Research Article

Cancer Prevention Research

Exercise After Diagnosis of Breast Cancer in Association with Survival

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Abstract

It has been suggested that exercise following breast cancer diagnosis is inversely associated with mortality. However, controversy exists regarding the causality of such associations. We evaluated associations of exercise after breast cancer diagnosis with total mortality and recurrence/disease-specific mortality, accounting for conditions that restrict exercise participation. The analysis included 4,826 women with stage I to III breast cancer identified 6 months after diagnosis through the population-based Shanghai Cancer Registry and recruited into the study between 2002 and 2006. Exercise was assessed approximately 6, 18, and 36 months postdiagnosis, and metabolic equivalent (MET) scores were derived. Information on medical history, cancer diagnosis, treatments, quality of life (QOL), anthropometrics, and lifestyles were obtained by in-person interviews at 6 months postdiagnosis. Medical charts were abstracted to verify clinical information. During the median follow-up of 4.3 years, 436 deaths and 450 recurrences/cancer-related deaths were documented. After adjustment for QOL, clinical prognostic factors, and other covariates, exercise during the first 36 months postdiagnosis was inversely associated with total mortality and recurrence/disease-specific mortality with HRs of 0.70 (95% CI: 0.56–0.88) and 0.60 (95% CI: 0.47–0.76), respectively. Significant dose–response relationships between total and recurrence/disease-specific mortality rates and exercise duration and MET scores were observed (all values for $P_{\text{trend}} < 0.05$). The exercise–mortality associations were not modified by menopausal status, comorbidity, QOL, or body size assessed at approximately 6 months postdiagnosis. An interaction between disease stage and hormone receptor status and total mortality was noted. Our study suggests that exercise after breast cancer diagnosis may improve overall and disease-free survival. *Cancer Prev Res; 4(9); 1409–18. ©2011 AACR.*

Introduction

Approximately 4.4 million women worldwide live with a diagnosis of breast cancer (1, 2). In the United States, there are currently more than 2 million breast cancer survivors, and the number continues to increase (3). Identifying modifiable lifestyle factors associated with prognosis could provide an additional means of improving outcomes for cancer survivors that both complement and extend the effects of pharmacologic treatments.

There is a growing body of evidence suggesting a link between exercise and breast cancer prognosis (4–14). Several studies, all conducted in Western countries, have evaluated the association of exercise after cancer diagnosis with breast cancer survival and provided some positive but inconsistent evidence (5, 7–9, 11–13, 15). Most studies assessed exercise at a single time point after cancer diagnosis (5, 7–9), even though exercise levels are known to vary over time after diagnosis (16). The major predictors of mortality, including cancer stage, progression of cancer, and poor quality of life (QOL; ref. 17), may limit exercise participation. These factors have not been adequately considered in previous studies. We have previously reported that exercise after cancer diagnosis is associated with improved QOL and decreased depression among breast cancer survivors (18, 19).

We present a detailed analysis of associations of exercise participation after breast cancer diagnosis with overall and disease-free survival, using data from a cohort study of 4,826 women diagnosed with stage I to III breast cancer in China, the Shanghai Breast Cancer Survival Study (SBCSS).

Materials and Methods

Study population

Details of the study design of the SBCSS have been described elsewhere (20). Briefly, through the population-based Shanghai Cancer Registry, we recruited 5,042

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incident breast cancer cases approximately 6 months after cancer diagnosis. Women were aged 20 to 75 years and were diagnosed between March 2002 and April 2006 (response rate, 80.0%). Study participants are being followed through in-person interviews administered approximately 18, 36, and 60 months after cancer diagnosis (20). Information on survival status is also obtained by annual linkage with the Shanghai Vital Statistics database.

We excluded cases with stage 0 ($n = 156$) and stage IV ($n = 28$) breast cancer from this study. To minimize the effect of existing and potential medical conditions and cancer treatments on exercise participation after cancer diagnosis, we also excluded cases or events (death, recurrence/metastasis) that occurred within the first year of follow-up. After excluding 32 cases who died during the 12-month period following cancer diagnosis, 4,826 women remained for the total mortality analysis. We further excluded from the recurrence analysis 315 cases (leaving 4,511 cases) who developed an event during the 12-month period following the cancer diagnosis. The study was approved by the Institutional Review Boards of all institutions involved, and all participants provided written informed consent prior to interview.

