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Sedentary Behaviors and Biomarkers Among Breast Cancer Survivors

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Abstract

Background—Sedentary behavior is associated with increased risk of poor outcomes in breast cancer survivors, but underlying mechanisms are not well understood. This pilot study explored

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associations between different aspects of sedentary behaviors (sitting, prolonged sitting, sit-to-stand transitions, and standing) and breast cancer risk-related biomarkers in breast cancer survivors (n = 30).

Methods—Sedentary behavior variables were objectively measured with thigh-worn activPALs. Breast cancer risk-related biomarkers assessed were C-reactive protein (CRP), insulin, and homeostatic model assessment of insulin resistance (HOMA-IR) and were measured in fasting plasma samples. Linear regression models were used to investigate associations between sedentary behavior variables and biomarkers (log CRP, insulin, and HOMA-IR).

Results—Sit-to-stand transitions were significantly associated with insulin resistance biomarkers ($P < .05$). Specifically, each 10 additional sit-to-stand transitions per day was associated with a lower fasting insulin concentration ($\beta = -5.52$; 95% CI, −9.79 to −1.24) and a lower HOMA-IR value ($\beta = -0.22$; 95% CI, −0.42 to −0.03). Sit-to-stand transitions were not significantly associated with CRP concentration ($P = .08$). Total sitting time, long sitting bouts, and standing time were not significantly associated with CRP, insulin, or HOMA-IR ($P > .05$).

Conclusions—Sit-to-stand transitions may be an intervention target for reducing insulin resistance in breast cancer survivors, which may have favorable downstream effects on cancer prognosis.

Keywords

sitting; insulin resistance; inflammation; sit-to-stand transitions

Due to improvements in screening and treatment, there are now over 3 million breast cancer survivors in the United States.[1] This large population of survivors will continue to grow as our population ages, requiring increased efforts to promote healthy long-term survivorship. Among women diagnosed with breast cancer, low levels of physical activity are associated with poorer outcomes, including lower quality of life, fatigue, and increased risk of breast cancer recurrence and morality.[2–5] Although the health benefits of increasing physical activity have been well documented in the literature,[6–8] more recent evidence points to sedentary behavior as a novel yet understudied predictor of health outcomes—even after adjusting for physical activity.[9] Sedentary activities are commonly defined as those with a low energy expenditure (<1.5 metabolic equivalents) and performed in a sitting or reclining posture (excluding sleeping). Common forms of sedentary behaviors include sitting for work and during transportation, eating, and leisure (eg, watching television or relaxing). Sedentary time is associated with higher numbers of comorbid conditions, higher tumor stage, and greater severity of fatigue in breast cancer survivors.[10] Some, but not all, studies have observed an inverse association between sedentary time and health-related quality of life.[11,12] A potentially important feature of sedentary time is the frequency with which it is interrupted. Specifically, a growing body of evidence in noncancer populations suggests that breaking up sedentary time is positively associated with improved health outcomes.[13–16]

Excessive sedentary time is associated with systemic inflammation [generally assessed using C-reactive protein (CRP)] and insulin resistance [as measured using the homeostatic model assessment of insulin resistance (HOMA-IR)], which are both implicated in promoting the development and progression of breast cancer.[17,18] Cross-sectional data indicate that healthy

women who spend more time sitting have higher levels of CRP and higher HOMA-IR scores compared with their less sedentary counterparts, suggesting a higher risk for breast cancer in sedentary women.[19] Further, longitudinal data from the Australian Diabetes, Obesity and Lifestyle Study demonstrated that changes in duration of television viewing time were accompanied by changes in obesity, fasting insulin, and HOMA-IR, all of which are associated with breast cancer risk.[20] These findings suggest that reducing sedentary time may be a useful target for breast cancer prevention.

