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Research Article

Recent Recreational Physical Activity and Breast Cancer Risk in Postmenopausal Women in the E3N Cohort

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Abstract

Background: Physical activity probably protects against the risk of breast cancer after menopause, but questions remain about how rapidly and for how long this protective effect exists.

Methods: We analyzed data from 59,308 postmenopausal women (2,155 incident invasive breast cancers) followed between 1993 and 2005 (8.5 years postmenopause on average) through biennial questionnaires. Multivariable Cox models included time-varying exposure data, using levels of recreational physical activity self-reported in 1993, 1997, and 2002.

Results: Women with recent (within the previous 4 years) recreational physical activity levels ≥12 metabolic equivalent task-hours (MET-h)/week had a lower risk of invasive breast cancer than women with lower levels [HR, 0.90; 95% confidence interval (CI), 0.82–0.99], with no apparent dose–response relation beyond 12 MET-h/week. Associations did not vary significantly across ER/PR subtypes. Risk reductions were of the same magnitude order regardless of weight change, body mass index, waist circumference, or less recent (5–9 years earlier) physical activity levels. Among women with levels of physical activity ≥12 MET-h/week 5 to 9 years earlier, those who became less active (<12 MET-h/week) had a significantly increased risk of breast cancer compared with those who did not (HR, 1.16; 95% CI, 1.01–1.35). And, compared with the least active women at both time points, they had no significantly decreased risk of breast cancer (HR, 1.06; 95% CI, 0.87–1.29).

Conclusions: Our results suggest a decrease in risk associated with recent recreational physical activity even of modest levels.

Impact: Starting or maintaining physical activity after menopause may be beneficial regarding breast cancer risk. *Cancer Epidemiol Biomarkers Prev; 23(9); 1893–902. ©2014 AACR.*

Introduction

Physical activity is among the few modifiable risk factors for breast cancer (1, 2), the most common cancer in women in high-income countries (3). Despite inconsistencies between epidemiologic studies, physical activity is currently considered to have a "probable" protective effect after menopause (4). Possible reasons for the inconsistencies include the fact that the associations may be different according to some characteristics of women, such as body mass index (BMI) or weight changes (1, 2). In particular, recent energy balance variation and weight changes induced by physical activity might be important (5). Questions also remain about whether the association between physical activity and breast cancer risk differs according to tumor receptor status (1, 2).

Furthermore, it is not clear how rapidly this association is observed after regular physical activity is initiated, or for how long it lasts after exercise stops (1, 2). A possible way to elucidate these two questions is to perform epidemiologic studies able to distinguish between recent and less recent physical activity habits. Some studies have assessed physical activity at inclusion and more than 10 years before inclusion (6–12), and all but two (6, 12) took these two assessments into account simultaneously. Their results were conflicting: two reported no association of breast cancer risk with either past or recent physical activity (7, 9); one showed an association with recreational physical activity at the age of 12 to 22 years, but not after the age of 35 years (8); and two reported an association with physical activity at baseline, but not earlier (10, 11). To our knowledge, only one prospective study (13) has investigated both past (at baseline, close to menopause)

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and recent (during the previous 2–4 years) physical activity in postmenopausal women. In that study, which had a 20-year follow-up period, only recent physical activity was inversely associated with breast cancer risk. Nonetheless, the separation of the two assessments of physical activity by up to 20 years hampers our comprehension of the impact of shorter term variations in physical activity on the phases of breast carcinogenesis (1, 4).

We therefore used information on self-reported physical activity in the large E3N cohort, regularly updated during follow-up, to examine the association between recent (within the previous 4 years) recreational physical activity and postmenopausal breast cancer risk taking into account less recent (5–9 years earlier) recreational physical activity, BMI, waist circumference, and recent weight changes.

Materials and Methods

The E3N cohort

E3N, the French component of the European Prospective Investigation into Cancer and Nutrition (EPIC; ref. 14), is a prospective cohort including 98,995 women born between 1925 and 1950 and insured by a national health insurance fund that primarily covers teachers. The National Commission for Data Protection and Privacy approved the study.

