original reports

Physical Activity Patterns and Relationships With Cognitive Function in Patients With Breast Cancer Before, During, and After Chemotherapy in a Prospective, Nationwide Study

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abstract

PURPOSE Physical activity (PA) is a promising intervention for cancer-related cognitive decline, yet research assessing its use during chemotherapy is limited. This study evaluated patterns of PA before, during, and after chemotherapy in patients with breast cancer and the association between PA and cognitive function.

METHODS In a nationwide, prospective cohort study, we assessed PA (Aerobics Center Longitudinal Study PA measure) and perceived and objectively measured cognitive functioning (Functional Assessment of Cancer Therapy–Cognitive, Delayed Match to Sample, and Rapid Visual Processing measures) at prechemotherapy (T1), postchemotherapy (T2), and 6 months postchemotherapy (T3) in patients with breast cancer and cancer-free, age-matched controls at equivalent time points. Longitudinal linear mixed-effects models (LMMs) characterized PA changes over time between patients and controls, adjusting for demographic and clinical factors. LMMs further estimated the role of prechemotherapy PA and changes in PA during chemotherapy on cognitive changes over time.

RESULTS Patients with stage I-IIIC breast cancer (n = 580; age M [standard deviation] = 53.4 [10.6] years) and controls (n = 363; age M [standard deviation] = 52.6 [10.3] years) were included. One third of patients met national PA guidelines at T1, dropping to 21% at T2 before rising to 37% at T3. LMMs revealed declines in PA from T1 to T2 in patients compared with controls (all $P < .001$). Patients meeting guidelines at T1 demonstrated better cognitive scores over time on the Functional Assessment of Cancer Therapy–Cognitive and Rapid Visual Processing (all $P < .05$), with similar patterns of objectively-measured cognitive function as controls. In patients, greater moderate-to-vigorous PA at the previous time point was significantly associated with better cognitive trajectories (all $P < .05$), and adherence to PA guidelines throughout chemotherapy was associated with better self-reported cognition ($P < .01$).

CONCLUSION This nationwide study demonstrates that PA maintenance before and during chemotherapy is associated with better cognitive function immediately and 6 months after chemotherapy completion.

J Clin Oncol 39:3283-3292.

INTRODUCTION

Cancer-related cognitive decline (CRCD) is an important clinical problem. Upward of 75% of patients with breast cancer report cognitive problems during chemotherapy,[1-5] and evidence suggests that CRCD may persist years after chemotherapy completion.[6] The onset of CRCD contributes to an accelerated aging phenotype, increasing morbidity and, subsequently, mortality.[7,8]

We previously reported on the impact of chemotherapy on cognition in patients with breast cancer compared with individuals without a cancer diagnosis serving as controls.[1,9] This large, nationwide study examined trajectories of cognitive change from prechemotherapy (T1) to postchemotherapy (T2) and 6 months post-chemotherapy completion (T3) in a cohort of 943 women with breast cancer and age- and sex-matched cancer-free controls. We showed that cognitive function declined in patients compared with controls from T1 to T3[1,9]; domains of sustained attention (ie, Rapid Visual Processing [RVP]) and visual memory (ie, Delayed Match-to-Sample [DMS]) were among those revealing significant performance reductions in patients relative to controls, where patients either declined or improved less over time. Cognitive complaints (ie, Functional Assessment of Cancer Therapy–Cognitive [FACT-Cog]) among patients increased significantly compared with controls.[1]

ASSOCIATED CONTENT

Appendix

Author affiliations and support information (if applicable) appear at the end of this article.

Accepted on June 30, 2021 and published at ascopubs.org/journal/jco on August 18, 2021: DOI https://doi.org/10.1200/JCO.20.03514

CONTEXT

Key Objective

Cancer-related cognitive decline is an important clinical problem for which interventions are needed. Physical activity (PA) is a promising intervention; however, its use in patients undergoing active treatment is limited. This study sought to investigate timing and dose of PA in a large nationwide, prospective cohort study in patients with breast cancer as well as its relationship to cognitive function. To our knowledge, this is one of the largest analyses of PA and cognitive function before and after chemotherapy in patients with breast cancer.

Knowledge Generated

PA in patients declined during chemotherapy before recovering to pretreatment levels 6 months after chemotherapy completion; however, most patients remained insufficiently active. More PA prechemotherapy, and adhering to national PA guidelines during chemotherapy, were associated with better cognition over time.

Relevance

This study supports the use of PA before and during chemotherapy for maintaining cognitive function.

Physical activity (PA) in cancer survivors has been consistently associated with improved health outcomes, including better physical function and quality of life, and improved survival.[10,11] Although PA following primary treatments has shown the greatest evidence for benefits on CRCD,[6,10,12-18] the American College of Sports Medicine and others have recommended more research on the timing and dose of PA[10]; studies focusing on PA before and during chemotherapy are lacking.[12] It remains unclear whether PA before (ie, prehabilitation) or during chemotherapy may provide lasting cognitive benefits.[19]

To address these gaps, we conducted an analysis of PA and cognition in a cohort of patients with breast cancer and controls.[1,9] We investigated the patterns and trajectories of PA in patients with breast cancer undergoing chemotherapy compared with age-matched, cancer-free controls. We then examined how prechemotherapy PA was associated with changes in cognitive functioning in both patients and controls, as well as how change in PA from prechemotherapy to postchemotherapy was associated with cognitive trajectories in patients only. We hypothesized that (1) patients would engage in lower levels of PA compared with controls, (2) PA levels in patients would decline from prechemotherapy to postchemotherapy, and (3) patients with high levels of prechemotherapy PA, and those who maintained high levels postchemotherapy, would demonstrate better cognitive functioning, comparable to controls, compared with those who were less active.

METHODS

Participants and Study Design

Details of the study design, sample size determination, and enrollment procedures have been previously reported.[1,9] All available data were used in the current analysis. Herein, cancer survivors are women diagnosed with breast cancer, and are referred to as patients throughout, given their entry into the study began before receiving curative intent treatment. Participants were recruited from 22 NCI Community Oncology Research Program (NCORP) sites nationwide to participate in a longitudinal study assessing the impact of chemotherapy on cognitive function in female patients with breast cancer. Eligibility criteria for patients included female with stage I-IIIC disease, at least 21 years of age, ability to write and speak English, not pregnant, chemotherapy-naïve, scheduled for chemotherapy with no plan to receive concurrent radiation therapy during chemotherapy, free from central nervous system disease, no neurodegenerative disease, and no hospitalization because of major psychiatric illness within the last year. Controls were eligible if they were cancer-free, within 5 years of age of the matched patients, and met non–cancer-specific eligibility criteria. The study was approved by all institutional review boards at each NCORP site and the University of Rochester Cancer Center NCORP Research Base (ClinicalTrials.gov identifier: NCT01382082). All participants provided written informed consent.