Early studies of sedentary time in breast cancer survivors relied on self-report questionnaires, which are subject to recall and social desirability biases.[9] More recently, sedentary time has been estimated in large cohort studies using hip-worn accelerometers.[19] Accelerometers worn on the hip, however, do not change position relative to the plane of the ground; therefore, when the wearer moves from a sitting to a standing position, it is difficult to derive thigh and body posture from a hip-worn accelerometer signal.[21] This measurement limitation is important because sedentary behavior dimensions such as sit-to-stand postural transitions and time spent standing may influence metabolic biomarkers and health outcomes.[15,16] In particular, standing results in a postural change that, in laboratory studies, has been show to increase blood flow, contract muscles, and break up sitting time, which may reduce concentrations of circulating markers of inflammation.[22] Although there has been limited research on increasing sit-to-stand transitions, 2 randomized trials using standing to break up prolonged sitting resulted in improvements in insulin[23] and glucose control[24] compared with the prolonged sitting condition. To our knowledge, no published studies have examined the association of sit-to-stand transitions with biomarkers of breast cancer prognosis. The objective of this pilot study was to assess the associations between multiple dimensions of sedentary behavior and CRP, fasting insulin, and HOMA-IR in posttreatment breast cancer survivors. Data are presented for total daily sedentary time and the accumulated patterns of behavior (time spent in uninterrupted sedentary bouts, time spent standing, and number of sit-to-stand transitions).

Methods

Study Design and Sample

Breast cancer survivors were enrolled in this cross-sectional pilot study designed to examine the associations between sedentary behavior and breast cancer-related biomarkers among breast cancer survivors. Eligible participants were women diagnosed with stages I–III breast cancer within the past 5 years who had completed active treatment (eg, radiation, chemotherapy) and were fluent in English. Women were excluded if they had a primary or recurrent invasive cancer within the last 10 years (other than nonmelanomic skin cancer or carcinoma of the cervix in situ), were over 85 years of age, recently had bariatric surgery, were taking insulin or corticosteroid medications, or were diabetic.

Participants attended one in-person study visit where they provided a fasting blood specimen and completed a series of assessments. Participants were asked to wear an ActiGraph GT3X + accelerometer (ActiGraph, Pensacola, FL) positioned on their right hip and an activPAL positioned on their thigh for 7 days after the clinic visit. All study procedures and measures

were approved by the Human Research Protections Program at the University of California, San Diego, and all subjects provided written informed consent.

Measures

Objective Assessment of Sedentary Behavior Dimensions—The activPAL (activPAL3; PAL Technologies, Glasgow, Scotland) is a small and lightweight triaxial accelerometer worn on the anterior aspect of the thigh. The activPAL combines acceleration data and accelerometer orientation to estimate time spent in different body postures (sitting/lying down, standing) and to estimate the number of sit-to-stand transitions.[25] The activPAL has demonstrated good reliability and validity.[26–28] Participants were asked to wear the device continuously for 24 hours a day for 7 days and instructed to remove the device during water-based activities or bathing. The activPAL data were downloaded and processed using activPAL Professional Research Edition software package using the 15-second Epoch. The 15-second Epoch data were summed to the day level and then divided by 60 to determine the minutes in different sedentary behaviors. To filter nighttime sleeping from activPAL-derived data, activPAL data were matched to the concurrently worn ActiGraph data (see below for more details), and overnight nonwear time periods on the ActiGraph were removed as “sleep time” from the activPAL. Time in long sitting bouts was defined as continuous periods of sitting that last at least 20 minutes with no interruptions. Time spent standing per day was approximated by summing the minutes in a day spent in a vertical posture. We also estimated the number of sit-to-stand transitions. Day-level approximations were averaged across measurement days for each participant to yield the average daily time spent in sedentary behavior.