Women were enrolled when they replied to a questionnaire sent in 1990 and gave written informed consent. They thereafter received questionnaires every 2 to 3 years for follow-up. The questionnaire mailed in July 2005 is the last used for this analysis.

Identification of breast cancer cases

Occurrence of breast cancer was identified mainly from self-reports in the questionnaires; a few additional cases came from next-of-kin reports and the national cause-of-death registry. Pathology reports were retrieved for 94% of the incident cases, and information on estrogen receptor (ER) and progesterone receptor (PR) status was extracted from them. The proportion of false-positive self-reports was <5%. We therefore included cases for which pathology reports were unobtainable in the analyses that do not take the hormone receptor status of breast cancers into account.

Assessment of recreational physical activity

Questions derived from a modified version of the Baecke questionnaire (14–16) were used to collect data on recreational physical activity in the 1993, 1997, and 2002 questionnaires. Duration (hours/week) that participants spent walking (including walking to work, shopping, and leisure time), cycling (including cycling to work, shopping, and leisure time), and engaging in sports during 2 typical weeks over the past year, one in summer and one in winter, was self-reported by the participants. We averaged the time reported during these 2 weeks. We assigned metabolic equivalent task (MET) values of 3.0 for one hour walking and 6.0 for one hour cycling or engaging in other sports (14, 16–18). For each woman, the MET-h/week obtained for walking, cycling, and sports activities was added to derive overall recreational physical activity.

Population for analysis and follow-up

The study population was restricted to postmenopausal women. Menopausal status and date of menopause were determined from regularly updated data on menstrual periods, hysterectomy, oophorectomy, use of menopausal hormone therapy, self-reported menopausal status, and menopausal symptoms, as detailed elsewhere (19). Follow-up started either at the date the 1993 questionnaire was returned for already postmenopausal women, or at the date menopause was first reported. The end of the observation period was set at July 2005, that is, the mailing date of the questionnaire following the last assessment of physical activity. Women contributed person-years of follow-up until the date of diagnosis of any cancer, the date of the last completed questionnaire, or of the end of the observation period, whichever occurred first.

The questionnaire sent in 1993 was returned completed by 74,531 women. After we excluded women who reported a prevalent cancer at baseline or before menopause other than basal cell carcinoma (n = 6,405), had never menstruated (n = 23), had missing information on physical activity in the 1993 questionnaire (n = 488) or an outlying value (i.e., in the top 1 percent) of walking, cycling, or sports activities in any questionnaire (n = 3,648), and women with no follow-up after menopause (n = 4,659), 59,308 women remained in the analysis. Because waist circumference was assessed only in the questionnaires sent in 1994 and 2002, follow-up for analyses stratified by waist circumference started on the date the 1994 questionnaire was mailed or at the date menopause was first reported then; these analyses, from which women who reported a prevalent cancer other than basal cell carcinoma before that modified start of follow-up were excluded, included 52,077 women. In the analyses evaluating recreational physical activity in the distant past (5–9 years earlier), follow-up could not start before the first questionnaire assessing physical activity since 1993, that is, the 1997 questionnaire; these analyses included 54,925 women with information on recreational physical activity available in at least two consecutive questionnaires, and excluded women who reported a prevalent cancer other than basal cell carcinoma before that modified start of follow-up.

Statistical analysis

Cox proportional hazard models stratified by 5-year interval birth cohorts, with age as the time-scale, were used to estimate HR and 95% confidence intervals (CI) for primary invasive breast cancer. The proportional hazards hypothesis was verified by including an interaction term between exposure and age and comparing the interaction model with the model without the interaction term by

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means of a likelihood ratio test. The proportional hazards assumption was not violated.

