitors and tamoxifen have shown evidence as factors influencing cognitive impairment in cancer survivors [9,10]. The most common aromatase inhibitors examined in the literature are anastrozole, letrozole, and exemestane, which are given to post-menopausal women, while tamoxifen is primarily given to pre-menopausal women [11]. Cognitive function, such as perception, planning, and memory, is impaired by anticancer treatments [12]. Verbal memory and psychomotor speed in women with breast cancer is impaired by the use of aromatase inhibitors and tamoxifen treatment [10,13]. Perceived cognition is associated with neuropsychological measures of executive function, immediate and delayed verbal memory, and depressive symptoms in breast cancer survivors [14]. Less is known about the impact of these deficits on cognitive function in everyday life. The evidence for anticancer treatment effects on depression and how it effects the etiology of cognitive dysfunction needs to be clarified. A meta-analysis of depression in cancer survivors found a pooled effect of 20% of breast cancer survivors meeting the diagnostic criteria for depression [15]. Depression in breast cancer survivors presents limitations in cognitive functions regardless of cause [16]. A recent study of endocrine treatment, depression, and chemotherapy on cognition in breast cancer survivors concluded that depression had the largest effect in predicting cognitive impairments [16]. However, endocrine treatment was also significantly associated with cognitive impairments in the model [16]. Older adults enrolled in a four-month exercise program experienced improvements in executive function and memory, along with a decrease in depressive symptoms [17]. Quality of life is also negatively affected by the experience of cognitive declines. However, physical activity may have the potential to reduce depressive symptoms and improve cognition in breast cancer survivors [18].

While treatment negatively impacts mood and cognition in breast cancer survivors, it is known that lifestyle interventions mitigate these effects. According to the American College of Sports Medicine (ACSM), the general exercise requirement for cancer survivors is 150 min of moderate-to-vigorous physical activity (MVPA) per week [19]. However, breast cancer survivors significantly reduce their physical activity level from pre-to post-diagnosis [20]. This places them at higher risk for neurodegeneration and cognitive impairment due to physical inactivity [21]. Implementing physical activity during, and post treatment, could preempt these declines in breast cancer survivors. Specifically, moderate to vigorous physical activity in breast cancer survivors has been shown to have a complimentary effect on information processing speed [22]. This suggests that physical activity may be a preventative measure for cognitive decline in breast cancer survivors [23].

Physical activity has similar benefits for depressive symptoms [24]. The role of physical activity on depression and cognitive function in breast cancer survivors is not well documented and therefore more research is needed to examine potential pathways underlying these complex effects. The purpose of this study is to examine the role of depression in mediating the effects of breast cancer treatment on cognitive function (perceived cognitive impairment, PCI; perceived cognitive ability, PCA). In addition, this study will examine the role of physical activity in mitigating these adverse effects of cancer treatment. The proposed model of anticancer treatment effects on depression and cognition and the pathways tested are outlined in Fig. 1. We hypothesize that breast cancer treatments will increase the severity of depressive symptoms, and that these symptoms will be associated with greater cognitive impairment. We also hypothesize that breast cancer survivors who engage in higher levels of physical activity will have less depressive symptoms and better cognitive function post treatment.

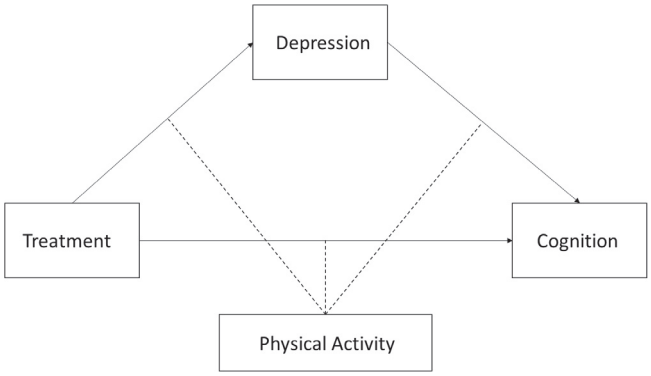

Fig. 1. Proposed model of cancer treatment effects and physical activity on depression and cognition.

2. Methods

2.1. Participants and recruitment

Breast cancer survivors were recruited via the Army of Women (AOW), a national non-profit breast cancer organization, which is an initiative of the Dr. Susan Love Research Foundation. Participants were women between 40 and 75 years old who had stage 0 (in situ) to stage IIIc breast cancer and were less than 10 years post diagnosis. In order to complete study evaluations and assessments the ability to read English and have access to a smartphone, tablet, ipad, computer, or laptop was required. We administered the surveys via Qualtrics, an online research survey platform. Surveys assessed demographics, treatment, cognitive function, depression, and self-reported physical activity of each breast cancer survivor. The Syracuse University Institutional Review Board (IRB) and the DSLRF Scientific Advisory Committee approved all procedures. Participants were recruited via an e-blast, which was sent out to eligible AOW members describing the study and inclusion criteria.