Measurements were assessed prechemotherapy—within 7 days before the first chemotherapy administration (T1); postchemotherapy—within 1 month of the last chemotherapy administration (T2); and 6 months postchemotherapy—6 months after the final chemotherapy administration (T3) — and at equivalent time points for controls. Covariates were assessed once at T1.

Measures

Physical activity. PA was assessed using the validated leisure time PA questionnaire from the Aerobics Center Longitudinal Study.[20] Participants indicated the frequency of varying activities over the past 3 months, ranging from household activities to vigorous sports. When applicable, a statistician (E.C.) calculated intensity using reported frequency and distance. Two researchers (E.A.S. and A.S.K.) independently assigned metabolic equivalent of task (MET)

hours for each activity classification based on the updated Physical Activity Compendium.[21] Disagreements were discussed among all three researchers until consensus was achieved based on existing literature, erring on the side of conservative MET assignment. MET assignments then estimated the energy cost of individual activities: light-intensity (1.6-2.9 METs),[22] moderate-intensity (3.0-5.9 METs), and vigorous-intensity (≥ 6.0 METs).[22,23] Moderate-to-vigorous-intensity physical activity (MVPA) included all activities ≥ 3.0 METs. In line with the current Physical Activity Guidelines for Americans,[23] MVPA was categorized to either meeting PA guidelines (≥ 150 min/wk MVPA) or not (< 150 min/wk MVPA). Analytic variables included index-specific minutes and MET h/wk, index-specific intensities (eg, exercise MVPA), and dichotomous meeting guidelines (yes or no).

Cognitive measures. For this analysis, we selected a combination of validated objective and self-reported cognitive measures administered in person and previously identified as being significantly reduced in patients with breast cancer compared with controls across T1-T3 in this cohort.[1,9] The FACT-Cog (version 2.0) Perceived Cognitive Impairment (PCI; assessing perceived impairments) and FACT-Cog Total Score (assessing all four domains) were studied.[24] The RVP assessed sustained attention[25,26] and the DMS assessed visual memory after a 12-second delay[26]—both from the CANTAB eclipse software (Cambridge Cognition, Cambridge, United Kingdom). Changes over time of more than 1/2 standard deviation of the FACT-Cog measured at baseline were considered to be clinically meaningful.[1,27]

Covariates. Age, race, and menopausal status were self-reported by participants. Body mass index (BMI) was calculated using the standard kg/m^2 calculation. Reading ability, a proxy for cognitive reserve, was assessed by the Wide Range Achievement Test, 4th Edition, reading subscale.[28] Anxiety was assessed by the Spielberger State-Trait Anxiety Inventory State score.[29] Depressive symptoms were assessed by a single item on the Multidimensional Fatigue Symptom Inventory.[30] Chemotherapy regimens were categorized as anthracycline-containing or non–anthracycline-containing from clinic notes, based on previous anthracycline-cognition literature.[31,32]

Statistical Analysis

Physical activity patterns. To investigate PA patterns and trajectories in patients with cancer compared with controls, we conducted *t* and χ^2 tests. To account for the full trajectory of PA in patients and controls, we used longitudinal linear mixed-effects models (LMMs) with PA at T1, T2, and T3 as the outcome. Fixed effects were assessment (T1, T2, and T3 treated nominally), group (patient or control), and group × time interaction. The random effect (independent of residual error) was participant-specific PA at the three time points, represented as an unstructured covariance matrix. Estimation was performed using the restricted maximum likelihood method. Marginal adjusted means quantified the between-group difference (patients *v* control) at T1, T2, and T3, changes from T1 to T2 and T1 to T3, and between-group differences in these changes. Models were adjusted for age, race, BMI, menopausal status, cognitive reserve, anxiety, and depressive symptoms.

Physical activity and cognitive functioning in patients and controls over time. We first explored how the PA-cognition association differed between patients and controls. Longitudinal LMMs estimated the association between pre-chemotherapy PA and change in cognitive functioning over time using three-way interactions between time (T1, T2, and T3), group (patients and controls), and PA (meeting guidelines at T1 and not meeting guidelines at T1), with cognition at T2 and T3 as outcome variables. Between-group differences in trajectories of cognitive tests were evaluated using linear contrasts (eg, patients meeting guidelines compared with controls not meeting guidelines). Analyses were adjusted for age, race, BMI, menopausal status, cognitive reserve, anxiety, and depressive symptoms.

Physical activity and cognitive functioning in patients only. For patient-only analyses, we conducted repeated-measures longitudinal LMMs with minutes of MVPA activities at T1 and T2 as lagged time-varying covariates and cognition at T2 and T3 as outcomes. Then, we categorized patients into four groups based on change in meeting PA guidelines from T1 to T2 (never met guidelines, went from meeting to not meeting guidelines, went from not meeting to meeting guidelines, and always met guidelines). This four-level group variable, time (nominal T1, T2, T3), and group × time interaction were fixed effects in longitudinal LMMs with cognition at T1, T2, and T3 as the outcome. Between-group differences in trajectories of cognitive tests were evaluated using linear contrasts. Estimation used restricted maximum likelihood and assumed unstructured covariance matrices for the random effects. Analyses were adjusted for all previous covariates plus treatment type (anthracycline yes or no). The significance level for all models was set to 0.05, and analyses were conducted using SAS (SAS Institute, Cary, NC) and SPSS (IBM Corp, Chicago, IL).

RESULTS

Participant characteristics are detailed in Table 1. Briefly, participants (N = 943) included 580 patients with breast cancer (53.4 ± 10.6 years) and 363 controls (52.6 ± 10.3 years) who provided complete cognitive data at each time point with minimal missing data (< 5%) on the PA questionnaire at each time point (Fig 1). Participants were mostly White (91.2%), completed at least some college training (80.4%), and postmenopausal (51.0%) at T1. Patients had mostly stage II disease (49.1%) and almost half had chemotherapy regimens containing anthracycline (45.9%).

