Supportive Care in Cancer (2019) 27:1435–1441
https://doi.org/10.1007/s00520-018-4459-8

ORIGINAL ARTICLE

Dimensions of sedentary behavior and objective cognitive functioning in breast cancer survivors

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Received: 21 March 2018 / Accepted: 30 August 2018 / Published online: 17 September 2018

Abstract

Purpose To examine associations between dimensions of sedentary behavior and cognitive function in breast cancer survivors.
Methods Sedentary behavior variables were measured using thigh-worn activPALs, and included total daily sitting time, time in long sitting bouts, sit-to-stand transitions, and standing time. Cognitive function was assessed using the NIH Toolbox Cognitive Domain. Separate multivariable linear regression models were used to examine associations between sedentary behavior variables with the cognitive domain scores of attention, executive functioning, episodic memory, working memory, and information processing speed.
Results Thirty breast cancer survivors with a mean age of 62.2 (SD = 7.8) years who were 2.6 (SD = 1.1) years since diagnosis completed study assessments. In multivariable linear regression models, more time spent standing was associated with faster information processing (b: 5.78; $p = 0.03$), and more time spent in long sitting bouts was associated with worse executive function (b: −2.82; $p = 0.02$), after adjustment for covariates. No other sedentary behavior variables were statistically significantly associated with the cognitive domains examined in this study.
Conclusions Two important sedentary constructs that are amenable to intervention, including time in prolonged sitting bouts and standing time, may be associated with cognitive function in breast cancer survivors. More research is needed to determine whether modifying these dimensions of sedentary behavior will improve cognitive function in women with a history of breast cancer, or prevent it from declining in breast cancer patients.

Keywords Sitting · Standing · Sedentary · Cognitive impairment · Breast cancer

Background

Breast cancer is one of the most common cancers among women in the US [1] and accounts for the largest group of cancer survivors [2]. Breast cancer survivors experience higher rates of cognitive impairment compared to women without a history of cancer due to a variety of factors [3] that may include cancer treatments [4] and psychosocial factors related to receiving a cancer diagnosis [5]. These impairments can last for years after treatment has been completed and may impact quality of life [6, 7]. There is a lack of effective pharmacologic treatments for cognitive impairment among breast cancer survivors [8], motivating the search for lifestyle strategies that may be leveraged to improve cognitive function and prevent future decline.

Sedentary behavior has become increasingly recognized as an important health behavior in recent years, with considerable epidemiologic evidence indicating that it has deleterious

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effects on a variety of health outcomes [9]. Sedentary behavior is distinct from physical inactivity, and refers to any waking behavior characterized by an energy expenditure ≤ 1.5 metabolic equivalents (METs), while in a sitting, reclining or lying posture [10]. While the impact of sedentary behavior has been widely studied in the context of conditions such as cardiovascular disease and diabetes [9], much less is known about the effect of sedentary behavior on cognitive function in cancer populations. In a 2016 systematic review of the literature, Falck and colleagues identified eight studies examining the association between sedentary behavior and aspects of cognition—all in non-cancer populations—and concluded that the [limited] existing evidence suggests that sedentary behavior is negatively associated with cognitive function [11]. Notably, this trend was particularly consistent in studies that used total TV time as a proxy for sedentary time. Several other studies in non-cancer populations have been published since that review was conducted, and largely observed the same associations [12, 13]. However, it is notable that the overwhelming majority of studies to date on the topic have used self-reported measures of sedentary behavior, which have well-known biases [14] and generally cannot be used to capture information on dimensions of sedentary behavior, such as time spent sitting, time spent in long sitting bouts, time spent standing, and the frequency of sit-to-stand transitions, which may be informative for sedentary behavior intervention development.