The regular updates during follow-up of the level of recreational physical activity were taken into account by including time-varying exposure variables in our statistical models. For recent level of physical activity, information reported in a given questionnaire (sent in 1993, 1997, or 2002) was used to categorize participants prospectively for the period between completion of that questionnaire and the subsequent questionnaire or end of follow-up. We defined as recent recreational physical activity that reported in the last considered questionnaire, and as less recent recreational physical activity that reported in the next-to-last considered questionnaire. As information on physical activity was updated approximately every 4 to 5 years, recent recreational physical activity corresponded approximately to that within the previous 4 years and less recent activity to that within the previous 5 to 9 years.

We systematically controlled for known breast cancer risk factors by adjusting models for the variables listed in Table 1 (except for weight gain), according to the categories there. BMI, history of benign breast disease, and use of menopausal hormone therapy were included in the models as time-varying variables, because they were regularly updated during follow-up. The information reported in questionnaire n or earlier was used to categorize women prospectively for the period between questionnaires n (Q_n) and n + 1 (Q_{n+1}).

Tests for linear trends used the level of recreational physical activity (in MET-h/week) as a continuous variable.

Breast cancer cases with no information on hormone receptor status ($n = 462$) were excluded from specific analyses on hormone receptor-defined breast cancers. Separate models were used for each specific type of breast cancer, and cases with an invasive cancer other than that under study were censored at the date of diagnosis. Tests for homogeneity of the association between recreational physical activity and risk of different types of breast cancer were based on Wald χ^2 statistics (19).

Whether the relation between recent recreational physical activity and breast cancer risk varied according to BMI, waist circumference, variation in weight, or less recent (5–9 years earlier) physical activity levels was assessed by testing the equality of the HR associated with recent recreational physical activity in the two groups in question (e.g., women with a BMI < and $\geq$25 kg/m^2). Recent variation in weight was calculated as (weight at Q_n − weight at Q_{n-1})/number of years elapsed between completion of Q_n and Q_{n-1}.

When information on recreational physical activity (exposure data) was missing in a questionnaire assessing recreational physical activity level, the woman did not contribute to the models until the next questionnaire without missing information. Missing values for adjustment factors were replaced by the modal or median value when data were missing for less than 5% of women, or else by a missing category.

Model parameters were estimated and compared with likelihood methods and Wald tests. All tests of statistical significance were two sided. All analyses were performed with SAS software, version 9.3 (SAS Institute, Inc.).

Results

Characteristics of the study population

Table 1 reports the baseline characteristics of the 59,308 women. A first primary invasive breast cancer was diagnosed in 2,155 of them, during a total of 505,321 person-years of follow-up (mean duration: 8.5 years; SD 3.4).

The distributions of the levels of recreational physical activities both at the start and at the end of follow-up are shown in Table 2, with recent physical activity levels categorized according to approximate quartiles.

Among the 54,925 women with information on recreational physical activity available in at least two consecutive questionnaires, 21% had moved from $\geq$12 MET-h/week of total recreational physical activity to <12 MET-h/week at least once, and 20% had moved from <12 MET-h/week to a higher level at least once (data not shown).

Recent recreational physical activity and breast cancer risk

Overall, compared with women in the category of lowest recent (within the previous 4 years) recreational activity, women in all other categories had a lower risk of breast cancer (Table 3). Given the absence of heterogeneity beyond the category of lowest recreational physical activity ($P_{\text{homogeneity}} = 0.27$, 0.77, and 0.38 for walking, cycling/sports, and total recreational physical activity, respectively), we have grouped the last three categories together hereafter. Moreover, because risk reductions did not vary appreciably according to type of activity (walking or cycling/sports) even if the risk decrease appeared slightly stronger with walking (Table 3), we have grouped them together in all subsequent analyses. Accordingly, breast cancer risk was lower in women with levels of recent recreational physical activity $\geq$12 MET-h/week compared with women with lower levels (HR, 0.90; 95% CI, 0.82–0.99; Table 3).

