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ARTICLE

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Epidemiology

Association between physical activity and neoadjuvant chemotherapy completion and pathologic complete response in primary breast cancer: the CANTO study

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BACKGROUND: Regular physical activity is associated with improved symptom control in patients with breast cancer but its association with chemotherapy completion or response is unclear.
METHODS: Using a prospective design, 1075 breast cancer patients receiving neoadjuvant chemotherapy between March 2012 and February 2017 were studied. Physical activity was assessed using the Global Physical Activity Questionnaire [GPAQ-16], quantified in standardised MET-h/wk. Chemotherapy completion was defined as the proportion of patients completing planned treatment course, requiring dose reduction, or requiring dose delay. Response was evaluated by pathologic complete response (pCR). Associations between physical activity and primary outcomes were assessed using multivariable logistic regression models.
RESULTS: There was no differences between any chemotherapy completion outcome on the basis of physical activity classification. The percent of patients not completing planned treatment was 5.7% for ≦0.33 MET-h/wk, compared with 6.8% for 0.34–16.65 MET-h/wk, and 4.6% for ≥16.6 MET-h/wk ($p = 0.52$). No significant relationships were observed between physical activity dose classification and pCR for the overall cohort or upon stratification by clinical subtype.
CONCLUSION: Future studies are required to further investigate the relationship between pre-treatment levels of physical activity and function on treatment completion and response in breast and other cancer populations.
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INTRODUCTION

Receipt of full chemotherapy dose in the adjuvant and neoadjuvant treatment is a strong, independent predictor of overall survival and disease-free survival in primary breast cancer [1–3]. However, dose reductions and dose delays remain frequent, resulting in suboptimal outcomes among patients with potentially curable disease [4]. In a nationwide study of 1243 community oncology practices including 20,799 patients with primary breast cancer treated with adjuvant chemotherapy, dose reductions ≥15% occurred in 36.5% of patients, whereas treatment delays ≥7 days occurred in 24.9%. Overall, 55.5% received a relative dose intensity (RDI) of <85% [4]. Identifying factors that can reliably identify patients at higher risk of lower dose-intensity chemotherapy as well as guide application of supportive measures are of high clinical relevance.

A common clinical perception is that "fit" patients tolerate planned chemotherapy more effectively than their "unfit"/deconditioned counterparts although data to support this notion are limited [5]. Two retrospective analyses of pooled data from randomised trials performed by two independent groups showed that breast cancer patients with higher cardiorespiratory fitness (CRF), measured before or shortly following the initiation of chemotherapy, were more likely to receive a RDI ≥85% [6, 7]. Evaluating CRF, however, requires specialised equipment and personnel, which significantly hampers widespread clinical application [8]. In contrast, measurement of self-reported physical

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activity, the major determinant of CRF [9], is feasible to implement in most oncology settings and may provide important prognostic information. Patients engaging in higher amounts of pre-diagnosis regular physical activity would be expected to exhibit higher inherent cardiovascular reserve capacity, rendering such individuals better able to adapt to, tolerate, and/or recover from chemotherapy-induced multisystem physiological toxicity [10] and therefore higher RDI of chemotherapy.

A highly relevant corollary line of investigation that is gaining increasing attention is whether physical activity improves chemotherapy efficacy. Exercise improves intratumoural blood vessel density and function, resulting in higher perfusion (i.e., physiologic angiogenesis) and lower hypoxia [11]. Since intratumoural hypoxia is a major barrier to chemotherapy delivery and efficacy, the normalising properties of exercise may enhance efficacy. Whether pre-treatment physical activity links with tumour response to chemotherapy has received minimal attention.

We leveraged data from the CANcer TOxicities (CANTO) prospective primary breast cancer surveillance study to examine whether physical activity at diagnosis (prior to chemotherapy administration) was associated with neoadjuvant chemotherapy completion and/or response in 1075 patients with primary breast cancer. Neoadjuvant provides an ideal setting to address these questions given the use of relatively uniform chemotherapy regimens, limited use of additional cytotoxic therapies (e.g., radiation) that confound treatment delivery and response, and capacity to evaluate tumour response with an objective end point [i.e., pathologic complete response (pCR)].