TABLE 1. Participant Demographics and Cancer-Specific Clinical Characteristics at Baseline

Characteristic	Breast Cancer, n = 580	Control, n = 363	Total, N = 943
	No. (%) or M (SD)	No. (%) or M (SD)	No. (%) or M (SD)
Age, years	53.4 (10.6)	52.6 (10.3)	53.1 (10.5)
Race			
White	517 (89.1%)	343 (94.5%)	860 (91.2%)
Black	47 (8.1%)	16 (4.4%)	63 (6.7%)
Other	16 (2.8%)	4 (1.1%)	20 (2.1%)
Education			
< High school	11 (1.9%)	0 (0%)	11 (1.2%)
High school or GED	131 (22.6%)	43 (11.8%)	174 (18.5%)
≥ Partial college	438 (75.5%)	320 (88.2%)	758 (80.4%)
BMI	30.3 (7.3)	29.0 (6.8)	29.7 (7.2)
Anxiety score	36.0 (12.4)	28.3 (9.2)	33.0 (11.8)
Depression item	0.68 (0.93)	0.39 (0.76)	0.56 (0.88)
Cognitive reserve (WRAT-4)	62.8 (6.0)	64.0 (4.4)	63.2 (5.5)
Menopausal status			
Premenopausal	181 (31.2%)	104 (28.7%)	285 (30.3%)
Postmenopausal	303 (52.2%)	178 (49.0%)	481 (51.0%)
Perimenopausal	45 (7.8%)	43 (11.8%)	88 (9.3%)
Medically induced	51 (8.8%)	38 (10.5%)	89 (9.4%)
Stage		—	—
I	158 (27.3%)	—	—
II	285 (49.1%)	—	—
III	108 (18.6%)	—	—
Unknown	29 (5.0%)	—	—
Chemotherapy		—	—
Anthracycline	266 (45.9%)	—	—
Nonanthracycline[a]	314 (54.1%)	—	—

Abbreviations: BMI, body mass index; GED, test of General Education Development; M, mean; SD, standard deviation; WRAT-4, Wide Range Achievement Test, 4th Edition.

[a]This group includes 32 cases for which we were unable to confirm chemotherapy regimen from clinic notes mostly because of dropout after T1; when adjusting for regimen in patient-only analyses, these 32 patients were not included in multivariate models.

PA Patterns

One third of patients with breast cancer met PA guidelines at T1, dropping to 21% at T2 before returning to 37% at T3. Figure 2 details the proportion of patients and controls meeting guidelines over time. At T1, patients reported an average of 11.1 ± 15.7 exercise MET h/wk and 10.4 ± 15.6 MVPA exercise MET h/wk, significantly lower than controls (both Ps = .02; Appendix Table A1 [online only, unadjusted]). These levels declined significantly in patients from T1 to T2 (both Ps < .001), remaining substantially lower than those in controls. Patients also reported significantly lower levels of total minutes and MET h/wk for all activities combined at T2 (all P < .01). Mean levels and group differences for all other PA outcomes are depicted in Table 2 (adjusted), Appendix Table A1, and Appendix Figure A1 (online only). Appendix Table A2 (online only) details the most common activities in patients and controls at T1. Longitudinal LMMs indicated several significant group × time interactions, confirming a decline in patients with breast cancer from T1 to T2 for all PA outcomes compared with controls (all P < .001). From T2 to T3, patients reported significantly increased PA across all outcomes compared with controls (all P < .03), with no significant difference in exercise levels between groups at T3 (all P > .64).

PA and Cognitive Functioning in Patients and Controls Over Time

Unadjusted changes in cognitive functioning over time in patients and controls by meeting PA guidelines at baseline are detailed in Appendix Figure A2 (online only). Longitudinal LMM linear contrasts indicated that patients meeting national

