Cardiorespiratory Fitness, Physical Activity, Sedentary Behavior, and Diabetes Risk Among Breast Cancer Survivors Treated with Endocrine Therapies

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ABSTRACT

LEACH, H. J., M. BOLT, E. W. CLARK, S. E. HULL, J. R. DIAMOND, K. LYDEN, and R. L. SCALZO. Cardiorespiratory Fitness, Physical Activity, Sedentary Behavior, and Diabetes Risk Among Breast Cancer Survivors Treated with Endocrine Therapies. *Med. Sci. Sports Exerc.*, Vol. 58, No. 1, pp. 70–77, 2026. **Purpose:** Endocrine therapies for breast cancer (BC) (i.e., selective estrogen receptor modulators (SERMs) or aromatase inhibitors (AI)) lower the risk for cancer recurrence but are linked to an increased risk of type 2 diabetes (T2D). This study examined associations between cardiorespiratory fitness (CRF), physical activity (PA), and sedentary behavior with T2D risk markers, and whether the magnitude of these associations varied between SERM and AI. **Methods:** This study was a cross-sectional study. Participants were BC survivors receiving either SERM or AI for ≥1 yr. A graded exercise test determined CRF (peak oxygen consumption). Participants wore an accelerometer for 14 d to assess time in sedentary behavior, light PA, moderate to vigorous PA, and number of sit-to-stand transitions. T2D risk was measured by an oral glucose tolerance test to determine fasting glucose, glucose area under the curve, insulin sensitivity (Matsuda Index), and insulin resistance (homeostatic model assessment of insulin resistance). Regression models estimated associations between CRF/activity behaviors and markers of T2D by endocrine therapy type adjusting for age, fat mass (measured using dual-energy x-ray absorptiometry scan, time receiving therapy, and amount of moderate or vigorous PA. **Results:** Participants (SERM (n = 19) or AI (n = 20)) were M = 54 ± 12 yr old and had received therapy for M = 3.2 ± 2.8 yr. Sit-to-stand transitions were associated with lower glucose tolerance (−221.52; 95% confidence interval (CI), −442.44 to −0.59; P = 0.049), higher insulin sensitivity (0.45; 95% CI, 0.25 to 0.66; P < 0.001), and lower insulin resistance (−0.06; 95% CI, −0.13 to 0; P = 0.047) but only for those on SERMs. **Conclusions:** Breaking up sedentary time may be a promising intervention target to lowering T2D risk among BC survivors treated with SERMs. Further studies are needed to better understand how SERMS and AI are differentially influencing glucoregulatory pathways. **Key Words:** NEOPLASM, EXERCISE, METABOLIC DISEASE, PREVENTION

Breast cancer is the second most common cause of death among women, and more than 70% of patients are diagnosed with estrogen receptor (ER)–positive tumors (1). In premenopausal women with ER positive cancer, treatment frequently includes a selective ER modulator (SERM) with or without ovarian function suppression (2). In postmenopausal women, or those receiving ovarian function suppression, the recommended treatment for ER-positive breast cancer is an aromatase inhibitor (AI) that blocks peripheral estrogen production (2,3). Both AIs and SERMs are associated with significantly lower risk for breast cancer recurrence (4,5); however, use of these agents is linked to an increased risk for the development of type 2 diabetes (T2D) (6–10).

Breast cancer survivors receiving endocrine therapy are 2.4 times more likely to develop T2D (11), and some adverse metabolic effects of treatment appear to be more prevalent in women with overweight and obesity (12,13). The mechanisms of elevated T2D risk in women treated with endocrine therapy are unclear, but data from clinical studies suggest that endocrine therapy is associated with greater adiposity (14,15), hepatic steatosis (16,17), and insulin resistance (13). (18). Exercise is a key component of breast cancer survivorship (19–21) and an established lifestyle modification in the prevention of T2D