2.2. Demographic/treatment questionnaire

This measure was used to acquire anthropometric data, specifically height and weight. The treatment questionnaire was used to assess the time of diagnosis, recurrences, stage of breast cancer and cancer treatment for all participants.

2.3. Functional Assessment of Cancer Therapy-Cognitive function (FACT-Cog)

This is a 37-item questionnaire assessing cognitive function. Two of the four subscales, perceived cognitive impairment (PCI) and perceived cognitive ability (PCA), were used to measure cognition in the participants. Participants responded to each question based on the occurrence over the past 7 days using a 5-point Likert scale, 0 (never/not at all) to 4 (several times a day/very much). Negatively worded PCI items were reverse scored prior to summation. Higher scores on the FACT-Cog are indicative of greater cognitive function. PCI and PCA scores can range from 0 to 132. The FACT-Cog has been found to be a valid and reliable measure to evaluate cognition in cancer patients [25,26].

2.4. International Physical Activity Questionnaire (IPAQ)

The IPAQ long form was used to determine self-reported hours per week spent in moderate-to vigorous-intensity sports and recreational activities. A comprehensive set of domains including: leisure time physical activity, domestic and gardening activities, work-related physical activity, and transport-related physical activity were used to compute total scores including the summation of the duration (in minutes) and frequency (days) for all types of activities. The volume of activity was then computed by weighting each type of activity dependent upon its energy requirement, defined in metabolic equivalents (METs), to yield a total score in MET-minutes. The IPAQ is a measure that has been found to be valid and reliable in evaluating self-reported physical activity [27].

2.5. Center for epidemiologic studies depression (CES-D)

The 20-item CES-D assesses depressive symptoms over the last 7 days. Scores can range from 0 to 60, with higher scores indicative of greater depressive symptoms. In previous studies, a score of 16 indicates a clinically significant level of depression. The CES-D has been previously used in cancer patients, shown strong internal consistency, and correlation with other measures of depression [28]. Cronbach's alpha for the present study is 0.931.

Table 1
Demographics.

Age (yrs)	59.1 (7.9)
Years Since Diagnosis	5.7 (2.8)
Stage	
0	16.9
I	35.8
II	33.9
III	13.4
BMI (kg/m^2)	28.7 (6.9)
Ethnicity (%)	
White	92.5
African-American	4.8
Asian Pacific Islander	2.7
Education Level (%)	
Some High School/Diploma or G.E.D.	2.8
Vocational/Some College/Associates	17.5
College Degree	23.2
Some grad school/Master's Degree	47.1
Doctoral Degree	9.4
Treatment (%)	
Surgery	98.4
Radiation	67.4
Aromatase Inhibitors	56.1
Estrogen Modulator	46.1
Chemotherapy	60.2
Tamoxifen	44.7
CES-D	11.6 (10.9)

N = 317. Means and SD or percentile.

3. Statistical analysis

PROCESS macro regressions were used to predict perceived cognitive impairment and perceived cognition function for all pathways in Fig. 1. Mediation effects were tested via 5000 bootstrap samples to generate 95% confidence intervals. We included treatments which previously have been identified as having a potential effect on cognition: aromatase inhibitors, chemotherapy, and tamoxifen. Moderate and vigorous physical activity (MPA; VPA), as quantified by the IPAQ, were also included in each model. Based on associations in the literature with cognition, physical activity, or treatment, we also included ethnicity, years since diagnosis, and stage of cancer as covariates. Age was not included as a covariate due to the recommended use of different anticancer treatments dependent on age of diagnosis [29–32]. Depression as measured by the CES-D was entered as a mediator of the relationship between treatment and cognition. Physical activity was tested as a moderator of cancer treatment effects on depression, depression on cognition, and treatment on cognition in all models. Due to the number of models run, we report significance at $p < .05$ and note the findings that survive a Bonferroni correction at $p < .017$. All analyses were conducted through IBM SPSS version 24 and PROCESS v3.1 [33].

4. Results

Four hundred and thirty four (434) participants were recruited for the study. Three hundred and seventeen (317) breast cancer survivors completed the study. There were no significant differences in demographics between those who were recruited and those who completed. The mean age of the sample was 59 years old, and the average years since diagnosis were 5.72 years. On average the women had a body mass index (BMI) of 28.7 kg/m^2 and approximately a third were diagnosed with Stage I (35.8%) and a third with Stage II (33.9%) breast cancer. The majority of women identified as white (92.5%) and had completed some form of graduate education (56.5%). Almost all women had received surgery as part of their treatment (98.4%) and over half (67.4%) of the women received radiation during their treatment. On average the women had a score of 11.6 on the CES-D [See Table 1].