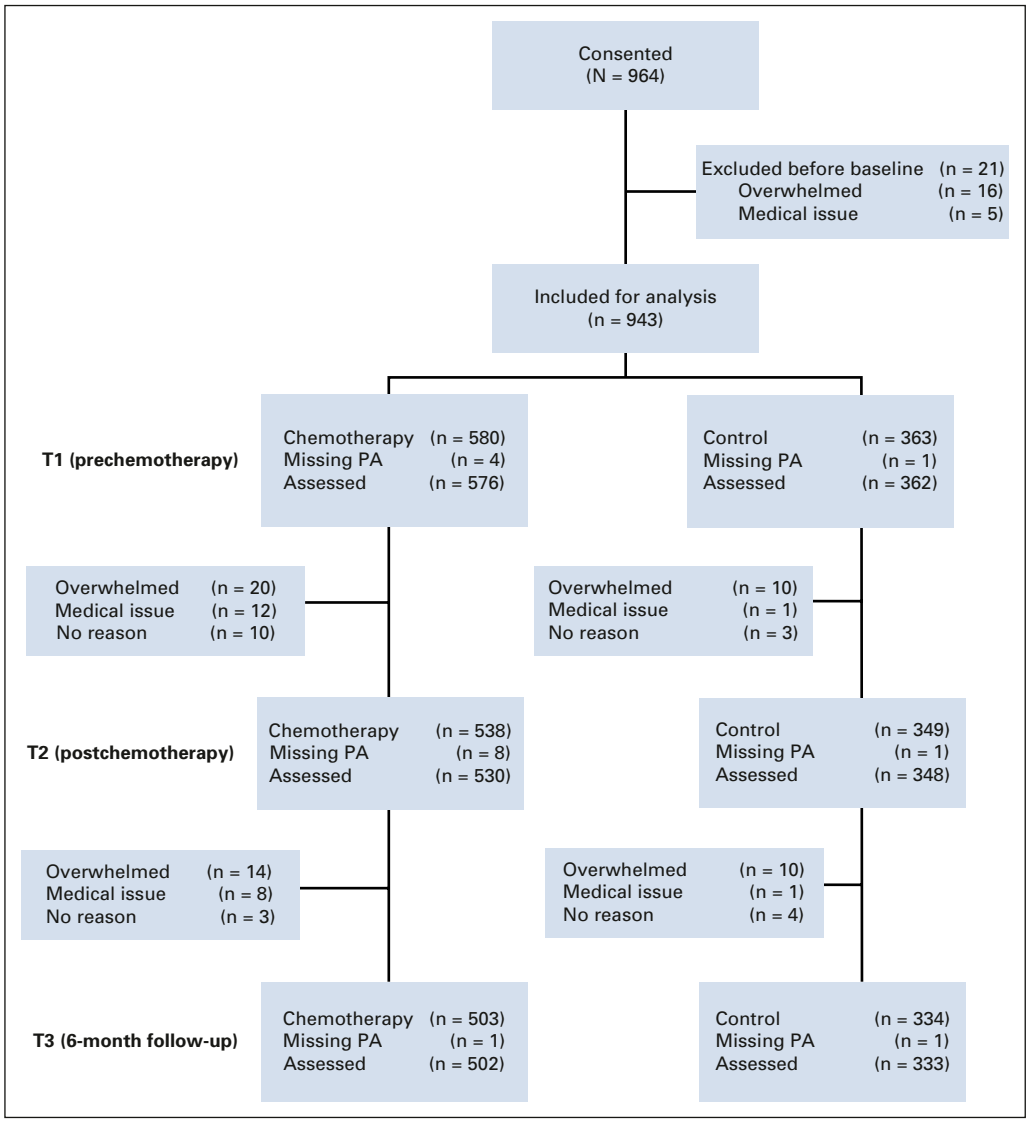

FIG 1. CONSORT diagram. PA, physical activity.

PA guidelines at baseline demonstrated comparable cognitive scores as controls who did not meet guidelines for RVP ($\beta = -1.5$, $P = .14$) and DMS ($\beta = -1.2$, $P = .33$). For the FACT-Cog PCI and Total scores, patients meeting PA guidelines at baseline scored lower (ie, worse function; than controls who did not meet guidelines, ($\beta = 7.2$, $P < .001$) and ($\beta = 9.6$, $P < .001$). Comparing patients and controls who both met PA guidelines at baseline, patients demonstrated comparable scores as controls on RVP and DMS, ($\beta = -2.0$, $P = .07$) and ($\beta = -0.7$, $P = .57$), respectively, but still reported more problems than controls on the FACT-Cog (Ps $< .001$). Similar findings were evident when comparing patients and controls who both did not meet PA guidelines at baseline (Appendix Fig A2).

PA and Cognitive Functioning in Patients Only

In patients only, meeting PA guidelines at baseline was associated with significantly higher scores (ie, better function or perceived function) on the FACT-Cog PCI ($\beta = 2.7$, $P = .05$), FACT-Cog Total ($\beta = 4.9$, $P = .02$), and RVP ($\beta = 2.2$, $P = .01$) over time, compared with patients not meeting PA guidelines at baseline. A similar pattern emerged for the DMS ($\beta = 1.9$, $P = .07$), albeit not statistically significant. Longitudinal LMMs with PA as a lagged time-varying covariate indicated that more minutes of MVPA measured at the previous time point was significantly associated with better cognitive function trajectories on the FACT-Cog PCI ($P = .01$), FACT-Cog Total ($P = .04$), and RVP ($P = .05$). No significant associations emerged between all activities and cognition (all $P > .23$). Assessing the association between change in meeting PA guidelines from T1 to T2, 316 patients never met guidelines, 102 patients went from meeting to not meeting guidelines, 36 patients went from not meeting to meeting guidelines, and 76 patients always met guidelines

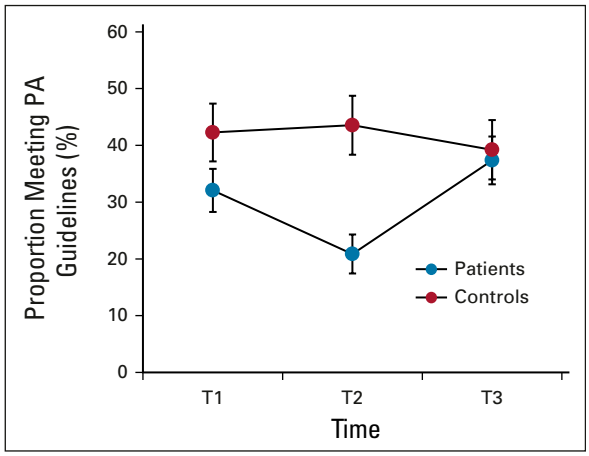

FIG 2. Proportion of patients with cancer and controls meeting PA guidelines over time. Error bars represent 95% CIs. PA, physical activity; T1, prechemotherapy; T2, postchemotherapy; T3, 6 months postchemotherapy or equivalent time points for controls.

(Fig 3 and Appendix Table A3, online only). On the FACT-Cog, patients who maintained guidelines demonstrated better cognitive function scores at T2 ($P = .01$), better cognitive recovery at T3 (T1 *v* T3 scores, $P = .97$), and a higher mean score at T3 compared with the other three groups ($P < .01$). Importantly, this group did not experience a clinically meaningful decline on the FACT-Cog from T1 to T3, as assessed by effect size (ES; difference in scores standardized to the baseline score standard deviation; PCI ES = 0.08, $P = .57$; Total ES = −0.06, $P = .97$). On the RVP, patients who met guidelines at T1 scored higher at all three time points regardless of meeting guidelines at T2 ($P = .05$). On the DMS, patients who never met guidelines performed worse than the other groups ($P = .12$). Indeed, patients who never met guidelines experienced clinically meaningful declines on the FACT-Cog (PCI ES = −0.45, $P < .001$; Total ES = −0.46, $P < .001$).

DISCUSSION

To our knowledge, this study provides one of the largest assessments of PA and cognitive function before and after chemotherapy in patients with breast cancer. Our results suggest that chemotherapy negatively affects the ability to maintain optimal PA levels, and higher levels of PA before initiating chemotherapy are associated with better perceived and objectively assessed cognitive functioning after chemotherapy completion. Although patients in the current sample returned to prechemotherapy PA levels 6 months postchemotherapy, more than two thirds of patients still did not meet PA guidelines. Importantly, patients who met PA guidelines pretreatment had comparable cognitive scores, at least for certain domains, as their cancer-free peers. Our results suggest that maintaining higher levels of MVPA from prechemotherapy to postchemotherapy, or at least meeting national PA guidelines before treatment, may assist in alleviating CRCD.