METHODS

Study cohort and design

CANTO is a French prospective cohort study with longitudinal follow-up of patients diagnosed and treated for stage I–III breast cancer (cT0–3 cN0–3 M0) at 26 institutions in France. Details of the study design, methods, and cohort characteristics have been reported previously [12]. Informed consent was obtained prior to study participation at each institution. Between March 2012 and February 2017, data from 9595 eligible patients was collected for analysis, of which 8072 were excluded for not receiving neoadjuvant chemotherapy, 96 with missing tumour or treatment information, and 127 with missing pre-treatment physical activity data for a final analytic cohort of 1075 patients.

Physical activity assessment

At CANTO baseline enrollment, physical activity exposure was assessed using the Global Physical Activity Questionnaire [GPAQ-16], developed by the World Health Organisation (WHO) [13]. The GPAQ-16 consists of 16 questions designed to estimate an individual's level of physical activity in three domains (work, transport, and leisure time) and time spent in sedentary behaviour; in this study, only physical activity reported in leisure time of at least a moderate- or vigorous-intensity (i.e., exercise) and moderate-intensity transport was analysed. The rationale for inclusion of these domains, and exclusion of occupation-related physical activity, was that moderate-intensity transport comprised a significant component of weekly physical activity in our cohort, and we wanted to focus on components of physical activity that were, at least to some extent, modifiable, to facilitate translation to the clinic. For completeness, we also calculated total physical activity and analysed association with study outcomes. Results were similar and hence only data corresponding to our aforementioned definition of physical activity are presented. Physical activity exposure was calculated according to the standardised WHO GPAQ guidelines. Specifically, standardised metabolic equivalent task (MET) values were assigned to moderate (4 METs) or vigorous (8 METs) physical activity, with dose being calculated by multiplying the frequency of activity sessions per week by average session duration, weighted by the appropriate standardised MET value. Individual activities were summed to derive a total MET-hours per week (MET-h/wk) categorised using a tertile split (≦0.33 MET-h/wk, 0.34–16.65 MET-h/wk, and ≥16.66 MET-h/wk). We also calculated the proportion of patients meeting global WHO physical activity recommendations (i.e., ≥150 min of moderate or ≥75 min of vigorous physical activity per week, respectively, or an equivalent combination of the two [i.e., ≥10 MET-h/wk]) [14]. Validity and reliability of the GPAQ has been established across multiple countries [15].

Outcomes

The main outcomes were neoadjuvant therapy completion and tumour response. Treatment completion was defined as: the proportion of patients: (1) completing planned treatment course, (2) requiring a dose reduction, or (3) requiring a dose delay. Completion of planned treatment was defined as a function of chemotherapy regimen and total number of cycles completed, specifically: (a) anthracycline (AC)/docetaxel (≥8 cycles), (b) carboplatin/docetaxel (≥4 cycles), (c) epirubicin/docetaxel (≥6 cycles), (d) 5 fluorouracil, epirubicin, and cyclophosphamide (FEC) (≥4 cycles), and (e) FEC/docetaxel (≥6 cycles). Dose reduction was defined as whether a patient had at least occurrence of a dose reduction in one or more cycles (yes vs. no). Dose delay was defined as a function of chemotherapy regimen and total cycles completed/duration of therapy greater than: (a) AC/docetaxel [21 days multiplied by (cycles completed $= 8 - 1) + 7$ days], (b) carboplatin/docetaxel [21 days multiplied by (total cycles completed $= 4 - 1) + 7$ days], (c) epirubicin/docetaxel [21 days multiplied by (total cycles completed $= 4 - 1) + 7$ days], (d) FEC (21 days multiplied by (total cycles completed $= 4 - 1) + 7$ days], and (e) FEC/docetaxel (FEC-T) (21 days multiplied by (total cycles completed $= 6 - 1) + 7$ days]. Tumour response was evaluated by pCR, defined as the absence of residual invasive and in situ cancer on haematoxylin and eosin evaluation of the complete resected breast specimen and all sampled regional lymph nodes following completion of neoadjuvant systemic therapy (i.e., ypT0 ypN0 in the current AJCC staging system) [16].