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(22). Previous randomized controlled trials among breast cancer survivors have found significant reductions in markers of T2D such as fasting insulin and glucose among exercisers compared with controls (23–25). However, the effects of exercise independent of changes in weight or body composition, and the differential relationship between exercise and markers of T2D among breast cancer survivors receiving SERMs versus AIs are still unknown. In exercise trials conducted by Irwin et al. (25) and Harrigan et al. (24), *post-hoc* analyses found greater reductions in fasting insulin among those with body mass index ≥30 $kg \cdot m^{-2}$ versus body mass index <30 $kg \cdot m^{-2}$ and those who lost >5% of their body weight. In the same study by Irwin et al. (25), among subjects who completed the exercise intervention, those on tamoxifen (SERM) versus no hormone therapy saw greater reductions in fasting insulin. In a more recent exercise trial by Dieli-Conwright et al. (23), the exercise group showed significant improvements in fasting blood glucose, insulin, and homeostatic model assessment of insulin resistance (HOMA-IR), but also had significant reductions in weight, fat mass, percent body fat, and the number of participants receiving endocrine therapy was not reported. Another study by Viskochil et al. (26) found a significant interaction with AI use following a 12-wk aerobic exercise intervention, with limited to no effects on peak insulin and insulin area under the curve (AUC) among participants who had past or present use of AI. Thus, when examining the potential impact of exercise for improving markers of T2D risk among breast cancer survivors, these studies suggest that it may be important to account for body weight and/or composition and consider the potential for differential effects of exercise depending on the type of endocrine therapy (i.e., SERM vs AI).

In addition, more recent studies have also begun to explore the spectrum of other activity behaviors (e.g., light-intensity physical activity (PA), time spent sitting and/or standing), aside from, or in addition to, exercise for reducing T2D risk (27–30). These behaviors have been shown to influence markers of T2D risk such as glucose tolerance and insulin resistance (28,30–32). Light-intensity activity and standing have been shown to increase blood flow, activate skeletal muscle, and break up sitting time, which may increase glucose uptake (33) and reduce concentrations of circulating markers of inflammation, which can result in improved insulin and glucose control (34). One previous study found that the number of sit-to-stand transitions was inversely associated with fasting insulin and insulin resistance among breast cancer survivors (35), and another in postmenopausal breast cancer survivors found that more replacing sedentary behavior with moderate to vigorous PA (using isotemporal substitution models) was associated with lower fasting glucose and better insulin resistance (36). Although these studies provide promising data to support potential associations between these nonexercise activity behaviors and markers of T2D risk among breast cancer survivors, some important limitations should be noted. In the Hartman et al. (35) study, endocrine therapy use was not reported, and in the Full et al. (36) study, all participants were postmenopausal, but models did control for AI use. Furthermore, in both studies, the measures of T2D risk were dependent on fasting variables and did not incorporate the dynamic response to insulin or glucose (i.e., hyperinsulinemic–euglycemic clamp or oral glucose tolerance test).

Taken together, there is a need for studies that will enhance our understanding of the effects of the full spectrum of activity behaviors (i.e., sitting through exercise) on markers of T2D risk among breast cancer survivors who are receiving endocrine therapy, while accounting for the type of endocrine therapy (i.e., SERM vs AI) and the important confounder of body composition. This information has implications for not only advancing mechanistic knowledge but also designing future interventions that seek to target one or more of these behaviors (i.e., breaking up sitting time requires a vastly different intervention from aerobic exercise).

Therefore, the aims of this study were to 1) evaluate whether associations between cardiorespiratory fitness (CRF), light PA, moderate–vigorous PA, sedentary behavior, and markers of T2D risk (i.e., glucose tolerance and insulin sensitivity) differ by endocrine therapy type (AIs vs SERMs); 2) if associations *do not* differ by therapy type, describe such associations independent of therapy type; and 3) if associations *do* differ by therapy type, describe such associations by endocrine therapy type. Our overarching hypothesis was that higher CRF, more time spent in moderate and vigorous PA, and/or less sitting time would be associated with greater insulin sensitivity and glucose tolerance in women treated with endocrine therapies for breast cancer, and that these associations may be of a lower magnitude among those being treated with AIs.

METHODS

This study was a cross-sectional study. The University of Colorado Institutional Review Board (IRB #21-3245) approved this study. Informed consent was obtained from all participants, and study data were collected and managed using REDCap electronic data capture tools hosted at the University of Colorado (37). Participants attended two in-person study visits where they completed 1) an oral glucose tolerance test to measure glucose tolerance/insulin sensitivity and body composition, and 2) a graded exercise test to measure CRF. At the end of the second visit, participants wore an accelerometer for the next 14 d to measure PA and sedentary behavior.