Results for all mediation models are presented in Tables 2 and 3. Depression was significantly associated with impaired cognition in all models. Of all treatments that were examined, only tamoxifen was significantly associated with greater depression. In addition, tamoxifen was the only treatment for which depression mediated the effects of treatment on cognition (PCI: −2.665, 95% CI = −5.113 to −0.447; PCA: −3.332, 95% CI = −6.396 to −0.516).

Results for all models of moderated mediation are presented in Tables 4–7. Across models, the total effect accounted for approximately 40% of the variance in cognition. None of the covariates were significant predictors in the models. For all models,

Table 2
Mediation model of treatment effects on depression and cognition.

Model $R^2 = 0.055$ $F(8,304) = 2.22$, $p = .026$	CES-D			PCI		
	Coefficient	SE	P	Coefficient	SE	P
Chemotherapy	0.581	1.478	0.695	−4.919	2.259	**0.030**
Tamoxifen	2.837	1.255	**0.024**	−3.208	1.918	0.096
Anastrozole	−2.122	1.324	0.110	0.302	2.024	0.882
Letrozole	−0.072	1.462	0.961	−1.071	2.235	0.632
Exemstane	−1.678	1.865	0.369	−0.812	2.851	0.776
CES-D	–	–	–	−0.921	0.070	**<0.001***

Values in bold are significant at $p < .05$; * indicates values which survived Bonferroni correction. Covariates also included in the model: years since diagnosis, stage of cancer at diagnosis, ethnicity, and all other forms of treatment.

Table 3
Mediation model of treatment effects on depression and cognition.

Model $R^2 = 0.058$ $F(8,304) = 2.34$, $p = .019$	CES-D			PCA		
	Coefficient	SE	P	Coefficient	SE	P
Chemotherapy	0.581	1.478	0.695	−7.278	2.837	**0.011***
Tamoxifen	2.837	1.255	**0.024**	−4.033	2.408	0.095
Anastrozole	−2.122	1.324	0.110	0.339	2.541	0.894
Letrozole	−0.072	1.462	0.961	−0.515	2.807	0.855
Exemstane	−1.678	1.865	0.369	−0.965	3.580	0.788
CES-D	–	–	–	−1.151	0.088	**<0.001***

Values in bold are significant at $p < .05$; * indicates values which survived Bonferroni correction. Covariates also included in the model: years since diagnosis, stage of cancer at diagnosis, ethnicity, and all other forms of treatment.

depression was significantly associated with cognitive impairments and abilities.

There was a significant interaction effect of MPA on the effect of chemotherapy on depression. Increasing MPA was associated with decreasing depressive symptoms in those who had received chemotherapy. There was no significant interaction of MPA and depression effects on cognitive function. There was a significant moderation by MPA on the direct effect of chemotherapy on PCI at moderate and high levels of MPA (−4.597, $p = .012$; −7.303, $p = .004$, respectively). Increasing amounts of MPA were associated with improved PCI but only for those who did not undergo chemotherapy. The above effects were all replicated with PCA for both moderate and high levels of MPA (−6.997, $p = .002$, −11.017, $p < .001$, respectively). There was no significant effect in the models for anastrozole and letrozole for both PCI and PCA. However, depression significantly mediated the effect of exemestane on PCI and PCA, but only for those with high levels of MPA (PCI: 6.345, 95% CI = 2.648–11.241; PCA: 4.960, 95% CI = 2.032–9.293). For those who received exemestane and engaged in more MPA, depression was decreased and perceived cognition improved. Depression

Table 4
Moderated mediation model of treatment effects on perceived cognitive impairment, moderated by total mets of moderate physical activity.