Measurement of Plasma Biomarkers—A 12-mL blood specimen was collected by venipuncture after a minimum 12-hour fast. Plasma was immediately isolated by centrifugation and stored at −80°C. CRP and insulin concentrations were measured using the Meso Scale Discovery platform (Kit Nos. K15198 and K15164, respectively; Meso Scale Discovery, Gaithersburg, MD). Glucose was measured using an YSI 2900 Biochemistry Analyzer (YSI, Yellow Springs, OH). HOMA-IR was calculated using the standard equation [HOMA-IR = glucose (mg/dL) × insulin (mU/L)/405].[29]

Other Assessments—Sociodemographic data were obtained through a self-report questionnaire. Body mass index (BMI, kg/m^2) was calculated from height and weight measured at the clinic visit. Medical records were reviewed to ascertain information related to breast cancer diagnosis and treatment including stage of cancer at diagnosis, date of diagnosis, and cancer treatments received.

Moderate to vigorous physical activity (MVPA) was measured with the ActiGraph GT3X+ accelerometer (ActiGraph). Accelerometers are a well-validated[30] wearable sensor that provides an indication of the frequency, duration, and intensity of physical activity. Participants were instructed to wear the accelerometer on their right hip during waking hours only for 7 days and to take it off for swimming or bathing. ActiLife v6.11 software (ActiGraph Corp, Pensacola, FL) was used to screen for sufficient wear time using guidelines outlined by Choi et al.[31] The sufficient wear time was defined as 5 days with

≥600 minutes of wear time or 3000 minutes (50 h) across 4 days. Time spent in MVPA was derived from accelerometer data using published cut points.[32] MVPA was defined as 1952 or more counts per minute (≥3 metabolic equivalents).

Statistical Analysis

Descriptive statistics characterized the study population. CRP was log transformed to better approximate a Gaussian distribution. One outlier for insulin and HOMA-IR was identified (243.7 pmol/L for insulin and 14.2 for HOMA-IR) and was removed from analyses given the small sample size. Separate multivariable linear regression models were used to examine associations between activPAL-derived variables and biomarker outcomes. Covariates were selected a priori and included MVPA, BMI, and total device wear time. For sit-to-stand transitions, total sitting time was also included in the model. We considered additional adjustment for other breast cancer and demographic variables including time since diagnosis and age. However, the addition of these variables in the models did not meaningfully change the magnitude or statistical significance of the findings, and these variables were not included in final models. To enhance the interpretability of the parameter estimates, a 30-minute unit of analysis was used for the time spent in MVPA variable, as well as the sedentary behavior and standing variables. Sit-to-stand transitions were modeled in units of 10. Parameter estimates for log CRP were back transformed for interpretability. The back-transformed parameter estimates should be interpreted as the percent change in CRP associated with a one unit increase in the exposure of interest (eg, sedentary time, MVPA).

Results

Of the 132 women who were contacted about the study, 30 were eligible and completed the clinic visit and fasting blood draw. The most frequent reason for ineligibility was not being able to commit to study requirements. Table 1 shows the relevant characteristics of the study participants. Participants were a mean of 62 years old (SD = 8), and 67% of women had been diagnosed with stage I breast cancer. The average time spent sedentary per day was a mean of 499 minutes (SD = 83), and the average time spent standing per day was a mean of 248 minutes (SD = 74). Participants had an average of 60.4 sit-to-stand transitions per day (SD = 17). Average wear time of the ActiGraph, to which activPAL wear time was matched, was 844.2 minutes per day (SD = 53). Sit-to-stand transitions were not significantly correlated with total sedentary time ($r = -.06$; $P = .72$; data not shown).

Table 2 shows biomarker association assessments for sedentary behavior dimensions measured by the activPAL. The number of sit-to-stand transitions was significantly and inversely associated with fasting insulin and HOMA-IR (Table 2) in analyses controlling for MVPA, BMI, and total sitting time. Specifically, each 10 additional sit-to-stand transitions per day was associated with a 5.5-unit lower concentration of fasting insulin ($\beta = -5.52$; 95% CI, −9.79 to −1.24). Additionally, each 10 additional sit-to-stand transitions was associated with a 0.22-unit lower HOMA-IR value ($\beta = -0.22$; 95% CI, −0.42 to −0.03). The number of sit-to-stand transitions was not significantly associated with CRP concentration ($P = .08$).