TABLE 2. Adjusted[a] Mean Physical Activity Levels for Patients and Controls Over Time

	Patients	Controls	
Physical Activity Outcome	**M (SE)**	**M (SE)**	***P***
All activities, MET h/wk			
T1	45.3 (2.6)	40.8 (3.0)	.14
T2	34.9 (2.6)	43.9 (3.0)	.004*
T3	44.5 (2.5)	38.4 (2.9)	.03*
All activities, min/wk			
T1	712.6 (40.0)	618.7 (46.2)	.04*
T2	561.7 (41.0)	663.0 (47.0)	.03*
T3	690.4 (39.6)	580.8 (44.8)	.01*
Exercise, MET h/wk			
T1	10.4 (1.0)	11.8 (1.1)	.19
T2	6.6 (0.9)	12.0 (1.0)	< .001**
T3	11.6 (1.0)	11.1 (1.1)	.64
Exercise, min/wk			
T1	143.1 (11.9)	154.7 (13.8)	.40
T2	95.1 (11.1)	152.3 (12.5)	< .001**
T3	155.8 (11.8)	142.1 (13.4)	.30
MVPA exercise, MET h/wk			
T1	9.8 (1.0)	11.3 (1.1)	.16
T2	5.9 (0.9)	11.5 (1.0)	< .001**
T3	10.9 (1.0)	10.7 (1.1)	.79
MVPA exercise, min/wk			
T1	124.2 (11.3)	138.6 (13.1)	.27
T2	74.4 (10.6)	137.7 (12.0)	< .001**
T3	136.0 (11.3)	128.4 (12.8)	.55

Abbreviations: M, mean; MET, metabolic equivalent of task; MVPA, moderate-to-vigorous physical activity; T1, prechemotherapy, T2, postchemotherapy; T3, 6 months postchemotherapy or equivalent time points for controls.

[a]Adjusted for age, race, body mass index, menopausal status, cognitive reserve, and anxiety and depressive symptoms.

*Significant at $P < .05$.

**Significant at $P < .001$.

Our finding that PA significantly declined during chemotherapy is consistent with the documented detrimental effects of chemotherapy on lifestyle behaviors after cancer.[33-36] Most of this work has been conducted cross-sectionally,[35,36] with time frames centered around diagnosis rather than treatment,[33,34] and without comparison to appropriate controls. This large, longitudinal cohort allowed us to determine how PA levels changed before, during, and acutely postchemotherapy. Despite a recovery to baseline activity 6 months after chemotherapy completion, 63% of patients were insufficiently active, emphasizing the need to encourage activity regardless of time on or off chemotherapy. Further understanding of behavioral factors underlying this PA recovery (eg, renewed motivation or

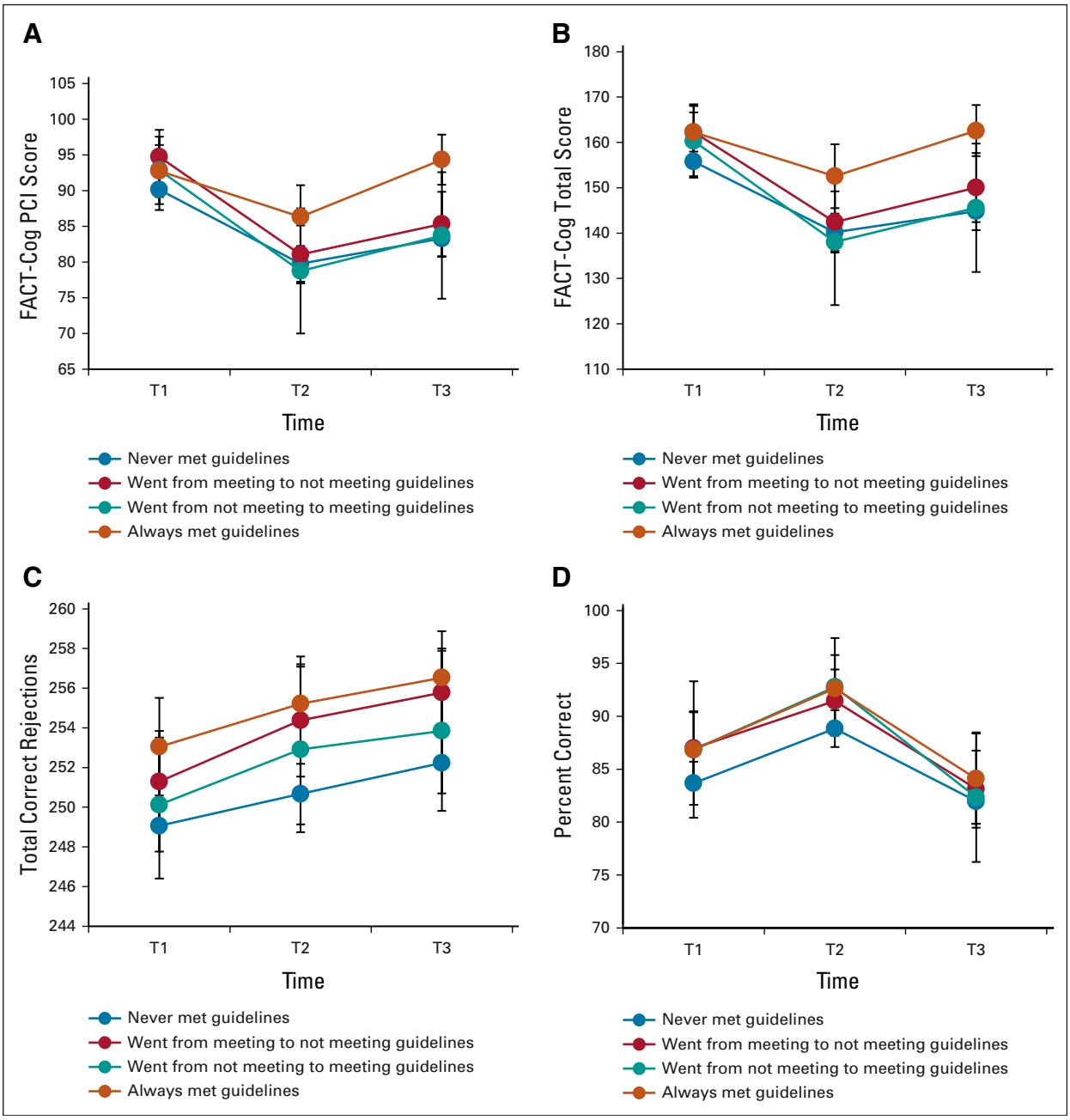

FIG 3. Change in cognitive functioning over time by changing levels of PA in patients with breast cancer. (A) FACT-Cog PCI, (B) FACT-Cog total score, (C) RVP, and (D) DMS. Error bars represent 95% CIs, unadjusted data, higher scores = better function. DMS, Delayed Match-to-Sample; FACT-Cog, Functional Assessment of Cancer Therapy–Cognitive; PCI, Perceived Cognitive Impairment; RVP, Rapid Visual Processing; T1, prechemotherapy; T2, postchemotherapy; T3, 6 months postchemotherapy.

postchemotherapy improved health status) will be important to shape behavioral interventions in this population.

