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Effect of Physical Activity on Women at Increased Risk of Breast Cancer: Results from the E3N Cohort Study

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Abstract

Purpose: **There is a need to investigate the type, duration, frequency, and intensity of physical activity that are critical to reduce the risk of breast cancer, and if this relation differs among subgroups of women.**
Methods: **We analyzed the relation between physical activity and breast cancer incidence between 1990 and 2002 (n = 3,424 cases), among 90,509 women of the French E3N cohort, ages between 40 and 65 years in 1990. We gave special attention to effect modification by body mass index (BMI), family history of breast cancer, parity, and hormone replacement therapy (HRT).**
Results: **A linear decrease in risk of breast cancer was observed with increasing amounts of moderate (P_{trend} < 0.01) and vigorous (P_{trend} < 0.0001) recreational activities. Compared with women who reported no recreational activities, those with more than five weekly hours of vigorous recreational activity had a relative risk of 0.62 (0.49-0.78). This decrease was still observed among women who were overweight, nulliparous, had a family history of breast cancer, or used HRT. Compared with the whole cohort, among nulliparous women, the reduction of risk observed was of a higher magnitude, although the test for heterogeneity did not reach statistical significance.**
Conclusion: **A risk reduction of breast cancer was particularly observed with vigorous recreational activity. Further investigations are needed to confirm that intensity is an important variable to consider in risk reduction and to identify the precise biological mechanisms involved in such a risk reduction.** (Cancer Epidemiol Biomarkers Prev 2006; 15(1):57–64)

Introduction

In 1998, Dorgan (1) underlined that although a decrease in risk of breast cancer with increasing levels of physical activity is intuitively appealing, there was at that time a disappointing lack of consistency in the findings of epidemiologic studies. Since 1998, numerous additional studies have been published, and the evidence of an inverse association between breast cancer risk and physical activity was in 2002 classified as ''convincing'' (2, 3). The risk reduction is, on average, 30% to 40% for the most physically active women compared with the least active women, and there is also evidence for a dose-response relation (2-4). Several biological mechanisms have been postulated for how physical activity may influence breast cancer risk, including an effect on endogenous estrogens, insulin, insulin-like growth factors, obesity and weight control, immune function, and other metabolic factors (3, 5, 6). Further research is needed, however, to define more precisely the exact nature of this association. It is still unclear which type, duration, frequency, and intensity of physical activity are needed to reduce breast cancer risk, and whether or not the relation between physical activity and breast cancer risk differs among subgroups of women.

To address some of the remaining issues in the association between physical activity and breast cancer risk, we examined this association in the E3N cohort study with particular emphasis on the issues of the level of activity and on the potential effect modification by other breast cancer risk factors.

Materials and Methods

The E3N cohort is composed of 98,995 women living in France, who are insured with the Mutuelle Générale de l'Education Nationale, a national health insurance scheme primarily covering teachers. Participants were ages 40 to 65 years when first recruited into the cohort between June 1990 and November 1991. The baseline questionnaire contained questions on reproductive life history, menopause, history of benign breast disease, first-degree family history of breast cancer, and anthropometric measures. Women were also asked to report their current physical activity habits. Specifically, they reported their recreational and household activity in separate questions that also asked about the frequency and duration of the activities that were done.

Self-administered follow-up questionnaires, with updates on some baseline exposures, were sent out approximately every 2 years thereafter. All of them asked participants whether or not breast cancer had been diagnosed, requesting the addresses of their physicians and permission to contact them to obtain pathology reports. Deaths in the cohort were ascertained from reports by family members and by searching the insurance company (Mutuelle Générale de l'Education Nationale) file that contains information on vital status. Information on cause of death was obtained from the French National Service on Causes of Deaths (http://sc8.vesinet.inserm.fr:1080/accueil_fr.html). Information on nonrespondents was obtained from the Mutuelle Générale de l'Education Nationale file on reimbursement of hospital fees. The third questionnaire was on dietary intake in the previous