	CES-D			PCI		
Model 1 $R^2 = .408$ $F(12,300) = 17.24$, $p < .001$	Coefficient	SE	p	Coefficient	SE	p
Chemotherapy	3.159	1.937	.104	−1.734	2.381	.467
Moderate PA	.001	.001	.119	.002	.001	.124
Chemotherapy x Moderate PA	-.002	.001	.042	-.002	.001	.091
CES-D	–	–	–	-.966	.103	**<.001***
CES-D x Moderate PA	–	–	–	.000	.000	.682
Model 2 $R^2 = .404$ $F(12,300) = 16.97$, $p < .001$						
Tamoxifen	2.608	1.829	.155	−2.126	2.249	.345
Total Moderate PA	-.000	.001	.859	.000	.001	.941
Tamoxifen x Total Moderate PA	.000	.001	.866	.001	.001	.327
CES-D	–	–	–	-.958	.105	**<.001***
CES-D x Total Moderate PA	–	–	–	.000	.000	.629
Model 3 $R^2 = .403$ $F(12,300) = 16.88$, $p < .001$						
Anastrozole	−1.639	1.979	.408	−2.922	2.425	.229
Total Moderate PA	.000	.001	.906	.000	.001	.914
Anastrozole x Total Moderate PA	-.000	.001	.749	.001	.001	.576
CES-D	–	–	–	-.975	.104	**<.001***
CES-D x Total Moderate PA	–	–	–	.000	.000	.472
Model 4 $R^2 = .404$ $F(12,300) = 16.93$, $p < .001$						
Letrozole	−1.208	2.079	.562	−2.436	2.552	.341
Total Moderate PA	-.000	.001	.679	.000	.001	.749
Letrozole x Total Moderate PA	.001	.001	.445	.001	.002	.421
CES-D	–	–	–	-.959	.105	**<.001***
CES-D x Total Moderate PA	–	–	–	.000	.000	.637
Model 5 $R^2 = .403$ $F(12,300) = 16.85$, $p < .001$						
Exemestane	2.141	2.768	.439	−1.374	3.399	.686
Total Moderate PA	.000	.001	.602	.001	.001	.593
Exemestane x Total Moderate PA	-.003	.002	.063	-.001	.002	.779
CES-D	–	–	–	-.971	.104	**<.001***
CES-D x Total Moderate PA	–	–	–	.000	.000	.526

Values in bold are significant at $p < .05$; * indicates values which survived Bonferroni correction. Covariates also included in the model: years since diagnosis, stage of cancer at diagnosis, ethnicity, and all other forms of treatment.

Table 5
Moderated mediation model of treatment effects on perceived cognitive ability, moderated by total mets of moderate physical activity.

	CES-D			PCA		
Model 1 $R^2 = .411$ $F(12,300) = 17.45, p < .001$	Coefficient	SE	p	Coefficient	SE	p
Chemotherapy	3.159	1.937	.104	−2.744	2.987	.359
Moderate PA	.001	.001	.119	.003	.002	**.033**
Chemotherapy x Moderate PA	-.002	.001	**.042**	-.003	.002	**.046**
CES-D	–	–	–	−1.173	.130	**<.001***
CES-D x Moderate PA	–	–	–	.000	.0001	.985
Model 2 $R^2 = .407$ $F(12,300) = 17.15, p < .001$						
Tamoxifen	2.608	1.829	.155	−3.446	2.824	.223
Moderate PA	-.000	.001	.859	.001	.001	.667
Tamoxifen x Moderate PA	.000	.001	.866	.002	.002	.171
CES-D	–	–	–	−1.159	.131	**<.001***
CES-D x Total Moderate PA	–	–	–	.000	.000	.942
Model 3 $R^2 = .404$ $F(12,300) = 16.97, p < .001$						
Anastrozole	−1.639	1.979	.408	−4.215	3.047	.168
Moderate PA	.000	.001	.906	.001	.001	.637
Anastrozole x Moderate PA	-.000	.001	.749	.001	.002	.459
CES-D	–	–	–	−1.188	.131	**<.001***
CES-D x Moderate PA	–	–	–	.000	.000	.693
Model 4 $R^2 = .403$ $F(12,300) = 16.89, p < .001$						
Letrozole	−1.208	2.079	.562	-.853	3.211	.791
Moderate PA	-.000	.001	.679	.001	.001	.342
Letrozole x Moderate PA	.001	.001	.445	.001	.002	.794
CES-D	–	–	–	−1.176	.132	**<.001***
CES-D x Moderate PA	–	–	–	.000	.000	.806
Model 5 $R^2 = .403$ $F(12,300) = 16.89, p < .001$						
Exemestane	2.141	2.768	.439	−3.116	4.272	.466
Moderate PA	.000	.001	.602	.001	.001	.355
Exemestane x Moderate PA	-.003	.002	.063	.000	.002	.866
CES-D	–	–	–	−1.179	.131	**<.001***
CES-D x Moderate PA	–	–	–	.000	.000	.750

Values in bold are significant at $p < .05$; * indicates values which survived Bonferroni correction. Covariates also included in the model: years since diagnosis, stage of cancer at diagnosis, ethnicity, and all other forms of treatment.

significantly mediated tamoxifen's effects on cognitive function, but only for those with moderate levels of MPA (PCI: −2.613, 95% CI = −5.033 to −0.354, PCA: −3.269, 95% CI = −6.327 to −0.514).