Survey interviews

In-person interviews were conducted to collect information on cancer diagnosis and treatment, sociodemographics, menstrual and reproductive history, diet, comorbidity, exercise, complementary and alternative medicine use, weight history, and QOL. In addition, height, weight, and waist and hip circumferences were measured at the baseline interview following a standard protocol. Body mass index (BMI) and waist-to-hip ratio were calculated on the basis of these measurements.

Disease- and treatment-related information, including stage of tumor-node-metastasis (TNM), estrogen receptor (ER) and progesterone receptor (PR) status, type of surgery, and chemotherapy, radiotherapy, immunotherapy, and tamoxifen use, was collected during in-person interviews and verified by reviewing medical charts. ER and PR status were included in the analyses in the following joint categories: ER^+/PR^+ (receptor-positive), ER^-/PR^- (receptor-negative), and ER^-/PR^+ or ER^+/PR^- (mixed). A Charlson comorbidity index was created on the basis of a validated comorbidity scoring system (21) and the diagnostic codes from the International Classification of Disease, 9th Revision (ICD-9; ref. 22).

Exercise assessment

At each interview, participants were asked whether they participated in exercise regularly (at least twice a week) or not. If the woman answered "Yes", she was further asked to report up to 5 of the most common activities in which she participated. At the baseline, 6-month postdiagnosis interview, women reported activities that took place during the 6 months preceding the interview. At subsequent interviews, women reported activities since the last interview (i.e., for the preceding 12 or 18 months). No women reported participating in more than 4 types of exercise during the first 18 months after diagnosis, and only 0.1% of women engaged in 5 types of exercise at the 36-month postdiagnosis interview. The 60-month postdiagnosis interviews are still ongoing; thus, the current analyses include only information from the first 36 months postdiagnosis.

Information on frequency and duration was obtained for all exercise activities. Each activity was assigned a metabolic equivalent (MET) score [3 MET-hours is equivalent to an average walking pace (2–2.5 mph) for 1 hour; 2 MET-hours is equal to moderate bicycling for half an hour], based on the method proposed by Ainsworth and colleagues (23). The score for MET-hours per week for each activity was calculated from the hours per week the participant reported engaging in that activity multiplied by the assigned MET score. The values from individual activities were summed to derive a total exercise MET score. The exercise questionnaire has been validated (24). Significant correlations between exercise measurements derived from the exercise questionnaire and criterion measures [e.g., physical activity log ($r = 0.74$) and 7-day physical activity questionnaire survey] were observed. The reproducibility of exercise participation ($\kappa = 0.64$) was reasonably high (24).

Assessment of other lifestyle factors and QOL

Habitual dietary intakes, tea and alcohol consumption, and smoking habits were also obtained through in-person interviews using validated questionnaires at baseline (19, 25).

The SBCSS was originally designed to recruit 2,250 breast cancer patients and was expanded to include about 5,000 patients. Two QOL instruments, the General Quality of Life Inventory-74 (GQOLI-74) and the 36-item Short Form Health Survey (SF-36), were administered as part of the 6-month postdiagnosis interview. The GQOLI-74 was administered first (44.2% cases) and the SF-36 second (55.8% cases). Women's responses on the 2 QOL instruments were converted to scores on a 0 to 100 scale, with higher scores reflecting better QOL. The GQOLI-74 has shown a satisfactory level of reliability and validity (26). Details about the GQOLI-74 have been described in our previous reports (27). The SF-36 has been used in epidemiologic studies of breast cancer patients and survivors (28, 29) and has been validated in the Chinese population (30). The instrument-specific QOL distribution of general health was used to categorize the QOL scores. The mean QOL score for general health on the GQOLI-74 was comparable with that on the SF-36 (score: 56.2 vs. 56.0) in this study.

Statistical analyses

Differences in sociodemographic and medical characteristics between exercisers and nonexercisers at baseline were evaluated using Student's t test or the χ^2 test. The endpoints for the analyses were any death for total mortality (overall survival analysis) and cancer recurrence/metastasis or death related to breast cancer for recurrence/disease-specific mortality (disease-free survival analysis).

