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Article

Physical Activity Before, During, and After Chemotherapy for High-Risk Breast Cancer: Relationships With Survival

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Abstract

Background: Although physical activity has been consistently associated with reduced breast cancer mortality, evidence is largely based on data collected at one occasion. We examined how pre- and postdiagnosis physical activity was associated with survival outcomes in high-risk breast cancer patients. **Methods:** Included were 1340 patients enrolled in the Diet, Exercise, Lifestyle and Cancer Prognosis (DELCaP) Study, a prospective study of lifestyle and prognosis ancillary to a SWOG clinical trial (S0221). Activity before diagnosis, during treatment, and at 1- and 2-year intervals after enrollment was collected. Patients were categorized according to the Physical Activity Guidelines for Americans as meeting the minimum guidelines (yes/no) and incrementally as inactive, low active, moderately active (meeting the guidelines), or high active. **Results:** In joint-exposure analyses, patients meeting the guidelines before and 1 year after diagnosis experienced statistically significant reductions in hazards of recurrence (hazard ratio [HR] = 0.59, 95% confidence interval [CI] = 0.42 to 0.82) and mortality (HR = 0.51, 95% CI = 0.34–0.77); associations were stronger at 2-year follow-up for recurrence (HR = 0.45, 95% CI = 0.31 to 0.65) and mortality (HR = 0.32, 95% CI = 0.19 to 0.52). In time-dependent analyses, factoring in activity from all time points, we observed striking associations with mortality for low- (HR = 0.41, 95% CI = 0.24 to 0.68), moderate- (HR = 0.42, 95% CI = 0.23 to 0.76), and high-active patients (HR = 0.31, 95% CI = 0.18 to 0.53). **Conclusions:** Meeting the minimum guidelines for physical activity both before diagnosis and after treatment appears to be associated with statistically significantly reduced hazards of recurrence and mortality among breast cancer patients. When considering activity from all time points, including during treatment, lower volumes of regular activity were associated with similar overall survival advantages as meeting and exceeding the guidelines.

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Over the past decade, a large body of epidemiological evidence has demonstrated an inverse association between prediagnosis (1–14) and postdiagnosis (4,8,9,15–25) recreational physical activity (RPA) with mortality among breast cancer patients. Collectively, data show that patients reporting the highest levels of prediagnosis RPA experienced a 26%–27% reduction in mortality in comparison to their least active counterparts (26,27), whereas the highest levels of postdiagnosis RPA

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associated with even stronger protection, with reduced hazards of mortality ranging from 39% to 48% in comparison to the least active women (26,27). However, data describing the associations of RPA with breast cancer recurrence remains limited, conflicting, and not well understood (11,21,25,27,28).

An important limitation of the extant literature is that it is based almost entirely on data collected on one occasion, reflecting either pre- or postdiagnosis activity. Few publications have reported how activity measured on multiple occasions is associated with breast cancer survival (8,17), and none have described how pre- and postdiagnosis RPA, queried prospectively on 4 occasions before, during, and after chemotherapy, is associated with disease recurrence and mortality. Yet this remains a clinically significant area of inquiry given that many breast cancer patients decrease activity or become entirely inactive during or after cancer treatment (29–32). As such, we investigated the associations of pre- and postdiagnosis RPA with disease recurrence and mortality for patients with high-risk breast cancer. Specifically, we sought to examine whether meeting the Physical Activity Guidelines for Americans (PAGAs) before diagnosis, during treatment, and after treatment was associated with disease recurrence and/or mortality.

Methods

Study Population and Data Collection

The Diet, Exercise, Lifestyle and Cancer Prognosis Study (DELCaP) was a questionnaire-based study ancillary to a breast cancer intergroup phase III clinical trial (SWOG 0221; NCT00070564) led by SWOG (33). DELCaP was initiated to assess lifestyles of women with high-risk, pathologic stage I to III breast cancer at multiple times throughout survivorship, including at study enrollment (before treatment), during treatment, and after chemotherapy completion (34,35).

Patients were excluded from enrollment in the S0221 therapeutic trial if they received prior chemotherapy or radiation treatment, had any heart disease or abnormal organ function, were HIV positive, were pregnant, or had a Zubrod performance status greater than 1. Patients with a history of hypertension and/or patients ages 60 years and older must have undergone diagnostic testing to demonstrate at least a normal left ventricle ejection fraction. Patients experiencing unacceptable treatment toxicities or treatment delays (>3 weeks) were removed from the trial.

DELCaP was initiated after S0221 began, and formal approval to conduct the study was obtained in June 2005 from the institutional review boards at Roswell Park and all participating institutions that enrolled patients to S0221. As shown in Figure 1, a total of 2014 patients were eligible to participate in DELCaP, and 1607 (79.8%) consented to participate. All participants provided written informed consent.