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Table 1. Baseline (1990) characteristics of breast cancer according to total physical activity, E3N study

Total physical activity (MET-h/wk)	Quartile 1, <28.3 (n = 15,351), % or mean (SD)*	Quartile 2, [28.3-41.8](n = 14,855), % or mean (SD)	Quartile 3, [41.8-57.8](n = 15,052), % or mean (SD)	Quartile 4, ≥57.8 (n = 15,041), % or mean (SD)
Age at inclusion, y	48.9 (6.6)	48.6 (6.4)	48.7 (6.5)	49.5 (6.8)
Age at menarche, y	12.7 (1.4)	12.7 (1.4)	12.8 (1.4)	12.8 (1.4)
Age at FFTP, y	25.2 (4.2)	24.9 (4.0)	24.7 (4.0)	24.4 (3.8)
Age at menopause †, y	48.9 (4.4)	48.9 (4.4)	48.9 (4.4)	49.0 (4.5)
Years of education	13.6 (2.5)	13.5 (2.5)	13.5 (2.5)	13.2 (2.7)
Nulliparous	2,314 (15.1%)	1,669 (11.2%)	1,393 (9.3%)	1,454 (9.7%)
Employed	13,337 (87.2%)	12,287 (82.9%)	11,475 (76.5%)	9,459 (63.1%)
Married	11,501 (74.9%)	11,778 (79.3%)	12,193 (81.0%)	12,309 (81.8%)
Oral contraceptives users	6,829 (44.5%)	6,771 (45.6%)	6,643 (44.1%)	6,018 (40.0%)
Benign breast disease history	3,686 (24.0%)	3,470 (23.4%)	3,559 (23.6%)	3,382 (22.5%)
First-degree relative breast cancer	1,806 (11.8%)	1,685 (11.4%)	1,724 (11.5%)	1,657 (11.1%)

*Mean (SD) or %, calculated from participants with nonmissing data for each variable.
†Among the 37,932 postmenopausal women at baseline.

12 months. More details on this questionnaire are provided elsewhere (7). Participants of the E3N cohort who responded to it (n = 74,524) were included in the European Prospective Investigation into Cancer and Nutrition (8).

Menopause was recorded in each follow-up questionnaire. To ensure that the constructed menopause variables were as accurate as possible, the whole set of answers on date and type of menopause (natural or the result of bilateral oophorectomy, chemotherapy, radiotherapy, or other treatments), date of last menstruation, date of start of menopausal symptoms, and date of hysterectomy, if appropriate, were taken into account. Postmenopause was defined as the cessation of periods for natural or other reasons. Women for whom age at menopause could not be determined (e.g., women that reported a hysterectomy but gave no information on oophorectomy or menopausal symptoms, or women that indicated they were postmenopausal without any other information) were considered as menopausal at age 47 if menopause was artificial and at 51 otherwise, ages that corresponds to the median age at menopause when artificial or natural, in our cohort. We also excluded from the analyses 33 women who never menstruated.

Endpoints and Assessments of Breast Cancer Cases. Follow-up time for the present analysis was between return of the baseline questionnaire in 1990 to 1991 and July 2002. Person-years were accrued up to the date of breast cancer diagnosis, date of death, date of last questionnaire returned, or July 2002 (for replies to the questionnaire received after July 2002), whichever occurred first. Women lost to follow-up between the baseline questionnaire and the second questionnaire (n = 2,601) were excluded. We also excluded women that declared a prevalent cancer at baseline other than a basal cell carcinoma or an incident first cancer other than a breast cancer (n = 5,447) and women that declared an incident ductal carcinoma *in situ* (n = 405). Finally, 90,509 women were included in the present analysis, and 85.7% (n = 77,565) were

Table 2. Baseline (1990) physical activity characteristics of breast cancer cases and noncases, E3N study