Table 1. Sociodemographic and clinical characteristics of breast cancer cases at study enrollment

Characteristic	Total (n = 4,826)[a]	Exercisers (n = 3,115)[a]	Nonexercisers (n = 1,711)[a]	P^b
Age at diagnosis, y	53.5 (10.0)	53.4 (10.0)	53.6 (10.1)	0.452
Education, %				
<High school	46.5	45.0	49.2	0.003
High school	37.6	38.0	37.0	
>High school	15.9	17.1	13.8	
Income (yuan/mo/capita), %				
<1,000	57.7	56.5	59.9	0.008
1,000–1,999	30.4	30.6	30.0	
≥2,000	11.9	12.9	10.1	
Married/living with partner, %	88.0	88.1	87.8	0.801
Interval from diagnosis to study enrollment, mo	6.5 (0.7)	6.5 (0.7)	6.5 (0.8)	0.755
Charlson comorbidity index ≥1	19.8	19.5	20.5	0.377
TNM stage, %				
I	34.8	36.4	31.9	<0.001[c]
IIa	33.9	34.0	33.8	
IIb	17.2	16.5	18.4	
III	9.4	8.4	11.2	
Unknown	4.7	4.7	4.9	
ER/PR status, %				
Positive (ER^+/PR^+)	50.3	50.2	50.3	0.651[c]
Negative (ER^-/PR^-)	27.4	27.1	27.9	
Mixed (ER^+/PR^- or ER^-/PR^+)	20.4	20.8	19.8	
Unknown	1.9	1.8	2.0	
Ever received chemotherapy, %	92.2	91.2	94.0	<0.001
Ever received radiotherapy, %	32.4	29.6	37.5	<0.001
Ever received immunotherapy, %	14.8	15.1	14.4	0.580
Ever used tamoxifen, %	51.9	54.3	48.0	<0.001
Type of surgery, %				
Mastectomy	94.1	94.7	93.8	0.352
Conservation	2.6	2.5	2.8	
Others	3.0	2.8	3.3	
Family history of breast cancer, %	5.6	5.5	5.7	0.695
BMI, kg/m^2	24.1 (3.4)	24.1 (3.3)	24.2 (3.6)	0.174
Waist-to-hip ratio	0.83 (0.05)	0.83 (0.05)	0.84 (0.06)	<0.001
Cigarette smoking, %	2.6	2.2	3.3	0.020
Alcohol consumption, %	3.1	2.9	3.5	0.271
Tea consumption, %	23.6	25.3	20.5	<0.001
Postmenopausal, %	51.1	51.1	51.2	0.935
Meat intake, g/d	82.7 (57.8)	83.6 (56.8)	81.1 (59.0)	0.148
Cruciferous vegetable intake, g/d	74.6 (53.0)	78.3 (52.1)	68.0 (54.0)	<0.001
Soy protein intake, g/d	11.4 (8.6)	12.0 (8.8)	10.1 (8.0)	<0.001
QOL score	58.1 (14.2)	59.3 (13.6)	55.9 (14.9)	<0.001

[a]Unless otherwise specified, means (SD) are presented.
[b]For tests of differences between women with and without exercise participation.
[c]For the χ^2 test, "unknown" group was excluded.

Survival rates were calculated starting at the time of cancer diagnosis to the endpoints of the study, censoring at the date of last contact or noncancer death (for disease-free survival only). The Kaplan–Meier method was used to generate survival curves for a preliminary examination of the data. The log-rank tests were applied to evaluate differences in survival rates for women with different exercise levels.

Multivariable Cox proportional hazards models were used to estimate the HRs and 95% CIs in association with exercise participation. Exercise was treated as a time-dependent variable. Survival was modeled as a function of age at entry into and exit from the study. Entry time was defined as age at cancer diagnosis and exit time was defined as age at death or censoring (31). The following covariates were related to exposure (exercise) or outcome (mortality) and were adjusted for: education; income; menopausal status; BMI; waist-to-hip ratio; QOL; intakes of cruciferous vegetables and soy protein; tea consumption; use of chemotherapy, radiotherapy, or tamoxifen; TNM stage; and ER/PR status. Type of surgery and immunotherapy were not related to exercise or mortality and were not included in the models. Regular exercisers were categorized by 2.5 hours per week and 8.3 MET-hours per week, the medians for exercise duration and exercise-MET score at 6 months postdiagnosis, levels similar to recent recommendations for physical activity for Americans and for cancer patients (32). Analyses of mortality and exercise participation over the first 36 months postdiagnosis were further stratified by TNM stage, ER/PR status, menopausal status, QOL, BMI, waist-to-hip ratio, comorbidity, and cancer-related treatments.