DELCaP Questionnaire

The DELCaP questionnaire, a self-administered epidemiological survey assessing demographic and lifestyle factors, was adapted from an extensive instrument used with patients participating in the DataBank and BioRepository at Roswell Park Comprehensive Cancer Center (36). The baseline questionnaire (Q1) was administered at the time of study enrollment and queried lifestyle behaviors in the month prior to diagnosis. Among the 1607 consented patients, 1340 (83.4%) completed and returned Q1. The second questionnaire (Q2) assessed lifestyles during chemotherapy and was administered to patients returning Q1 6 months after study enrollment when treatment was scheduled to be completed; among the 1340 patients receiving Q2, 1134 (84.6%) completed the questionnaire. The third questionnaire (Q3) was administered to patients completing Q1 and Q2 approximately 1 year after study enrollment and assessed lifestyles in the preceding year; 921 patients (81.2%) completed Q3. Lastly, the fourth questionnaire (Q4) was administered 2 years after study enrollment to patients completing Q1–Q3 and queried lifestyles in the preceding year; 81.5% of eligible participants completed Q4.

Recreational Physical Activity Assessment

The DELCaP questionnaire assessed mode, frequency, and duration of RPA and was adapted from the Lifetime Physical Activity Questionnaire, a self-administered survey with established reliability among adult women (37). Total metabolic equivalent of task (MET) minutes/hours were calculated for each person at each time based on corresponding codes and MET values published in the Physical Activity Compendium (38). Activities were included in the analysis if performed at least once a week throughout the exposure window assessed and if the compendium MET value was at least 3.0 or higher (38–40).

We parameterized RPA as a categorical variable using three approaches. First, in light of emerging evidence showing that lower volumes of regular, weekly activity have been associated with decreased all-cause and cancer mortality in comparison to inactivity (41,42), we examined whether engaging in any regular, weekly RPA (i.e., at least once per week, yes/no) was associated with outcomes. We further examined relationships according to the minimum PAGAs (the MET hour equivalent of 150 minutes of moderate-intensity RPA per week, yes/no) (43). Lastly, in accordance with the incremental physical activity levels outlined in the PAGAs, we classified patients as inactive (no regular and/or weekly RPA); low active (some activity but insufficiently active according to minimum recommendations); moderate active (the equivalent of meeting the recommended range of RPA in the PAGAs); or high active (exceeding the minimum recommended range of RPA in the PAGAs) (43).

Clinical Outcome Ascertainment

The primary analytic outcomes were disease recurrence and all-cause mortality. Recurrence data were assessed via post-treatment follow-up visits in which patients underwent physical examination every 6 months for the first 5 years and annually for up to 15 years until death, whichever occurred first. Additional studies (eg, imaging, biopsy) to investigate and document suspected disease recurrence were performed as clinically indicated, and results were noted on the appropriate study forms. For disease recurrence, disease-free survival time was defined as time from randomization to first instance of disease recurrence, new breast primary tumor, or death from any cause, whichever came first. Vital status was ascertained from medical records, phone calls and/or letters to patient homes, obituaries, and national death records. For all-cause mortality, survival time was defined as time from randomization to death from any cause. Patients who had not recurred and who were still alive at the time of analysis were censored on the date of their last clinical contact.