Despite the low proportion of patients meeting PA guidelines and exercising prechemotherapy, those who did had substantially better cognitive outcomes after chemotherapy. Few observational studies have examined the association between PA and cognitive functioning in patients with cancer,[12] and most were conducted in small samples[37] or after chemotherapy completion.[38-40] Our findings reveal the importance of prechemotherapy PA on changes in cognitive function after chemotherapy in more than 500 patients with breast cancer. Future work should explore whether this association is the result of an epidemiologic relationship between precancer PA accumulated across the lifespan and cognition, or rather if increasing PA within a discrete time window before treatment (eg, prehabilitation) can effectively reduce CRCD. Further exploration of prechemotherapy PA change is warranted.[12,19,41,42]

The importance of prechemotherapy PA is underscored by our finding of comparable scores on objective measures of cognition (eg, RVP and DMS) over time between patients who met PA guidelines at baseline and controls. These associations did not emerge for self-reported cognition, where active patients still scored lower than controls on the FACT-Cog. Many self-reported cognitive measures, such as the FACT-Cog, are multidimensional and capture additional psychosocial and emotional symptoms,[43,44] which may explain this discrepancy. The fact that active patients scored similarly to both inactive and active controls on objective measures of cognitive functioning suggests that PA may help attenuate accelerated cognitive aging. These results point to potential aging-specific mechanisms that warrant further exploration.

The robust PA-cognition relationship persisted in our analysis of patients only. Lagged analyses indicated that higher levels of recent PA were associated with better cognition for most cognitive domains assessed. This finding was consistent over time, emphasizing the importance of PA across the entire chemotherapy window. Patients who adhered to PA guidelines from prechemotherapy to post-chemotherapy had the highest cognitive functioning across domains with no clinically meaningful declines in self-reported cognitive functioning. Regardless of PA change during treatment, those who met guidelines pre-chemotherapy had the highest scores on attention. Those who never met guidelines scored worse on visual memory than all other groups. These findings demonstrate the importance of PA both before and during chemotherapy for preventing meaningful declines in self-reported cognition. However, it remains unclear as to whether increasing PA during chemotherapy can improve cognition; only 36 patients increased their PA levels during chemotherapy. Further randomized controlled trials in this space are warranted. MVPA demonstrated the most robust associations with cognition, confirming the need to focus on PA dosing when designing such trials in cancer.[10]

Our findings should be interpreted in the context of their strengths and limitations. This study was conducted in a large, nationwide longitudinal sample within the NCORP network. We used multiple well-validated measures of cognitive function that have previously been identified as impaired by chemotherapy,[1,9] across the treatment window. The use of age-matched, cancer-free controls allowed for comparisons to the general population. We acknowledge that PA was self-reported, which may introduce recall or social desirability biases[45]; however, this cost-effective method surveyed a large cohort over time during a challenging life phase (cancer treatment) and captured contextual PA information. Both PA and cognitive function were assessed simultaneously in this sample. Although our statistical analyses accounted for and maintained temporality, it is possible that patients with better executive functioning and self-regulation were more likely to engage in PA behavior.[46]

In summary, patients with breast cancer resumed their pretreatment PA levels 6 months postchemotherapy; however, a majority of patients remained insufficiently active. Importantly, PA before and during chemotherapy was associated with better cognitive outcomes. Promoting PA across the treatment continuum should continue, and further research should focus on how PA both before and during chemotherapy may minimize CRCD.

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PRIOR PRESENTATION

Presented in part as a poster at the International Cognition and Cancer Task Force (ICCTF) meeting, February 4, 2020, Denver, CO.

SUPPORT

Supported by National Cancer Institute Grants No. U10CA037420 Supplement, UG1CA189961, DP2195765, K07CA168886, T32CA102618, and R01CA231014. E.A.S. was supported by the Cancer Prevention Fellowship Program (National Cancer Institute, National Institutes of Health) from 2017-2020.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at DOI https://doi.org/10.1200/JCO.20.03514.

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ACKNOWLEDGMENT

The authors thank the participants of this study and all staff at the University of Rochester Cancer Center NCORP Research Base and NCORP affiliate sites that recruited and observed participants. The authors thank the National Cancer Institute Clinical Community Oncology Program (CCOP) and NCORP programs for their funding and support of this project. The authors thank Dr Sue Rosenthal for providing feedback on this manuscript.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Physical Activity Patterns and Relationships With Cognitive Function in Patients With Breast Cancer Before, During, and After Chemotherapy in a Prospective, Nationwide Study

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No other potential conflicts of interest were reported.