Total sitting time, time spent in long sitting bouts, and total standing time were not significantly associated with CRP, insulin, or HOMA-IR when controlling for MVPA and BMI ($P > .05$; see Table 2).

Conclusions

This study is one of the first to test in cancer survivors the association of sedentary time and dimensions of sedentary behavior with biomarkers linked to cancer risk and prognosis. In this sample of primarily early stage breast cancer survivors, the number of sit-to-stand transitions was significantly and positively associated with lower levels of fasting insulin and HOMA-IR. Importantly, these associations were independent of MVPA and BMI. These findings suggest that sit-to-stand transitions may be an important behavioral target for reducing insulin resistance among breast cancer survivors.

Much of the experimental studies to date investigating the health benefits of breaking up prolonged sitting have used short intervals of physical activity to break up sedentary time and have been conducted in noncancer populations.[33] These studies have found that in general, breaking up sedentary time with physical activity is associated with improvements in postprandial metabolic parameters including insulin—particularly for adults who are not physically active on a regular basis.[33] The health benefits of breaking up sitting time with standing have been less extensively studied. Our finding that more sit-to-stand transitions (which may be analogous to breaking up sitting with standing) are favorably associated with insulin and insulin resistance parameters is consistent with a recent intervention trial.[23] In that randomized trial of 22 overweight/obese dysglycemic postmenopausal women, compared with a sitting-only condition, the standing breaks condition improved a number of metabolic parameters including postprandial insulin.[23] Another study among 23 overweight men and women in the workplace reported that standing breaks improved glucose control parameters but not insulin.[24] In contrast, a study with 10 nonobese adults found that standing breaks had no benefit on any metabolic parameters assessed.[34] It is possible that the discrepancies in the literature in regards to the impact of breaking up sitting time with standing are due to differences in subject characteristics (eg, less metabolically healthy individuals may be more likely to benefit), as postulated by Benatti and Ried-Larsen.[33] More research in larger samples and broader populations of adults, including cancer survivors, are needed before any firm conclusions can be drawn.

Previous research in noncancer survivor populations have demonstrated that greater total sedentary time is associated with biomarkers of metabolic dysfunction and inflammation.[19,35–37] Total sedentary time was not significantly associated with inflammation or insulin resistance in our sample. It may be that the relationship between total sedentary time and these biomarkers differs between cancer survivors and populations without cancer, or this could be an artifact of the modest sample size and limited power of this pilot study.

Other limitations of this study include the cross-sectional design and the relatively homogenous population of the participants. Strengths of this study include the detailed measurement of multiple dimensions of sedentary behavior using an activPAL that can more accurately detect postural changes.

In conclusion, these data provide preliminary support that increasing the number of daily sit-to-stand transitions may be a key intervention target for reducing fasting insulin and insulin resistance in breast cancer survivors. This study is an important first step in examining associations between sedentary behavior and the mechanisms by which it seems to influence breast cancer prognosis. The study provides preliminary findings on which larger studies can be built. Additional insight from larger observational studies and intervention trials examining the impact of multiple dimensions of sedentary time on biomarker outcomes are needed to clarify these associations. If confirmed, interventions to increase the number of sit-to-stand transitions could be a strategy to improve breast cancer prognosis in women.

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Table 1

Characteristics of Breast Cancer Survivors in the Study Sample (n = 30)

	Mean (SD) unless otherwise noted
Age, y	62.2 (7.8)
White, non-Hispanic,[a] n (%)	28 (93.3)
Completed college, n (%)	17 (57.0)
BMI, 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)
ER positive,[a] n (%)	21 (70.0)
PR positive,[a] n (%)	20 (66.7)
MVPA, min/d	27.9 (22.2)
ActivPAL-derived sedentary behavior and transition variables	
Total sitting time, min/d	498.9 (82.8)
Time in long sitting bouts,[b] min/d	288.7 (93.1)
Total standing time, min/d	248.4 (73.8)
Sit-to-stand transitions, n/d	60.4 (16.7)
CRP, median (Q1, Q3), mg/L	0.8 (0.5, 1.6)
Fasting insulin,[c] pmol/L	49.0 (20.3)
HOMA-IR[c]	2.1 (0.9)

Abbreviations: BMI, body mass index; CRP, C-reactive protein; ER, estrogen receptor; HOMA-IR, homeostatic model assessment of insulin resistance; MVPA, moderate to vigorous physical activity; PR, progesterone receptor; Q1, 1st quartile; Q3, 3rd quartile.

