Physical Activity and Survival After Breast Cancer Diagnosis

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Context Physical activity has been shown to decrease the incidence of breast cancer, but the effect on recurrence or survival after a breast cancer diagnosis is not known.

Objective To determine whether physical activity among women with breast cancer decreases their risk of death from breast cancer compared with more sedentary women.

Design, Setting, and Participants Prospective observational study based on responses from 2987 female registered nurses in the Nurses' Health Study who were diagnosed with stage I, II, or III breast cancer between 1984 and 1998 and who were followed up until death or June 2002, whichever came first.

Main Outcome Measure Breast cancer mortality risk according to physical activity category (<3, 3-8.9, 9-14.9, 15-23.9, or ≥24 metabolic equivalent task [MET] hours per week).

Results Compared with women who engaged in less than 3 MET-hours per week of physical activity, the adjusted relative risk (RR) of death from breast cancer was 0.80 (95% confidence interval [CI], 0.60-1.06) for 3 to 8.9 MET-hours per week; 0.50 (95% CI, 0.31-0.82) for 9 to 14.9 MET-hours per week; 0.56 (95% CI, 0.38-0.84) for 15 to 23.9 MET-hours per week; and 0.60 (95% CI, 0.40-0.89) for 24 or more MET-hours per week (*P* for trend = .004). Three MET-hours is equivalent to walking at average pace of 2 to 2.9 mph for 1 hour. The benefit of physical activity was particularly apparent among women with hormone-responsive tumors. The RR of breast cancer death for women with hormone-responsive tumors who engaged in 9 or more MET-hours per week of activity compared with women with hormone-responsive tumors who engaged in less than 9 MET-hours per week was 0.50 (95% CI, 0.34-0.74). Compared with women who engaged in less than 3 MET-hours per week of activity, the absolute unadjusted mortality risk reduction was 6% at 10 years for women who engaged in 9 or more MET-hours per week.

Conclusions Physical activity after a breast cancer diagnosis may reduce the risk of death from this disease. The greatest benefit occurred in women who performed the equivalent of walking 3 to 5 hours per week at an average pace, with little evidence of a correlation between increased benefit and greater energy expenditure. Women with breast cancer who follow US physical activity recommendations may improve their survival.

JAMA. 2005;293:2479-2486 www.jama.com

PHYSICAL ACTIVITY AFTER A breast cancer diagnosis has been strongly linked to improved quality of life.[1-3] There is reason to believe that physical activity might extend survival in women with breast cancer.

Physical activity also has been linked to a lower risk of breast cancer. An expert panel of the International Agency for Research on Cancer of the World Health Organization estimated a 20% to 40% decrease in the risk of developing breast cancer among the most physically active women, regardless of menopausal status, type, or intensity of activity.[4]

Physical activity has been linked to lower levels of circulating ovarian hormones, which may explain the relationship between physical activity and breast cancer.[5-7] Lower estrogen levels among physically active women with breast cancer could potentially improve survival, although few data exist to support this hypothesis.[8,9]

Lack of physical activity has been shown to be related to weight gain during breast cancer survival.[10] Weight gain after a breast cancer diagnosis is a common adverse effect of treatment.[10-12] This is important because both being overweight at the time of breast cancer diagnosis[13-21] and weight gain after diagnosis[14,22] are linked to poorer survival in many studies. Lack of physical activity is believed to be as important a factor as changes in food intake in the ongoing obesity epidemic.[23]

Few have studied associations between physical activity and survival and no studies have assessed physical activity level after diagnosis. Rohan et al[24] found no association between physical activity before diagnosis and survival in a population-based prospective study of 412 women with breast cancer. We hypothesized that higher levels of physical activity after a breast cancer diagnosis would be associated with longer survival.

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METHODS

Study Participants

In 1976, the Nurses' Health Study (NHS) cohort was established when 121 700 female registered nurses from across the United States, aged 30 to 55 years, answered a mailed questionnaire on risk factors for cancer and cardiovascular disease. Follow-up questionnaires have been sent every 2 years until 2004 to the NHS participants. This study was approved by the human subjects committee at Brigham and Women's Hospital in Boston, Mass. Completion of the self-administered questionnaires was considered to imply informed consent.