APPENDIX

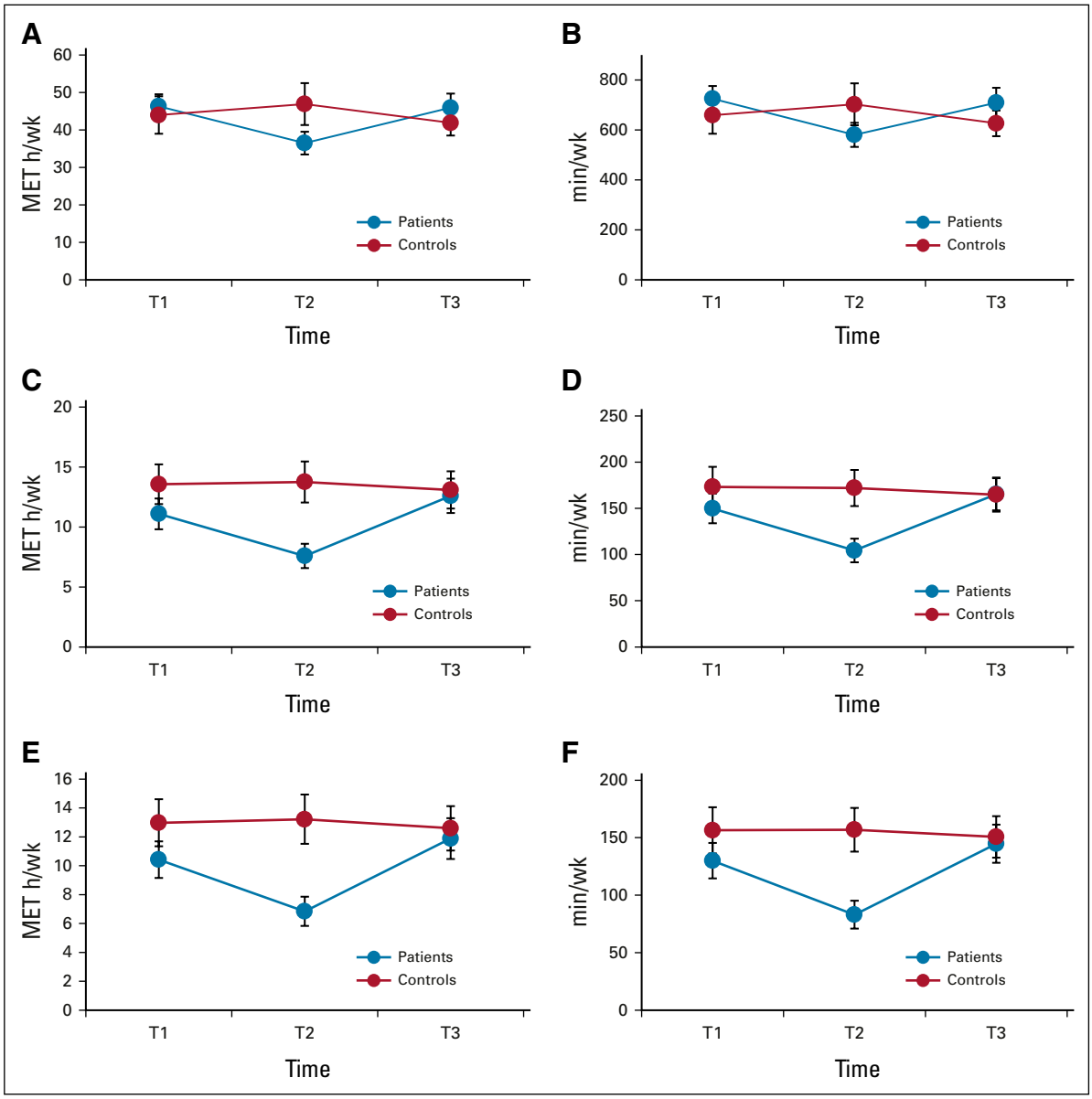

FIG A1. PA levels for patients and controls over time: (A and B) all activities, (C and D) exercise, and (E and F) moderate-to-vigorous physical activity. Error bars represent 95% CIs. MET, metabolic equivalent of task; T1, prechemotherapy; T2, postchemotherapy; T3, 6 months postchemotherapy or equivalent time points for controls.

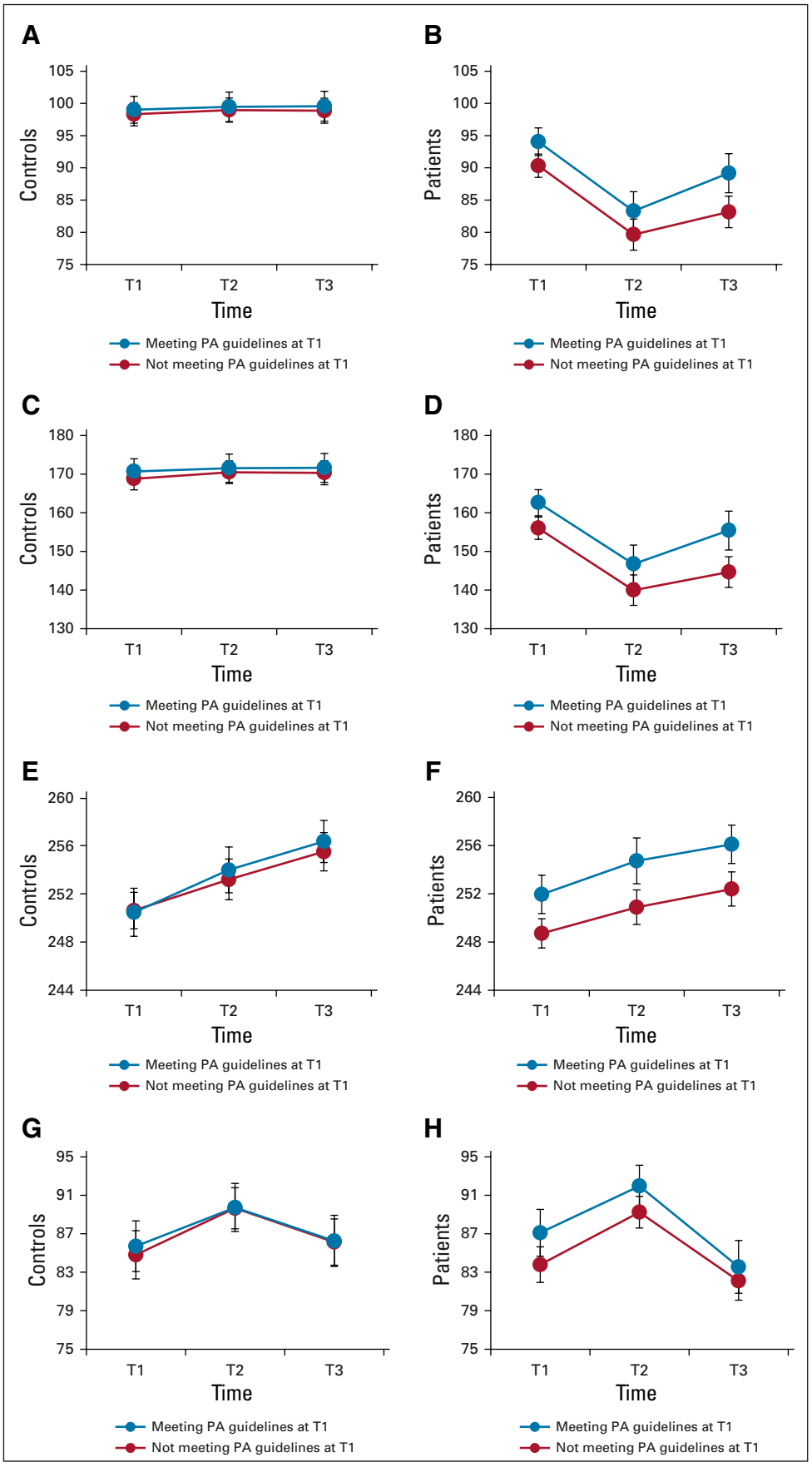
A
Controls
105
100
95
90
85
80
75
T1
T2
T3
Time
Meeting PA guidelines at T1
Not meeting PA guidelines at T1
B
Patients
105
100
95
90
85
80
75
T1
T2
T3
Time
Meeting PA guidelines at T1
Not meeting PA guidelines at T1
C
Controls
180
170
160
150
140
130
T1
T2
T3
Time
Meeting PA guidelines at T1
Not meeting PA guidelines at T1
D
Patients
180
170
160
150
140
130
T1
T2
T3
Time
Meeting PA guidelines at T1
Not meeting PA guidelines at T1
E
Controls
260
256
252
248
244
T1
T2
T3
Time
Meeting PA guidelines at T1
Not meeting PA guidelines at T1
F
Patients
260
256
252
248
244
T1
T2
T3
Time
Meeting PA guidelines at T1
Not meeting PA guidelines at T1
G
Controls
95
91
87
83
79
75
T1
T2
T3
Time
Meeting PA guidelines at T1
Not meeting PA guidelines at T1
H
Patients
95
91
87
83
79
75
T1
T2
T3
Time
Meeting PA guidelines at T1
Not meeting PA guidelines at T1

