



Recreational physical activity and breast cancer risk by menopausal status and tumor hormone receptor status: results from the Nurses' Health Studies

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Abstract

Purpose Physical activity is associated with lower breast cancer risk, especially in postmenopausal women. Associations in premenopausal women are less well established.

Methods We evaluated recreational physical activity and breast cancer risk in the Nurses' Health Study (NHS) and NHSII (187,278 women; n = 12,785 breast cancers; follow-up: NHS = 1986–2016, NHSII = 1989–2017) by menopausal status and estrogen (ER) and progesterone (PR) receptor status. Physical activity was evaluated as updated cumulative average of metabolic equivalent of task (MET)-h/week. Cox proportional hazards models were used to estimate multivariable hazard ratios (HR) and 95% confidence intervals (CI).

Results Recreational physical activity was inversely associated with breast cancer risk in pre- and postmenopausal women. Higher activity levels were associated with lower risk of ER+/PR+ breast cancer in both pre- and postmenopausal women (e.g., total recreational activity, ≥ 27 vs < 3 MET-h/week, premenopausal HR = 0.83, 95%CI = (0.70–0.99), postmenopausal HR = 0.86 (0.78–0.95); $p_{\text{heterogeneity}} = 0.97$). Results were attenuated with adjustment for current body mass index (BMI) among postmenopausal, but not premenopausal, women (e.g., ≥ 27 vs < 3 MET-h/week, premenopausal HR = 0.83 (0.69–0.98); postmenopausal HR = 0.95 (0.85–1.05); $p_{\text{heterogeneity}} = 0.99$). In analyses of moderate-vigorous activity and breast cancer risk, no heterogeneity by menopausal status was observed ($p_{\text{het}} \geq 0.53$; e.g., ≥ 27 vs < 3 MET-h/week, ER+/PR+, premenopausal HR = 0.88 (0.69–1.11); postmenopausal HR = 0.71 (0.58–0.88). No associations were observed for ER–/PR– disease.

Conclusions Recreational physical activity was associated with lower breast cancer risk in both pre- and postmenopausal women, supporting recreational physical activity as an accessible, modifiable exposure associated with reduced breast cancer risk regardless of menopausal status.

Keywords Breast cancer · Risk · Physical activity · Menopausal status · Hormone receptor status

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Introduction

Higher levels of physical activity are consistently associated with lower risk of breast cancer for postmenopausal women, while associations for premenopausal women remain less clear [1], in large part due to the relatively small number of premenopausal cases with pre-diagnosis activity data in individual prospective cohort studies. The World Cancer Research Fund International (WCRF): Continuous Update Project (CUP) 2018 Expert Report [2] summarized associations between physical activity and breast cancer and reported inverse associations between vigorous activity and both pre- and postmenopausal breast cancer, while total and recreational activity were only significantly associated with postmenopausal disease and with the associations for premenopausal women classified as “limited-suggestive” [1, 2]. In contrast, a more recent study in the UK Biobank reported a 17–23% lower breast cancer risk with higher levels of activity in pre- and postmenopausal women [3]. Inverse associations for pre-/perimenopausal [4] and postmenopausal women are further supported by results from Mendelian randomization studies [5].

Beyond the somewhat conflicting results by menopausal status for breast cancer overall, few studies have evaluated physical activity and breast cancer risk by hormone receptor status in premenopausal women [6]. Differing associations in pre- and postmenopausal women by tumor hormone receptor status may be evident given differences in hormone metabolism and divergent associations between adiposity and breast cancer risk by menopausal status [1, 7]. A meta-analysis including both prospective cohorts and retrospective case–control studies, evaluated 4 studies with estrogen (ER) and progesterone (PR) receptor status and premenopausal breast cancer, and observed inverse associations for both ER+/PR+ and ER–/PR– disease [6]. Analyses by ER/PR status were not included in the recent UK Biobank study [3], and in the WCRF meta-analysis [1] analyses by hormone receptor status were limited to the more common outcome of postmenopausal breast cancer (ER+/PR+, 6 studies and 5117 cases; ER–/PR–, 5 studies 1236 cases; restricted to prospective studies).

Given the relatively sparse data on physical activity in premenopausal women by hormone receptor subtype, we provide a comprehensive evaluation of recreational physical activity, overall and of moderate-vigorous intensity, and breast cancer risk by menopausal status and hormone receptor status in 187,278 women, including 12,785 breast cancer diagnoses, from two well-characterized cohorts with up to three decades of follow-up. The results of this study provide an update of prior findings from the Nurses’ Health Study (NHS) and NHSII, with more than double the number of cases and more than a decade of further follow-up [8, 9].

Methods

Study population: the Nurses’ Health Study (NHS) and Nurses’ Health Study II (NHSII)

The NHS was initiated in 1976 when 121,700 registered nurses in the United States, ages 30–55, completed and returned a mailed questionnaire [10, 11]. The NHSII was initiated in 1989 with 116,429 female registered nurses ages 25–42 and uses the same protocols. Participants in both cohorts complete mailed biennial questionnaires and provided updated information on lifestyle factors and disease diagnoses, including cancers. The studies were approved by the institutional review boards at Brigham and Women’s Hospital and Harvard T.H. Chan School of Public Health, and participating registries as required.

Breast cancer case ascertainment

Participants reported disease status on the biennial NHS and NHSII questionnaires. Eligible cases reported no prior cancer diagnosis before baseline and were diagnosed with invasive breast cancer through June 2016 (NHS) or June 2017 (NHSII). A total of 12,785 eligible breast cancer cases were identified. A study physician confirmed cases through medical record review. Invasiveness, hormone receptor status, and tumor characteristics were abstracted from medical records. Vital status was ascertained through June 1, 2016 (NHS) or June 1, 2017 (NHSII) using next of kin reports, death certificates, and the National Death Index. Given the high confirmation rate by medical record for breast cancer in this cohort (99%) [12], we included both medical record and participant-confirmed cases in this study.