VPA significantly moderated chemotherapy's direct effect on cognitive function for those with moderate and high levels of VPA (PCI: −4.495, p = .013; −6.894, p = .005, respectively; PCA: −6.740, p = .003; −9.985, p = .001, respectively). For those who do not engage in VPA, depression significantly mediated anastrozole's effect on cognitive impairment and ability (PCI: 3.618, 95% CI = 0.895–6.516; PCA: 4.414, 95% CI = 0.938–7.828). As depression increased in those who received anastrozole, cognitive function decreased significantly, but only for those who did not engage in VPA. There was no significant effect in the models for letrozole and exemestane. For those who engage in moderate levels of VPA, depression significantly mediated tamoxifen's effect on cognitive impairment and ability (PCI: −2.970, 95% CI = −5.994 to −0.079; 95% CI = −2.765, −5.206 to −0.586; PCA: −3.472, 95% CI = −6.457 to −0.669).

5. Discussion

This study examined the role of depression in mediating the effects of breast cancer treatment on cognition as well as the role of physical activity in moderating each of these effects. Given that breast cancer survivors experience adverse effects from treatment, such as depressive symptoms and cognitive dysfunction, it is important to identify the process by which these effects occur. Additionally, physical activity may alter these effects.

Our findings demonstrate the role of depressive symptoms on cognitive function in breast cancer survivors, regardless of treatment type. Impairments in cognition, specifically associated with tamoxifen treatment were, in part, due to tamoxifen's significant association with depressive symptoms. We also demonstrated that chemotherapy's effect on depression varies depending on the level of moderate and vigorous physical activity. To further understand the association of depression and moderate physical activity, clinicians should screen for depressive symptoms associated with cognitive impairments in breast cancer survivors. Breast cancer survivors who engaged in higher levels of moderate or vigorous physical activity had significantly improved cognitive ability. While moderate physical activity was effective at improving cognition in those who did not receive chemotherapy, those who did showed only minimal improvements in cognition with increasing levels of moderate physical activity. The results of our study suggest that the effects of chemotherapy on the brain may not be mitigated by moderate levels of physical activity. Applying more targeted exercise protocols may be necessary to show improvements in cognition and depressive symptoms in those who received

Table 6
Moderated mediation model of treatment effects on perceived cognitive impairment, moderated by total mets of vigorous physical activity.

	CES-D			PCI		
Model 1 $R^2 = .408$ $F(12,300) = 17.28, p < .001$	Coefficient	SE	p	Coefficient	SE	p
Chemotherapy	1.198	1.652	.469	−3.306	2.019	.131
Vigorous PA	-.000	.001	.683	.001	.001	.419
Chemotherapy x Vigorous PA	-.001	.001	.426	-.002	.002	.129
CES-D	–	–	–	-.973	.081	**<.001***
CES-D x Vigorous PA	–	–	–	.000	.000	.168
Model 2 $R^2 = .406$ $F(12,300) = 17.15, p < .001$						
Tamoxifen	3.032	1.468	.039	.119	1.809	.947
Vigorous PA	-.001	.001	.195	.000	.001	.805
Tamoxifen x Vigorous PA	.000	.001	.949	-.002	.002	.249
CES-D	–	–	–	-.979	.0801	**<.001***
CES-D x Vigorous PA	–	–	–	.000	.000	.101
Model 3 $R^2 = .407$ $F(12,300) = 17.14, p < .001$						
Anastrozole	−3.757	1.512	.014*	-.907	1.884	.631
Vigorous PA	-.002	.001	.005*	-.002	.002	.253
Anastrozole x Vigorous PA	.003	.001	.022	.001	.001	.576
CES-D	–	–	–	-.963	.081	**<.001***
CES-D x Vigorous PA	–	–	–	.000	.000	.128
Model 4 $R^2 = .404$ $F(12,300) = 16.97, p < .001$						
Letrozole	−1.081	1.705	.527	−1.469	2.094	.484
Vigorous PA	-.001	.001	.045	-.000	.001	.738
Letrozole x Vigorous PA	.002	.002	.300	.000	.002	.854
CES-D	–	–	–	-.969	.081	**<.001***
CES-D x Vigorous PA	–	–	–	.000	.000	.162
Model 5 $R^2 = .406$ $F(12,300) = 17.05, p < .001$						
Exemestane	−1.593	2.198	.469	−1.089	2.689	.686
Vigorous PA	-.001	.001	.112	-.000	.001	.960
Exemestane x Vigorous PA	-.000	.001	.963	-.002	.002	.428
CES-D	–	–	–	-.968	.081	**<.001***
CES-D x Vigorous PA	–	–	–	.000	.000	.171

Values in bold are significant at $p < .05$; * indicates values which survived Bonferroni correction. Covariates also included in the model: years since diagnosis, stage of cancer at diagnosis, ethnicity, and all other forms of treatment.

chemotherapy.