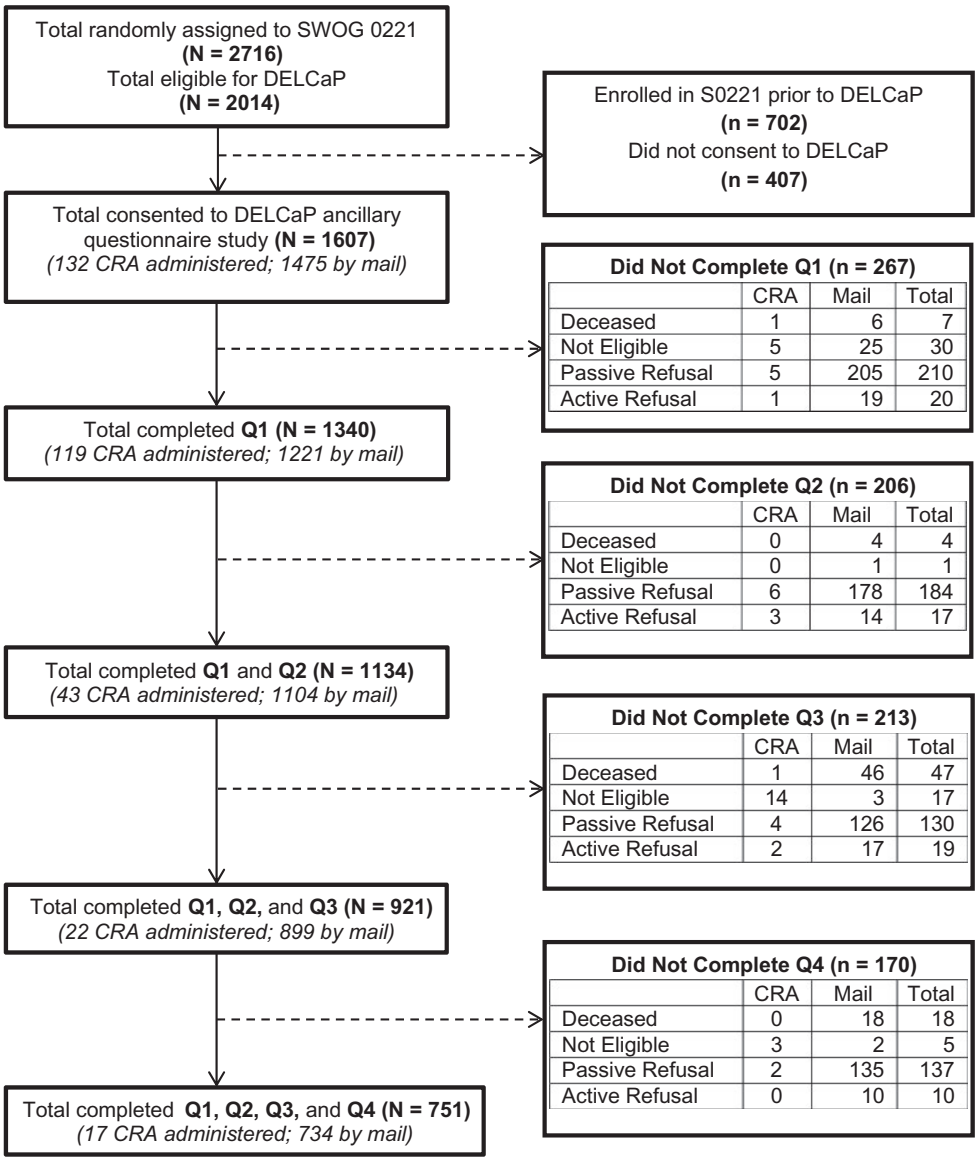

Figure 1. Study schema for participants included in the physical activity and survival analysis from the Diet, Exercise, Lifestyle and Cancer Prognosis (DELCaP) Study, an observational questionnaire study ancillary to S0221, a randomized treatment trial for high-risk breast cancer. Questionnaire 1 (Q1) was completed at the time of S0221 registration, prior to the initiation of chemotherapy. Q2 was completed at the completion of active treatment (approximately 6 months after trial registration). Q3 was completed 1 year after trial registration, approximately 6 months after treatment completion. Q4 was completed 2 years after trial registration, approximately 1 year after treatment completion. CRA = Clinical Research Associate.

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Statistical Analysis

Standard Cox models were used to estimate associations of prediagnosis RPA with disease recurrence and mortality and to assess associations representing the joint exposure of pre- and postdiagnosis RPA with disease recurrence and mortality. Time-dependent models were used to consider RPA as a time-varying exposure across all exposure windows and to appropriately account for the possibility of immortal time bias (44,45). Sensitivity landmark analyses were conducted to further account for the possibility of immortal time bias and to examine associations at each independent exposure window. However, we used time-dependent analyses in the primary analyses because with each successive questionnaire, the landmark time became shorter and data points were lost, providing an incomplete picture of the exposure-outcome association (45).

We a priori defined age at baseline and a stratification factor corresponding to the original randomization treatment assignment from the SWOG clinical trial as important covariates in all multivariable analyses. We examined additional relevant prognostic variables for confounding using stepwise regression models and the 10% change-in-estimate method (46). Based on these approaches, we determined that body mass index, menopausal status, race, ethnicity, and education were not statistically significant factors. The number of positive nodes, HER2 status, and estrogen receptor and/orprogesterone receptor status were statistically significant factors in stepwise regression but did not change the minimally adjusted hazard ratios (HRs); thus, we present minimally adjusted models as our primary results.

We used standard diagnostic methods to examine our model-building process to detect any substantial departures

Table 1. Baseline demographic and clinical characteristics of the Diet, Exercise, Lifestyle and Cancer Prognosis Study study population according to overall and disease-free survival status (n = 1340)

Patient characteristic	Overall survival, No. (%)			Disease-free survival, No. (%)		
	Alive (n = 1118, 83%)	Deceased (n = 222, 17%)	P*	Disease-free (n = 1030, 77%)	Recurrence (n = 310, 23%)	P*
Demographic characteristics						
Age, mean (SD), y	50.89 (9.72)	53.39 (10.47)	<.001	50.87 (9.64)	52.75 (10.56)	.005
Body mass index, mean (SD)	29.15 (6.77)	30.49 (7.07)	.008	29.14 (6.75)	30.16 (7.05)	.02
Menopausal status			.006			.006
Premenopausal	545 (86.51)	85 (13.49)		506 (80.32)	124 (19.68)	
Postmenopausal	563 (80.89)	133 (19.11)		515 (73.99)	181 (26.01)	
Self-reported race			.10			.37
White	937 (83.81)	181 (16.19)		864 (77.28)	254 (22.72)	
Black	69 (73.40)	25 (26.60)		64 (68.09)	30 (31.91)	
Multiracial	38 (84.44)	7 (15.56)		35 (77.78)	10 (22.22)	
American Indian	11 (84.62)	2 (15.38)		10 (76.92)	3 (23.08)	
Asian/Pacific Islander	44 (91.17)	4 (.08)		40 (83.33)	8 (16.67)	
Other	15 (83.33)	3 (16.67)		14 (77.78)	4 (22.22)	
Self-reported ethnicity			.73			.51
Non-Hispanic	1059 (83.32)	212 (16.68)		978 (76.95)	293 (23.05)	
Hispanic	51 (85.00)	9 (15.00)		44 (73.33)	16 (26.67)	
Education			.03			.06
Grade school or some high school	69 (74.19)	24 (25.81)		61 (65.59)	32 (34.41)	
High school graduate or GED	234 (81.53)	53 (18.47)		219 (76.31)	68 (23.69)	
Some college or technical school	412 (85.12)	72 (14.88)		380 (78.51)	104 (21.49)	
College graduate	248 (86.71)	38 (13.29)		227 (79.37)	59 (20.63)	
Advanced degree	149 (80.98)	35 (19.02)		137 (70.46)	47 (25.54)	
Clinical characteristics						
Nodal status			<.001			<.001
Negative	309 (88.54)	40 (11.46)		290 (83.09)	59 (16.91)	
1–3 positive nodes	433 (86.25)	69 (13.75)		406 (80.88)	96 (19.12)	
≥4 positive nodes	374 (76.80)	113 (23.20)		332 (68.17)	155 (31.83)	
ER/PgR status			<.001			.01
Positive (either or both positive)	751 (86.03)	122 (13.97)		690 (79.04)	183 (20.96)	
Negative (both negative)	365 (78.66)	99 (21.34)		338 (72.84)	126 (27.16)	
HER2 status			.03			.007
Negative	867 (82.18)	188 (17.82)		793 (75.17)	262 (24.83)	
Positive	245 (87.81)	34 (12.19)		231 (82.80)	48 (17.20)	