It remains unclear whether the previously reported associations between sedentary time and cognitive function are generalizable to women with a history of breast cancer, whose cognitive decline may stem from other sources [3]. It is also notable that breast cancer survivors have been shown to have lower than expected cognitive performance compared to age-matched controls [15], and are more sedentary than individuals without a history of cancer [16]. We therefore tested whether sedentary behaviors were associated with cognitive function in a sample of early-stage breast cancer survivors. We used a computerized assessment of objectively measured cognitive function via the NIH Toolbox (nihtoolbox.org); and used objective measures of different dimensions of sedentary behavior, which included time spent sitting, time spent in long sitting bouts, time spent standing, and the frequency of sit-to-stand transitions. These dimensions are of particular interest given the existing evidence that time spent in long sedentary bouts may be a stronger predictor of health outcomes in breast cancer survivors than total sedentary time [17], and given the growing interest in incorporating standing and sit-to-stand transitions as strategies to "break up" or reduce sedentary time in intervention research [18, 19]. Findings generated from these analyses are positioned to contribute important preliminary insight into the role that sedentary behaviors, and strategies to break up sedentary behaviors, have on cognitive function in breast cancer survivors.

Methods

Participants were women enrolled in a cross-sectional pilot study designed to examine associations between objectively measured sedentary behavior and health outcomes among early-stage breast cancer survivors [20]. Women were recruited from the greater San Diego, CA area, using registries of breast cancer survivors who had previously consented to be contacted for research. Eligibility was assessed by telephone interview. To be eligible for the study, women had to have been diagnosed with stage I-III breast cancer within 5 years of study enrollment, have completed primary treatment, and had to speak English fluently. Women were excluded if they had a primary or recurrent invasive cancer in the past 10 years (except non-melanoma skin cancer or carcinoma of the cervix in situ), were over 85 years of age, recently had bariatric surgery within the past year, were taking insulin or corticosteroid medications, or were diabetic.

Eligible participants attended an in-person study visit at the Moores UC San Diego Cancer Center, where they self-reported socio-demographic factors, and completed physical assessments of height and weight and an objective assessment of cognitive functioning. Participants were also asked to wear an activPAL3 positioned on their thigh for 7 days after the clinic visit, and had an ActiGraph GT3X+ accelerometer positioned at their right hip during the same 7-day measurement period. The Human Research Protections Program at the University of California, San Diego, approved all procedures and measures (IRB# 130815) and all subjects provided written informed consent.

Cognitive function Cognitive function was assessed objectively using the National Institutes of Health (NIH) Toolbox Cognitive Domain (nihtoolbox.org). The NIH Toolbox Cognitive Domain is comprised of a series of interviewer-administered, computer-adaptive tests that take approximately 45 min to complete. The adaptive feature of the test is intended to minimize practice effects, as well as floor- and ceiling-effects. We examined age-standardized scores of five tests, representing distinct cognitive sub-domains. These tests and domains included: the Dimensional Change Card Sort Test of executive functioning, the Flanker Inhibitory Control and Attention Test of attention, the Picture Sequence Memory Test of episodic memory, the List Sorting Working Memory Test of working memory, and the Pattern Comparison Test of information processing speed. Detailed descriptions of these tests have been previously published [21], and the battery has been validated in adults [22].

Objective assessment of sedentary behavior dimensions The activPAL3 (PAL Technologies, Glasgow, Scotland), hereafter, referred to more generally as an "activPAL," is a small and lightweight accelerometer worn on the thigh. The activPAL produces a signal related to thigh inclination, which is used to estimate time spent in different body postures (sitting/lying down, standing) and to estimate the number of sit-to-stand transitions [23]. The activPAL has demonstrated good reliability and validity [24–26]. Participants were asked to wear the device continuously, 24 hours a day, for 7 days and instructed to remove the device during water-based activities or bathing. ActivPAL data were downloaded and processed using the activPAL Professional Research Edition software package using the 15-second Epoch. To filter nighttime sleeping, activPAL data were matched to the hip-worn ActiGraph data, which was worn concurrently with the activPAL except that participants were instructed to remove the ActiGraph for sleep. Overnight non-wear time periods on the ActiGraph were thus removed from activPAL time as "sleep time." Time in long sitting bouts was defined as continuous periods of sitting that lasted at least 20 minutes [17, 20]. To approximate time spent standing per day, we summed the minutes in a day spent in a vertical posture. We also estimated the number of sit-to-stand transitions, which reflect both transitions from sit-to-stand and sit-to-walking behaviors. Day-level approximations were averaged across measurement days for each participant to create a daily average during the wear-period.