Measurement of Breast Cancer

In the NHS, incident breast cancer was ascertained by biennial mailing of the questionnaire to participants. For any report of breast cancer, written permission was obtained from study participants to review their medical records. Physicians, blinded to exposure information from questionnaires, subsequently reviewed medical records and pathology reports. Overall, 99% of self-reported invasive breast cancers for which medical records were obtained have been confirmed. The individuals in this analysis were NHS participants with stages I, II, or III invasive breast cancer that was diagnosed between 1984 and 1998. The 1984 start date was chosen to assess physical activity at least 2 years after diagnosis and physical activity was first assessed as MET-hours per week in 1986.

Measurement of Mortality

Women were followed up until death or June 2002, whichever came first. Ascertainment of deaths included reporting by the family or postal authorities. In addition, the names of persistent nonresponders were searched in the National Death Index,[25] which has been shown to be a reliable resource.[26] The cause of death was assigned by physician reviewers. In the case of a woman who died from breast cancer not previously reported, medical records were obtained to record details of her breast cancer diagnosis. More than 98% of deaths in the NHS have been identified by these methods.[27]

Measurement of Breast Cancer Recurrence

If, after having a breast cancer diagnosis, women reported a second cancer diagnosis on a routine NHS follow-up, it was assumed that breast cancer recurred if cancer was reported in the lung, liver, bone, or brain because these are the most common sites of recurrence. In addition, women who died from breast cancer were considered to have had a breast cancer recurrence 2 years prior to death. The numbers of cases of recurrent breast cancer calculated in this manner are similar to the numbers expected given the recurrence rates found in a large (N=5569) trial of early stage breast cancer.[28]

Exclusions

Women were excluded if they were diagnosed with breast or any other cancer (other than nonmelanoma skin cancer) prior to 1984, missing information on physical activity at least 2 years after diagnosis or unable to walk, or had stage IV disease at diagnosis. Women with 4 or more positive nodes but who lacked a complete metastatic workup were also excluded because of concerns about occult metastatic disease. A complete metastatic workup consisted of a negative chest x-ray (or chest computed tomographic scan), bone scan, and liver function tests (or liver scan) or documentation from a treating physician that the patient did not have metastatic disease. Women were also excluded if information on disease stage was missing. No women had implausible levels of physical activity, which was defined as more than 100 MET-hours per week.

Exposure Assessment

We assessed leisure-time physical activity in MET-hours per week beginning in 1986. Women were asked: "During the past year, what was your average time per week spent at each of the following activities?" Choices included the following 8 activities: walking or hiking outdoors (including walking while playing golf); jogging (>10 minutes per mile); running (≤10 minutes per mile); bicycling (including stationary bike); swimming laps; tennis; calisthenics, aerobics, aerobic dance, or rowing machine; or squash or racquetball. These activities were the most common ones reported by women in the College Alumni Health Study.[29] To characterize duration, women chose 1 of 11 categories ranging from zero to 11 or more hours per week. In addition, participants were asked their usual walking pace: easy or casual (<2 mph), normal or average (2-2.9 mph), brisk (3-3.9 mph), very brisk (≥4 mph), or unable to walk. Physical activity was reassessed in 1988, 1992, 1994, 1996, 1998, and 2000. The 1992 through 2000 questionnaires included other vigorous activities (eg, lawn mowing) and lower-intensity exercise (eg, yoga, stretching). For this analysis, the first physical activity assessment collected at least 2 years after the breast cancer diagnosis was used to avoid assessment during the period of active treatment. Although only women with stage I, II, and III disease were included in these analyses, it is presumed that those who eventually died from breast cancer first experienced metastatic disease. To avoid bias due to declining physical activity immediately prior to and after diagnosis with metastatic breast cancer, physical activity was not updated.

Each activity on the questionnaire was assigned a metabolic equivalent task (MET) score based on the classification by Ainsworth et al.[30] One MET is the energy expenditure for sitting quietly. MET scores for specific activities are defined as the ratio of the metabolic rate associated with that activity divided by the resting metabolic rate. For example, walking at an average pace was assigned an MET score of 3; jogging, 7; and running, 12. MET scores for walking were assigned based on the pace reported; for other activities, a leisurely to moderate intensity score was selected. The scores for MET-hours per week for each activity were calculated from the reported hours per week engaged in that activity multiplied by the assigned MET score. The values from the individual activities were summed for a total MET-hours per week score. Categories of MET-hours per week were defined as less than 3, 3 to 8.9, 9 to 14.9, 15 to 23.9, and 24 or more. These categories were chosen to correspond to the equivalent of less than 1, 1 to less than 3, 3 to less than 5, 5 to less than 8, and 8 or more hours per week of walking at an average pace. Walking was the most popular activity in this cohort, contributing 66% of the total MET-hours per week.[31]