Further adjustment for other potential confounders, including other types of physical activities or levels of physical activity during childhood, modified HR estimates only very marginally: in a model with further adjustment for years of schooling (<13/13+), geographic area (into 6 categories), recent mammogram (i.e., performed during the preceding follow-up cycle: yes/no), previous use of oral progestagens (yes/no) or of oral contraceptives (never/less than 10 years ago/more than 10 years ago/ever but unknown recency of use), level of household activities in 1990 (less than 6/6-12/13-22/23+ MET-h/week), recent level of gardening activities (less than 5/5+ MET-h/week), recent level of do-it-

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Table 1. Selected characteristics of participants at the start of postmenopausal follow-up

	Among non cases (n = 57,153) *n* (%)	Among cases (n = 2,155) *n* (%)
Y of birth		
1925–1929	4,623 (8.1)	169 (7.8)
1930–1934	7,856 (13.7)	385 (17.9)
1935–1939	11,616 (20.3)	579 (26.9)
1940–1944	14,435 (25.3)	610 (28.3)
1945–1949	18,623 (32.6)	412 (19.1)
Family history of breast cancer in first-degree relatives		
No	50,598 (88.5)	1,779 (82.6)
Yes	6,555 (11.5)	376 (17.4)
Age at menarche, y		
<13	26,029 (45.5)	1,011 (46.9)
≥13	31,124 (54.5)	1,144 (53.1)
Parity and age at first full-term pregnancy		
Nulliparous	6,649 (11.6)	290 (13.5)
1 or 2 children and first full-term pregnancy at age <30	29,278 (51.2)	1,081 (50.2)
3 or more children and first full-term pregnancy at age <30	16,235 (28.4)	558 (25.9)
First full-term pregnancy at age ≥30	4,991 (8.7)	226 (10.5)
BMI (kg/m^2)		
<18.5	1,871 (3.3)	64 (3.0)
18.5 to <22	21,033 (36.8)	783 (36.3)
22 to <25	20,628 (36.1)	815 (37.8)
≥25	13,621 (23.8)	493 (22.9)
History of benign breast disease		
No	39,783 (69.6)	1,333 (61.9)
Yes	17,370 (30.4)	822 (38.1)
Age at menopause, y		
<49	14,554 (25.5)	528 (24.5)
49 to <51	13,722 (24.0)	566 (26.3)
51 to <53	16,270 (28.5)	578 (26.8)
≥53	12,607 (22.1)	483 (22.4)
Use of menopausal hormone therapy		
Never	23,313 (40.8)	696 (32.3)
Ever	33,840 (59.2)	1,459 (67.7)
Total energy intake[a] in 1993 (cal/d)		
Quartile 1 (≤1,703)	14,335 (25.1)	492 (22.8)
Quartile 2 (1,704–2,039)	15,062 (26.4)	569 (26.4)
Quartile 3 (2,040–2,410)	13,495 (23.6)	528 (24.5)
Quartile 4 (≥2,411)	14,261 (25.0)	566 (26.3)
Alcohol intake in 1993 (g/d)		
Quartile 1 (≤1.4)	14,361 (25.1)	488 (22.6)
Quartile 2 (1.5–6.1)	14,760 (25.8)	521 (24.2)
Quartile 3 (6.2–15.2)	13,797 (24.1)	553 (25.7)
Quartile 4 (≥15.3)	14,235 (24.9)	593 (27.5)
Weight gain during the previous follow-up cycle (kg/y)		
≤1	39,372 (68.9)	1,504 (69.8)
>1	12,234 (21.4)	453 (21.0)
Not known	5,547 (9.7)	198 (9.2)

NOTE: E3N Cohort, 1993–2005 (n = 59,308).
[a]Excluding alcohol.