*P values reflect pooled t test for age and body mass index, otherwise χ^2 test and are rounded to the nearest 100th place except where <0.01. ER = estrogen receptor; PgR = progesterone receptor.

from model assumptions that may have influenced our estimates (ie, examining residuals, ad hoc time-varying covariates of a discretized time scale, and Kaplan–Meier curves for the main effects under consideration). No interaction terms were statistically significant relative to our final conclusions.

Missing data from nonresponse (at least one missing survey) were assumed to be missing not at random. To account for the missing data mechanism, Taylor series variance estimation was employed and observations that had missing values were included in computing the degrees of freedom (47).

All statistical tests were two-sided, and a *P* value of less than .05 was considered statistically significant. All analyses were performed using SAS 9.4 (SAS Institute, Cary, NC).

Results

The demographic and clinical characteristics of the DELCaP study population according to overall and disease-free survival are summarized in Table 1. At the time of analysis, with a mean follow-up time of 89 months, 222 patients had died and 310 experienced recurrence. Table 2 characterizes the prevalence of RPA according to survival outcomes at each exposure window. We observed expected decreases in activity during chemotherapy, with 54.5% of patients reporting RPA, in contrast to 73.2% before diagnosis; the highest prevalence of activity was at 2-year follow-up (75.1%).

Table 3 presents the associations of prediagnosis RPA with cancer outcomes. In comparison to inactive patients, patients reporting any regular RPA experienced a 19% and 22% decreased hazard of recurrence and mortality, respectively, although estimates weren't statistically significant. Patients meeting or exceeding the minimum PAGAs experienced a statistically significant reduced hazard of mortality compared with those not meeting the PAGAs (HR = 0.74, 95% CI = 0.56 to 0.96); there was a similar, non-statistically significant reduction in the hazard of recurrence (HR = 0.82, 95% CI = 0.66 to 1.03). When incremental activity levels were examined, only moderately active patients experienced a statistically significant reduced hazard of recurrence (HR = 0.62, 95% CI = 0.43 to 0.88) and mortality (HR = 0.48, 95% CI = 0.31 to 0.75).

Joint exposure models representing the associations of pre- and postdiagnosis RPA with outcomes are presented in Table 4. The primary finding from these analyses is that patients

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Table 2. The prevalence of regular, weekly pre- and postdiagnosis recreational physical activity as queried before, during, and after treatment in the Diet, Exercise, Lifestyle and Cancer Prognosis Study study population according to disease-free and overall survival

			Disease-free survival			Overall survival		
Questionnaire/Time period (N)*	Regular RPA	No. (%)	Disease free No. (%)	Recurred No. (%)	P†	Alive No. (%)	Deceased No. (%)	P†
Q1, before diagnosis (n = 1340)	Yes	981 (73.2)	765 (74.3)	216 (69.7)	.11	828 (84.4)	153 (80.8)	.11
	No	359 (26.8)	265 (25.7)	94 (30.3)		290 (15.6)	69 (19.2)	
Q2, during treatment (n = 1147)	Yes	625 (54.5)	493 (55.3)	132 (51.6)	.29	528 (54.7)	97 (53.3)	.72
	No	522 (45.5)	398 (44.7)	124 (48.4)		437 (45.3)	85 (46.7)	
Q3, 1 year after enrollment (n = 936)	Yes	640 (68.4)	519 (69.2)	121 (65.1)	.28	560 (69.3)	80 (62.5)	.12
	No	296 (31.6)	231 (30.8)	65 (34.9)		248 (30.7)	48 (37.5)	
Q4, 2 years after enrollment (n = 769)	Yes	577 (75.1)	483 (76.4)	94 (68.6)	.06	512 (75.5)	65 (71.4)	.39
	No	192 (24.9)	149 (23.6)	43 (31.4)		166 (24.5)	26 (28.6)	

*Total N for each questionnaire presented herein does not exactly coincide with Figure 1 because patients/deaths were excluded for the purposes of Landmark survival analyses for each successive exposure assessment and because 2 patients who completed Q3 did not complete Q2, and 5 patients who completed Q4 did not complete all prior questionnaires. RPA = recreational physical activity; Q = questionnaire.
†P values reflect two-sided χ^2 test.