The ability of the activity questionnaire to assess total activity over the previous year was tested in a sample of 151 women.[32] Compared with four 7-day activity diaries, the questionnaire underestimated total activity by approximately 20%. However, the correlation for total MET-hours per week of activity was excellent (r=0.62; 95% confidence interval [CI], 0.44-0.75), suggesting that the questionnaire is a valid tool for categorical ranking of respondents. The activity questionnaire was also compared with 4 past-week questionnaires collected seasonally during the year. For walking, the primary activity among women of this age, the intraindividual correlation was 0.70 (95% CI, 0.49-0.84).

Covariates

Covariates included factors previously associated with breast cancer survival in this cohort.[33] The following covariates were extracted from the medical record: tumor size and the presence and number of metastatic lymph nodes; and estrogen receptor and progesterone receptor status. Women also reported method of treatment (radiation, chemotherapy, or tamoxifen). The time interval between breast cancer diagnosis and assessment of physical activity was also adjusted for in this analysis. The following were taken from the questionnaire most immediately preceding the breast cancer diagnosis: menopausal status, age at first pregnancy, parity, postmenopausal hormone use, oral contraceptive use, and body mass index (BMI; calculated as weight in kilograms divided by the square of height in meters). Diet was assessed using validated food frequency questionnaires in 1986, 1990, 1994, and 1998.[34,35] We controlled for energy and protein intake taken from the dietary assessment that most immediately followed the breast cancer diagnosis, which were shown in a previous analysis of this cohort to be associated with survival.[33]

Statistical Analysis

Cox proportional hazards models with time since questionnaire report of diagnosis in months as the underlying time variable were used to calculate the relative risk (RR) of death, death from breast cancer, or recurrence adjusted for other risk factors for survival. In the main analysis, death from breast cancer was the end point and deaths from any other cause were censored. In a secondary analysis, death from any cause was the end point. In another secondary analysis, breast cancer recurrence was the end point and all deaths were censored. Each participant accumulated person-time beginning with the date of breast cancer diagnosis report that was censored at the end point (death, death from breast cancer, or breast cancer recurrence) or study end in June 2002, whichever came first. The RRs are shown for categories of MET-hours per week of physical activity. The less than 3 MET-hours per week category was the reference group. The 2-tailed P value for the linear trend test across categories was calculated by assigning the median value to each category. P = .05 was considered statistically significant. All analyses were performed using SAS version 8.0 (SAS Institute Inc, Cary, NC).

RESULTS

There were 4484 women diagnosed with breast cancer during the selected period. Women were excluded from the analysis for (1) recurrence prior to first follow-up or at the same time as physical activity assessment (n = 38); (2) diagnosis of cancer prior to the first follow-up period (n = 305); (3) no report of physical activity after diagnosis (n = 829); (4) stage IV disease at diagnosis (n = 140); (5) having 4 or more positive lymph nodes at diagnosis and no report of metastatic workup (n = 78); and (6) missing disease stage (n = 107). Women may have been excluded for more than 1 reason but only the first reason is reported.

A total of 2987 women with stages I, II, or III breast cancer were included in the analyses. There were 463 deaths: 280 were from breast cancer. There were 370 breast cancer recurrences. Physical activity assessment occurred a median of 38 months after diagnosis; the 10th and 90th percentiles were 27 and 59 months, respectively. The median length of follow-up for the breast cancer mortality analyses was 96 months; the 10th and 90th percentiles were 47 and 187 months, respectively.

Age-standardized covariates according to category of physical activity are shown in **TABLE 1**. Women who were more active had a lower BMI, consumed more protein, and were less likely to have gained weight between time of diagnosis and time of activity assessment. Women who engaged in little to no physical activity (<3 MET-hours per week) were more likely to have been smokers prior to diagnosis than women who engaged in higher levels of activity. Women in the 2 highest categories of physical activity were less likely to have stage I disease and were more likely to have stage II disease than women in the lower activity categories.