[a] Missing data on race for n = 1 participant, and ER and PR status for n = 1 participant.

[b] Long sitting bouts: Continuous periods of sitting that last at least 20 minutes.

[c] One outlier removed from the sample (see Methods section).

Table 2

Associations[a] of ActivPAL-Derived Variables, MVPA, and BMI With Breast Cancer Biomarkers

	Log CRP (mg/L)		Insulin (pmol/L)[f]		HOMA-IR[f]	
	Exp[b] β (95% CI)	*P*-value	β (95% CI)	*P*-value	β (95% CI)	*P*-value
Total sitting time[c]	0.92 (0.84–1.01)	.10	0.42 (−2.55 to 3.39)	.78	0.05 (−0.08 to 0.18)	.48
MVPA[c]	1.00 (0.70–1.42)	.996	−0.67 (−11.33 to 9.99)	.90	−0.03 (−0.50 to 0.45)	.91
BMI, kg/m^2	**1.18 (1.10–1.26)**	**<.001**	1.89 (−0.33 to 4.10)	.11	0.03 (−0.07 to 0.13)	.57
Time in long sitting bouts[c,d]	0.98 (0.90–1.07)	.66	1.87 (−0.56 to 4.30)	.15	0.09 (−0.02 to 0.20)	.11
MVPA[c]	1.06 (0.73–1.52)	.77	−0.30 (−10.37 to 9.78)	.95	−0.03 (−0.48 to 0.42)	.90
BMI, kg/m^2	**1.18 (1.09–1.27)**	**<.001**	2.06 (−0.06 to 4.18)	.07	0.03 (−0.06 to 0.13)	.48
Total standing time[c]	1.11 (0.99–1.23)	.08	−1.96 (−5.21 to 1.30)	.25	−0.13 (−0.27 to 0.01)	.07
MVPA[c]	1.14 (0.81–1.62)	.46	−2.53 (−13.1 to 8.01)	.64	−0.17 (−0.63 to 0.29)	.48
BMI, kg/m^2	**1.19 (1.11–1.28)**	**<.001**	1.78 (−0.36 to 3.92)	.12	0.02 (−0.07 to 0.11)	.68
Sit-to-stand transitions[e]	0.87 (0.76–1.01)	.08	**−5.52 (−9.79 to −1.24)**	**.02**	**−0.22 (−0.42 to −0.03)**	**.04**
MVPA[c]	0.97 (0.69–1.35)	.84	−1.86 (−11.54 to 7.81)	.71	−0.08 (−0.52 to 0.37)	.74
BMI, kg/m^2	**1.18 (1.11–1.27)**	**<.001**	2.09 (0.09 to 4.10)	.05	0.04 (−0.05 to 0.13)	.43

Abbreviations: BMI, body mass index; CI, confidence interval; CRP, C-reactive protein; Exp, exponentiated; HOMA-IR, homeostatic model assessment of insulin resistance; MVPA, moderate to vigorous physical activity.

[a] Associations presented were derived using multivariable linear regression models. Models were run separately for each outcome variable and adjusted for device wear time.

[b] Values presented have been back transformed (ie, exponentiated).

[c] A 30-minute unit of analysis was used.

[d] Long sitting bouts: Continuous periods of sitting that last at least 20 minutes.

[e] Sit-to-stand transitions were modeled in units of 10 and controlled for total sitting time.

[f] One outlier was removed for insulin and HOMA-IR.