Participants. To be included in the study, participants had to be female; diagnosed with breast cancer; aged 18–80 yr old; completed surgery, chemotherapy, and/or radiation therapy; and prescribed an AI or SERM for at least 1 yr from the time of screening. Exclusion criteria were having type I or II diabetes, prescribed antihyperglycemic medication, insulin, or sulfonylurea, pregnant, breastfeeding or planning to become pregnant in next 2 months, have absolute contraindications to exercise testing (e.g., unstable angina, recent myocardial infarction, cardiac surgery, or vascular surgery (<3 months)), uncontrolled high blood pressure, severe arthritis or mobility impairment that would interfere with exercise testing, or suspected cognitive impairment

that would prevent understanding or comprehension of study procedures.

Participants were recruited via study flyers sent to providers and support groups or survivorship care leaders at the University of Colorado Cancer Center, Rocky Mountain Cancer Centers, Saint Joseph Hospital, and at various cancer care clinics, and community locations in the Denver metro area. Emails advertising the study were sent to local advocacy groups (e.g., Colorado Cancer Coalition, Susan G Komen) to advertise the study via social media, and website, and the study was listed on the cancer center's research study web portal (https://researchstudies.cuanschutz.edu).

Study visits. Study visit 1 consisted of an oral glucose tolerance test and a dual-energy x-ray absorptiometry scan. For the oral glucose tolerance test, participants fasted 8–12 h. An IV was placed and a baseline blood drawn. After the blood draw, participants were instructed to drink a 75 g glucola beverage within 5 min. Blood draws occurred at 30, 60, 90, and 120 min to collect measures of plasma glucose (glucose colorimetric assay; Cayman Chemical, Ann Arbor, MI) and insulin (enzyme-linked immunosorbent assay; ALPCO Diagnostics, Salem, NH) concentration. The HOMA-IR was calculated according to the formula: fasting insulin ($\mu U \cdot L^{-1}$) × fasting glucose ($mmol \cdot L^{-1}$)/22.5. Insulin sensitivity was calculated with the Matsuda Index (PMID: 10480510).

Total fat mass and fat-free mass were measured by dual-energy x-ray absorptiometry scan. The Hologic Horizon W (software v Apex 5.6.05; Hologic, Inc., Bedford, MA) and standard manufacturer recommendations for line placement were used to delineate regions of interest (i.e., trunk and leg). In the Colorado Nutrition Obesity Research Center (NORC) Energy Balance Laboratory, the average intraindividual ($n = 50$) reproducibility (two scans same day, one scan separate day) for measurements of total fat mass and fat-free mass are 1.8% ± 1.2% and 1.2% ± 0.8%, respectively. Immediately following study visit 1, participants were sent questionnaires to complete on their own via RedCap to gather information on cancer diagnosis and treatment and sociodemographics.

Study visit 2 occurred within 1 wk of study visit 1 and consisted of a graded exercise test to determine CRF (peak oxygen consumption ($\dot{V}O_{2peak}$)). $\dot{V}O_{2peak}$ was determined during a graded bicycle protocol to exhaustion using graded watt steps, and the value was between 10 and 25 $W \cdot min^{-1}$. $\dot{V}O_{2peak}$ was defined by meeting two of the following three criteria: plateau of $\dot{V}O_2$ with increasing workload, RER > 1.1, and/or achievement of a heart rate >85% of age-predicted max. Immediately following study visit 2, participants received an ActivPal accelerometer (Pal Technologies, Glasgow, United Kingdom) to measure PA and sedentary time (i.e., activity behaviors). The activPAL™ quantifies free-living sedentary and ambulatory activities, has previously been used in cancer survivors (38), and has been validated as one of the most accurate wearable activity monitors (39). The activPAL is a small device worn on the thigh that uses information about static and dynamic acceleration to (1) distinguish body posture as sitting/lying, standing, and stepping and (2) estimate energy expenditure (expressed as metabolic equivalents (METs)) (40). Participants wore the activPAL for 14 consecutive days, 24 $h \cdot d^{-1}$ immediately following the study visit 2. Participants were asked to record time of activPAL removal and sleep/wake up times. Data were downloaded using PAL Analysis, and all activity variables were processed using proprietary activPAL algorithms in the PAL Software Suite version 8 (www.palt.com/softwaresuite.com). A valid day of data collection was defined as at least 10 h of waking wear time. All activPAL outcomes were calculated as minutes per day, averaged across all valid days. Sedentary time was defined as time spent sitting or lying while awake, light PA was defined as time upright (standing or walking) <75 or ≥75 steps per minute for <1 min in duration, and moderate to vigorous PA was defined as walking or running ≥75 steps per minute for ≥1 min in duration.