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Table 2. Distribution of recent recreational physical activity levels

	At the start of follow-up		At the end of follow-up	
	n (%)	Mean (SD)	*n* (%)	Mean (SD)
Walking (MET-h/wk)		15.2 (12.8)		15.4 (12.7)
<6	12,598 (21.2)		11,694 (20.8)	
6 to <12	16,100 (27.1)		14,624 (26.0)	
12 to <24	18,239 (30.8)		17,837 (31.7)	
≥24	12,371 (20.9)		12,118 (21.5)	
Cycling and other sports (MET-h/wk)		10.8 (13.6)		10.5 (13.9)
0	20,936 (35.3)		22,927 (40.7)	
>0 to <12	15,358 (25.9)		12,093 (21.5)	
12 to <24	13,781 (23.2)		12,605 (22.4)	
≥24	9,233 (15.6)		8,648 (15.4)	
Total recreational physical activity (MET-h/wk)		26.0 (19.9)		25.9 (19.9)
<12	14,226 (24.0)		13,793 (24.5)	
12 to <24	17,847 (30.1)		16,637 (29.6)	
24 to <36	12,298 (20.7)		11,632 (20.7)	
≥36	14,937 (25.2)		14,211 (25.3)	

NOTE: For 3,035 women, information on recent recreational physical activity levels was missing at the end of follow-up.
E3N Cohort, 1993–2005 ($n = 59{,}308$).

yourself activities (less than 5/5+ MET-h/week), sports activities between ages 8 years and 15 years outside school (in hours/week: none/1-4/5+/not known), walking between ages 8 years and 15 years (in hours/week: 2 or less/3-4/5+/not known), the HR associated with levels of recent recreational physical activity ≥12 MET-h/week compared with lower levels was equal to 0.89 (95% CI, 0.81–0.99).

Adding recent variation in weight in our model did not modify our results: the HR associated with levels of recent recreational physical activity ≥12 MET-h/week compared with lower levels was equal to 0.90 (95% CI, 0.82–0.99). Removing BMI from the model produced similarly marginal modifications: the HR associated with levels of recent recreational physical activity ≥12 MET-h/week compared with lower levels was equal to 0.90 (95% CI, 0.81–0.99).

In a model including simultaneously recent (within the previous 4 years) and less recent (5–9 years earlier) recreational physical activity, activity 5 to 9 years earlier was not significantly associated with breast cancer risk ($HR_{\geq 12\ \text{MET-h/week vs.} <12\ \text{MET-h/week}}$, 1.04; 95% CI, 0.92–1.18), whereas breast cancer risk was still significantly lower in women with levels of recent activity ≥12 MET-h/week compared with women with lower levels of recent activity (HR, 0.88; 95% CI, 0.78–0.98).

Recent recreational physical activity and breast cancer risk by ER/PR subtype

Cancer cases were cross-classified by hormone receptor status (Table 4). Nonsignificant inverse associations were observed for all types of breast cancer except ER^-/PR^- ($P_{\text{homogeneity}} = 0.57$).

Interactions between recent recreational physical activity and BMI, waist circumference, weight changes, and less recent physical activity

Risk reductions associated with recent recreational physical activity were of the same order of magnitude regardless of BMI, waist circumference, or recent weight gain ($P_{\text{homogeneity}}$ between 0.43 and 0.93; Table 5).

Less recent (5–9 years earlier) recreational physical activity did not either modify the association between recent recreational physical activity and breast cancer risk ($P = 0.92$; Table 5). Among women with low levels of physical activity (<12 MET-h/week) 5 to 9 years earlier, those who became more active (≥12 MET-h/week) recently had a nonsignificantly decreased risk of breast cancer compared with those who did not (HR, 0.88; 95% CI, 0.72–1.09). Conversely, among women with levels of physical activity ≥12 MET-h/week 5 to 9 years earlier, those who became less active (<12 MET-h/week) had a significantly increased risk of breast cancer compared with those who did not (HR, 1.16; 95% CI, 1.01–1.35; Table 5).

A supplementary model with the reference category comprising the least active women at both time points (within the previous 4 years and 5–9 years earlier) showed that women who were active 5 to 9 years earlier but became less active had no significantly reduced risk of breast cancer (HR, 1.06; 95% CI, 0.87–1.29; data not shown).