Table 3. Hazard ratios representing the associations of prediagnosis recreational physical activity with disease recurrence and mortality in the Diet, Exercise, Lifestyle and Cancer Prognosis Study (n = 1340)

		Disease recurrence			All-cause mortality		
Multivariable models*	Parameterization of recreational physical activity†	No. of events/total	HR (95% CI)‡	P	No. of Events/total	HR (95% CI)‡	P
Minimally-adjusted models	Any regular, weekly RPA						
	No	94/359	1.00 (Referent)		69/359	1.00 (Referent)	
	Yes	216/981	0.81 (0.64 to 1.03)	.08	153/981	0.78 (0.59 to 1.04)	.09
	Meet the minimum PAGAs						
	No	174/689	1.00 (Referent)		131/689	1.00 (Referent)	
	Yes	136/651	0.82 (0.66 to 1.03)	.09	91/651	0.74 (0.56 to 0.96)	.02
	Incremental activity categories (PAGAs)						
	No weekly RPA	94/359	1.00 (Referent)		69/359	1.00 (Referent)	
	Low weekly activity	80/330	0.87 (0.65 to 1.18)	.38	62/330	0.92 (0.65 to 1.29)	.61
	Moderate activity	45/257	0.62 (0.43 to 0.88)	.008	26/257	0.48 (0.31 to 0.75)	.001
	High activity	91/394	0.88 (0.66 to 1.18)	.39	65/394	0.87 (0.62 to 1.22)	.41
Fully-adjusted models	Any regular, weekly RPA						
	No	94/359	1.00 (Referent)		69/359	1.00 (Referent)	
	Yes	216/981	0.80 (0.63 to 1.02)	.07	153/981	0.76 (0.57 to 1.01)	0.06
	Meet the minimum PAGAs						
	No	174/689	1.00 (Referent)		131/689	1.00 (Referent)	
	Yes	136/651	0.84 (0.67 to 1.05)	.12	91/651	0.76 (0.58 to 0.99)	0.04
	Incremental activity categories (PAGAs)						
	No weekly RPA	94/359	1.00 (Referent)		69/359	1.00 (Referent)	
	Low weekly activity	80/330	0.85 (0.63 to 1.15)	.38	62/330	0.87 (0.62 to 1.24)	0.45
	Moderate activity	45/257	0.65 (0.46 to 0.93)	.01	26/257	0.51 (0.32 to 0.80)	0.003
	High activity	91/394	0.85 (0.64 to 1.15)	.29	65/394	0.85 (0.60 to 1.19)	0.33

*Minimally adjusted models are adjusted for age and stratified by treatment arm. Fully adjusted models are adjusted for age, HER2 status, hormone receptor status, number of positive nodes, and stratified by treatment arm. CI = confidence interval; HR = hazard ratio; MET = metabolic equivalent of task; PAGAs = Physical Activity Guidelines for Americans; RPA = recreational physical activity.
†METs are expressed as average MET hours per week. Any regular, weekly RPA (yes/no) denotes at least 1 session per week throughout the exposure window assessed. Meeting the minimum PAGAs (yes/no) uses 8.3 MET hours per week as the cutoff and assumes the equivalent of 150 minutes per week of moderate-intensity activity, such as brisk walking at 3.0 miles per hour. Incremental physical activity levels are defined as inactive (reference group), low active (<8.3 MET hours per week), moderately active (8.3–16 MET hours per week), and high active (>16 MET hours per week).
‡Standard Cox models were used to estimate HRs and 95% CIs.

meeting the minimum PAGAs (yes/no) before diagnosis and at 1-year follow-up experienced statistically significantly reduced hazards of recurrence (HR = 0.59, 95% CI = 0.42 to 0.82) and mortality (HR = 0.51, 95% CI = 0.34 to 0.77); observed associations became stronger at the 2-year follow-up for both recurrence (HR = 0.45, 95% CI = 0.31 to 0.65) and mortality (HR = 0.32, 95% CI = 0.19 to 0.52). Importantly, we also observed statistically significant reduced hazards of recurrence (46%) and mortality (43%) among patients not meeting the PAGAs before diagnosis but who met the PAGAs at the 2-year follow-up.

Table 4. Multivariable models representing the joint exposure of prediagnosis and postdiagnosis recreational physical activity with disease recurrence and all-cause mortality in the Diet, Exercise, Lifestyle and Cancer Prognosis Study