Statistical analyses. Sample characteristics are described with means and standard deviations for continuous variables and with counts and proportions for categorical variables. With markers of T2D risk as outcomes, two classes of linear regression models were constructed, one with an interaction between endocrine therapy type and CR/activity behaviors and the other with endocrine therapy type and CRF/activity behaviors as independent variables but without an interaction between them. Likelihood ratio tests (LRTs) were then used to compare the two classes of models and evaluate whether associations between CRF/activity behaviors and markers of T2D risk differed by endocrine therapy type.

For relationships between CRF/activity behaviors and markers of T2D risk that did not appear to differ by endocrine therapy type as designated by the LRTs, simple unadjusted models with markers of T2D risk as dependent variables and only the CRF/activity behavior of interest as the independent variable were constructed. Unadjusted associations between markers of T2D risk and CRF/activity behavior with P values of less than 0.1 were then modeled with additional adjustments for covariates in multivariable models, where covariates (age in years, body fat percentage, time receiving therapy in years, and minutes per day of moderate or vigorous PA) were selected *a priori* based on clinical relevance, with the expectation that minutes per day of moderate or vigorous PA would serve as a covariate in models with activity behaviors as dependent variables but not in models with CRF as the dependent variable.

For relationships between activity behaviors and markers of T2D risk that did appear to differ by endocrine therapy type, additional multivariable modeling was conducted to adjust for covariates with continued inclusion of the interaction effect between endocrine therapy type and activity behavior. LRTs were then used again to determine whether associations between activity behaviors and markers of T2D risk differed by endocrine therapy type considering additional covariates (via comparison to models without interaction effects), and general linear hypothesis tests were used to estimate and test marginal effects between activity behaviors and markers of T2D risk by endocrine therapy type. Activity behaviors were mean-centered in multivariable modeling to allow for interpretation

of coefficients associated with endocrine therapy class (after accounting for interaction) under mean activity behavior values rather than at no activity behavior. When plotting predicted values of markers of T2D risk to visualize estimated relationships with activity behaviors, means of continuous covariates and the most prevalent category of categorical covariates were assumed for prediction. A complete-case approach was used to handle missing data. R version 4.4.0 in RStudio 2024.04.0 was used for all analyses along with various associated R packages (41).

RESULTS

Participants ($N = 39$) were, on average, 54 yr old (SD, 12; range, 31–79 yr) and had been on endocrine therapy for an average duration of 3.2 yr (SD, 2.8; range, 1–15.2 yr). Nineteen participants were prescribed SERM, and 20 were prescribed AIs (49% and 51%, respectively). Additional participant characteristics and summaries of activity behaviors and markers of T2D risk are shown in Table 1.

Evaluation of whether associations differed by endocrine therapy type. In LRTs comparing models with interactions between CRF/activity behaviors and endocrine therapy type as independent variables with markers of T2D risk as outcomes against models with CRF/activity behaviors adjusting for (but not interacting with) endocrine therapy type as independent variables with markers of T2D risk as outcomes, only the number of sit-to-stand transitions per day consistently appeared to have differing associations with markers of T2D risk dependent on endocrine therapy type (Table 2). Relationships between all other CRF/activity behaviors and markers of T2D risk appeared to be unaffected by endocrine therapy type. As such, further models with activity behaviors or CRF besides number of sit-to-stand transitions did not include interactions with endocrine therapy type.

TABLE 1. Participant characteristics ($N = 40$).