Discussion

In this large prospective study, recent (within the previous 4 years) recreational physical activity was associated with a decrease of approximately 10% in breast cancer

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Table 3. HRs for invasive breast cancer according to levels of recreational physical activity within the previous 4 years

	No. of cases	Multivariable HR[a]	95% CI
Walking (MET-h/wk)			
<6	453	1.00	(reference)
6 to <12	476	0.84	0.74–0.96
12 to <24	645	0.87	0.77–0.98
≥24	523	0.93	0.82–1.06
P_{trend}[b]		0.93	
<6	453	1.00	(reference)
≥6	1,644	0.88	0.79–0.98
Cycling and other sports (MET-h/wk)			
0	853	1.00	(reference)
>0 to <12	468	0.94	0.84–1.06
12 to <24	452	0.94	0.84–1.06
≥24	324	0.99	0.87–1.12
P_{trend}[b]		0.66	
0	853	1.00	(reference)
>0	1,244	0.95	0.87–1.04
Total recreational physical activity (MET-h/wk)			
<12	521	1.00	(reference)
12 to <24	567	0.86	0.76–0.97
24 to <36	440	0.92	0.81–1.05
≥36	569	0.93	0.83–1.05
P_{trend}[b]		0.69	
<12	521	1.00	(reference)
≥12	1,576	0.90	0.82–0.99

NOTE: Fifty-eight breast cancer cases occurred among women with missing information on level of recreational physical activity within the previous 4 years. E3N Cohort, 1993–2005 ($n = 59,308$).

[a]Adjusted for age (time scale), family history of breast cancer in first-degree relatives, age at menarche, parity and age at first full-term pregnancy, BMI, history of benign breast disease, age at menopause, use of menopausal hormone therapy, total energy intake excluding alcohol, and alcohol intake. Further stratified by year of birth. See Table 1 for categories/cutoffs used. Walking and cycling/sports activities are mutually adjusted.

[b]Tests for linear trends were performed with level of recreational physical activity (in MET-h/wk) as a continuous variable.

risk, with no apparent dose–response relation beyond 12 MET-h/week. This association was independent of the level of less recent (5–9 years earlier) recreational physical activity, itself not associated with breast cancer risk. It was also independent of BMI, waist circumference, and recent weight gain. Associations did not vary significantly across ER/PR subtypes. Our findings of a modest decrease in risk associated with recent recreational physical activity appeared slightly more marked with walking than with cycling and other sports activities, but there was no significant heterogeneity between these two types of physical activity.

The decrease in risk observed with a ≥12 MET-h/week exercise level is consistent with the World Cancer Research Fund recommendations of walking at least 30 minutes daily (4). On the other hand, most studies have found stronger associations (1, 2) and an inverse dose–response relation (1, 2, 4). However, it is difficult to compare reports, because of differences in the types and timing of the activities investigated and genetic and anthropometric differences in populations (1). The questions used to assess the level of physical activity in the E3N questionnaires sent in 1993, 1997, and 2002 may contribute to the absence of a dose–effect relation in this study. They were indeed derived from the short EPIC questionnaire (20), which was found to rank participants satisfactorily with regard to their physical activity level (14–16), but to be less suitable for estimating energy expenditure (15), due to limited information on the intensity of leisure-time physical activity.

Our results were consistent with those of most (2) but not all (21–23) of the studies examining BMI, in that they did not find it to be an intermediate factor or a potential effect modifier in the relation between physical activity and breast cancer risk. However, the leanness of E3N women did not allow to explore the effect in higher categories of BMI or waist circumference. Similarly, most studies did not observe modifications in this relation according to hormone receptor status during postmenopause (6, 10, 13, 22–26). The risk reduction was limited to ER^- (27) and PR^+ (28) subtypes in two prospective studies and apparent only for postmenopausal ER^+/PR^- (29) and ER^+/PR^+ (25) cancers in two other studies (no tests for homogeneity). However, in our study, the fact that the association with recreational physical activity did not vary significantly between ER/PR subtypes may also be due to a lack of statistical power, owing to the small number of cases in ER^- subtypes.