Physical activity assessment

Recreational physical activity data was reported approximately every 4 years via self-administered questionnaire beginning in 1986 (NHS) and 1989 (NHSII). In the NHS, updated physical activity was reported in 1988, 1990 (walking only), 1992, 1994, 1996, 1998, 2000, 2004, 2006, 2008, 2010, 2012 and 2014 (2006, 2010: walking, jogging and running only). In the NHSII, physical activity was updated in 1991, 1997, 2001, 2005, 2009, and 2013.

Participants reported time spent (ten categories ranging from: 0 min/week to 11 + h/week), engaging in the following activities: walking or hiking outdoors; jogging (≥ 10 min/mile); running (< 10 min/mile); bicycling; calisthenics/aerobics; aerobic dance/rowing machine; tennis/squash/racquetball; lap swimming; and other aerobic recreation. Participants estimated walking pace (easy, casual (< 2 miles per hour (mph)); normal, average (2–2.9 mph); brisk (3–3.9

mph); very brisk/ striding (≥ 4 mph)). Energy expenditure was estimated by multiplying metabolic equivalent task (MET) values by reported duration for each activity [13] giving MET-h/week (e.g., 3–9 MET-h/week corresponds to approximately 1–3 h/week of walking at a pace of 2.5 mph).

Summary exposures included: total reported recreational physical activity (“total” activity in the current study refers to all recreational activities reported on the participant questionnaires) and moderate-vigorous activity (activities > 3 METs per hour: walking at pace ≥ 3 miles/hour, jogging, or running). Physical activity data was carried forward from the previous questionnaire year only in years when it was not queried (i.e., for 2002, activity reported in 2000 was used).

Covariate assessment

Data on covariates was available from the baseline and/or biennial questionnaires. Age at each questionnaire was calculated using date of birth and questionnaire return date. Age at menarche and height were collected on the baseline questionnaires. Further covariates (date of collection) included: weight at age 18 (NHS: 1980; NHSII: 1989), weight (biennially), oral contraceptive use (OC; NHS: biennially until 1982; NHSII: biennially until 2009), menopausal hormone therapy use (HT; biennially), smoking status (biennially), alcohol consumption (every four years, NHS: from 1980; NHSII: from 1991), parity (NHS: biennially until 1984; NHSII: biennially), age at first birth (NHS: 1976 and biennially until 1982; NHS: 1989 and biennially), age at menopause (biennially), diagnosis of benign breast disease (biennially), and family history of breast cancer (NHS: every 4 years beginning in 1988; NHS2: 1989, and every 4 years beginning in 1997). Body mass index (BMI) at age 18 and current BMI were calculated using self-reported weight and height (BMI = weight in kilograms (kg)/height in meters (m)²).

Statistical analysis

We calculated person-years beginning at date of baseline physical activity questionnaire return and ending at the earliest of date of diagnosis of any cancer (except non-melanoma skin cancer), death, or end of follow-up. We used multivariable Cox proportional hazards models to calculate hazard ratios (HR) using age in months as the time scale and stratified by follow-up year and cohort. Covariates were included in the models as time-varying covariates for variables with updated data throughout follow-up. Physical activity was evaluated using updated cumulative average over follow-up (i.e., average value across follow-up periods, with the average updated with each subsequent physical activity assessment). We used activity categories previously used in the cohorts (MET-h/week: < 3 , 3 to < 9 , 9 to < 18 ,

18 to < 27 , ≥ 27). The reference category was < 3 MET-h/week; this level of activity corresponds to less than one hour of walking reported at “normal” or “average” pace per week. Tests for trend were evaluated by including category medians as continuous variables in the models. Covariates included in final models were: age at first birth and parity combined, birth index [14], age at menarche, BMI at age 18, menopausal status and age at menopause, oral contraceptive use, hormone therapy use, smoking, alcohol use, family history of breast cancer, and history of benign breast disease. Adjustment for current BMI was assessed in an additional model.

Associations were evaluated in strata of menopausal status and hormone receptor status. Heterogeneity (p_{het}) in associations by hormone receptor status was assessed using a likelihood ratio test (LRT) comparing models assuming the same association between physical activity and breast cancer overall to one allowing different associations by receptor status using a competing risks model [15]. We evaluated heterogeneity in associations with overall, ER+/PR+, and ER-/PR- disease by menopausal status (premenopausal, postmenopausal) by comparing models with and without an interaction term using the LRT. Within each menopausal group, we also evaluated heterogeneity by BMI category (< 25 , ≥ 25 kg/m²). As a sensitivity analysis, we restricted analyses to women reporting a screening mammogram in the preceding two years to evaluate whether our results were impacted by differences in screening between physical activity subgroups (i.e., healthy behavior effect).

P values were considered statistically significant at < 0.05 ; all statistical tests are two-sided. Analyses were conducted in SAS 9.4 (Cary, NC).

Results

Baseline characteristics were generally similar across physical activity categories in both cohorts (Table 1), though women reporting higher levels of physical activity at baseline were leaner (e.g., mean BMI in NHS, ≥ 27 vs. < 3 MET-h/week: 24.4 vs. 26.2 kg/m²). Average age at baseline was 52 years for NHS participants and 34 years for NHSII participants. A total of 39% of participants in the NHS were premenopausal at first physical activity assessment and 95% were parous, whereas 97% of participants in the NHSII were premenopausal and a lower proportion parous (e.g., parous, < 3 MET-h/week: 77%; ≥ 27 : 65%). Median (interquartile range) reported activity at baseline was 7.7 MET-h/week (2.7–19.0) in the NHS and 13.7 MET-h/week (5.2–30.2) in the NHSII. Average activity at the first assessment across categories and ranged from e.g., 1.4 MET-h/week for individuals reporting < 3 MET-h/week of activity

Table 1 Baseline characteristics at first recreational physical activity assessment: Nurses' Health Study (1986) and Nurses' Health Study II (1989)