Statistical analysis

Demographic, disease and treatment characteristics were reported by physical activity categorisation and compared using chi-square/Fisher exact test for categorical variables and Wilcoxon rank sum/Kruskal–Wallis test for continuous variables, as appropriate. Multivariable logistic regression models were used to estimate odds ratios (ORs) and 95% confidence intervals (95% CIs) for the association between physical activity (categorised using the tertile split: ≦0.33 MET-h/wk [referent], 0.34–16.65 MET-h/wk, and ≥16.66 MET-h/wk; and dichotomous split comparing no physical activity and meeting WHO physical activity recommendations: 0 MET-h/wk [referent], ≥10 MET-h/wk) and treatment completion metrics and pCR at surgery. We also examined whether the relationship between physical activity and pCR differed according to clinical subtype categorised as follows: (1) ER^+, $PR^+/^-$ and $HER2^-$, (2) ER^+, $PR^+/^-$, $HER2^+$, (3) ER^-, PR^-, and $HER2^+$, and (4) ER^-, PR^-, and $HER2^-$. Finally, given the discovery nature of our study, we used descriptive statistics (mean, median, interquartile range) to further explore the physical activity–pCR relationship. No additional insights were observed (data not presented). Covariates were ascertained at the time of diagnosis via medical chart review; the final multivariable-adjusted model included age, body mass index (BMI), menopausal status, Charlson comorbidity score, tumour subtype, tumour grade, tumour size, tumour histology, cT, and cN. Statistical analyses were conducted using SAS Version 9.4 (Cary, NC). All tests were two-sided and p values of ≤0.05 were considered statistically significant.

RESULTS

Patient characteristics are presented in Table 1. Neoadjuvant chemotherapy consisted of standard FEC-T in 784 (73.0%) of patients. Exercising patients (i.e., >0.33 MET-h/wk) had a lower BMI and were more likely to be non-smokers. Fifty-five percent of patients reported meeting WHO exercise recommendations (≥10 MET-h/wk).

Treatment completion

Table 2 presents the multivariable-adjusted models for treatment completion metrics according to MET-h/wk tertiles. In multivariable analyses, no significant associations were observed between exercise dose and any treatment completion metric (Table 2). For instance, the percent of patients not completing planned treatment dose was 5.7% (referent) for ≦0.33 MET-h/wk, compared with 6.8% (OR: 0.64, 95% CI, 0.27–1.48) for 0.34–16.65 MET-h/wk and 4.6% (OR: 0.92, 95% CI, 0.40–2.25) for ≥16.6 MET-h/wk ($p = 0.52$). The corresponding data for rates of dose reduction

Table 1. Characteristics of the participants by physical activity classification.