Tamoxifen was associated with significantly higher depressive symptoms in breast cancer survivors. Although these symptoms were experienced in the week prior to the assessment, prior studies have found longitudinal changes in cognition and depressive symptoms immediately following tamoxifen treatment [34]. Similar to the effects of chemotherapy, VPA improved depressive symptoms, except in those who received anastrozole. Those who received anastrozole and engaged in VPA showed only minimal improvements in depressive symptoms. This fits with inconsistent findings in the literature on whether aromatase inhibitors and/or tamoxifen alter hippocampal function and connectivity to promote depressive symptoms and cognitive dysfunction [35]. This effect, however, was conditional on the level of physical activity. Therefore, prior inconsistent findings may be due to variable levels of physical activity between study groups. Across all models, higher levels of depressive symptoms were associated with impaired cognitive function. This indicates that breast cancer survivors may need to engage in vigorous levels of physical activity in order to improve depressive symptoms. This would in turn improve cognitive function, which may lead to improvements in overall quality of life for breast cancer survivors.

There were a few limitations in our study. In an effort to measure perceived cognitive function, the FACT-Cog was used. Although this measure is self-reported and responses may be biased, it has been well documented that perceived cognition in breast cancer survivors can be accurately measured using the FACT-Cog [25]. A second potential limitation was the use of the IPAQ to measure physical activity. Though self-report responses may reflect fluctuations in levels of physical activity over the past 7 days, the IPAQ has previously been found to be a valid and reliable measure of physical activity [27]. The third limitation is the use of the CES-D to measure depressive symptoms. Similar to the above measures, this self-report may reflect experiences of depressive symptoms and not necessarily clinical criteria for depression. However, depressive symptoms, not just depression, have been predictive of negative outcomes for breast cancer survivors [36]. Another potential limitation is that the models presented here did not control for age of participants. This is due to overlap between recommended anticancer treatments and age at diagnosis [29–32]. Therefore, future studies would benefit from testing pre- and post-treatment neuropsychological function and stratifying participants by different age groups. Additionally, some pathways did not remain significant when a Bonferroni correction was applied to the analyses. However, it is important to note that all moderated mediation paths remained significant. Finally, while the near term of self-report period allows for less inaccuracy in recollection of information for those measures, long-term measurement of

Table 7
Moderated mediation model of treatment effects on perceived cognitive ability, moderated by total mets of vigorous physical activity.

	CES-D			PCA		
Model 1 $R^2 = .408$ $F(12,302) = 17.19$, $p < .001$	Coefficient	SE	p	Coefficient	SE	p
Chemotherapy	1.198	1.653	.469	−4.794	2.543	.060
Vigorous PA	-.000	.001	.683	.002	.002	.181
Chemotherapy x Vigorous PA	-.001	.001	.426	-.003	.002	.103
CES-D	–	–	–	−1.187	.101	**<.001***
CES-D x Vigorous PA	–	–	–	.000	.000	.401
Model 2 $R^2 = .403$ $F(12,300) = 16.87$, $p < .001$						
Tamoxifen	3.032	1.468	**.039**	-.508	2.283	.824
Vigorous PA	-.000	.001	.195	.001	.002	.578
Tamoxifen x Vigorous PA	.000	.001	.949	-.001	.002	.542
CES-D	–	–	–	−1.189	.102	**<.001***
CES-D x Vigorous PA	–	–	–	.000	.000	.321
Model 3 $R^2 = .405$ $F(12,300) = 16.99$ $p < .001$						
Anastrozole	−3.757	1.512	**.014***	−1.070	2.374	.653
Vigorous PA	-.002	.001	**.005***	.001	.002	.428
Anastrozole x Vigorous PA	.003	.001	**.022**	-.002	.002	.257
CES-D	–	–	–	−1.175	.102	**<.001***
CES-D x Vigorous PA	–	–	–	.000	.000	.323
Model 4 $R^2 = .402$ $F(12,300) = 16.82$, $p < .001$						
Letrozole	−1.081	1.705	.527	-.561	2.638	.832
Vigorous PA	-.001	.001	**.045**	.000	.001	.747
Letrozole x Vigorous PA	.002	.002	.300	-.000	.002	.953
CES-D	–	–	–	−1.182	.102	**<.001***
CES-D x Vigorous PA	–	–	–	.000	.000	.379
Model 5 $R^2 = .403$ $F(12,300) = 16.87$, $p < .001$						
Exemestane	−1.593	2.198	.469	−1.688	3.390	.619
Vigorous PA	-.001	.001	.112	.001	.001	.627
Exemestane x Vigorous PA	-.000	.001	.963	-.002	.003	.537
CES-D	–	–	–	−1.181	.102	**<.001***
CES-D x Vigorous PA	–	–	–	.000	.000	.399

Values in bold are significant at $p < .05$; * indicates values which survived Bonferroni correction. Covariates also included in the model: years since diagnosis, stage of cancer at diagnosis, ethnicity, and all other forms of treatment.

behaviors and symptoms would be useful in clarifying the directionality of the findings.