Only a few studies simultaneously considered recent and earlier physical activity, and their results conflict (6–13). In line with our findings, in the Nurses' Health Study (13), women who were active close to menopause but not later did not have a lower risk of breast cancer than the least active women (<9 MET-h/week) during both periods, whereas women who were recently active had a risk 10% lower, regardless of whether or not they were active around menopause. However, the two assessments of physical activity might have been separated by a period of up to 20 years. To our knowledge, our study is the first to independently assess the association between breast cancer risk and recreational physical activity both 5 to 9 years earlier and within the previous 4 years, and we found that only recent recreational physical activity was associated with a significantly reduced risk. This suggests that starting recreational physical activity may be followed relatively rapidly by a reduction in breast cancer risk in postmenopausal women, a reduction that may disappear a few years after the activity stops.

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Table 4. HRs for hormone receptor–defined invasive breast cancer according to level of recreational physical activity within the previous 4 years

Recreational physical activity (MET-h/wk)	ER^+/PR^+ No. of cases	ER^+/PR^+ Multivariable HR[a]	ER^+/PR^+ 95% CI	ER^+/PR^- No. of cases	ER^+/PR^- Multivariable HR[a]	ER^+/PR^- 95% CI	ER^-/PR^+ No. of cases	ER^-/PR^+ Multivariable HR[a]	ER^-/PR^+ 95% CI	ER^-/PR^- No. of cases	ER^-/PR^- Multivariable HR[a]	ER^-/PR^- 95% CI
<12	238	1.00	(reference)	94	1.00	(reference)	16	1.00	(reference)	61	1.00	(reference)
≥12	721	0.90	0.78–1.05	284	0.87	0.69–1.10	33	0.62	0.34–1.13	205	1.00	0.75–1.33
$P_{homogeneity}$						0.57						

Recreational physical activity (MET-h/wk)	ER^+ No. of cases	ER^+ Multivariable HR[a]	ER^+ 95% CI	ER^- No. of cases	ER^- Multivariable HR[a]	ER^- 95% CI	PR^+ No. of cases	PR^+ Multivariable HR[a]	PR^+ 95% CI	PR^- No. of cases	PR^- Multivariable HR[a]	PR^- 95% CI
<12	332	1.00	(reference)	77	1.00	(reference)	254	1.00	(reference)	155	1.00	(reference)
≥12	1,005	0.89	0.79–1.01	238	0.92	0.71–1.19	754	0.88	0.77–1.02	489	0.92	0.77–1.10
$P_{homogeneity}$			0.87						0.74			

NOTE: Forty-one breast cancer cases occurred among women with missing information on level of recreational physical activity within the previous 4 years. E3N Cohort, 1993–2005 ($n = 58,846$).

[a]Adjusted for age (time scale), family history of breast cancer in first-degree relatives, age at menarche, parity and age at first full-term pregnancy, BMI, history of benign breast disease, age at menopause, use of menopausal hormone therapy, total energy intake excluding alcohol, and alcohol intake. Further stratified by year of birth. See Table 1 for the categories/cutoffs used.

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Table 5. HRs for invasive breast cancer according to level of recreational physical activity within the previous 4 years, stratified by BMI, waist circumference, variation in weight, and less recent level of recreational physical activity

Recent recreational physical activity (MET-h/wk)	No. of cases	Multivariable HR[a]	95% CI		No. of cases	Multivariable HR[a]	95% CI
	BMI < 25 kg/m²				BMI ≥25 kg/m²		
<12	364	1.00	(reference)		157	1.00	(reference)
≥12	1,220	0.88	0.78–0.98		356	0.96	0.80–1.16
$P_{\text{homogeneity}}$				0.43			
	WC < 75 cm				WC ≥75 cm		
<12	142	1.00	(reference)		283	1.00	(reference)
≥12	566	0.90	0.75–1.08		747	0.90	0.78–1.03
$P_{\text{homogeneity}}$				0.93			
	Recent annual weight gain[b] ≤ 1 kg				Recent annual weight gain[b] >1 kg		
<12	366	1.00	(reference)		119	1.00	(reference)
≥12	1,185	0.90	0.80–1.02		296	0.86	0.70–1.07
$P_{\text{homogeneity}}$				0.78			
	Recreational physical activity 5–9 y earlier <12 MET-h/wk				Recreational physical activity 5–9 y earlier ≥12 MET-h/wk		
<12	176	1.00	(reference)		220	1.00	(reference)
≥12	181	0.88	0.72–1.09		1,008	0.86	0.74–0.99
$P_{\text{homogeneity}}$				0.92			
<12					220	1.16	1.01–1.35
≥12					1,008	1.00	(reference)