Physical activity parameterization*	Joint exposure time periods assessed†	Disease recurrence		All-cause mortality	
		HR (95% CI)‡	*P*	HR (95% CI)‡	*P*
Any regular, weekly recreational physical activity	No regular RPA before diagnosis, No during treatment	1.00 (Referent)		1.00 (Referent)	
	No before diagnosis, Yes during treatment	1.20 (0.74 to 1.96)	.46	1.44 (0.83 to 2.50)	.19
	Yes before diagnosis, No during treatment	0.85 (0.60 to 1.21)	.37	0.83 (0.54 to 1.27)	.38
	Yes before diagnosis, Yes during treatment	0.73 (0.53 to 1.01)	.06	0.74 (0.51 to 1.10)	.13
	No regular RPA before diagnosis, No at 1 year	1.00 (Referent)		1.00 (Referent)	
	No before diagnosis, Yes at 1-year follow-up	0.78 (0.45 to 1.36)	.38	0.69 (0.36 to 1.34)	.27
	Yes before diagnosis, No at 1-year follow-up	0.72 (0.44 to 1.17)	.19	0.63 (0.35 to 1.12)	.11
	Yes before diagnosis, Yes at 1-year follow-up	0.70 (0.48 to 1.03)	.07	0.57 (0.36 to 0.88)	.01
	No regular RPA before diagnosis, No at 2 years	1.00 (Referent)		1.00 (Referent)	
	No before diagnosis, Yes at 2-year follow-up	0.73 (0.39 to 1.35)	.31	0.99 (0.48 to 2.04)	.99
	Yes before diagnosis, No at 2-year follow-up	0.84 (0.46 to 1.53)	.56	0.71 (0.32 to 1.56)	.39
	Yes before diagnosis, Yes at 2-year follow-up	0.61 (0.39 to 0.97)	.04	0.59 (0.33 to 1.06)	.08
Met the minimum PAGAs	No before diagnosis, No during treatment	1.00 (Referent)		1.00 (Referent)	
	No before diagnosis, Yes during treatment	1.18 (0.73 to 1.93)	.50	1.29 (0.75 to 2.21)	.36
	Yes before diagnosis, No during treatment	0.86 (0.67 to 1.11)	.25	0.78 (0.58 to 1.06)	.12
	Yes before diagnosis, Yes during treatment	0.78 (0.55 to 1.11)	.17	0.69 (0.45 to 1.06)	.09
	No before diagnosis, No at 1-year follow-up	1.00 (Referent)		1.00 (Referent)	
	No before diagnosis, Yes at 1-year follow-up	0.80 (0.54 to 1.20)	.29	0.81 (0.51 to 1.30)	.38
	Yes before diagnosis, No at 1-year follow-up	0.96 (0.74 to 1.25)	.76	0.86 (0.64 to 1.20)	.41
	Yes before diagnosis, Yes at 1-year follow-up	0.59 (0.42 to 0.82)	.001	0.51 (0.34 to 0.77)	.001
	No before diagnosis, No at 2-year follow-up	1.00 (Referent)		1.00 (Referent)	
	No before diagnosis, Yes at 2-year follow-up	0.54 (0.35 to 0.83)	.005	0.57 (0.35 to 0.94)	.03
	Yes before diagnosis, No at 2-year follow-up	0.94 (0.73 to 1.21)	.64	0.91 (0.68 to 1.23)	.55
	Yes before diagnosis, Yes at 2-year follow-up	0.45 (0.31 to 0.65)	<.001	0.32 (0.19 to 0.52)	<.001

*METs are expressed as average MET hours per week. Any regular, weekly RPA (yes/no) denotes at least 1 session per week throughout the exposure window assessed. Meeting the minimum PAGAs (yes/no) uses <8.3 MET hours per week as the cutoff for no, ≥8.3 for yes and assumes the equivalent of 150 minutes per week of moderate-intensity activity, such as brisk walking at 3.0 miles per hour. CI = confidence interval; HR = hazard ratio; MET = metabolic equivalent of task; PAGAs = Physical Activity Guidelines for Americans; RPA = recreational physical activity.

†RPA exposure during four time points was considered in joint-exposure analyses as follows: RPA before diagnosis (Q1); during treatment (Q2); 1-year follow-up (Q3); and 2-year follow-up (Q4).

‡Multivariable hazard models are adjusted for age and stratified by treatment arm. Standard Cox models were used to estimate HRs and 95% CIs.

In time-dependent analyses, striking statistically significant inverse associations between RPA and mortality were observed, but the association for disease recurrence was attenuated (Table 5). In comparison to inactive patients, patients reporting any regular weekly activity experienced a 63% reduced hazard of mortality. Additionally, patients meeting the minimum PAGAs experienced a 60% reduced hazard of mortality in comparison to those who didn't meet the PAGAs. When participants were categorized according to incremental activity levels, patients reporting low and moderate volumes of activity experienced similar overall survival advantages (HR = 0.41, 95% CI = 0.24 to 0.68 and HR = 0.42, 95% CI = 0.23 to 0.76, respectively). However, highly active patients experienced the greatest survival advantage with a 69% reduced hazard of mortality (HR = 0.31, 95% CI = 0.18 to 0.53).

Sensitivity landmark analyses confirmed the validity of the inverse associations between RPA and mortality observed in time-dependent models. Patients meeting the PAGAs during treatment and at 1-year follow-up experienced a 44% and 36% reduced hazard of mortality, respectively, in comparison to those not meeting the PAGAs; but as expected, precision decreased as the landmark time became shorter and data points were lost (Supplementary Table 1, available online).