Nurses' Health Study					
	Physical Activity in 1986 (MET-h/week)				
	<3 (n=21,830)	3- <9 (n=20,869)	9- <18 (n=14,919)	18- <27 (n=8263)	≥27 (n=6453)
Age, 1986	52.2 (7.0)	52.4 (7.1)	52.4 (7.1)	52.4 (7.1)	52.6 (7.1)
Total Activity, MET-h/wk	1.4 (0.9)	5.4 (1.8)	12.9 (2.7)	22.1 (2.5)	34.0 (4.3)
BMI (current), kg/m ²	26.2 (5.4)	25.6 (4.8)	25.0 (4.4)	24.6 (4.0)	24.4 (4.1)
BMI (age 18), kg/m ²	21.5 (3.1)	21.3 (2.8)	21.3 (2.7)	21.3 (2.6)	21.3 (2.8)
Age at Menarche, Years	12.5 (1.4)	12.5 (1.4)	12.5 (1.4)	12.5 (1.4)	12.5 (1.4)
Parous, %	95	95	95	95	94
Parity (among parous women)	3.2 (1.5)	3.2 (1.5)	3.1 (1.5)	3.1 (1.4)	3.1 (1.5)
Age at First Birth, Years	25.2 (3.4)	25.1 (3.3)	25.0 (3.3)	25.0 (3.2)	25.0 (3.1)
Smoking, %					
Never	44	47	46	46	44
Past	31	33	36	38	39
Current	25	20	17	16	17
Family history of breast cancer, %	7	8	8	8	7
History of benign breast disease, %	33	34	35	36	35
Menopausal status, %					
Premenopausal	39	39	39	40	39
Postmenopausal	54	54	54	53	54
Perimenopausal/Unknown	7	7	7	7	7
Current HRT use, % (if postmenopausal)	23	25	27	29	29
Nurses' Health Study II					
	Physical Activity in 1989 (MET-h/week)				
	<3 (n=17,408)	3- <9 (n=26,020)	9- <18 (n=23,994)	18- <27 (n=15,079)	≥27 (n=32,443)
Age, 1989	34.9 (4.6)	34.5 (4.6)	34.4 (4.6)	34.3 (4.6)	33.7 (4.8)
Total Activity, MET-h/wk	1.4 (0.90)	5.7 (1.7)	13.0 (2.6)	22.1 (2.5)	62.5 (51.0)
BMI, kg/m ²	25.2 (6.1)	24.6 (5.3)	24.0 (4.8)	23.7 (4.4)	23.2 (4.3)
BMI (age 18), kg/m ²	21.4 (3.6)	21.3 (3.3)	21.3 (3.3)	21.3 (3.2)	21.2 (3.3)
Age at Menarche, Years	12.9 (1.0)	12.9 (1.0)	12.9 (1.0)	12.9 (1.0)	13.0 (1.0)
Parous, %	77	75	73	69	65
Parity (among parous women)	2.1 (0.9)	2.1 (0.9)	2.1 (0.9)	2.1 (0.9)	2.1 (0.9)
Age at First Birth, Years	25.5 (4.1)	25.6 (4.0)	25.5 (3.9)	25.5 (4.0)	25.3 (4.1)
Smoking, %					
Never	65	66	66	66	65
Past	20	20	21	22	23
Current	16	14	12	12	12
Family History of Breast Cancer, %	6	6	5	6	6
History of Benign Breast Disease, %	8	8	8	8	8
Menopausal status, %					
Premenopausal	97	97	97	97	97
Postmenopausal	2	2	2	2	2
Perimenopausal/Unknown	1	1	1	1	1
Current HT use, % (postmenopausal)	86	91	90	87	87

Values are means (SD) or percentages and are standardized to the age distribution of the study population

Values of polytomous variables may not sum to 100% due to rounding

3–9 MET-h/week corresponds to approximately 1–3 h/week of walking at a pace of 2.5 mph

*Value is not age adjusted

to 33.7 MET-h/week for women reporting ≥ 27 MET-h/week of activity in the NHS.

Total reported recreational physical activity was inversely associated with overall breast cancer risk in pre- and postmenopausal women (premenopausal: HR = 0.91, 95%CI = (0.80–1.04); postmenopausal, 0.87 (0.80–0.94)). Recreational physical activity was inversely associated with ER+/PR+ breast cancer risk, with similar associations observed in both pre- and postmenopausal women (≥ 27 vs < 3 MET-h/week, premenopausal HR = 0.83, 95%CI = (0.70–0.99), $p_{\text{trend}} = 0.06$; postmenopausal HR = 0.86 (0.78–0.95), $p_{\text{trend}} < 0.01$; $p_{\text{heterogeneity}} = 0.97$) (Table 2). The association in premenopausal women was unchanged with adjustment for current BMI (≥ 27 vs < 3 MET-h/week, 0.83 (0.69–0.98), $p_{\text{trend}} = 0.05$), while the association in postmenopausal women was attenuated after adjustment (0.95 (0.85–1.05), $p_{\text{trend}} = 0.09$). We observed limited evidence of heterogeneity in the association between moderate-vigorous activity and ER+/PR+ breast cancer risk by menopausal status ($p_{\text{het}} \geq 0.58$; e.g., ≥ 27 vs < 3 MET-h/week, premenopausal HR = 0.88 (0.69–1.11); postmenopausal HR = 0.71 (0.58–0.88)). No associations were observed for ER-/PR- breast cancer. Among women reporting a mammogram in the prior 2 years associations with total and moderate-vigorous activity were similar to the overall analyses (Table S1).

We evaluated heterogeneity in associations by BMI separately in pre- (Table 3) and postmenopausal women (Table 4). In premenopausal women, associations comparing highest to lowest activity subgroup were similar in both BMI subgroups (e.g., total activity, ER+/PR+, ≥ 27 vs. < 3 MET-h/week, BMI < 25 : 0.84 (0.66–1.08) $p_{\text{trend}} = 0.01$; ≥ 25 : 0.86 (0.67–1.11) $p_{\text{trend}} = 0.99$) (Table 3). Among postmenopausal women, inverse associations between total activity and ER+/PR+ breast cancer were only observed in women with BMI ≥ 25 kg/m² (e.g., ≥ 27 vs. < 3 MET-h/week, BMI ≥ 25 : 0.80 (0.69–0.92) $p_{\text{trend}} < 0.001$; < 25 : 0.96 (0.80–1.15) $p_{\text{trend}} = 0.74$) (Table 4). Moderate-vigorous activity results were similar in both strata of BMI among postmenopausal women.