TABLE 2 shows the age-adjusted and multivariable-adjusted RR of death from any cause, death from breast cancer, and breast cancer recurrence according to the category of physical activity. Each category of activity above the reference category (<3 MET-hours per week) was associated with a decreased risk of an adverse breast cancer outcome. Compared with women who participated in less than 3 MET-hours per week of activity, the multivariable RR of death from breast cancer was 0.80 (95% CI, 0.60-1.06) for 3 to 8.9 MET-hours per week; 0.50 (95%

CI, 0.31-0.82) for 9 to 14.9 MET-hours per week; 0.56 (95% CI, 0.38-0.84) for 15 to 23.9 MET-hours per week; and 0.60 (95% CI, 0.40-0.89) for 24 or more MET-hours per week (*P* for trend = .004). Despite a significant linear trend, the RR was relatively flat in the 3 highest activity categories. Similar results were found for overall survival and breast cancer recurrence. In each analysis, adjustment for covariates strengthened the results slightly more than the age-adjusted results.

The association of physical activity was collapsed into 2 categories with death from breast cancer as the outcome. The cutoff of 9 MET-hours per week was chosen for these analyses because this was the predetermined category that divided the cohort almost in half. The RR of death for women who engaged in 9 or more MET-hours per week of physical activity was 0.63 (95% CI, 0.48-0.81) compared with less than 9 MET-hours per week.

The 5-year survival for women who engaged in 9 or more MET-hours per week was 97%; 3 to 8.9 MET-hours per week, 97%; and less than 3 MET-hours per week, 93% (FIGURE). The corresponding 10-year survival rates were 92%, 89%, and 86%, respectively. The absolute unadjusted risk reduction was 4% at 5 years and 6% at 10 years for women who engaged in 9 or more MET-hours per week of physical activity compared with less than 3 MET-hours per week.

The protective benefit of physical activity was similar among overweight women (BMI ≥25) and normal weight (BMI <25) women (TABLE 3). Among overweight women, the RR of death from breast cancer for women who engaged in 24 or more MET-hours per week of physical activity compared with less than 3 MET-hours per week was 0.52 (95% CI, 0.26-1.06; *P* for trend = .01). Among normal weight women, the RR of death from breast cancer for women who engaged in 24 or more MET-hours per week of physical activity compared with less than 3 MET-hours per week was 0.61 (95% CI, 0.37-0.99; *P* for trend = .10). Among women with a BMI of 30 or higher and compared with women who engaged in less than 3 MET-hours per week of physi-

Table 1. Age-Standardized Covariates According to Physical Activity Category After Breast Cancer Diagnosis

	Physical Activity After Diagnosis, MET-h/wk (N = 2987)				
	<3 (n = 959)	3-8.9 (n = 862)	9-14.9 (n = 335)	15-23.9 (n = 428)	≥24 (n = 403)
BMI, mean*†	26.4	25.3	24.7	24.6	24.6
Current smoker, %*	25.8	16.7	15.4	17.5	15.8
Medication use, %					
Oral contraceptives (ever)*	41.4	39.6	51.0	42.3	46.3
Hormone therapy (current; postmenopausal women only)*	30.7	30.2	44.0	33.3	35.5
Chemotherapy‡	31.4	33.9	37.5	33.4	32.1
Family history of breast cancer, %*	22.6	20.5	25.3	20.8	25.5
Intake, mean‡					
Energy, kcal/d	1699	1738	1828	1761	1748
Energy-adjusted protein, g/d	73.1	74.3	73.1	75.0	75.2
Cancer stage, %‡					
I	58.7	57.9	58.6	56.5	57.0
II	34.1	35.2	33.9	36.1	36.2
III	7.2	6.9	7.4	7.5	6.8
Weight gain (BMI increase of >0.5), %‡	52.9	52.6	56.4	51.3	46.5

Abbreviations: BMI, body mass index; MET, metabolic equivalent task.
*Determined prior to diagnosis.
†Calculated as weight in kilograms divided by the square of height in meters.
‡Determined after diagnosis.