Tests for trend were conducted by entering the categorical variables as continuous parameters in the corresponding models. Tests for effect modification were examined on a multiplicative scale. All tests were conducted by using Statistical Analysis Software (SAS, version 9.1; SAS Institute, Inc.). The significance levels were set at $P < 0.05$ for 2-sided analyses.

Results

During the median follow-up period of 4.3 years, 436 deaths and 450 recurrences or breast cancer-related deaths were documented. At 6 months postdiagnosis, 65% of women reported exercising regularly with a median of 8.3 MET-hours per week of exercise. The corresponding rates were 74% (median MET = 15.4) and 74% (median MET = 15.8) at 18 and 36 months postdiagnosis, respectively. At 6 months postdiagnosis, women engaged in an average of 1.5 exercise activities. Walking was the most common type of regular exercise carried out in this study population (52%), followed by gymnastics (14%), body building (7%), and traditional Chinese exercises (5%, including Qigong and Tai Chi). Similar results were observed at 18 and 36 months postdiagnosis.

At baseline, exercisers had higher levels of education and household income, were more likely to have earlier-stage disease, to have used tamoxifen, and had higher QOL than nonexercisers (Table 1). In addition, exercisers had lower waist-to-hip ratio and higher intakes of meats, cruciferous vegetables, soy protein, and tea. Women who engaged in exercise regularly during the first 6 months postdiagnosis had higher overall (Fig. 1) and disease-free (Fig. 2) survival rates than nonexercisers. After adjustment for QOL, clinical factors, and other confounders, the HRs were 0.80 (95% CI: 0.65–0.97) for total mortality and 0.91 (95% CI: 0.75–1.11) for recurrence/breast cancer–related mortality

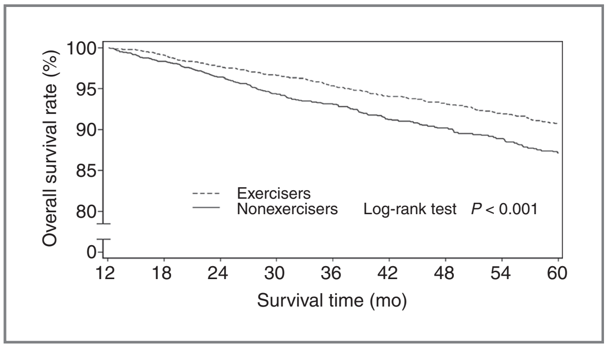

Figure 1. Overall survival curves among Chinese women diagnosed with breast cancer by regular exercise participation during the first 6 months after breast cancer diagnosis (n = 4,826).

for those who exercised regularly during the first 6 months postdiagnosis compared with nonexercisers (Table 2). When exercise levels during the first 18- and 36-month postdiagnosis periods were taken into consideration, a dose–response relationship was observed for both overall and disease-free survival rates (all $P_{\text{trend}} < 0.05$).

Table 3 presents associations of exercise over the first 36 months postdiagnosis with mortality stratified by TNM stage and ER/PR status. An inverse association between exercise and total mortality was observed among women with early (I–IIa) and advanced disease stage (IIb–III), although the trend test was only significant for the latter. Exercise was significantly associated with recurrence/disease-specific mortality, regardless of disease stage. Exercise was associated with reduced total mortality only among women with ER/PR-negative, but not ER/PR-positive, cancer ($P_{\text{interaction}} = 0.004$). No significant interaction was observed for recurrence/disease-specific mortality.

Associations of exercise with total mortality and recurrence/disease-specific mortality were not modified by menopausal status, BMI, or comorbidity (Table 4), nor were associations of mortality modified by waist-to-hip ratio, chemotherapy, radiotherapy, or tamoxifen use (data not shown).

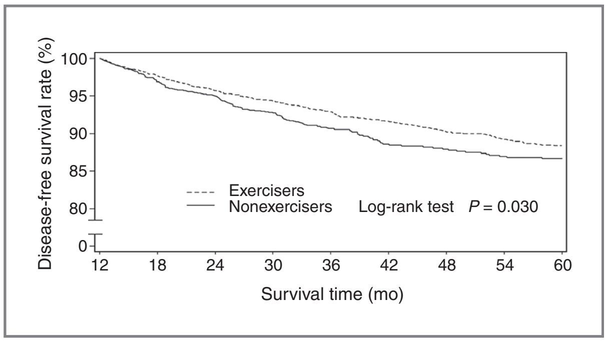

Figure 2. Disease-free survival curves among Chinese women diagnosed with breast cancer by regular exercise participation during the first 6 months after breast cancer diagnosis (n = 4,511).