Discussion

Higher levels of recreational physical activity were associated with lower risk of hormone receptor-positive breast cancer in this large prospective study. These findings provide support for a role for physical activity in primary prevention of breast cancer. Inverse associations were observed regardless of menopausal status, though while associations for premenopausal disease were robust to adjustment for BMI, associations for postmenopausal disease were attenuated by BMI adjustment. This study adds

to the relatively sparse literature on recreational physical activity and breast cancer in premenopausal women by hormone receptor status, observing similar inverse associations in pre- and postmenopausal women.

Prior studies have reported lower risk of breast cancer with higher levels of total recreational physical activity, with a recent meta-analysis of prospective studies noting an inverse association of similar magnitude in pre- and postmenopausal women (e.g., “high” vs. “low” recreational activity, premenopausal, relative risk (RR) = 0.89 (0.74–1.04); postmenopausal, 0.88 (0.82–0.94)) [1]. A limited number of studies with results by hormone receptor status precluded meta-analyses by hormone receptor status among premenopausal women. A lower risk of ER+/PR+ postmenopausal breast cancer was reported with higher recreational activity (n = 6 studies, 5117 cases, RR = 0.89 (0.82–0.96)), and the association ER-/PR- breast cancer was of the same magnitude (n = 5 studies, 1236 cases, 0.89 (0.76–1.04)) [1]. We observed heterogeneity when examining overall physical activity and breast cancer risk by hormone receptor status only among postmenopausal women; however, in both pre- and postmenopausal women, associations were only observed for ER+/PR+ disease. Heterogeneity by hormone receptor status has largely not been observed in prior studies of physical activity and breast cancer risk [8, 16–20], though associations are more consistently observed for hormone responsive disease. The current study includes more postmenopausal ER+/PR+ cases (n = 5598) than the prior published meta-analysis [1], and a substantial number of ER-/PR- cases (n = 1106), and adds needed data on physical activity and breast cancer in premenopausal women (n = 1729 ER+/PR+, n = 372 ER-/PR-).

Findings from prior studies have suggested vigorous activity may have differential effects on breast cancer risk by menopausal status, with a prior meta-analysis of prospective studies [1] reporting a suggestively stronger inverse association for vigorous activity among premenopausal women, (“high” vs. “low”, premenopausal, 0.79 (0.74–1.04); postmenopausal, 0.90 (0.85–0.95)). A separate meta-analysis [6] on moderate-vigorous activity including both retrospective and prospective studies observed lower risk of ER+/PR+ and ER-/PR- in premenopausal women, as compared to postmenopausal women (e.g., ER+/PR+: premenopausal, 4 studies, RR = 0.60 (0.45–0.81); postmenopausal, 13 studies, 0.79 (0.71–0.89)). We did not observe this pattern for moderate-vigorous activity in the current study, with a somewhat stronger association observed in postmenopausal women (ER+/PR+, ≥ 27 vs. < 3 MET-h/week, 0.71 (0.58–0.88)) and an inverse association observed in premenopausal women (0.88 (0.69–1.11)); associations in the current study were similar when considering all cases (i.e., regardless of ER/PR status).

Table 2 Association between overall and moderate-vigorous recreational physical activity and risk of breast cancer by tumor hormone receptor status and menopausal status: NHS (1986–2016) and NHSII (1989–2017)

	MET-h/week		P _{read}		P _{int} memo	
	<3	3 to <9	9 to <18	19 to <27	≥27	HR (95% CI)
Premenopausal						
	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	
Overall recreational physical activity						
All cases (n = 2,935)						
n cases/person-years	352/210158	754/437474	712/460348	449/282961	668/472417	
Multivariable	Ref	1.02 (0.90–1.17)	0.91 (0.80–1.00)	0.95 (0.82–1.10)	0.91 (0.80–1.04)	0.90
Multivariable+ current BMI	Ref	1.02 (0.89–1.16)	0.91 (0.80–1.04)	0.95 (0.82–1.10)	0.91 (0.79–1.04)	0.93
ER+/PR+ (n = 1,729)						
n cases/person-years	212/210158	435/437474	420/460348	274/282961	388/472417	
Multivariable	Ref	0.94 (0.79–1.11)	0.85 (0.72–1.01)	0.91 (0.76–1.09)	0.83 (0.70–0.99)	0.97
Multivariable+ current BMI	Ref	0.94 (0.79–1.11)	0.85 (0.71–1.00)	0.90 (0.75–1.09)	0.83 (0.69–0.98)	0.99
ER–/PR– (n = 372)						
n cases/person-years	39/210158	98/437474	98/460348	60/282961	77/472417	
Multivariable	Ref	1.21 (0.83–1.77)	1.18 (0.80–1.72)	1.21 (0.80–1.82)	1.00 (0.67–1.48)	0.47
Multivariable+ current BMI	Ref	1.22 (0.84–1.78)	1.19 (0.81–1.74)	1.23 (0.81–1.86)	1.03 (0.69–1.53)	0.46
Moderate-vigorous activity						
All cases (n = 2935)						
n cases/person-years	1772/1131584	584/346409	327/203911	128/85241	124/96215	
Multivariable	Ref	0.98 (0.89–1.08)	0.95 (0.84–1.06)	0.94 (0.78–1.12)	0.85 (0.71–1.03)	0.82
Multivariable+ current BMI	Ref	0.98 (0.89–1.08)	0.94 (0.84–1.06)	0.93 (0.78–1.12)	0.85 (0.71–1.02)	0.90
ER+/PR+ (n = 1,729)						
n cases/person-years	1028/1131584	362/346409	184/203911	81/85241	74/96215	
Multivariable	Ref	1.01 (0.90–1.14)	0.89 (0.76–1.04)	1.02 (0.81–1.28)	0.88 (0.69–1.11)	0.58
Multivariable+ current BMI	Ref	1.01 (0.89–1.14)	0.88 (0.75–1.04)	1.01 (0.81–1.27)	0.87 (0.68–1.11)	0.68
ER–/PR– (n = 372)						
n cases/person-years	226/1131584	73/346409	42/203911	20/85241	11/96215	
Multivariable	Ref	1.02 (0.78–1.34)	1.02 (0.73–1.42)	1.18 (0.74–1.87)	0.65 (0.35–1.19)	0.55
Multivariable+ current BMI	Ref	1.04 (0.79–1.36)	1.04 (0.75–1.46)	1.21 (0.76–1.92)	0.67 (0.36–1.23)	0.53
Postmenopausal						
Overall recreational physical activity						
All cases (n = 9850)						
n cases/person-years	1153/345134	2551/779156	2773/864669	1557/504052	1816/657671	
Multivariable	Ref	0.98 (0.91–1.05)	0.96 (0.89–1.03)	0.93 (0.86–1.01)	0.87 (0.80–0.94)	<0.01
Multivariable+ current BMI	Ref	1.00 (0.93–1.08)	1.00 (0.93–1.07)	0.99 (0.91–1.07)	0.94 (0.87–1.01)	0.04