Table 2. Age-Adjusted and Multivariable-Adjusted Relative Risks According to Physical Activity Category After Breast Cancer Diagnosis

		Physical Activity After Diagnosis, MET-h/wk					
	Total (N = 2987)	<3 (n = 959)	3-8.9 (n = 862)	9-14.9 (n = 335)	15-23.9 (n = 428)	≥24 (n = 403)	*P* for Trend
Total deaths	463	188	126	38	51	60	
Age-adjusted RR (95% CI)		1.00	0.69 (0.55-0.87)	0.53 (0.37-0.75)	0.56 (0.41-0.77)	0.67 (0.50-0.90)	.004
Multivariable-adjusted RR (95% CI)*		1.00	0.71 (0.56-0.89)	0.59 (0.41-0.84)	0.56 (0.41-0.77)	0.65 (0.48-0.88)	.003
Breast cancer deaths	280	110	84	20	32	34	
Age-adjusted RR (95% CI)		1.00	0.79 (0.60-1.06)	0.47 (0.29-0.76)	0.60 (0.41-0.89)	0.64 (0.44-0.94)	.01
Multivariable-adjusted RR (95% CI)*		1.00	0.80 (0.60-1.06)	0.50 (0.31-0.82)	0.56 (0.38-0.84)	0.60 (0.40-0.89)	.004
Recurrence	370	137	108	29	45	51	
Age-adjusted RR (95% CI)		1.00	0.82 (0.64-1.06)	0.53 (0.35-0.79)	0.66 (0.47-0.93)	0.76 (0.55-1.04)	.05
Multivariable-adjusted RR (95% CI)*		1.00	0.83 (0.64-1.08)	0.57 (0.38-0.85)	0.66 (0.47-0.93)	0.74 (0.53-1.04)	.05

Abbreviations: CI, confidence interval; MET, metabolic equivalent task; RR, relative risk.
*Adjusted for age (months); interval between diagnosis and physical activity assessment (28-33, 34-40, ≥41 mo); smoking status (never, current, past); body mass index (<21, 21-22.9, 23-24.9, 25-28.9, ≥29), which was calculated as weight in kilograms divided by the square of height in meters; menopausal status and hormone therapy use (premenopausal, postmenopausal, and never use; postmenopausal and current use; postmenopausal and past use; uncertain menopausal status; missing); age at first birth and parity (nulliparous, <25 y and 1-2 births, <25 y and ≥3 births, ≥25 y and 1-2 births, ≥25 y and ≥3 births); oral contraceptive use (never, ever, missing); energy intake (quintiles); energy-adjusted protein intake (quintiles); disease stage (I, II, III); radiation treatment (yes or no); chemotherapy (yes or no); and tamoxifen treatment (yes or no).

cal activity, the RR of death from breast cancer was 0.63 (95% CI, 0.26-1.52) for 3 to 8.9 MET-hours per week; 0.78 (95% CI, 0.20-3.04) for 9 to 14.9 MET-hours per week; 0.22 (95% CI, 0.03-1.82) for 15 to 23.9 MET-hours per week; and 0.36 (95% CI, 0.08-1.55) for 24 or more MET-hours per week (*P* for trend =.09). These results suggest additional benefit of physical activity for obese women; however, this analysis was limited by the small number of breast cancer deaths (n = 38) among women with a BMI of 30 or higher.

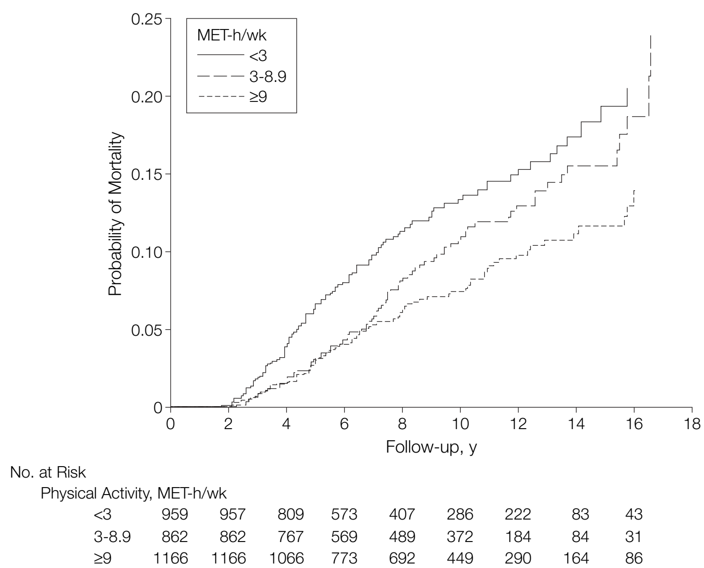
Analyses of breast cancer death stratified by menopausal status, hormone receptor status, and disease stage appear in TABLE 4. Because of the small number of deaths in some activity categories, the exposure in these analyses was dichotomous (<9 and ≥9 MET-hours per week). There were no substantial differences by menopausal status. Physical activity appeared beneficial to women whose tumors had both estrogen and progesterone receptors (RR, 0.50; 95% CI, 0.34-0.74) and not to women whose tumors lacked hormone receptors (RR, 0.91; 95% CI, 0.43-1.96). However, this finding was based on a small number of deaths.