Table 2. Associations of exercise after breast cancer diagnosis with total mortality and relapse/disease-specific mortality

Characteristics	Total	Events	HR (95% CI)		
			First 6 mo postdiagnosis[a]	First 18 mo postdiagnosis[b]	First 36 mo postdiagnosis[b]
Total mortality	4,826	436			
Exercise participation					
No	1,711	185	1.00	1.00	1.00
Yes	3,115	251	0.80 (0.65–0.97)	0.70 (0.56–0.87)	0.70 (0.56–0.88)
Exercise participation per week, h					
No exercise	1,711	185	1.00	1.00	1.00
<2.5	1,654	126	0.78 (0.62–0.98)	0.75 (0.59–0.96)	0.84 (0.66–1.08)
≥2.5	1,461	125	0.82 (0.64–1.04)	0.66 (0.51–0.84)	0.64 (0.49–0.82)
P_{trend}			0.168	0.004	0.002
Exercise energy expenditure, MET-hours per week					
No exercise	1,711	185	1.00	1.00	1.00
<8.3	1,566	122	0.79 (0.63–0.99)	0.77 (0.60–0.99)	0.81 (0.63–1.05)
≥8.3	1,549	129	0.80 (0.63–1.02)	0.65 (0.51–0.83)	0.65 (0.51–0.84)
P_{trend}			0.198	0.004	<0.001
Relapse/disease-specific mortality	4,511	450			
Exercise participation					
No	1,580	174	1.00	1.00	1.00
Yes	2,931	276	0.91 (0.75–1.11)	0.71 (0.57–0.90)	0.60 (0.47–0.76)
Exercise participation per week, h					
No exercise	1,580	174	1.00	1.00	1.00
<2.5	1,552	133	0.84 (0.66–1.05)	0.70 (0.54–0.90)	0.63 (0.48–0.82)
≥2.5	1,379	143	1.01 (0.80–1.27)	0.73 (0.57–0.94)	0.57 (0.44–0.74)
P_{trend}			0.522	0.341	0.030
Exercise energy expenditure, MET-hours per week					
No exercise	1,580	174	1.00	1.00	1.00
<8.3	1,468	128	0.85 (0.67–1.07)	0.70 (0.54–0.91)	0.60 (0.46–0.78)
≥8.3	1,463	148	0.98 (0.78–1.24)	0.72 (0.57–0.93)	0.59 (0.45–0.76)
P_{trend}			0.471	0.324	0.006

[a]Adjusted for date of birth, BMI at baseline, waist-to-hip ratio at baseline, menopausal status, income, education, QOL, cruciferous vegetable intake, soy protein intake, tea consumption, chemotherapy, radiotherapy, tamoxifen use, TNM status, and ER/PR status.
[b]Adjusted for the same variables as above, but exercise was treated as a time-dependent variable.

Discussion

Exercise may affect breast cancer prognosis by enhancing immune function and reducing levels of estrogen and growth factors, insulin resistance, and hyperinsulinemia and by decreasing depression and increasing QOL (18, 19, 33–35). In this large, population-based cohort study, we found that regular exercise after breast cancer diagnosis was significantly associated with improved overall and disease-free survival following a dose–response pattern. We also observed that breast cancer patients increased their participation in exercise or their level of exercise over the first 36 months postdiagnosis. The exercise–survival association varied little by type of cancer-related treatment, BMI, QOL, comorbidity, or menopausal status and was more evident among women with advanced disease stage and with ER/PR-negative breast cancer.