Characteristic	Physical activity classification (MET-h/wk)				*p*
	Overall	≦0.33	0.34–16.65	≥16.66	
No. (%)	1075	366 (34)	356 (33)	353 (33)	
Age (years)—mean (SD)	48 (11)	49 (11)	48 (11)	48 (11)	0.47
BMI (kg/m^2)—mean (SD)	25 (5)	26 (5)	25 (5)	25 (5)	0.004
Smoking—no. (%)					
Current	239 (23)	102 (28)	70 (20)	67 (20)	0.03
Former	223 (21)	71 (20)	82 (24)	70 (20)	
Never	584 (56)	185 (52)	194 (56)	205 (60)	
Menopausal status—no. (%)					
Premenopausal	675 (64)	228 (63)	230 (66)	217 (63)	0.57
Tumour size—no. (%)					
T0	29 (3)	13 (4)	10 (3)	6 (2)	0.04
T1	141 (15)	36 (11)	51 (16)	54 (17)	
T2	630 (65)	207 (63)	207 (64)	216 (67)	
T3	170 (17)	71 (22)	54 (17)	45 (14)	
Tumour grade—no. (%)					
High	599 (57)	200 (56)	195 (56)	204 (58)	0.73
Low/intermediate	456 (43)	160 (44)	151 (44)	145 (42)	
Tumour subtype—no. (%)					
ER$^+$, PR$^+$/$^-$, and HER2$^-$	230 (22)	79 (22)	85 (24)	66 (19)	0.40
ER$^+$, PR$^+$/$^-$, HER2$^+$	389 (36)	129 (35)	129 (37)	131 (37)	
ER$^-$, PR$^-$, and HER2$^+$	133 (12)	49 (13)	46 (13)	38 (11)	
ER$^-$, PR$^-$, and HER2$^-$	315 (30)	108 (30)	92 (26)	115 (33)	
Tumour histology—no. (%)					
Ductal	948 (89)	319 (88)	317 (90)	312 (89)	0.88
Lobular	37 (3)	12 (3)	12 (3)	13 (4)	
Mixed and others	84 (8)	33 (9)	25 (7)	26 (7)	
Charlson comorbidity—no. (%)					
Score 0	867 (88)	283 (87)	289 (87)	295 (90)	0.53
Score ≥1	118 (12)	41 (13)	43 (13)	34 (10)	
Chemotherapy—no. (%)					
Anthracycline only	9 (1)	3 (1)	3 (1)	3 (1)	0.55
Anthracyclines–taxanes[a]	1033 (96)	352 (96)	338 (95)	343 (97)	
Taxane only	33 (3)	11 (3)	15 (4)	7 (2)	
Nodal involvement—no. (%)					
No	624 (61)	213 (61)	202 (60)	209 (62)	0.85

Numbers may not sum to 100% due to missing data.
MET metabolic equivalent task, *BMI* body mass index, *HR* hormone receptor, *HER2* human epidermal growth factor receptor 2.
[a]FEC-T in $n = 786$ (73.0%) of patients.

were 16.9, 17.6, and 18.2% for ≦0.33, 0.34–16.65, and ≥16.6 MET-h/wk, respectively ($p = 0.92$). Similar trends were observed for rates of dose delay (Table 2). No significant associations were indicated for the dichotomous stratification of exercise dose (0 MET-h/wk, ≥10 MET-h/wk) (data not shown).

Tumour response

Table 3 presents multivariable-adjusted models for pCR rates according to MET-h/wk tertiles. In multivariable analyses, no significant associations were observed between physical activity classification and pCR for either the overall cohort or upon stratification by clinical subtype (Table 3). For instance, in the overall cohort the percent of patients achieving a pCR was 26.2% (referent) for ≦0.33 MET-h/wk, compared with 29.2% (OR: 0.94, 95% CI, 0.63–1.42) for 0.34–16.65 MET-h/wk and 26.9% (OR: 0.87, 95% CI, 0.58–1.31) for ≥16.6 MET-h/wk ($p = 0.80$). No significant associations were indicated on the basis of dichotomous physical activity dose stratification (data not shown).

DISCUSSION

In this large population-based cohort, higher levels of pre-treatment physical activity was not associated with higher rates of treatment completion in patients undergoing standard contemporary neoadjuvant chemotherapy for primary breast cancer. No associations were also observed between physical activity and tumour response for the overall cohort or by clinical subtype. Our findings have important implications for future

Table 2. Chemotherapy completion metrics by physical activity classification.