Table 2 (continued)

Postmenopausal										
ER+/PR+ (n = 5598)										
n cases/person-years	621/345144	1432/779163	1648/864649	886/504052	1011/657671					
Multivariable	Ref	0.99	1.01	0.93	0.86	(0.84–1.03)	(0.78–0.95)	<0.01	0.02	
Multivariable + current BMI	Ref	1.02	1.06	1.00	0.95	(0.90–1.11)	(0.85–1.05)	0.09	0.05	
ER-/PR- (n = 1106)										
n cases/person-years	113/345144	291/779163	283/864649	206/504052	213/657671					
Multivariable	Ref	1.13	1.01	1.27	1.05	(1.00–1.61)	(0.83–1.33)	0.64		
Multivariable + current BMI	Ref	1.14	1.02	1.29	1.08	(1.02–1.64)	(0.85–1.37)	0.49		
Moderate-Vigorous Activity										
All cases (n = 9850)										
n cases/person-years	6356/1956010	1918/641259	1055/349125	333/118321	188/85966					
Multivariable adjusted	Ref	0.95	0.96	0.89	0.76	(0.79–0.99)	(0.66–0.88)	<0.01		
Multivariable adjusted + current BMI	Ref	0.99	1.01	0.95	0.83	(0.85–1.07)	(0.72–0.96)	0.06		
ER+/PR+ (n = 5598)										
n cases/person-years	3575/1956010	1136/641259	615/349125	172/118321	100/85966					
Multivariable	Ref	0.98	0.97	0.81	0.71	(0.70–0.95)	(0.58–0.88)	<0.01	0.22	
Multivariable + current BMI	Ref	1.03	1.05	0.89	0.80	(0.76–1.04)	(0.65–0.98)	0.10	0.40	
ER-/PR- (n = 1106)										
n cases/person-years	691/1956010	212/641259	131/349125	44/118321	28/85966					
Multivariable	Ref	0.93	1.04	1.07	1.05	(0.79–1.46)	(0.70–1.50)	0.65		
Multivariable + current BMI	Ref	0.94	1.06	1.09	1.05	(0.80–1.50)	(0.72–1.54)	0.50		

Multivariable models adjusted for age at first birth and parity (nulliparous, 1–2 birth ≤25y, 1–2 births >25y, 3+ births ≤25y, 3+ births >25y), birth index, age at menarche (categorical), family history of breast cancer, history of benign breast disease, oral contraceptive use (categorical, premenopausal only), current smoking status, alcohol (categories), hormone therapy use (categorical, postmenopausal only), age at menopause (postmenopausal only), BMI at age 18 (continuous)

Note: 3–9 MET-h/week corresponds to approximately 1–3 h/week of walking at a pace of 2.5 mph

Table 3 Association between overall and moderate-vigorous recreational physical activity and risk of breast cancer by tumor hormone receptor status and BMI (<25 , ≥ 25 kg/m²): NHS (1986–2016) and NHSII (1989–2017) among premenopausal women

	MET-h/week						HR (95% CI)	P _{trend}	P _{het} ERPR	P _{int} BMI [†]				
	<3		3 to <9		9 to <18						19 to <27		≥27	
	n cases/person-years	HR (95% CI)	n cases/person-years	HR (95% CI)	n cases/person-years	HR (95% CI)					n cases/person-years	HR (95% CI)	n cases/person-years	HR (95% CI)
BMI < 25 kg/m²														
Overall recreational physical activity														
All cases (n = 1599)	159/100296	385/217761	398/247183	248/161708	409/302046									
Multivariable	Ref	1.12 (0.93–1.35)	1.02 (0.85–1.23)	0.97 (0.79–1.19)	0.92 (0.76–1.11)	0.02	0.52							
Multivariable + current BMI	Ref	1.12 (0.93–1.35)	1.02 (0.85–1.23)	0.97 (0.79–1.19)	0.92 (0.76–1.11)	0.02	0.54							
ER+/PR+ (n = 932)	93/100296	232/217761	227/247183	149/161708	231/302046									
Multivariable	Ref	1.11 (0.87–1.42)	0.94 (0.74–1.21)	0.94 (0.72–1.22)	0.84 (0.66–1.08)	0.01	0.25							
Multivariable + current BMI	Ref	1.11 (0.87–1.42)	0.94 (0.74–1.21)	0.94 (0.72–1.22)	0.84 (0.65–1.08)	0.01	0.26							
ER-/PR- (n = 194)	14/100296	48/217761	59/247183	31/161708	42/302046									
Multivariable	Ref	1.60 (0.88–2.93)	1.79 (0.99–3.24)	1.46 (0.76–2.77)	1.10 (0.59–2.05)	0.20	0.60							
Multivariable + current BMI	Ref	1.60 (0.88–2.93)	1.79 (0.99–3.25)	1.46 (0.77–2.79)	1.12 (0.60–2.08)	0.23	0.56							
Moderate-Vigorous Activity														
All cases (n = 1599)	874/576024	359/198532	196/125932	77/56437	93/72070									
Multivariable	Ref	1.06 (0.93–1.20)	0.93 (0.80–1.09)	0.85 (0.67–1.08)	0.84 (0.68–1.05)	0.04	0.73							
Multivariable + current BMI	Ref	1.06 (0.93–1.20)	0.93 (0.80–1.09)	0.85 (0.67–1.08)	0.85 (0.57–1.05)	0.04	0.74							
ER+/PR+ (n = 932)	509/576024	213/198532	108/125932	48/56437	54/72070									
Multivariable	Ref	1.04 (0.89–1.23)	0.85 (0.69–1.05)	0.90 (0.67–1.22)	0.83 (0.62–1.11)	0.08	0.48							
Multivariable + current BMI	Ref	1.04 (0.89–1.23)	0.85 (0.69–1.05)	0.90 (0.67–1.22)	0.83 (0.62–1.11)	0.08	0.50							
ER-/PR- (n = 194)	105/576024	49/198532	25/125932	7/56437	8/72070									
Multivariable	Ref	1.28 (0.91–1.81)	1.08 (0.69–1.68)	0.66 (0.30–1.42)	0.65 (0.31–1.33)	0.16	0.16							
Multivariable + current BMI	Ref	1.29 (0.91–1.82)	1.08 (0.70–1.69)	0.66 (0.31–1.43)	0.66 (0.32–1.36)	0.18	0.18							
BMI ≥ 25 kg/m²														
Overall recreational physical activity														
All cases (n = 1316)	190/109403	367/217305	310/209221	197/118445	252/165356									
Multivariable	Ref	0.94 (0.78–1.12)	0.82 (0.68–0.99)	0.94 (0.77–1.16)	0.94 (0.78–1.15)	0.91	0.91							
Multivariable + current BMI	Ref	0.94 (0.78–1.12)	0.82 (0.68–0.99)	0.94 (0.76–1.15)	0.94 (0.77–1.14)	0.88	0.88							