FIG A2. Change in cognitive functioning over time for patients and controls, by meeting PA guidelines at baseline: (A and B) FACT-Cog: perceived cognitive impairment (PCI), (C and D) FACT-Cog: total score, (E and F) rapid visual processing (RVP), and (G and H) delayed match to sample (DMS). Error bars represent 95% CIs, unadjusted data, higher scores = better function. DMS, Delayed Match-to-Sample; FACT-Cog, Functional Assessment of Cancer Therapy–Cognitive; PA, physical activity; PCI, Perceived Cognitive Impairment; RVP, Rapid Visual Processing; T1, prechemotherapy; T2, postchemotherapy; T3, 6 months postchemotherapy or equivalent time points for controls.

TABLE A1. Unadjusted Mean Physical Activity Levels for Patients and Controls Over Time

	Patients	Controls	
Physical Activity Outcome	**M (SD)**	**M (SD)**	***P***
All activities, MET h/wk			
T1	46.3 (39.0)	44.0 (48.4)	.43
T2	36.5 (35.5)	46.9 (52.9)	.001**
T3	45.9 (43.1)	41.9 (31.2)	.12
All activities, min/wk			
T1	725.1 (613.5)	658.9 (721.2)	.15
T2	580.2 (562.5)	702.2 (797.2)	.01*
T3	708.7 (678.9)	626.3 (473.4)	.04*
Exercise, MET h/wk			
T1	11.1 (15.7)	13.6 (16.0)	.02*
T2	7.6 (11.9)	13.8 (16.3)	< .001**
T3	12.6 (16.3)	13.1 (14.4)	.64
Exercise, min/wk			
T1	149.8 (196.6)	173.3 (210.3)	.09
T2	104.4 (150.7)	172.0 (185.4)	< .001**
T3	165.2 (199.3)	164.8 (170.4)	.98
MVPA exercise, MET h/wk			
T1	10.4 (15.6)	13.0 (15.7)	.02*
T2	6.8 (11.8)	13.2 (16.2)	< .001**
T3	11.9 (16.1)	12.6 (14.3)	.50
MVPA exercise, min/wk			
T1	129.9 (188.0)	156.4 (194.1)	.04*
T2	83.0 (142.5)	156.9 (180.3)	< .001**
T3	144.7 (189.5)	150.7 (166.8)	.63

Abbreviations: M, mean; MET, metabolic equivalent of task; MVPA, moderate-to-vigorous physical activity; SD, standard deviation; T1, prechemotherapy; T2, postchemotherapy; T3, 6 months postchemotherapy or equivalent time points for controls.

*Significant at $P < .05$.

**Significant at $P < .001$.

TABLE A2. Most Common Activities at T1 in Patients and Cancer-Free Controls

Physical Activity Type	Patients (%)	Controls (%)
Household	95.5	97.0
Stairs	56.2	66.6
Walking	56.2	63.8
Lawn or garden	39.5	47.0
Aerobic	12.1	16.9
Weights	10.9	17.7
Treadmill	10.5	16.6
Biking	9.7	13.8
Jogging	4.0	6.6
Swimming	2.2	3.9

Abbreviation: T1, prechemotherapy or equivalent time point for controls.

TABLE A3. Unadjusted Change in Cognitive Functioning Over Time by Changing Levels of Physical Activity in Patients With Breast Cancer

	Never Met Guidelines	Meeting to Not Meeting	Not Meeting to Meeting	Always Met Guidelines
Cognitive Function Outcome	M (SD)	M (SD)	M (SD)	M (SD)
FACT-Cog PCI				
T1	90.1 (18.4)	94.7 (14.4)	92.9 (16.6)	92.8 (15.9)
T2	79.8 (22.8)	81.1 (20.8)	78.8 (25.9)	86.3 (19.5)
T3	83.3 (22.4)	85.3 (22.5)	83.7 (25.8)	94.3 (15.0)
FACT-Cog total score				
T1	155.8 (29.5)	162.3 (22.2)	160.3 (23.9)	162.3 (25.3)
T2	140.2 (37.6)	142.4 (24.6)	138.0 (41.1)	152.6 (30.7)
T3	144.9 (36.7)	150.1 (38.0)	145.6 (40.6)	162.6 (24.2)
RVP				
T1	249.1 (11.7)	251.3 (11.3)	250.1 (10.7)	253.1 (10.8)
T2	250.7 (13.8)	254.4 (14.5)	252.9 (12.2)	255.2 (10.4)
T3	252.2 (13.4)	255.8 (10.9)	253.9 (11.4)	256.5 (10.0)
DMS				
T1	83.7 (18.4)	87.0 (17.9)	86.9 (18.9)	86.8 (15.5)
T2	88.8 (15.9)	91.5 (15.2)	92.8 (13.7)	92.6 (13.8)
T3	82.0 (18.7)	83.1 (18.0)	82.4 (17.6)	84.1 (18.2)

Abbreviations: DMS, Delayed Match-to-Sample; FACT-Cog, Functional Assessment of Cancer Therapy-Cognitive; M, mean; PCI, Perceived Cognitive Impairment; RVP, Rapid Visual Processing; SD, standard deviation; T1, prechemotherapy; T2, postchemotherapy; T3, 6 months postchemotherapy.