Outcome	Overall ($n = 1075$)	≦0.33 ($n = 369$)	0.34–16.65 ($n = 356$)	≥16.66 ($n = 353$)	*p*
Median (IQR) Met-h/wk)		0.0 (0.0–0.0)	8.0 (4.0–12.0)	32.7 (24.0–48.0)	
Completion of planned dose[a]					
No. (%)	780 (94)	266 (94)	246 (93)	268 (95)	0.53[b]
Multivariable-adjusted[c] OR (95% CI)		Ref.	0.64 (0.27–1.48)	0.92 (0.40–2.25)	0.52
Dose reduction[d]					
No. (%)	188 (18)	62 (17)	62 (18)	64 (18)	0.91[b]
Multivariable-adjusted[c] OR (95% CI)		Ref.	1.10 (0.68–1.74)	1.08 (0.68–1.72)	0.92
Dose delay[e]					
No. (%)	109 (13)	38 (14)	33 (13)	38 (14)	0.94[b]
Multivariable-adjusted[c] OR (95% CI)		Ref.	1.20 (0.66–2.19)	1.19 (0.66–2.16)	0.79

MET metabolic equivalent task, *OR* odds ratio.
[a]Treatment completion is defined as the number (%) of patients completing planned neoadjuvant therapy.
[b]Chi-square/Fisher exact test, as appropriate.
[c]Adjusted for age, body mass index, smoking, menopausal status, comorbidities (Charlson), subtype, tumour size, nodal involvement, grade, tumour histology.
[d]Dose reduction is defined as the number (%) of patients requiring a dose reduction during neoadjuvant therapy.
[e]Dose delay is defined as the number (%) of patients requiring a dose delay during neoadjuvant therapy.

studies investigating whether pre-treatment evaluation of lifestyle factors such as physical activity and/or objective measures of patient physiology predict treatment outcomes in patients initiating cancer therapy.

Findings of the present study showing no impact of pre-treatment physical activity are contrary to the hypothesised relationship between physical activity, CRF, and tolerance of chemotherapy-related physiological toxicity. In corroboration of our findings, An et al. found no relationship between self-reported exercise (i.e., leisure-time physical activity) and RDI, analysed as both a continuous variable and on the basis of several categorical classifications [7]. Unfortunately, calculation of RDI was not possible in the present study. In the only other study evaluating the impact of pre-treatment physical activity and treatment completion in breast cancer, Usiskin et al. reported that patients reporting ≥7.5 MET-h/wk in the year prior to a diagnosis were more likely to complete planned dose of neoadjuvant chemotherapy [17]. These data are limited, however, by the retrospective recall of exercise over a 12-month period and small sample size ($n = 67$). Overall, based on the current evidence conclusions regarding the link between pre-treatment physical activity or CRF and risk of chemotherapy-related toxicity/completion rates are premature. Studies leveraging measures of physical activity and exercise together with objective assessment of patient physiology/function are required to better understand and evaluate the potential importance of such data for prediction and monitoring of treatment toxicity/tolerability in diverse oncology settings [8]. In terms of the latter, adjuvant therapy for lung, colorectal, ovarian, or first-line treatment for metastatic disease in which completion of planned therapy is generally much lower (50–80%) may be ideal settings to conduct such studies. These are also settings in which identification of robust pre-treatment prognostic markers are of urgent clinical need [8].