Table 3 (continued)

	MET-h/week						P _{trend}	P _{het} ERPR	P _{int} BMI [†]				
	<3		3 to <9		9 to <18					19 to <27		≥27	
	HR (95% CI)	n	HR (95% CI)	n	HR (95% CI)	n				HR (95% CI)	n	HR (95% CI)	n
ER+/PR+ (n = 781)	117/109403	202/217305	190/209221	121/118445	151/165356								
n cases/person-years	Ref	0.80	(0.64–1.01)	0.78	(0.62–0.99)	0.88	(0.68–1.15)	0.86	(0.67–1.11)	0.99	0.90		
Multivariable	Ref	0.80	(0.63–1.01)	0.78	(0.61–0.99)	0.88	(0.67–1.14)	0.86	(0.66–1.10)	0.94	0.88		
Multivariable + current BMI													
ER-/PR- (n = 178)	25/109403	50/217305	39/209221	29/118445	35/165356								
n/person-years	Ref	0.96	(0.59–1.56)	0.78	(0.46–1.30)	1.08	(0.62–1.88)	1.03	(0.61–1.74)	0.65	0.65		
Multivariable	Ref	0.97	(0.60–1.58)	0.79	(0.47–1.33)	1.11	(0.64–1.93)	1.06	(0.62–1.80)	0.57	0.57		
Multivariable + current BMI													
Moderate-Vigorous Activity													
All cases (n = 1316)													
n cases/person-years	886/549231	223/143772	128/75403	50/27961	29/23364								
Multivariable	Ref	0.88	(0.76–1.03)	0.99	(0.82–1.19)	1.12	(0.84–1.49)	0.84	(0.58–1.22)	0.72	0.72		
Multivariable + current BMI	Ref	0.88	(0.76–1.02)	0.98	(0.81–1.19)	1.12	(0.84–1.49)	0.83	(0.57–1.21)	0.69	0.69		
ER+/PR+ (n = 781)	510/549231	147/143772	74/75403	32/27961	18/23364								
n cases/person-years	Ref	0.97	(0.80–1.17)	0.95	(0.74–1.22)	1.25	(0.87–1.79)	0.89	(0.55–1.43)	0.92	0.32		
Multivariable	Ref	0.97	(0.80–1.17)	0.94	(0.74–1.21)	1.24	(0.86–1.77)	0.88	(0.55–1.42)	0.97	0.32		
Multivariable + current BMI													
ER-/PR- (n = 178)	121/549231	24/143,772	17/75403	13/27961	3/23364								
n cases/person-years	Ref	0.75	(0.48–1.16)	1.02	(0.61–1.71)	2.21	(1.24–3.96)	0.66	(0.21–2.10)	0.35	0.35		
Multivariable	Ref	0.76	(0.48–1.19)	1.05	(0.63–1.76)	2.27	(1.26–4.08)	0.69	(0.22–2.17)	0.29	0.29		
Multivariable + current BMI													

Multivariable models adjusted for age at first birth and parity (nulliparous, 1–2 birth ≤25y, 1–2 births >25y, 3+ births ≤25y, 3+ births >25y), birth index, age at menarche (categorical), family history of breast cancer, history of benign breast disease, oral contraceptive use (categorical), current smoking status, alcohol (categories), BMI at age 18 (continuous)

[†] p value for heterogeneity tests model with BMI (high v. low) in place of continuous BMI vs. interaction model

Note: 3–9 MET-h/week corresponds to approximately 1–3 h/week of walking at a pace of 2.5 mph

Table 4 Association between overall and moderate-vigorous recreational physical activity and risk of breast cancer by tumor hormone receptor status and BMI (<25, ≥25 kg/m²): NHS (1986–2016) and NHSII (1989–2017) among postmenopausal women