Characteristic	AI ($N = 20$)	SERM ($N = 19$)	Overall ($N = 39$)
Fasting glucose (mg·dL^{-1})	77 (10)	80 (11)	79 (10)
Glucose (AUC)	13,755 (3707)	13,210 (3129)	13,490 (3404)
HOMA-IR	1.30 (0.92)	1.31 (1.02)	1.30 (0.96)
(Missing)	1	0	1
Matsuda Index	7.0 (3.1)	7.3 (4.0)	7.1 (3.6)
(Missing)	3	0	3
Age (yr)	55 (14)	53 (9)	54 (12)
Ethnicity			
White/Caucasian	19 (95%)	16 (84%)	35 (90%)
Other	1 (5.0%)	3 (16%)	4 (10%)
Education			
Graduate degree	10 (50%)	10 (53%)	20 (51%)
4-yr college degree	9 (45%)	8 (42%)	17 (44%)
Some college or associate's degree	1 (5.0%)	1 (5.3%)	2 (5.1%)
Body fat (%)	39.8 (6.2)	35.2 (5.8)	37.6 (6.4)
Time on therapy (yr)	3.27 (3.08)	3.16 (2.46)	3.22 (2.76)
$\dot{V}O_2$ peak (ml/kg/min)	22 (6)	26 (7)	24 (6)
Light-intensity PA (min·d^{-1})	309 (97)	312 (74)	310 (85)
Moderate to vigorous PA (min·d^{-1})	28 (16)	45 (21)	37 (20)
Sedentary time (min·d^{-1})	562 (90)	573 (84)	567 (86)
Sit to stand transitions (number per day)	51 (9)	49 (7)	50 (8)
Time spent sedentary for ≥60 min continuously (min·d^{-1})	122 (62)	129 (48)	126 (55)
Had chemotherapy treatment	12 (60%)	12 (63%)	24 (62%)
Had radiation treatment	15 (75%)	12 (63%)	27 (69%)
HER2+	7 (35%)	6 (32%)	13 (33%)
ER+	19 (95%)	19 (100%)	38 (97%)
PR+	17 (85%)	14 (74%)	31 (79%)
Stage of diagnosis			
0	1 (5.0%)	2 (11%)	3 (7.7%)
1	8 (40%)	13 (68%)	21 (54%)
2	6 (30%)	4 (21%)	10 (26%)
3	3 (15%)	0 (0%)	3 (7.7%)
4	2 (10%)	0 (0%)	2 (5.1%)
Time from diagnosis to study consent	4.42 (3.39)	3.97 (2.65)	4.19 (3.00)
(Missing)	2	0	2

Mean (SD) or *n* (%) shown.

Examination of associations not differing by endocrine therapy type. After determination that all associations between CRF/activity behaviors and markers of T2D risk did not differ by endocrine therapy type, apart from sit-to-stand transitions, relationships between CRF/activity behaviors and markers of T2D risk without interaction with endocrine therapy type were tested. Table 3 presents *P* values for these tests of associations unmodified by endocrine therapy type. Only the associations between $\dot{V}O_2$ peak and glucose under the curve (AUC) ($\beta = -193.87$; 95% CI, −357.77 to −29.98; $P = 0.02$) and $\dot{V}O_2$ peak and MATSUDA ($\beta = 0.17$; 95% CI, −0.01 to 0.35; $P = 0.06$) appeared to differ significantly from what would have been expected by chance. However, after adjusting these associations for age (years), body fat percentage, years receiving endocrine therapy, and endocrine therapy type in a multivariable model, we found that $\dot{V}O_2$ had no meaningful association with glucose AUC ($\beta = -181.87$; 95% CI, −445.1 to 81.37; $P = 0.17$) or with MATSUDA ($\beta = 0.19$; 95% CI, −0.11 to 0.5; $P = 0.20$).

Examination of associations differing by endocrine therapy type. Finally, to examine the association between the number of sit-to-stand transitions per day and markers of T2D by endocrine therapy type, multivariable models with an interaction between endocrine therapy type and number of sit-to-stand transitions and adjusting for age (years), body fat percentage, years receiving therapy, and minutes per day of moderate to vigorous PA were constructed. Results from these models are displayed in Table 4, where each column represents a separate multivariable model. The association of the number of sit-to-stand transitions per day with each marker of T2D risk differed significantly by endocrine therapy type (LRT *P* values: fasting glucose, $P = 0.01$; glucose AUC, $P = 0.01$; HOMA-IR, $P = 0.03$; MATSUDA, $P < 0.001$). For those on AI, number of sit-to-stand transitions did not have significant associations with any markers of T2D risk (Table 4), whereas for those on SERM, number of sit-to-stand transitions per day had negative associations with fasting glucose ($\beta = -0.67$; 95% CI, −1.36 to 0.02; $P = 0.057$), glucose AUC ($\beta = -221.52$; 95% CI, −442.44 to −0.59; $P = 0.049$), and HOMA-IR ($\beta = -0.06$; 95% CI, −0.13 to 0; $P = 0.047$), and a positive association with MATSUDA $\beta = (0.45$; 95% CI, 0.25 to 0.66; $P < 0.001$). These relationships are visualized in Figure 1. Other covariates and markers of T2D risk that were significantly or suggestively associated