The effect of postdiagnosis exercise on breast cancer survival has drawn considerable attention in recent years, because exercise is a modifiable behavior (5, 7–9, 11, 36). The Nurses' Health Study (NHS) reported a decreased risk of breast cancer-related death among stage I to III breast cancer patients participating in physical activity at levels comparable with our study (5). The Life After Cancer Epidemiology (LACE) study and another recent U.S. study also found that women with higher levels of recreational physical activity after diagnosis had decreased risk of mortality from breast cancer (9). However, the Women's Healthy Eating and Living (WHEL) study found that only when combined with higher fruit and vegetable intakes was exercise at 2 years postdiagnosis associated with favorable

Table 3. Associations of exercise over the first 36 months after breast cancer diagnosis with total mortality and relapse/disease-specific mortality, stratified by disease stage and hormone receptor status

	Total mortality			Relapse/disease-specific mortality		
	Total	Events	HR (95% CI)	Total	Events	HR (95% CI)
Stratified by TNM[a]						
TNM I–IIa stage	3,316	166		3,124	190	
MET-hours per week[b]						
No exercise	1,123	67	1.00	1,044	69	1.00
<8.3	1,097	44	0.79 (0.51–1.22)	1,032	50	0.52 (0.32–0.80)
≥8.3	1,096	55	0.89 (0.59–1.36)	1,048	71	0.62 (0.41–0.92)
P_{trend}			0.333			0.444
TNM IIb–III stage	1,282	249		1,176	241	
MET-hours per week[b]						
No exercise	505	110	1.00	461	102	1.00
<8.3	395	73	0.83 (0.60–1.15)	364	71	0.57 (0.40–0.82)
≥8.3	382	66	0.52 (0.37–0.72)	351	68	0.45 (0.32–0.64)
P_{trend}			<0.001			<0.002
$P_{interaction}$			0.037			0.218
Stratified by ER/PR[c]						
ER^+PR^+ (positive)	2,426	161		2,308	189	
MET-hours per week[b]						
No exercise	861	70	1.00	815	80	1.00
<8.3	809	39	1.41 (0.87–2.27)	771	46	0.72 (0.47–1.12)
≥8.3	756	52	1.32 (0.83–2.12)	722	63	0.79 (0.53–1.19)
P_{trend}			0.935			0.540
ER^-PR^- (negative)	1,323	171		1,213	155	
MET-hours per week[b]						
No exercise	478	76	1.00	428	62	1.00
<8.3	429	50	0.58 (0.39–0.86)	392	45	0.40 (0.25–0.63)
≥8.3	416	45	0.40 (0.29–0.59)	393	48	0.36 (0.24–0.56)
P_{trend}			<0.001			0.002
ER^+PR^-/ER^-PR^+ (mixed)	986	87		911	94	
MET-hours per week[b]						
No exercise	338	31	1.00	308	28	1.00
<8.3	299	28	0.78 (0.42–1.43)	282	32	0.62 (0.32–1.23)
≥8.3	349	28	0.67 (0.36–1.22)	321	34	0.51 (0.27–1.00)
P_{trend}			0.051			0.166
$P_{interaction}$			0.004			0.375

[a]Adjusted for date of birth, BMI at baseline, waist-to-hip ratio at baseline, menopausal status, income, education, QOL, cruciferous vegetable intake, soy protein intake, tea consumption, chemotherapy, radiotherapy, tamoxifen use, and ER/PR receptor status.
[b]Exercise was treated as a time-dependent variable.
[c]Further adjusted for TNM status instead of ER/PR receptor status.

survival (7). A small study of 603 breast cancer patients in Canada showed no association of breast cancer survival with exercise shortly after surgery (36). Most previous studies were based on a single-exercise measurement at or after cancer diagnosis (7–9, 11, 36). In our study, exercise was assessed at multiple time points after cancer diagnosis. In addition, we accounted for the possible confounding effect of QOL and other lifestyle factors. Although we cannot completely rule out chance findings caused by other confounders, the consistency of the association and the dose–response pattern we found provide the strongest epidemiologic evidence to date that exercise after breast cancer diagnosis is associated with improved overall and disease-free survival.