	MET-h/week						P _{total}	P _{het} ERPR	P _{int} BMI [†]				
	<3		3 to <9		9 to <18					19 to <27		≥27	
	n cases/person-years	HR (95% CI)	n cases/person-years	HR (95% CI)	n cases/person-years	HR (95% CI)				n cases/person-years	HR (95% CI)	n cases/person-years	HR (95% CI)
BMI < 25 kg/m²													
Overall recreational physical activity													
All cases (n = 3573)													
n cases/person-years	347/105553	800/242395	419/242395	549/294278	967/294278	598/188820	861/281187						
Multivariable	Ref	0.97 (0.85–1.11)	0.93 (0.78–1.11)	0.96 (0.81–1.14)	0.95 (0.84–1.08)	0.94 (0.82–1.08)	0.96 (0.84–1.09)			0.10			
Multivariable + current BMI	Ref	0.97 (0.85–1.10)	0.92 (0.77–1.10)	0.96 (0.80–1.14)	0.95 (0.84–1.08)	0.94 (0.82–1.08)	0.96 (0.85–1.10)			0.27			
ER+/PR+ (n = 1938)													
n cases/person-years	179/105553	419/242395	419/242395	549/294278	967/294278	311/188820	480/281187						
Multivariable	Ref	0.93 (0.78–1.11)	0.93 (0.78–1.11)	0.96 (0.81–1.14)	0.95 (0.84–1.08)	0.87 (0.72–1.05)	0.96 (0.80–1.15)			0.09			
Multivariable + current BMI	Ref	0.92 (0.77–1.10)	0.92 (0.77–1.10)	0.96 (0.80–1.14)	0.95 (0.84–1.08)	0.87 (0.72–1.05)	0.97 (0.81–1.16)			0.27			
ER–/PR– (n = 455)													
n cases/person-years	42/105553	98/242395	98/242395	115/294278	115/294278	95/188820	105/281187						
Multivariable	Ref	0.98 (0.68–1.43)	0.98 (0.68–1.43)	1.00 (0.69–1.44)	1.00 (0.69–1.44)	1.29 (0.88–1.90)	1.02 (0.70–1.48)			0.88			
Multivariable + current BMI	Ref	0.98 (0.68–1.43)	0.98 (0.68–1.43)	1.00 (0.69–1.44)	1.00 (0.69–1.44)	1.30 (0.88–1.90)	1.02 (0.70–1.49)			0.91			
Moderate-Vigorous Activity													
All cases (n = 3573)													
n cases/person-years	2019/611222	774/243069	774/243069	490/152195	490/152195	176/58598	114/47148						
Multivariable	Ref	0.97 (0.89–1.06)	0.97 (0.89–1.06)	0.99 (0.90–1.10)	0.99 (0.90–1.10)	0.94 (0.81–1.11)	0.83 (0.69–1.01)			0.73			
Multivariable + current BMI	Ref	0.98 (0.89–1.06)	0.98 (0.89–1.06)	1.00 (0.90–1.11)	1.00 (0.90–1.11)	0.96 (0.82–1.12)	0.85 (0.70–1.04)			0.98			
ER+/PR+ (n = 1938)													
n cases/person-years	1062/611222	450/243069	450/243069	281/152195	281/152195	84/58598	61/47148						
Multivariable	Ref	1.03 (0.92–1.15)	1.03 (0.92–1.15)	1.06 (0.93–1.22)	1.06 (0.93–1.22)	0.85 (0.68–1.07)	0.84 (0.64–1.09)			0.64			
Multivariable + current BMI	Ref	1.03 (0.92–1.16)	1.03 (0.92–1.16)	1.07 (0.94–1.23)	1.07 (0.94–1.23)	0.87 (0.69–1.09)	0.87 (0.67–1.14)			0.95			
ER–/PR– (n = 455)													
n cases/person-years	255/611222	93/243069	93/243069	58/152195	58/152195	28/58598	21/47148						
Multivariable	Ref	0.93 (0.72–1.19)	0.93 (0.72–1.19)	0.93 (0.69–1.26)	0.93 (0.69–1.26)	1.27 (0.85–1.88)	1.25 (0.80–1.97)			0.83			
Multivariable + current BMI	Ref	0.93 (0.73–1.19)	0.93 (0.73–1.19)	0.93 (0.69–1.26)	0.93 (0.69–1.26)	1.27 (0.85–1.89)	1.26 (0.80–1.97)			0.88			
BMI ≥ 25 kg/m²													
Overall recreational physical activity													
All cases (n = 5317)													
n cases/person-years	747/205142	1550/425769	1550/425769	1502/426489	1502/426489	772/225847	746/253964						
Multivariable	Ref	0.99 (0.90–1.08)	0.99 (0.90–1.08)	0.95 (0.87–1.04)	0.95 (0.87–1.04)	0.94 (0.85–1.04)	0.83 (0.75–0.93)			<0.001			
Multivariable + current BMI	Ref	1.00 (0.92–1.10)	1.00 (0.92–1.10)	0.97 (0.89–1.07)	0.97 (0.89–1.07)	0.97 (0.87–1.08)	0.87 (0.78–0.96)			0.003			

Table 4 (continued)

	MET-h/week					P _{net} ERPR	P _{net} BMI [†]
	< 3	3 to < 9	9 to < 18	19 to < 27	≥ 27		
	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)		
ER+/PR+ (n = 3061)							
n cases/person-years	409/205142	897/425769	891/426489	460/225847	404/253964		
Multivariable	Ref	1.02 (0.90–1.15)	0.99 (0.87–1.11)	0.97 (0.84–1.11)	0.80 (0.69–0.92)	<0.001	0.07
Multivariable+current BMI	Ref	1.04 (0.92–1.17)	1.02 (0.90–1.15)	1.01 (0.88–1.16)	0.84 (0.73–0.97)	0.005	0.09
ER–/PR– (n = 569)							
n cases/person-years	67/205142	178/425769	138/426489	98/225847	88/253964		
Multivariable	Ref	1.24 (0.93–1.65)	0.95 (0.70–1.29)	1.30 (0.94–1.80)	1.07 (0.77–1.49)	0.94	
Multivariable+current BMI	Ref	1.25 (0.93–1.67)	0.97 (0.71–1.31)	1.33 (0.96–1.84)	1.10 (0.78–1.53)	0.82	
Moderate-Vigorous Activity							
All cases (n = 5317)							
n cases/person-years	3782/1056710	901/278030	446/135321	122/41641	662/5509		
Multivariable	Ref	0.94 (0.88–1.02)	0.96 (0.87–1.06)	0.86 (0.72–1.04)	0.88 (0.69–1.12)	0.04	
Multivariable+current BMI	Ref	0.97 (0.90–1.04)	0.99 (0.89–1.09)	0.89 (0.74–1.07)	0.91 (0.71–1.17)	0.21	
ER+/PR+ (n = 3061)							
n cases/person-years	2169/1056710	528/278030	265/135321	64/41641	35/25509		
Multivariable	Ref	0.94 (0.85–1.04)	0.98 (0.86–1.11)	0.78 (0.60–1.00)	0.81 (0.57–1.14)	0.04	0.65
Multivariable+current BMI	Ref	0.97 (0.88–1.07)	1.02 (0.89–1.16)	0.81 (0.63–1.05)	0.85 (0.61–1.20)	0.18	0.74
ER–/PR– (n = 569)							
n cases/person-years	385/1056710	105/278030	58/135321	15/41641	6/25509		
Multivariable	Ref	1.01 (0.81–1.27)	1.12 (0.84–1.49)	0.97 (0.56–1.67)	0.77 (0.34–1.72)	0.97	
Multivariable+current BMI	Ref	1.03 (0.82–1.29)	1.14 (0.85–1.52)	0.99 (0.57–1.71)	0.79 (0.35–1.77)	0.92	