with one another were age and glucose AUC, body fat percentage and fasting glucose, time on medication and MATSUDA, and moderate to vigorous PA and glucose AUC, although because these covariates were included merely to serve either as precision variables or adjust for potential confounding, these associations are not further explored. Lastly, endocrine therapy type (SERM vs AI) was not found to have any additional association with markers of T2D risk beyond its association through the interaction with number of sit-to-stand transitions per day.

DISCUSSION

The study's primary finding was that more sit-to-stand transitions were associated with lower fasting glucose and greater glucose tolerance and insulin sensitivity for women prescribed SERMs but not those for prescribed AIs. CRF and other activity behaviors were not associated with markers of T2D risk in women prescribed SERMs or AIs. These data suggest that interventions targeting breaks in sedentary behavior may lower T2D risk in breast cancer survivors prescribed SERMs.

This finding is congruent with current literature, which demonstrates that sedentary behavior is related to glucose intolerance and lower insulin sensitivity (42,43), and that interventions that break up sedentary behavior improve glucose tolerance and insulin sensitivity (44–47). However, evidence to elucidate the mechanisms linking sedentary behavior and glucoregulatory processes is still emerging. A prominent hypothesis for this relationship is the important role of skeletal muscle. Skeletal muscle is the largest glucose sink in the body (48), accounting for roughly 80% of insulin-stimulated glucose disposal (49). The mechanical workload of each sit-to-stand transition activates skeletal muscle, suggesting that increasing breaks in sedentary behavior by standing up results in greater skeletal muscle oxidation of carbohydrates (50,51), which may improve glucose tolerance. Furthermore, when interventions to break up sedentary behavior were implemented among overweight/obese adults, signaling associated with glucose uptake and oxidation was augmented in skeletal muscle (33,52). Relevant to the current study population, one cross-sectional investigation in breast cancer survivors did find a similar, inverse relationship between sit-to-stand transitions and HOMA-IR (35), but did not delineate whether participants were receiving endocrine therapy.

In the current study, sit-to-stand transitions predicted T2D risk only in women prescribed SERMs. SERMs and AIs both improve breast cancer survival by restricting estrogen to the breast tumor but work through different mechanisms of action. AIs block estrogen production, whereas SERMs are ER antagonists in the breast and ER agonists in other tissues such as the bone, liver, and cardiovascular system (53). Evidence also shows that SERMs may also act as ER agonists in skeletal muscle (54). Important for this current study, ER signaling in skeletal muscle supports insulin sensitivity and glucose tolerance (55). Skeletal muscle ER signaling targets the same pathway as sit-to-stand transitions (56). Thus, it is possible that the permissive nature of SERMs on ER signaling in skeletal muscle could explain the differences observed between treatment groups in the current study.

Our finding that CRF, PA, and sedentary behavior variables do not predict T2D in women prescribed AIs is supported by previous research. It is suggested that AIs may interfere with the metabolic adaptations to exercise training (26). AIs primarily block estrogen production in peripheral tissues such as the adipose tissue and the brain and are often prescribed to postmenopausal women or women with suppressed ovarian function. In this context, the glucoregulatory processes reinforced by estrogen (i.e., skeletal muscle glucose uptake) are left unsupported in the context of AI treatment, leading therefore to a potential disassociation of fitness and activity behaviors and T2D risk markers.

Further studies are needed to determine viable lifestyle behaviors that can improve T2D risk in women prescribed AIs. One option may be resistance exercise training, which has been shown to augment insulin-stimulated glucose uptake in the skeletal muscle due to increased lean mass, insulin signaling, and glucose transporter protein expression (57). In postmenopausal women, resistance exercise has been shown to lower cumulative glucose load (58,59) and fasting glucose (60), suggesting that it may be possible that resistance exercise could be effective at lowering T2D risk in women prescribed AIs.