In our study, walking and other moderate exercises (e.g., Tai Chi) were the most common types of exercise. Consistent with our findings, Irwin and colleagues reported that among 933 U.S. women with breast cancer, exercising the recommended amounts of 2.5 hours per week of moderate-intensity physical activity compared

Table 4. Associations of exercise over the first 36 months after breast cancer diagnosis with total mortality and relapse/disease-specific mortality, stratified by menopausal status, QOL, and BMI

	Total mortality			Relapse/disease-specific mortality		
	Total	Events	HR (95% CI)	Total	Events	HR (95% CI)
Stratified by menopausal status[a]						
Premenopause	2,359	186		2,202	208	
MET-hours per week[b]						
No exercise	835	76	1.00	773	81	1.00
<8.3	764	49	0.87 (0.58–1.10)	714	55	0.59 (0.39–0.89)
≥8.3	760	61	0.86 (0.58–1.26)	715	72	0.69 (0.47–1.00)
P_{trend}			0.317			0.631
Postmenopause	2,467	250		2,309	242	
MET-hours per week[b]						
No exercise	876	109	1.00	807	93	1.00
<8.3	802	73	0.82 (0.59–1.14)	754	73	0.63 (0.44–0.91)
≥8.3	789	68	0.55 (0.40–0.77)	748	76	0.52 (0.36–0.74)
P_{trend}			<0.001			0.001
$P_{interaction}$			0.233			0.300
Stratified by QOL[c]						
QOL < median	2,278	205		2,138	222	
MET-hours per week[b]						
No exercise	902	101	1.00	827	99	1.00
<8.3	723	56	0.63 (0.44–0.90)	681	59	0.45 (0.31–0.65)
≥8.3	653	48	0.50 (0.35–0.71)	630	64	0.47 (0.33–0.66)
P_{trend}			<0.001			0.006
QOL ≥ median	2,548	231		2,373	228	
MET-hours per week[b]						
No exercise	809	84	1.00	753	75	1.00
<8.3	843	66	1.06 (0.73–1.55)	787	69	0.80 (0.53–1.21)
≥8.3	896	81	0.83 (0.58–1.21)	833	84	0.74 (0.50–1.10)
P_{trend}			0.111			0.289
$P_{interaction}$			0.294			0.218
Stratified by BMI[d]						
BMI<25	3,128	267		2,914	266	
MET-hours per week[b]						
No exercise	1,102	113	1.00	1,015	98	1.00
<8.3	999	76	0.76 (0.55–1.05)	932	81	0.70 (0.47–0.96)
≥8.3	1,027	78	0.62 (0.45–0.85)	967	87	0.66 (0.47–0.94)
P_{trend}			0.002			0.033
BMI ≥ 25	1,698	169		1,597	184	
MET-hours per week[b]						
No exercise	609	72	1.00	565	76	1.00
<8.3	567	46	0.91 (0.60–1.38)	536	47	0.53 (0.35–0.81)
≥8.3	522	51	0.70 (0.46–1.05)	496	61	0.50 (0.38–0.74)
P_{trend}			0.027			0.095
$P_{interaction}$			0.642			0.704
Stratified by Charlson comorbidity index						
Charlson comorbidity index <1	3,869	339		3,601	350	
MET-hours per week[b]						
No exercise	1,360	138	1.00	1,253	133	1.00
<8.3	1,258	98	0.89 (0.66,1.18)	1,172	101	0.65 (0.47–0.89)
≥8.3	1,251	103	0.68 (0.50–0.90)	1,176	116	0.66 (0.49–0.90)
P_{trend}			0.003			0.162

(Continued on the following page)

Table 4. Associations of exercise over the first 36 months after breast cancer diagnosis with total mortality and relapse/disease-specific mortality, stratified by menopausal status, QOL, and BMI (Cont'd)

	Total mortality			Relapse/disease-specific mortality		
	Total	Events	HR (95% CI)	Total	Events	HR (95% CI)
Charlson comorbidity index ≥1	957	97		910	100	
MET-hours per week[b]						
No exercise	351	47	1.00	327	41	1.00
<8.3	308	24	0.63 (0.36–1.10)	296	27	0.49 (0.26–0.78)
≥8.3	298	26	0.62 (0.37–1.05)	287	32	0.39 (0.23–0.66)
P_{trend}			0.050			0.009
$P_{interaction}$			0.198			0.651

[a]Adjusted for date of birth, BMI at baseline, waist-to-hip ratio at baseline, income, education, QOL, cruciferous vegetable intake, soy protein intake, tea consumption, chemotherapy, radiotherapy, tamoxifen use, TNM status, and ER/PR receptor status.
[b]Exercise was treated as a time-dependent variable.
[c]Further adjusted for TNM status instead of QOL.
[d]Further adjusted for QOL instead of BMI.

with no exercise was associated with 67% decreased risk of death (11).