The mechanistic rationale underpinning the concept that pre-treatment physical activity may be linked to receipt of full neoadjuvant chemotherapy dose centres on the notion that higher physical activity is generally associated with higher CRF. CRF, a measure of integrative multi-system cardiovascular reserve capacity (e.g., efficiency of oxygen delivery, extraction, and consumption), possesses remarkable adaptive capacity [10]. As such, patients with higher pre-treatment physical activity and CRF would be expected to better withstand chemotherapy-induced physiological toxicity reflected in higher RDI. Retrospective data analysis from two independent groups reported that CRF either before or within the first cycle of treatment was associated with chemotherapy completion rates in primary breast cancer [6, 7]. Specifically, pooling data from two randomised trials of exercise therapy among 543 patients initiating adjuvant breast cancer chemotherapy, An et al. found no difference in pre-treatment CRF between patients receiving a RDI ≥85% compared to those receiving a RDI <85%. In a sensitivity analysis stratifying patients at the phenotypic extremes of absolute CRF (CRF measurement not indexed to body weight), patients in the highest 80% were almost twice as likely to receive a RDI ≥85% compared to those in lowest 20%, although this was not statistically significant [7]. Using a similar approach, Groen et al. [6] found that patients with poor pre-treatment CRF had a 44% increased risk of not receiving a RDI ≥85% among 419 primary breast cancer patients. Findings from both these two studies should, however, be interpreted with caution since approximately two-thirds of patients received structured exercise therapy for the entire duration of chemotherapy, confounding any inference concerning the link between pre-treatment CRF and receipt of planned chemotherapy dose. Indeed, in separate publications, two of the four trials included in these pooled analyses found exercise therapy increased chemotherapy RDI compared with usual care [18, 19].

A secondary objective was to examine the link between pre-treatment physical activity and tumour response to chemotherapy (i.e., pCR). Although we observed no impact of physical activity on chemotherapy completion rates, investigation on tumour response remains germane since physical activity might influence chemotherapy efficacy independent of tolerability. Indeed, the concept that physical activity may improve treatment efficacy is biologically plausible. In a prior retrospective study among men with localised prostate cancer, higher pre-diagnosis exercise was associated with more normalised tumour microvessel morphology; higher blood vessel perfusion would be expected to correlate with lower intratumoural hypoxia [20]. Hypoxia is a major barrier to chemotherapy delivery and efficacy, thus the potential normalising effects of exercise on the tumour microenvironment may improve treatment efficacy [21]. Intriguingly, preclinical data demonstrate that exercise (concurrent with chemotherapy treatment) improves intratumoural blood vessel density and function, resulting in higher perfusion (i.e., physiologic angiogenesis), lower

Table 3. Treatment response by physical activity classification.

Outcome	Physical activity classification (MET-h/wk)				*p*
	Overall	**≦0.33**	**0.34–16.65**	**≥16.66**	
All patients ($n = 1075$)					
pCR—no. (%)	295 (27)	96 (26)	104 (29)	95 (27)	0.64[a]
Multivariable-adjusted[b] OR (95% CI)		Ref.	0.94 (0.63–1.42)	0.87 (0.58–1.31)	0.80
ER^+, $PR^+/^-$, and $HER2^-$ ($n = 230$)					
pCR—no. (%)	68 (30)	22 (28)	24 (28)	22 (33)	0.73[a]
Multivariable-adjusted[b] OR (95% CI)		Ref.	0.74 (0.31–1.75)	1.04 (0.42–2.56)	0.69
ER^+, $PR^+/^-$, $HER2^+$ ($n = 389$)					
pCR—no. (%)	55 (14)	17 (13)	23 (18)	15 (11)	0.31[a]
Multivariable-adjusted[b] OR (95% CI)		Ref.	1.14 (0.49–2.66)	0.69 (0.30–1.61)	0.50
ER^-, PR^-, and $HER2^+$ ($n = 133$)					
pCR—no. (%)	66 (50)	23 (47)	23 (50)	20 (53)	0.86[a]
Multivariable-adjusted[b] OR (95% CI)		Ref.	0.76 (0.24–2.4)	0.67 (0.19–2.34)	0.80
ER^-, PR^-, and $HER2^-$ ($n = 315$)					
pCR—no. (%)	102 (32)	33 (31)	33 (36)	36 (31)	0.69[a]
Multivariable-adjusted[b] OR (95% CI)		Ref.	0.84 (0.40–1.76)	0.81 (0.40–1.69)	0.84

MET metabolic equivalent task, *pCR* pathologic complete response (no invasive or in situ cancer in breast or axilla), *OR* odds ratio, *HR* hormone receptor, *HER2* human epidermal growth factor 2.
[a]Chi-square/Fisher exact test, as appropriate.
[b]Adjusted for age, BMI, smoking, menopausal status, comorbidities (Charlson), subtype, tumour size, nodal involvement, grade, tumour histology.

hypoxia, and improved tumour response to chemotherapy in mouse models of triple-negative breast cancer [11]. Several other preclinical studies corroborate these data [22].