Strengths of the current study include the delineation of participants by type of hormone therapy (i.e., AI vs SERM), and the high-quality measures of PA, sedentary behavior, CRF, and markers of T2D risk. Given the important role of weight loss in improving indices of insulin resistance among breast cancer survivors (61), another major strength of this study was the inclusion of body composition as a covariate in analyses. The use of a cross-sectional study limits conclusions on causality. It is possible that the directionality of the association of sit-to-stand transitions and glucose tolerance/insulin sensitivity is

TABLE 2. LRT *P* values comparing models with and without interaction terms.

	Markers of T2D Risk			
CRF/Activity Behaviors	Fasting Glucose	Glucose AUC	HOMA-IR	Matsuda Index
$\dot{V}O_2$ peak (mL·kg^{-1}·min^{-1})	0.81	0.99	0.63	0.76
Light-intensity PA	0.89	0.71	0.54	0.51
Number of sit-to-stand transitions per day	**0.01**	**0.07**	**0.05**	**<0.001**
Sedentary time	0.27	0.33	0.23	0.64
Time spent sedentary for ≥60 min continuously	0.11	0.35	0.59	0.37
Moderate to vigorous PA	0.86	0.91	0.19	0.48

Bold indicates statistical significance.

TABLE 3. *P* values for estimated slopes from simple, unadjusted models between activity variables and markers of T2D risk.

	Markers of T2D Risk			
CRF/Activity Behaviors	Fasting Glucose	Glucose AUC	HOMA-IR	Matsuda Index
$\dot{V}O_2$ peak (mL·kg^{-1}·min^{-1})	0.34	**0.02**	0.8	**0.06**
Light-intensity PA	0.49	0.64	0.97	0.5
Sedentary time	0.76	0.98	0.99	0.34
Time spent sedentary for ≥60 min continuously	0.72	0.5	0.35	0.31
Moderate to vigorous PA	0.97	0.67	0.69	0.35

Bold indicates statistical significance.

TABLE 4. Multivariable relationships between number of sit-to-stand transition transitions per day, covariates, and markers of T2D risk.

	Markers of T2D Risk											
	Fasting Glucose			Glucose AUC			HOMA-IR			MATSUDA		
	Estimate	95% CI	*P*	Estimate	95% CI	*P*	Estimate	95% CI	*P*	Estimate	95% CI	*P*
(Intercept)	42.58	(11.14 to 74.03)	0.01	879.81	(–9139.88 to 10,899.49)	0.86	–1.07	(–4.05 to 1.91)	0.47	9.41	(–0.54 to 19.35)	0.06
Age (yr)	0.06	(–0.23 to 0.35)	0.67	105.1	(12.31 to 197.88)	0.03	–0.01	(–0.04 to 0.02)	0.41	–0.04	(–0.12 to 0.05)	0.4
Body fat percentage	0.63	(–0.11 to 1.38)	0.09	130.68	(–106.93 to 368.29)	0.27	0.06	(–0.01 to 0.13)	0.11	0.05	(–0.2 to 0.3)	0.68
Time on current medication (yr)	0.22	(–1.15 to 1.58)	0.75	–135.49	(–570.19 to 299.21)	0.53	0.1	(–0.02 to 0.23)	0.1	–0.72	(–1.27 to –0.17)	0.01
Moderate to vigorous PA (mean min per day)	0.16	(–0.06 to 0.38)	0.14	77.32	(7.27 to 147.37)	0.03	0.01	(–0.01 to 0.03)	0.28	–0.01	(–0.08 to 0.06)	0.77
SERM (vs AI, not accounting for sit-to-stand)	3.11	(–4.06 to 10.29)	0.38	–1158.4	(–3443.23 to 1126.43)	0.31	0.03	(–0.63 to 0.69)	0.93	1.31	(–0.92 to 3.53)	0.24
LRT *P* value			0.01			0.01			0.03			<0.001
Marginal effect of the number of sit-to-stand transitions on AI:	0.52	(–0.1 to 1.13)	0.1	131.94	(–64.35 to 328.23)	0.18	0.02	(–0.03 to 0.08)	0.4	–0.13	(–0.32 to 0.06)	0.17
Marginal effect of the number of sit-to-stand transitions on SERM	–0.67	(–1.36 to 0.02)	0.057	–221.52	(–442.44 to –0.59)	0.049	–0.06	(–0.13 to 0)	0.047	0.45	(0.25 to 0.66)	<0.001