As with any study of exercise and mortality, there is a concern that low levels of exercise may be the result, rather than the cause, of a health condition that creates a predisposition to mortality. Breast cancer patients with late-stage or more aggressive forms of cancer may be too fatigued to participate in exercise during the period of active chemotherapy and radiotherapy (16, 37). To minimize this concern, we excluded women with stage IV breast cancer from the analyses. We also carefully evaluated the confounding and modifying effects of TNM stage, ER/PR status, QOL, comorbidity, and other covariates in our analyses. We observed strong associations among women with relatively advanced stage (IIb–III) and ER/PR-negative breast cancer, which supports a possible role for reverse causation. However, we found no evidence of significant interaction for QOL, comorbidity, or cancer-related treatment.

Several studies have reported a potential effect modification of hormone receptor status on the exercise–survival association (5, 7, 11). The Health, Eating, Activity, and Lifestyle (HEAL) study found a strong benefit of physical activity among women with ER-positive breast cancer (11), consistent with findings from the NHS (5). The WHEL study reported no survival advantage for ER/PR-negative breast cancer, a borderline advantage for ER^-/PR^+, and significant benefits for ER^+/PR^- and ER/PR-positive cancers (7). None of these studies had adequate statistical power to investigate ER/PR-negative breast cancer. In our study, we found stronger associations among women with ER/PR-negative breast cancer. Studies with large sample sizes are needed to address the possible differential effect of exercise on outcomes for subtypes of breast cancer.

The potential modifying effect of body size on the associations between exercise and breast cancer survival has been evaluated in several studies with inconsistent findings (5, 6, 8, 9, 13). The California Teachers Study reported that recreational physical activity was associated with lower risk for breast cancer–related death only among overweight women (13). Holick and colleagues also found a stronger effect of postdiagnosis recreational physical activity on breast cancer survival for women with a BMI of 25 or more, although no interaction was detected (8). In contrast, the LACE study reported a reduced risk of all-cause mortality associated with physical activity in women with a BMI less than 25, but not in overweight/obese women (9). In our study, we found little evidence that BMI or waist-to-hip ratio modified the exercise–survival association, although the prevalence of overweight and obesity was relatively lower (29.5% and 5.6%, respectively) than that in Western populations.

Our study has several strengths. First, it was designed specifically to evaluate the effect of postdiagnosis exercise on breast cancer prognosis. The population-based study design and the high response rate minimized selection bias. Second, multiple exercise assessments were implemented and detailed exercise information was collected. Third, information on sociodemographics, medical and lifestyle factors, QOL, and anthropometrics was collected using structured and/or validated questionnaires by health care professionals and was adjusted for in the analyses.

Our study also has limitations. First, exercise information was self-reported, which can be subject to recall bias or overreporting. However, our validation study indicated that the self-reported exercise questionnaire has high validity (24). Self-reported physical activity has been used widely in epidemiologic studies of breast cancer patients and survivors (5, 8, 9, 13). Second, 2 different QOL instruments were applied. However, we found that the average total QOL scores derived from these 2 measurements were comparable and should be sufficient for adjustment. Third, although chemotherapy and tamoxifen use rates differ from rates in the United States, they are in agreement with findings from previous independent research conducted in the same population (27). Systemic adjuvant therapy is commonly used in China for women with either early or advanced disease, but the rate of hormone therapy use, usually applied after chemotherapy and radiotherapy, is low in China (38). Not being able to investigate the influence of exercise changes from pre- to post–cancer diagnosis on survival outcomes is another limitation. Finally, the median of our follow-up period was less than 5 years, which is relatively short. Ongoing follow-up of our cohort will allow us to evaluate the long-term effect of exercise on breast cancer prognosis.

In summary, our study provides strong epidemiologic evidence that regular exercise during the first 3 years after cancer diagnosis, particularly at the currently recommended levels for breast cancer survivors of 2.5 hours per week for exercise duration and 8.3 MET-hours per week for exercise-MET score or higher (32, 39), has a beneficial effect on breast cancer survival. Health care professionals should encourage their patients to engage in regular exercise in accordance with current recommendations (32, 39) and guidelines for safe and effective exercise (39). Our finding of an increase in exercise participation or level among Chinese breast cancer survivors suggests that this goal is achievable.

Disclosure of Potential Conflicts of Interest

The authors have no conflicts of interest to disclose.

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