Physical activity was beneficial to women with stage I and II disease, but appeared particularly beneficial to women with stage III disease. For women with stage III cancer who had engaged in 9 or more MET-hours per week of physical activity compared with less than 9 MET-hours per week, the RR was 0.36 (95% CI, 0.19-0.71). However, these results were based on only 76 women and 15 breast cancer deaths. There was no significant difference in the proportion of estrogen receptor–positive and progesterone receptor–positive tumors by stage (80% for stage I, 76% for stage II, and 82% for stage III).

We assessed the comparative role of walking and vigorous exercise in relation to the risk of breast cancer death, which was similar to an analysis performed by Manson et al[36] on cardiovascular disease. Vigorous exercise was defined as participation in activities that required at least 6 METs per hour, including jogging, running, bicycling, swimming laps, racquet sports, and calisthenics. We cross-classified women's participation in walking and vigorous exercise in categories of MET-hours per week (TABLE 5). Both walking and vigorous activity contributed toward lowering the risk of breast cancer death.

Adjustment for category of physical activity prior to diagnosis did not change the association of physical activity after diagnosis with risk of breast cancer death. Compared with women who engaged in less than 3 MET-hours per week of physical activity after diagnosis, the multivariable RR of breast cancer death (adjusted for activity prior to diagnosis) was 0.76 (95% CI, 0.57-1.02) for 3 to 8.9 MET-hours per week; 0.54 (95% CI, 0.31-0.94) for 9 to 14.9 MET-hours per week; 0.57 (95% CI, 0.36-0.90) for 15 to 23.9 MET-hours per week; and 0.60 (95% CI, 0.38-0.95) for 24 or more MET-hours per week.

Figure. Kaplan-Meier Survival Curves



MET indicates metabolic equivalent task.

Table 3. Multivariable-Adjusted Relative Risk of Breast Cancer Death According to Activity Category Prior to Breast Cancer Diagnosis and BMI

		Physical Activity Prior to Diagnosis, MET-h/wk (N = 2987)					
	Total	**<3**	**3-8.9**	**9-14.9**	**15-23.9**	**≥24**	***P* for Trend**
BMI <25*							
No. of deaths/No. of participants	159/1629	59/437	42/459	11/215	23/272	24/246	
Multivariable-adjusted RR (95% CI)†		1.00	0.65 (0.43-0.97)	0.35 (0.18-0.68)	0.63 (0.39-1.04)	0.61 (0.37-0.99)	.10
BMI ≥25*							
No. of deaths/No. of participants	121/1358	51/522	42/403	9/120	9/156	10/157	
Multivariable-adjusted RR (95% CI)†		1.00	1.01 (0.66-1.55)	0.81 (0.38-1.72)	0.44 (0.21-0.93)	0.52 (0.26-1.06)	.01

Abbreviations: BMI, body mass index; CI, confidence interval; MET, metabolic equivalent task; RR, relative risk.
*Calculated as weight in kilograms divided by the square of height in meters.
†See asterisk footnote in Table 2 for list of variables.

COMMENT

We found that any category of activity higher than the reference category of less than 3 MET-hours per week was associated with a decreased risk of an adverse breast cancer outcome. Women who engaged in an amount of physical activity equivalent to walking 1 or more hours per week had better survival compared with those who exercised less than that or not at all. After adjusting for factors predictive of survival after breast cancer, the RRs of adverse outcomes including death, breast cancer death, and breast cancer recurrence were 26% to 40% lower comparing women with the highest to the lowest category of activity. The association was particularly apparent among women with hormone-responsive tumors. Our results suggest a possible hormonal mechanism for improved survival among women who are physically active.