Discussion

In this prospective observational study embedded in a SWOG clinical trial, we made 4 key observations that expand the current physical activity and breast cancer literature. First, high-risk breast cancer patients meeting the minimum PAGAs, both before and after diagnosis, experienced greater than 50% reduced hazards of recurrence and mortality compared with those not meeting the PAGAs at either time point. Second, patients not meeting the minimum PAGAs prior to diagnosis, but who reported meeting the PAGAs after treatment (ie, 2-year follow-up) experienced statistically significantly reduced hazards of recurrence and mortality in comparison to patients not meeting the PAGAs at that time. These findings have important implications in the clinical oncology setting because they suggest that a cancer diagnosis may serve as an impetus for increasing physical activity in some patients, and among these patients, beginning an exercise program after treatment completion resulted in a survival advantage. Third, in time-dependent analyses considering activity from all time points, striking inverse associations remained at all activity levels for mortality demonstrating that patients who consistently engaged in lower volumes of regular, weekly RPA experienced similar survival advantages as patients who met or exceeded the PAGAs. Lastly, the strong inverse relationship between prediagnosis RPA and outcomes among those meeting the recommended range of activity reveals the broader health impact of these findings by suggesting that even though exercise may not prevent breast cancer in all women, it is consistently associated with a survival advantage.

This is the first report of how pre- and postdiagnosis RPA participation measured before, during, and after chemotherapy

Table 5. Time-dependent multivariable risk models representing the associations of regular recreational physical activity sequentially measured before, during, and after treatment with disease recurrence and mortality in the Diet, Exercise, Lifestyle and Cancer Prognosis Study

		Disease recurrence		All-cause mortality	
Multivariable models*	Parameterization of recreational physical activity†	HR (95% CI)‡	*P*	HR (95% CI)‡	*P*
Minimally adjusted models	Any regular, weekly RPA				
	No	1.00 (Referent)		1.00 (Referent)	
	Yes	0.97 (0.72 to 1.29)	.81	0.37 (0.26 to 0.52)	<.001
	Meet the minimum PAGAs				
	No	1.00 (Referent)		1.00 (Referent)	
	Yes	1.01 (0.72 to 1.42)	.95	0.40 (0.27 to 0.61)	<.001
	Incremental activity categories (PAGAs)				
	No weekly RPA	1.00 (Referent)		1.00 (Referent)	
	Low weekly activity	0.90 (0.55 to 1.46)	.66	0.41 (0.24 to 0.68)	.001
	Moderate activity	1.01 (0.61 to 1.67)	.95	0.42 (0.23 to 0.76)	.004
	High activity	0.98 (0.63 to 1.54)	.95	0.31 (0.18 to 0.53)	<.001
Fully adjusted models	Any regular, weekly RPA				
	No	1.00 (Referent)		1.00 (Referent)	
	Yes	0.95 (0.71 to 1.29)	.75	0.38 (0.27 to 0.54)	<.001
	Meet the minimum PAGAs				
	No	1.00 (Referent)		1.00 (Referent)	
	Yes	1.00 (0.70 to 1.42)	.99	0.41 (0.27 to 0.63)	<.001
	Incremental activity categories (PAGAs)				
	No weekly RPA	1.00 (Referent)		1.00 (Referent)	
	Low weekly activity	0.89 (0.56 to 1.44)	.64	0.42 (0.25 to 0.69)	<001
	Moderate activity	1.06 (0.64 to 1.74)	.82	0.44 (0.24 to 0.80)	.007
	High activity	0.94 (0.60 to 1.49)	.80	0.31 (0.18 to 0.54)	<.001

[a]Minimally adjusted models are adjusted for age and stratified by treatment arm; fully adjusted models are adjusted for age, HER2 status, hormone receptor status, number of positive nodes, and stratified by treatment arm. CI = confidence interval; HR = hazard ratio; MET = metabolic equivalent of task; PAGAs = Physical Activity Guidelines for Americans; RPA = recreational physical activity.
[b]METs are expressed as average MET hours per week. Any regular, weekly RPA (yes/no) denotes at least 1 session per week throughout the exposure window assessed. Meeting the minimum PAGAs (yes/no) uses 8.3 MET hours per week as the cutoff and assumes the equivalent of 150 minutes per week of moderate-intensity activty, such as brisk walking at 3.0 miles per hour. Incremental physical activity levels are defined as inactive (reference group), low active (<8.3 MET hours per week), moderately active (8.3–16 MET hours per week), and high active (>16 MET hours per week).
[c]Time dependent models were used to estimate HRs and 95% CIs.

is associated with outcomes in high-risk breast cancer patients, expanding the current knowledge regarding the role of physical activity in breast cancer survivorship. The magnitudes of the associations observed herein for prediagnosis RPA are nearly identical to those previously reported (26,27). Additionally, time-dependent analyses showing patients meeting the minimum PAGAs experienced a 58%–60% reduced hazard of mortality are congruent with a report by Lahart et al. (27), who observed a 46% reduced hazard of all-cause mortality among survivors meeting the PAGAs after diagnosis.

Importantly, the finding suggesting that patients who began meeting the PAGAs after treatment experienced a statistically significant survival advantage coincides with previous work showing that inactive patients in the decade prior to diagnosis, who became active after diagnosis, experienced a statistically significantly reduced hazard of mortality in comparison to patients who remained inactive (41). Furthermore, the finding that lower volumes of activity were similarly protective as higher volumes of activity for overall survival is congruent with previous reports failing to show a linear dose–response association between RPA and cancer outcomes (41,48–50). Indeed, in the exercise science literature, it has been consistently reported that the association between RPA and health benefits is curvilinear (51), with the steepest increase in benefit occurring at the lower levels of activity and benefits plateauing or decreasing at higher levels of activity (51–53).