6. Conclusion

Future studies examining effects of chemotherapy on cognition should evaluate and control for levels of depressive symptoms. Additionally, further research should examine whether breast cancer survivors undergoing an exercise intervention experience beneficial changes in depressive symptoms and cognitive function over time. The effects of treatment on cognition in breast cancer survivors are partially explained by changes in depressive symptoms. However, these changes depend on the level of physical activity that survivors engage in. Clinicians working with breast cancer survivors post treatment should consider screening regularly for depressive symptoms and encourage patients to meet ACSM guidelines for moderate and vigorous physical activity. Future research and clinical work should consider the role of depressive symptoms and exercise in the trajectory of treatment related cognitive impairment in breast cancer survivors.

Conflicts of interest

The authors declare they have no conflicts of interest.

Ethical approval

Institutional review board approval and participant informed consent was obtained.

Funding

Funding for this study was provided by the Robert E. Leet and Clara Guthrie Patterson Trust (PI: Thomas).

References

[1] Selamat Hafsah Maryam, Yim Loh Siew, Mackenzie Lynette, Janette Vardy. Chemobrain experienced by breast cancer survivors: a meta-ethnography study investigating research and care implications. PLoS One 2014;9(9).
[2] Massie MJ. In: Pain. 1. Washington, DC: American Psychiatric Press; 2000 [u.a.].
[3] Lyon DE, Cohen R, Chen H, et al. Relationship of systemic cytokine concentrations to cognitive function over two years in women with early stage breast cancer. J Neuroimmunol 2016;301:74–82.
[4] Wefel Jeffrey S, et al. Acute and late onset cognitive dysfunction associated with chemotherapy in women with breast cancer. Cancer 2010;116(14):3348–56.
[5] Philipp Zimmer, Baumann Freerk T, Max Oberste, Wright Peter, Alexander Garthe, Alexander Schenk, Thomas Elter, Galvao Daniel A, William Bloch, Hubner Sven T, Wolf Florian. Effects of exercise interventions and physical activity behavior on cancer related cognitive impairments: a systematic review. BioMed Res Int 2016;2016:13.