Covariates Moderate-to-vigorous intensity physical activity (MVPA) was assessed using ActiGraph GT3X+ accelerometers (ActiGraph, LLC), which are well-validated wearable sensors that provide an indication of the frequency, duration, and intensity of physical activity. ActiLife v6.11 software was used to screen for sufficient wear-time using guidelines outlined by Choi and colleagues [27]. Sufficient wear-time was defined as 5 days with ≥ 600 min of wear time or 3000 min (50 hrs) across 4 days. Time spent in MVPA was derived from accelerometer data using published cut-points [28]. MVPA was defined as an intensity count of 1952 or more per minute. Socio-demographic data were obtained through self-report. Study staff also reviewed medical records to verify each woman's breast cancer diagnosis and to abstract clinical and treatment variables.

Statistical analysis

Separate multivariable linear regression models were used to assess whether sitting and standing time were associated with domains of cognitive function (attention, executive functioning, episodic memory, working memory, and information processing speed). Given the emerging interest in designing interventions to "break up" long bouts of sedentary behavior [19], we also examined whether the number of sit-to-stand transitions and time in long sitting bouts were associated with cognitive sub-domains. All models controlled for a set of a-priori identified confounders which included measurement device wear time, education, employment status, moderate to vigorous intensity physical activity (MVPA), and chemotherapy status (received vs. no). The model with sit-to-stand transitions as the primary exposure variable additionally adjusted for total sitting time. We did not adjust for body mass index (BMI), because it may lie on the causal pathway between sedentary behaviors and cognitive function [29]. Given the limited sample size and exploratory nature of this pilot study, we did not adjust our analyses for multiple comparisons.

Results

Participants ($n = 30$) were a mean age of 62.2 (SD = 7.8), were primarily White (93%), and were well educated, with over half of the sample having completed college (Table 1). Participants were enrolled in the study an average of 2.6 (SD = 1.1) years after their initial diagnosis of breast cancer,

Table 1 Characteristics of breast cancer survivors in the study sample ($n = 30$)

	Mean (SD)
Age	62.2 (7.8)
White, non-Hispanic[†], *n* (%)	28 (93.3%)
Completed college, *n* (%)	17 (57.0%)
Body mass index (kg/m^2)	23.7 (3.5)
Years since diagnosis	2.6 (1.1)
Cancer stage	
I	20 (66.7%)
II	9 (30.0%)
III	1 (3.3%)
Received chemotherapy, n(%)	17 (56.7%)
Estrogen receptor positive[†], n(%)	21 (70.0%)
Progesterone receptor positive[†], n(%)	20 (66.7%)
Moderate-to-vigorous intensity physical activity (min/day)	27.9 (22.2)
Sedentary behavior and transition variables	
Total sitting time (h/day)	8.3 (1.4)
Time in long sitting bouts[‡] (h/day)	4.8 (1.6)
Total standing time (h/day)	4.1 (1.2)
Sit-to-stand transitions (n/day)	60.4 (16.7)
Cognitive testing sub-domain scores	
Executive functioning: card sort	100.6 (9.2)
Attention: flanker	98.3 (9.9)
Memory: picture sequence	110.8 (19.4)
Working memory: list sorting	106.1 (12.9)
Information processing speed: pattern comparison test	98.4 (15.2)

[†] Missing data on race for $n = 1$ participant, and estrogen and progesterone receptor status for $n = 1$ participant

[‡] Long sitting bouts: continuous periods of sitting that last at least 20 min

had predominantly stage I or II breast cancer, and 57% of the sample received chemotherapy. On average, participants in the study spent over a third of their day sitting, 8.3 hours (SD = 1.4), with at least half, 4.8 hours (SD = 1.6), of the sitting time accumulated in long bouts of at least 20 minutes in duration.