Table 4. Multivariable-Adjusted Relative Risk of Breast Cancer Death According to 2 Physical Activity Categories After Breast Cancer Diagnosis*

	Physical Activity After Diagnosis, MET-h/wk	
	<9	≥9
Premenopausal†		
No. of deaths/No. of participants	39/289	19/242
Multivariable-adjusted RR (95% CI)‡	1.00	0.58 (0.32-1.04)
Postmenopausal†		
No. of deaths/No. of participants	140/1406	66/836
Multivariable-adjusted RR (95% CI)‡	1.00	0.73 (0.54-0.98)
Negative for estrogen and progesterone receptors§		
No. of deaths/No. of participants	27/272	13/149
Multivariable-adjusted RR (95% CI)‡	1.00	0.91 (0.43-1.96)
Positive for estrogen and progesterone receptors§		
No. of deaths/No. of participants	99/955	38/609
Multivariable-adjusted RR (95% CI)‡	1.00	0.50 (0.34-0.74)
Stage I‖		
No. of deaths/No. of participants	52/1083	26/685
Multivariable-adjusted RR (95% CI)‡	1.00	0.67 (0.41-1.09)
Stage II‖		
No. of deaths/No. of participants	94/609	45/405
Multivariable-adjusted RR (95% CI)‡	1.00	0.62 (0.43-0.90)
Stage III‖		
No. of deaths/No. of participants	48/129	15/76
Multivariable-adjusted RR (95% CI)‡	1.00	0.36 (0.19-0.71)

Abbreviations: CI, confidence interval; MET, metabolic equivalent task; RR, relative risk.
*The cutoff of 9 MET-h/wk was chosen because this was the predetermined category that divided the cohort almost in half.
†P = .34 for interaction between menopausal status.
‡See asterisk footnote in Table 2 for list of variables.
§P = .08 for interaction between estrogen and progesterone receptor status.
‖P = .15 for interaction between disease stage.

Table 5. Multivariable-Adjusted Relative Risk of Breast Cancer Death by Vigorous Exercise Category and Walking Category After Breast Cancer Diagnosis*

	Vigorous Exercise After Diagnosis, MET-h/wk†		
	0	0.1-6.9	≥7.0
Walking, MET-h/wk			
0-0.6	1.00	0.58 (0.27-1.23)	0.30 (0.07-1.25)
0.7-6.9	0.68 (0.42-1.09)	0.59 (0.38-0.93)	0.57 (0.34-0.97)
≥7.0	0.73 (0.44-1.20)	0.59 (0.35-0.99)	0.49 (0.28-0.85)

Abbreviation: MET, metabolic equivalent task.
*Values expressed as multivariable-adjusted relative risk (95% confidence interval). See asterisk footnote in Table 2 for list of variables.
†Defined as participation in activities that required at least 6 METs per hour, including jogging, running, bicycling, swimming laps, racquet sports, and calisthenics.

A randomized trial of physical activity among overweight postmenopausal women demonstrated declines in serum levels of androgen[37] and estrogen.[38] Evidence from breast cancer primary prevention studies suggests that increasing activity levels later in life may reduce risk of incident breast cancer.[39] We did not explicitly assess whether increasing physical activity after a breast cancer diagnosis is associated with improved survival. However, adjustment for physical activity prior to diagnosis did not change the risk estimates of mortality in women who engaged in physical activity after breast cancer diagnosis.

Physical activity might also improve survival through acute and chronic improvements in insulin resistance and reduction in hyperinsulinemia.[40] The associations we observed may change over time as the use of aromatase inhibitors to suppress hormone levels becomes more popular.

We addressed several methodological issues in our analyses. Women may feel too fatigued to exercise during the period of active chemotherapy and radiation treatment.[41,42] Therefore, we avoided the active treatment period for the physical activity assessments. Because women with metastatic disease may also not be well enough to exercise, we excluded women with stage IV cancer at diagnosis. Furthermore, we did not update the assessment of physical activity over time because physical activity decreases when a woman is diagnosed with metastatic disease.

Women with occult reasons for poor prognosis at the time of physical activity assessment could bias results. If this were true, we might expect physical activity to be associated with less benefit among women with a higher disease stage. In fact, we found the opposite, although the results are based on small numbers of events.