[6] Watson M, Haviland J, Greer S, Davidson J, Bliss J. Influence of psychological response on survival in breast cancer: a population-based cohort study. Lancet 1999;354(9187):1331–6.
[7] Janelsins MC, Heckler CE, Peppone LJ, et al. Cognitive complaints in survivors of breast cancer after chemotherapy compared with age-matched controls: an analysis from a nationwide, multicenter, prospective longitudinal study. J Clin Oncol: Official J Am Soc Clin Oncol 2017;35(5):506–14.
[8] Wefel Jeffrey S, Saleeba Angele K, Buzdar Aman U, Meyers Christina A. Acute and late onset cognitive dysfunction associated with chemotherapy in women with breast cancer. 2010.
[9] Jenkins VA, Ambroisine LM, Atkins L, Cuzick J, Howell A, Fallowfield LJ. Effects of anastrozole on cognitive performance in postmenopausal women: a randomised, double-blind chemoprevention trial (IBIS II). Lancet Oncol 2008;9(10):953–61.
[10] Boele FW, Schilder CMT, de Roode ML, Deijen JB, Schagen SB. Cognitive functioning during long-term tamoxifen treatment in postmenopausal women with breast cancer. Menopause 2015;22(1):17–25.
[11] Pistelli M, et al. Aromatase inhibitors in premenopausal women with breast cancer: the state of the art and future prospects. Curr Oncol 2018;25(2):e168–75.
[12] Lange M, Heutte N, Noal S, et al. Cognitive changes after adjuvant treatment in older adults with early-stage breast cancer. Oncol 2018:0570.
[13] Jenkins V, Shilling V, Fallowfield L, Howell A, Hutton S. Does hormone therapy for the treatment of breast cancer have a detrimental effect on memory and cognition? A pilot study. Psycho Oncol 2004;13(1):61–6.
[14] Von Ah, Diane PhD, RN|Tallman Eileen F, BS BA. Perceived cognitive function in breast cancer survivors: evaluating relationships with objective cognitive performance and other symptoms using the functional assessment of cancer therapy—cognitive function instrument. J Pain Symptom Manag 2015;49(4):697–706.
[15] Krebber AMH, Buffart LM, Kleijn G, et al. Prevalence of depression in cancer patients: a meta-analysis of diagnostic interviews and self-report instruments. Psycho Oncol 2014;23(2):121–30.
[16] Seliktar N, Polek C, Brooks A, Hardie T. Cognition in breast cancer survivors: hormones versus depression. Psycho Oncol 2015;24(4):402–7.
[17] Khatri P, Blumenthal JA, Babyak MA, et al. Effects of exercise training on cognitive functioning among depressed older men and women. J Aging Phys Activ 2001;9(1):43–57.
[18] Lawson Rachael A, Yarnall Alison J, Duncan Gordon W, Breen David P, Khoo Tien K, Williams-Gray Caroline H, Barker Roger A, Collerton Daniel, Taylor John-Paul, Burn David J. Cognitive decline and quality of life in incident Parkinson's disease: the role of attention. Park Relat Disord 2016;27:47–53.
[19] Schmitz KH, Courneya KS, Matthews C, et al. American College of Sports Medicine roundtable on exercise guidelines for cancer survivors. Med Sci Sports Exerc 2010;42(7):1409–26.
[20] Irwin ML, Crumley D, Mctiernan A, et al. Physical activity levels before and after a diagnosis of breast cancer: the health, eating, activity, and lifestyle (HEAL) study. 2003.
[21] Pedersen BK. Exercise-induced myokines and their role in chronic diseases. Brain Behav Immun 2011;25(5):811–6.
[22] Marinac C, Godbole S, Kerr J, Natarajan L, Patterson R, Hartman S. Objectively measured physical activity and cognitive functioning in breast cancer survivors. J Cancer Surviv 2015;9(2):230–8.
[23] Erickson KI, Leckie RL, Weinstein AM. Physical activity, fitness, and gray matter volume. Neurobiol Aging 2014;35:S28.
[24] Pareja-Galeano H, Sanchis-Gomar F, Lucia A. Physical activity and depression: type of exercise matters. JAMA Pediat 2015;169(3):288.
[25] Jacobs Sherri R. Validation of the functional assessment of cancer therapy cognitive scale with bone marrow transplant patients. Graduate Theses and Dissertations. 2004.
[26] Asher A, Myers JS. The effect of cancer treatment on cognitive function. Clin Adv Hematol Oncol : H&O 2015;13(7):441.
[27] Craig CL, Marshall AL, Sjöström M, Bauman AE, Booth ML, Ainsworth BE, Pratt M, Ekelund U, Yngve A, Sallis JF, Oja P. International physical activity questionnaire: 12-country reliability and validity. Med Sci Sports Exerc 2003 Aug;35(8):1381–95.
[28] Radloff LS. The CES-D scale. Appl Psychol Meas 1977;1(3):385–401.
[29] August David A, Rea Thomas, Sondak Vernon K. Age-related differences in breast cancer treatment. Ann Surg Oncol 1994;1(1):45–52.
[30] Yancik Rosemary, et al. Effect of age and comorbidity in postmenopausal breast cancer patients aged 55 years and older. Jama 2001;285(7):885–92.
[31] Lumachi Franco, Santeufemia Davide A, Basso Stefano MM. Current medical treatment of estrogen receptor-positive breast cancer. World J Biol Chem 2015;6(3):231.
[32] Suter Matteo B, Pagani Olivia. Should age impact breast cancer management in young women? Fine tuning of treatment guidelines. Therap Adv Med Oncol 2018;10. https://doi.org/10.1177/1758835918776923. 1758835918776923. 22 Jun.
[33] Hayes AF. Introduction to mediation, moderation, and conditional process analysis: a regression-based approach. second ed. New York: The Guilford Press; 2018.
[34] Espeland MA, Shumaker SA, Limacher M, et al. Relative effects of tamoxifen, raloxifene, and conjugated equine estrogens on cognition. J Women Health 2010;19(3):371–9 (2002).
[35] Kokras N, Pastromas N, Porto TH, Kafetzopoulos V, Mavridis T, Dalla C. Acute but not sustained aromatase inhibition displays antidepressant properties. Int J Neuropsychopharmacol 2014;17(8):1307–13.
[36] Park J, Bae SH, Jung Y, Jung Y. Prevalence and characteristics of chemotherapy-related cognitive impairment in patients with breast cancer. J Kor Acad Nurs 2015;45(1):118–28.