In multivariable linear regression models, longer time spent standing was associated with significantly faster information processing (Table 2). Specifically, each additional hour spent standing was associated with a 5.78-unit higher score on the Pattern Comparison processing speed test (b: 5.78; $p = 0.03$), after adjustment for measurement device wear time, education, employment status, MVPA, and chemotherapy use. We also observed a significant association between total time spent in long sitting bouts with executive functioning in a similar covariate-adjusted model, such that more time spent in long sitting bouts was associated with a lower score on the Card Sort executive functioning test (b: −2.82; $p = 0.02$). Several borderline-significant trends were also observed for the associations of sedentary variables with executive function: total sitting time was inversely associated with executive function as measured by the Card Sort Test (b: −2.75; $p = 0.06$), whereas standing time was positively associated with this measure of executive function (b: 2.84; $p = 0.08$). Finally, more sit-to-stand transitions were borderline-significantly associated with better working memory as assessed by the List Sorting Test (b: −0.36; $p = 0.051$). None of the other sedentary behavior or standing variables were associated with the cognitive domains examined in this study, at or below a significance of $p = 0.1$.

Conclusions

In this pilot sample of early-stage breast cancer survivors, two dimensions of sedentary behavior were significantly associated with domains of cognitive function. The strongest and most statistically significant effects were observed for the cognitive domains of information processing speed and executive function, which are domains that broadly refer to the amount of time it takes to process information, and the "top-down" cognitive modulation of goal-directed activities [21]. We observed that more time spent standing was associated with faster information processing, and found an inverse and potentially deleterious association between the time spent in long sitting bouts and executive function. Notably, these associations were independent of time spent in MVPA, which was controlled for in all models. Together, these findings offer preliminary insight into the unique role that dimensions of sedentary behavior may have on cognitive function in women who have been treated for breast cancer.

Our finding that more sedentary time is associated with worse executive functioning is consistent with the trends observed in non-cancer populations. For example, in a cross-sectional analysis of data from $n = 2579$ participants ages 45–60 years who were enrolled in a randomized trial assessing the efficacy of daily antioxidant supplementation on health, it was found that more self-reported time spent watching television (a commonly used proxy for total sedentary time) was associated with significantly worse executive function [30]. In that study, the measure of executive function was derived from a validated battery of six neuropsychological tests using principal component analysis. Similarly, a prospective study of $n = 3247$ adults ages 18–30 years enrolled in a longitudinal study designed to trace the development of risk factors for coronary heart disease, found that more self-reported television time during a 25-year exposure period was associated with worse executive function as measured by the Stroop Test [13]. It is notable, however, that these studies only focused on specific sedentary activities (e.g., television time) and did not utilize objective measures such as the activPAL used in the current study. We are not aware of studies that have

Table 2 Associations of sedentary activity variables with cognitive domain scores in breast cancer survivors

	Total standing time		Sit to stand transitions†		Total sitting time		Time in sitting bouts >= 20 min	
	b	*p* value	*b*	*p* value	*b*	*p* value	*b*	*p* value
Attention: flanker	2.06	0.18	0.14	0.27	0.21	0.88	−0.73	0.54
Executive functioning: card sort	2.84	0.08	0.16	0.20	−2.75	0.06	*−2.82*	*0.02*
Episodic memory: picture sequence	−1.33	0.68	−0.06	0.82	2.69	0.34	3.29	0.17
Working memory: list sorting	1.72	0.46	−0.36	0.051	−1.01	0.63	1.36	0.44
Information processing speed: pattern comparison test	*5.78*	*0.03*	0.07	0.77	−2.47	0.32	−1.21	0.57

Note: Models control for total device wear time, moderate-to-vigorous intensity physical activity, education, employment status, and whether the participant received chemotherapy. Unit of analysis for standing time, sitting time, and time in long sitting bouts is hours per day

† Models of sit-to-stand transitions additionally adjusted for total sitting time

examined associations between the dimensions of sedentary behavior such as time in long sitting bouts with cognition (which is difficult to self-report), which we found to be more significantly associated with executive function than total sitting time. Therefore, more studies that incorporate different dimensions of sedentary behavior, such as time in long sitting bouts, utilizing objective measures such as the activPAL used in this study, will be important for refining our understanding of how sedentary behavior influences cognition, and may inform the development of future interventions.