Findings from the present study fail to support that physical activity, at least immediately prior to chemotherapy administration and not concurrent with chemotherapy as in the preclinical studies, improves treatment response. Usiskin et al. also found no association between pre-treatment exercise and pCR rate to neoadjuvant chemotherapy in a small primary breast cancer cohort [17]. The lack of association between pre-treatment physical activity and pCR appears contradictory to other observational data indicating that pre-diagnosis physical activity is associated with a significant reduction in the risk of breast cancer mortality [23]. Clearly, physical activity-mediated improvements in treatment completion and/or response is one potential "mechanism" that could lead to reductions in cancer mortality (presumably occurring several years after treatment completion) but other non-treatment factors (e.g., adherence to post-treatment cancer surveillance) may also contribute. Additionally, in prior work physical activity has been typically assessed several years prior to a subsequent breast cancer diagnosis whereas in the present study physical activity was assessed at the point of diagnosis and therefore more proximal to adjuvant therapy initiation. In this context, findings of the present study that leveraged the neoadjuvant setting to perform accurate assessment of treatment completion and tumour response significantly adds to the current evidence base. Given emergent preclinical data demonstrating that exercise regulates hypoxia, metabolism, and immune milieu landscapes of solid tumours including breast cancer [11, 24, 25], translational-driven studies are required to interrogate how exercise and patient physiology influence tumour response to conventional and novel anticancer therapy.

Important limitations of our study require consideration. First, and perhaps most importantly, physical activity exposure was assessed by self-report—a method with well-established inherent limitations particularly misclassification of physical activity exposure and reverse causation bias. Second, we only assessed the relationship between physical activity and completion and response to a relatively uniform chemotherapy regimen (i.e., predominantly FEC-T), therefore generalisability to other chemotherapy regimens are imprudent. Third, given the high rate of treatment completion, we were underpowered to detect meaningful differences as a function of physical activity classification. Indeed, given the very high completion rates, studies designed to specifically detect meaningful differences would require a very large sample size further highlighting that adjuvant breast cancer is likely not the preferred population and setting in which to address this important clinical question. Finally, physical activity was assessed at only one time point, prior to the initiation of neoadjuvant chemotherapy. This is important for two reasons. First, physical activity levels reported at the point of diagnosis may have altered significantly due to the recent cancer diagnosis and therefore may not reflect normal mobility patterns levels. Second, such data do not address the clinical question whether change in physical activity or exercise during treatment is associated with treatment outcomes.

In conclusion, pre-treatment physical activity exposure was not associated with treatment completion or response to standard contemporary neoadjuvant chemotherapy in patients with primary breast cancer. However, given the highlighted limitations further research is required to better understand the intersection between lifestyle factors (such as exercise) and patient physiology both immediately prior to as well as during therapy and treatment outcomes in breast and other cancer populations.

DATA AVAILABILITY

Data will be made available upon reasonable request.

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AUTHOR CONTRIBUTIONS

JLB: Wrote the paper. ADM, ASG, MEM: Conceived and designed the analysis and performed the analysis. NMI: Conceived and designed the analysis. SM, PC, FL, CC, AL, OT, LV, CJ, IH, SE, A-LM, PA, AF: Collected the data. IV-L, LWJ: Conceived and designed the analysis and wrote the paper.

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COMPETING INTERESTS

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ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Informed consent was obtained from all patients prior to study participation at each institution.

ADDITIONAL INFORMATION

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