Multivariable models adjusted for age at first birth and parity (nulliparous, 1–2 births > 25 y, 3+ births ≤ 25 y, 3+ births > 25 y), birth index, age at menarche (categorical), family history of breast cancer, history of benign breast disease, current smoking status, alcohol (categories), hormone therapy use (categorical), age at menopause, BMI at age 18 (continuous)

[†] p value for heterogeneity tests model with BMI (high v. low) in place of continuous BMI vs. interaction model

Note: 3–9 MET-h/week corresponds to approximately 1–3 h/week of walking at a pace of 2.5 mph

We observed limited heterogeneity in associations by BMI in the current study, although the inverse association between total recreational activity and risk in the current study was predominantly observed in postmenopausal women with BMI ≥ 25 kg/m². This is in contrast to a meta-analysis evaluating total activity, which reported a stronger association among postmenopausal normal-weight women [1]. A recent study in the UK Biobank [3] observed no heterogeneity in associations by BMI, with similar associations in strata of BMI and an inverse association among (pre- and postmenopausal) women with BMI ≥ 25 kg/m². We observed that the associations between moderate-vigorous activity and breast cancer risk were similar in both strata of BMI. This is consistent with a meta-analysis on moderate-vigorous activity which reported similar associations in strata of BMI [6], though this was only observed for postmenopausal women.

Physical activity may influence breast cancer risk through its impact on adiposity, and adiposity-related mechanisms including sex steroid hormone metabolism, and inflammation and immune-related pathways. The associations between adiposity [21, 22] and physical activity [23, 24] and these mechanisms have been described previously with lower levels of adiposity and higher levels of physical activity, for example, associated with lower circulating estradiol, improvements in insulin resistance, and lower concentrations of inflammation marker C-reactive protein, and altered immune response.

We adjusted for current BMI in secondary models given that BMI may be on the causal pathway. BMI adjustment had essentially no impact on the association between physical activity and breast cancer in premenopausal women, but attenuated associations for ER+/PR+ postmenopausal disease (e.g., total activity unadjusted HR, 0.86 (0.78–0.95); adjusted, 0.95 (0.85–1.05)). The associations for postmenopausal breast cancer are in line with the well-established positive association between BMI and postmenopausal breast cancer [1]. In a recent study in the UK Biobank, accelerometer-based physical activity was evaluated, and analyses were adjusted for fat mass measured with bioimpedance [3]. Small changes in the associations between physical activity and breast cancer risk were noted after adjustment for body fatness, in the direction of strengthening associations in premenopausal women (RR per 5 milligravity units of activity, before adjustment, 0.82 (0.69–0.97); after adjustment, 0.79 (0.66–0.95)) and attenuating associations after adjustment in postmenopausal women (before adjustment, 0.79 (0.69–0.90); after adjustment, 0.84 (0.73–0.96)). Notably, BMI is associated with a lower risk of breast cancer in premenopausal women [7], likely explaining why this adjustment did not impact findings for physical activity and pre-menopausal breast cancer. It is plausible that the associations between physical activity and premenopausal breast cancer are underpinned by direct effects of physical activity on intermediate mechanistic pathways, and that associations are independent of adiposity.

Our study has strengths and limitations. The biennial follow-up enabled us to update physical activity and covariate data throughout the study period, and we used a cumulative average measure to represent habitual physical activity across follow-up. A limitation of using the cumulative average physical activity measure, together with time-varying covariates, is the potential conditioning on mediating variables across follow-up (i.e., those variables impacted by past activity as reflected in the cumulative average). Results from age-adjusted models were similar to those from the multivariable models, though with less precise confidence intervals, thus we do not expect this has had a substantial impact on our results. The BMI-adjusted models would be expected to be the most substantially impacted by this issue, and this may have led to an attenuation of the effect of adjustment for BMI. A limitation of the study is the use of self-reported activity, however, this approach has demonstrated reliability and validity [25] and has been associated with other outcomes [26–29]. The levels of recreational activity reported in the NHS and NHSII are similar to those reported in other prospective cohorts [30]. Further, our results describe associations with recreational, discretionary activity and not occupational or household and caregiving physical activity. Recreational activity may represent activity types that are most amenable to change, and thus with potential for intervention toward cancer prevention. However, lack of data on other activity types precludes an evaluation of total physical activity across domains. The results of this updated study within the NHS and NHSII are in line with earlier findings from these cohorts with shorter follow-up [8, 9]. Finally, while this study adds needed information on physical activity and breast cancer risk in premenopausal women by tumor hormone receptor status, sample size precluded an evaluation of more detailed tumor subtypes.

Higher levels of recreational physical activity were associated with lower risk of both pre- and postmenopausal hormone receptor-positive breast cancer, providing further support for the beneficial role of physical activity for cancer prevention. These results were robust to adjustment for current BMI in premenopausal women, whereas BMI adjustment attenuated the results in postmenopausal women, findings that are consistent with the established associations between adiposity-related mechanisms and postmenopausal breast cancer. These findings support recreational physical activity as a modifiable exposure associated with reduced breast cancer risk regardless of menopausal status.

Supplementary Information The online version contains supplementary material available at <https://doi.org/10.1007/s10549-023-07238-x>.

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Data availability Data used in this study are available by application at nurseshealthstudy.org.

Declarations

Competing interests The authors have no relevant financial or non-financial interests to disclose.

Ethical approval This study was approved by the Institutional Review Board of the Brigham and Women's Hospital (Boston, MA).

Consent to participate Participants provided informed consent.

Consent to publish Not applicable.

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