Our finding that more standing time is associated with faster information processing is intriguing given the popularization and commercialization of standing desks in recent years, and the scientific interest in testing the efficacy of standing interventions for reducing sedentary behavior in the workplace [18]. Despite the increasing interest in this area, there has been limited research into the possible effects of increased standing time on cognition in populations with high rates of cognitive impairment or who are at risk for cognitive decline. One study by Ebara and colleagues demonstrated in a study of 24 adults (12 undergraduate students and 12 older adults), that a sit-stand workstation that promotes increased standing resulted in a modestly (non-significantly) improved ability to maintain a steady task performance compared to performing the same activities in a sitting position [31]. Several studies conducted among samples of university students observed no benefit of increased standing time or sit-stand transitions on cognitive performance [32, 33]; however these samples of university students were presumably cognitively healthy and thus may have had minimal room for improvement.

There are several hypothesized mechanisms through which sedentary behavior may influence cognitive function and overall brain health. First, sedentary behavior may reduce cognitive function through its effects on metabolic factors known to be associated with cognitive impairment, such as glycemic control and obesity [29, 34]. Sedentary behavior may also accelerate cognitive decline by reducing cerebral blood flow [34]; and through processes including reduced neurogenesis, disrupting the modulation of synaptic plasticity and growth factors such as brain-derived neurotrophic factor (BDNF), and by increasing inflammation [29]. In addition, a recent study of 352 adults in the Age, Gene/Environment Susceptibility-Reykjavik (AGES-Reykjavik) Study, observed significant associations between sedentary behaviors with 5-year changes in white matter of the brain, suggesting that sedentary behavior may be associated with brain atrophy [35]. It is notable that a majority of the mechanistic evidence supporting a role of sedentary behavior on cognitive processes has been inferred from physical activity research, with the AGES-Reykjavik study being an exception, despite it being well-established that sedentary behaviors and physical inactivity are distinct risk factors for poor health outcomes [36]. Future studies that incorporate objective measures of both sedentary behavior and cognitive function and incorporate measures of mechanistic processes in the brain, such as those mentioned above, will contribute to a better understanding of these associations.

Limitations of this study include the modest sample size of this pilot with limited power to detect true associations or explore difference across population subgroups, such as women who had and had not received chemotherapy. Given the small sample, we did not adjust analyses for multiple comparisons out of concern that reducing the type I error rate in this pilot study via adjustment for multiple comparisons would further increase the type II error for associations that are not null [37]. In addition, although there are distinct advantages to using objective tools to assess sedentary behaviors, the objective measures of sedentary behavior used in the current study do not provide contextual information, and therefore do not enable us to differentiate between types of sedentary behaviors. This is potentially problematic, given the evidence that some types of sedentary behaviors have favorable effects on cognition (e.g., computer work) [12, 30]. Finally, participants in our study were predominantly White and well educated, and thus it is unclear whether our findings are generalizable to other more diverse sub-groups of breast cancer survivors. Notable strengths of this study include the detailed measurement of multiple dimensions of sedentary behavior, and use of an objective and standardized measure of cognitive function via the NIH Toolbox [22].

In conclusion, findings from this exploratory pilot study suggest that several dimensions of sedentary behavior, including time in prolonged sitting bouts and standing time, are associated with cognitive functioning in early stage breast cancer survivors, independent of MVPA. To our knowledge, this is the first published study to report associations between multiple dimensions of sedentary behavior and cognitive function in breast cancer survivors. Future research in larger samples should explore differences across subgroups of breast cancer survivors, such as women that had and had not received chemotherapy, and among more recent vs. longer term survivors. If these findings are confirmed in larger and prospective studies, it could motivate the development of behavior change interventions to improve cognitive functioning in breast cancer survivors that target key dimensions of sedentary behaviors, such as interventions designed to break up long sitting bouts and increase time spent standing.

Acknowledgements The content in this manuscript is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health or the American Cancer Society.

Funding information Research support was provided by pilot funding from the Department of Family Medicine and Public Health at UC San Diego. Research support was also provided by the National Cancer Institute of the National Institutes of Health under the following award numbers: K07CA181323 (SJH), K07CA178870 (LC-B), F31CA183125 (CRM), and F32CA220859 (CRM). CRM was also supported by an American Cancer Society Postdoctoral Fellowship under award number PF-17-231-01-CCE.

Compliance with ethical standards

Conflicts of interest The authors declare that they have no conflicts of interest to disclose.

Ethics approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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