Few reports have described the association of pre- or postdiagnosis RPA with breast cancer recurrence, and the relationship remains poorly understood (11,21,25). The mixed findings regarding the RPA–disease recurrence association reported herein are not entirely surprising given that time-dependent models assess short-term effects (ie, HRs represent weighted averages of the association between RPA and recurrence for each exposure window prior to an event), whereas standard models assess long-term effects of RPA from one time point (44). Inconsistencies in the literature could also be the result of varying definitions of recurrence (ie, including or excluding mortality) or the general lack of well-designed prospective studies assessing this outcome. Notably, there is a growing recognition that recurrences are not suitable proxies for mortality because they are independent outcomes that may not associate with RPA through the same underlying mechanisms (28,54).

As previously summarized (41), the most commonly cited mechanisms explaining the associations of RPA with cancer outcomes include improved body composition, a decrease in the bioavailability of sex hormones, improved insulin sensitivity, decreased inflammation, improved adipokine milieu, improved immune surveillance, and improved DNA repair (28). Data from mechanistic studies have also demonstrated that aerobic exercise in tumor-bearing mice enhances sensitivity to chemotherapy through decreased hypoxia, resulting in the direct suppression of tumor growth and recurrence across several mouse models including mammary cancer (55,56). Additional studies suggest that myokines (eg, SPARC and calprotectin) secreted from contracting skeletal muscle prevent carcinogenesis through the promotion of autophagy, apoptosis, and antitumor

immunity, while preventing invasion and metastases (57). It is also plausible that regular exercise decreases breast cancer recurrence and mortality by way of blunted adrenergic signaling and subsequently blunted immunosuppression (58,59). Research has also shown that RPA is associated with decreased treatment toxicities, decreased depressive symptoms, decreased cancer-related fatigue, decreased pain, and improved sleep and overall quality of life (60–62), all which have been shown to contribute to improved clinical outcomes in cancer patients.

A primary strength of our study was the availability of pre- and postdiagnosis RPA assessed at multiple times. Reliance on prediagnosis RPA alone would not account for changes in activity throughout follow-up, and reliance on postdiagnosis RPA cannot rule out a reverse causation bias. Thus, the incorporation of exposure data collected at multiple times throughout survivorship and the use of joint-exposure and time-dependent analyses helps offset some of the potential biases that might ensue from examining RPA at only one time.

An important limitation of our study remains the reliance on self-reported RPA data, which can result in recall error and misclassification. Despite this potential limitation, the DELCaP questionnaire yielded the expected prevalence of physical (in)-activity (57), including decreased activity during treatment (31), and we observed similar associations as have been previously reported for pre- and postdiagnosis activity with all-cause mortality (44), thus reinforcing our confidence in these data.

Although we assessed the role of several potential confounders, we cannot entirely rule out the possibility that residual confounding by measured or unmeasured factors influenced our results. We cannot account for comorbidities such as cardiovascular disease, a major competing cause of death among older breast cancer patients, which may have developed after treatment completion (63). Relatedly, the primary outcome herein was all-cause mortality, which is also inversely associated with RPA. However, several recently published meta-analyses have demonstrated that the point estimates representing associations for all-cause and breast-cancer specific mortality with RPA are of similar magnitudes (26,27,64), suggesting that all-cause mortality is a suitable proxy for breast-cancer mortality. Because this was a clinical trial for high-risk patients who at enrollment had no comorbidities and had normal organ function and good performance status, competing causes of mortality may have been less likely to contribute to events in comparison to previous studies. However, we also acknowledge that because these were high-risk patients, RPA may have been unable to mitigate the biology of aggressive disease, while still exerting an overall survival advantage.

An additional limitation of the current work is that we cannot describe the clinical, demographic, or survival characteristics of the subcohort of patients who did not participate in DELCaP. It is possible that patients who did not enroll were sicker, less active, and more likely to experience an event, whereas patients who were more active and more likely to survive enrolled in the study. That is, fewer patients in the reference category would inflate the observed associations reported herein. To examine this possibility, we compared the 5-year survival experience of patients enrolled in DELCaP with the survival experience in the overall SWOG trial (33), and the differences between the 2 groups were slight. Survival rates were 89% in the trial compared with 88% in DELCaP, with event rates of 0.023 and 0.026, respectively. Thus, we observed no convincing evidence of a healthy survivor bias in the current analysis.

Consistently meeting the PAGAs before diagnosis and after treatment was associated with statistically significantly reduced hazards of recurrence and mortality among high-risk breast cancer patients enrolled in the DELCaP Study. When factoring in activity before diagnosis, during treatment, and at 1- and 2-year follow-ups, patients reporting lower volumes of activity experienced similar overall survival advantages as those who met the PAGAs. These findings have valuable clinical and public health implications because they provide additional evidence to solidify the message that low-volume activity is associated with statistically significant overall survival benefits and is superior to inactivity. This is particularly encouraging given that patients and survivors may be overwhelmed by the most current PAGAs recommending 150–300 minutes per week of moderate-intensity RPA or 3 days per week of at least 30 minutes of moderate-intensity structured aerobic exercise for cancer survivors (43,65).

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