reversed considering the relationship between glycemic control and skeletal muscle function and strength (62). Additional limitations are a sample comprising mostly White/Caucasian, high socioeconomic status breast cancer survivors, absence of a measure of circulating estradiol, and a relatively small sample size. Although analyses had adequate statistical power to detect effects, we anticipate that the relationships found would have been stronger with a larger sample size and provide more clarity on the variability of our estimates. In addition, on average, the sample was fairly active, achieving recommendations for MVPA, and there may be potential for a larger magnitude of effect for sit-to-stand transitions on metabolic health among breast cancer survivors who are insufficiently active or sedentary.

CONCLUSIONS

In conclusion, more sit-to-stand transitions were associated with more favorable levels of fasting glucose, glucose tolerance, and insulin sensitivity in breast cancer survivors prescribed SERMs but not those prescribed AIs. These findings may represent the effect of SERMs to augment skeletal muscle glucose uptake in response to breaks in sedentary behavior. Further work is needed to test this hypothesis of the underlying mechanism, as

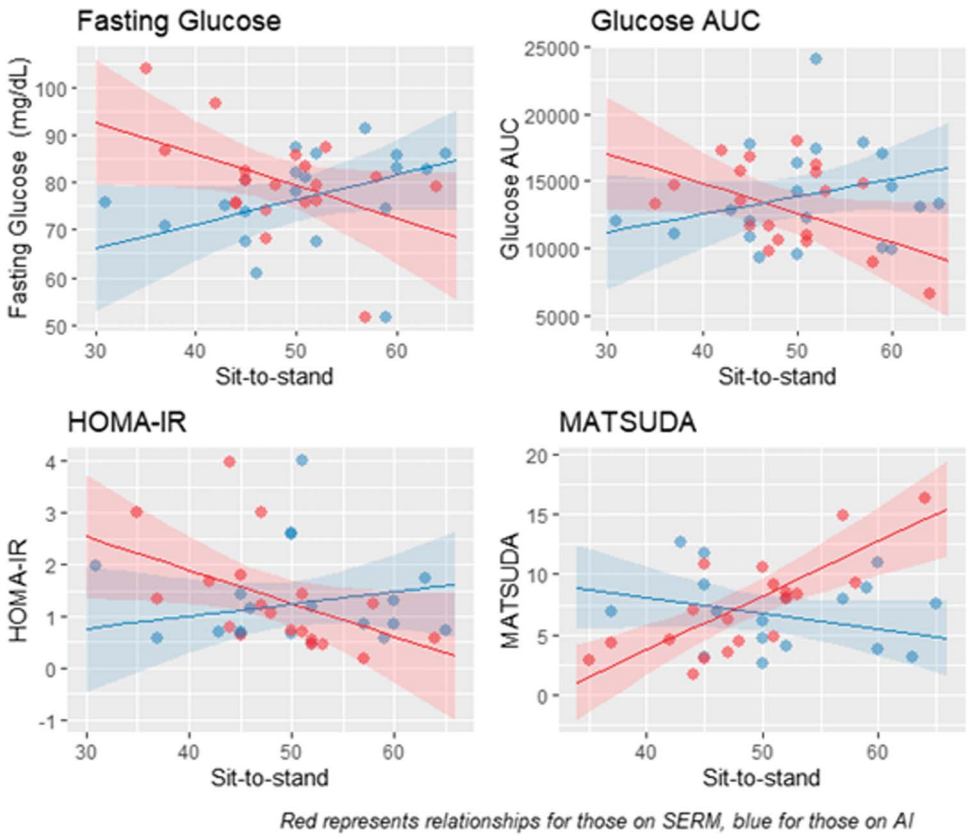

FIGURE 1—Associations between the number of sit-to-stand transitions per day and markers of T2D risk by endocrine therapy type.

well as to prospectively examine the effect of increasing sit-to-stand transitions on these markers of T2D risk among breast cancer survivors being treated with SERMs. Given the advances in breast cancer treatment that have reduced breast-cancer recurrence and mortality, mitigating risk for comorbidities such as T2D is an important target to improve survivorship outcomes.

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