NOTE: E3N Cohort, 1993–2005.

Abbreviation: WC, waist circumference.

[a]Adjusted for age (time scale), family history of breast cancer in first-degree relatives, age at menarche, parity and age at first full-term pregnancy, BMI, history of benign breast disease, age at menopause, use of menopausal hormone therapy, total energy intake excluding alcohol, and alcohol intake. Further stratified by year of birth. See Table 1 for the categories/cutoffs used.

[b]kg gained per year during the previous follow-up cycle.

Contrary to most studies, which have not found that the relation between physical activity and breast cancer risk was modified by weight changes before inclusion (9, 11, 13, 21, 30), three articles report that the risk decrease associated with baseline physical activity is restricted to postmenopausal women with limited weight gain between youth and baseline (22, 31, 32). However, a weight gain before baseline may be associated with a decrease in physical activity after baseline (33). A strength of our study is that weight variations were updated every 2 to 3 years, that allowed us to show that the relation between physical activity and breast cancer risk was similar regardless of recent weight changes.

The lack of significant change in associations according to ER subtype or after adjustment for BMI suggests that the mechanisms involved are also nonhormonal; they might thus include decreased inflammation (34), immunomodulation (34), interference with the glycolytic switch (35), or decreased DNA damage (34). Physical activity also improves insulin sensitivity independently of changes in body weight or composition (34): it decreases estradiol bioavailability by increasing SHBG levels (1). Most exercise intervention trials have reported a reduction in fat mass with at least 10 MET-h/week of physical activity, even without weight loss (36); the explanation probably lies in the decrease in plasma estradiol levels found by three exercise intervention studies in postmenopausal overweight/obese women (1).

Strengths of our study include its prospective design, updated anthropometric and physical activity data, large cohort size, large number of breast cancer cases and their high rate of histologic confirmation, and detailed information on potential confounders and effect modifiers. The main limitations are the probable underestimation of high levels of physical activity due to limited information on the intensity of recreational physical activity (15). Self-report of physical activity is another limitation, prone to nondifferential recall bias. ER assay results abstracted

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from pathology reports seem a reasonable alternative to central laboratory testing for large population-based studies seeking to assess ER/PR status, despite the numerous laboratories involved (37). Because early breast cancers are unlikely to affect physical activity levels before being diagnosed, and our cohort had very few breast cancer cases that were at an advanced stage at diagnosis, reverse causation is unlikely.

In summary, in our study, recent recreational physical activity, even at a modest level, was associated with a breast cancer risk reduction in postmenopause; this association seemed to attenuate a few years after activity stops. Because the women participating in the cohort are fairly slender teachers, our results should be replicated in populations with different genetic, anthropometric, and occupational characteristics.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Authors' Contributions

Conception and design: A. Fournier, G. Dos Santos, S. Mesrine
Development of methodology: A. Fournier, G. Dos Santos, S. Mesrine
Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): F. Clavel-Chapelon
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): A. Fournier, G. Dos Santos, G. Guillas
Writing, review, and/or revision of the manuscript: A. Fournier, J. Bertsch, M. Duclos, M.-C. Boutron-Ruault, F. Clavel-Chapelon, S. Mesrine
Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): A. Fournier, M.-C. Boutron-Ruault
Study supervision: J. Bertsch, M.-C. Boutron-Ruault, S. Mesrine

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