In the current study, the RR for each adverse outcome was lowest for intermediate levels—not the highest levels of physical activity. It is possible that some women at the highest levels of activity are motivated toward a healthy lifestyle after diagnosis because of a worse prognosis. A recent report of physical activity levels among breast cancer survivors in the Health, Eating, Activity, and Lifestyle (HEAL) study found that women diagnosed with a higher stage of disease reported 15% more time engaged in physical activity compared with women diagnosed with in situ disease, although this difference was accounted for by household and not by recreational activity.[43] Consistent with this hypothesis, women in the 2 highest categories of activity were slightly more likely to have stage II cancer, and slightly less likely to have stage I cancer compared with women in the lower categories of physical activity. This could create the appearance of a higher risk of adverse outcome in the highest compared with intermediate levels of physical activity.

High levels of vigorous activity (such as marathon training) have been linked to increased risk of upper respiratory tract infection due to reduced immune function.[44] The fact that the RR of mortality in the highest category of physical activity was not the lowest (although still lower than the reference group) raises the possibility that vigorous activity may be less beneficial than moderate activity for women with breast cancer. However, no such detrimental effect from vigorous activity was found (Table 5).

Women in the highest category of activity like the rest of the cohort were primarily walkers but they walked for longer periods. Forty-five percent reported walking 5 or more hours per week, 28% reported bicycling 1 or more hours per week, and 28% reported participating in aerobics classes 1 or more hours per week. We speculated that women in the highest physical activity categories were very active before their cancer diagnosis, and that if they developed breast cancer despite high levels of activity, their cancer might be resistant to the beneficial effects of activity on survival. However, among women participating in 15 or more MET-hours per week of activity after their diagnosis, 62% were less active prior to their diagnosis. Overall, given the uniform evidence of the benefits of moderate physical activity to health,[45-47] we believe that it is unlikely that exercise at the highest levels is detrimental to women with breast cancer.

Our study was limited by the fact that physical activity was self-reported. However, the association of other diseases with physical activity in this cohort including cardiovascular disease[48,49]; breast,[50] colon,[51] and pancreatic cancer[52]; infertility[53]; cholecystectomy[54]; hip fracture[31]; cognitive function[55]; and total mortality[56,57] suggest that our measure of physical activity is adequate to detect important disease relationships. We assessed only leisure-time activity. Occupational and household activity may also affect risk of adverse outcomes in women with breast cancer. In this occupationally homogenous group, we expected our inability to assess other types of activity would lead to nondifferential misclassification of the exposure. Therefore, the association incorporating all types of physical activity may be even stronger. Our assessment of recurrence may not be valid. However, our results for recurrence were similar to results for mortality, which is a more definitive end point. We were not able to determine adherence to therapy, which may be differential across categories of physical activity. Finally, our study population is professional and primarily non-Hispanic white, with 2% of the women self-defined as either Hispanic, black, or Asian when presented with those choices on the 1992 questionnaire. The range of physical activity engaged in by these women may be different from that of the general population. However, there is little reason to believe that the biological mechanisms by which physical activity could improve breast cancer survival would differ in women from other groups.

Our results suggest that physical activity after a breast cancer diagnosis may lower the risk of death from that disease. The benefit was seen particularly among women who had tumors overexpressing estrogen receptors and progesterone receptors. These results are consistent with a hormonal mechanism. The maximal benefit occurred among women who performed the equivalent of walking 3 to 5 hours per week at an average pace (2-2.9 mph) with little evidence of increased benefit for more exercise. It has been estimated that women decrease their levels of physical activity by 2 hours per week after a breast cancer diagnosis, with greater decreases among obese women,[41] and that less than one third of breast cancer survivors participate in levels of activity recommended by government agencies.[43] Women with breast cancer who follow the Centers for Disease Control and Prevention recommendations for all individuals in the United States to exercise at moderate intensity for 30 or more minutes per day for 5 or more days per week[58] may survive longer.

Author Contributions: Dr Holmes had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Holmes, Chen, Kroenke.
Acquisition of data: Holmes, Chen.
Analysis and interpretation of data: Holmes, Chen, Feskanich, Kroenke, Colditz.
Drafting of the manuscript: Holmes, Colditz.
Critical revision of the manuscript for important intellectual content: Chen, Feskanich, Kroenke.
Statistical analysis: Holmes, Feskanich.
Obtained funding: Holmes, Chen.
Administrative, technical, or material support: Holmes, Colditz.

Financial Disclosures: None reported.
Funding/Support: The research for this article was funded by grant CA87969 from the National Institutes of Health.
Role of the Sponsor: The National Institutes of Health had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; and preparation, review, or approval of the manuscript.
Acknowledgment: We acknowledge the invaluable programming assistance of Lisa Li, MD.

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