Total physical activity (MET-h/wk)	Quartile 1, <28.3 (n = 15,351), %	Quartile 2, [28.3-41.8](n = 14,855), %	Quartile 3, [41.8-57.8](n = 15,052), %	Quartile 4, ≥57.8 (n = 15,041), %
Walking (m/d)				
<500	23.1*	13.7	17.9	16.9
500-2,000	54.6	59.5	57.0	50.0
≥2,000	22.3	26.8	25.1	33.1
Flight stairs (n/d)				
0	54.3	35.2	33.0	20.2
1-4	41.6	54.5	54.7	55.6
≥5	4.1	10.3	12.3	24.1
Moderate recreational activity (h/wk)				
0	59.1	22.3	10.3	3.8
1-4	40.1	77.7	89.6	57.2
5-13	0.0	0.0	0.1	33.7
≥14	0.0	0.0	0.0	5.3
Vigorous recreational activity (h/wk)				
0	98.6	81.3	37.2	20.8
1-2	1.4	18.6	60.2	35.7
3-4	0.0	0.1	2.5	29.6
≥5	0.0	0.0	0.1	13.9
Light household activity (h/wk)				
0	7.4	2.3	0.7	0.8
1-4	91.6	84.8	63.9	38.1
5-13	1.0	12.7	33.3	46.5
≥14	0.0	0.2	2.1	14.6
Heavy household activity (h/wk)				
0	61.5	21.0	6.8	8.9
1-2	34.5	59.8	66.4	45.3
3-4	3.9	17.1	22.4	30.6
≥5	0.1	2.1	4.4	15.2

*%, calculated from participants with nonmissing data for each variable.

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still respondent to the 7th questionnaire. Among the 90,509 women included, 3,491 incident first primary breast cancers were reported during the follow-up (mean = 11.4 years, SD = 2.4 years). We obtained pathology reports for 94.9% of them (n = 3,031). Because the rate of histologic confirmation was very high (97.8%, n = 2,964), we decided to include in our analyses breast cancer cases whose pathology reports had not yet been obtained (n = 460). Our present study is based on 3,424 incident first primary breast cancers.

Assessment of Physical Activity. Assessment of habitual physical activity at baseline was based on six questions on the usual distance walked daily (<500, [500-2,000[, and ≥2,000 m), the average number of flights of stairs climbed daily (0, [1-4], and ≥5), the average amount of time spent weekly doing light household activity (0, [1-4], [5-13], and ≥14 hours) and heavy household activity (0, [1-4], and ≥5 hours), and the average amount of time spent weekly doing moderate recreational activity (0, [1-4], [5-13], and ≥14 hours) and vigorous recreational activity (0, [1-4], and ≥5 hours).

A recreational physical activity score was estimated by multiplying the metabolic equivalent cost (MET) of walking and moderate and vigorous recreational activities by their frequency and duration. A value of 3 METs for walking and 6 METs and 9 METs for moderate and vigorous recreational activities, respectively, was assigned, according to the Compendium of Physical Activities (9). Additionally, a total physical activity score was estimated in a similar way with all the variables describing physical activity in our questionnaire. A value of 8 METs for climbing stairs and 2.5 METs and four METs for light and heavy household activities, respectively, was assigned. The two scores expressed in MET-hours/wk were divided into quartiles for the analyses, based on their distribution in the total population.

Statistical Analyses. Risk estimates were obtained using Cox's proportional hazard models, with subjects' age as the time scale. For each physical activity variable, the least active women were considered as the reference category. Particularly, women who reported neither moderate nor vigorous

Table 3. RR estimates of breast cancer associated with indices of physical activity, cohort E3N, France, 1990 and 2002

Variable	Cases	Total person-years	Age-adjusted RR	Multivariate* RR
Walking (m/d)				
<500	1,185	351,880	1.00 (reference)	1.00 (reference)
[500-2,000]	1,738	501,050	1.00 (0.93-1.08)	1.03 (0.95-1.11)
≥2,000	402	130,171	0.86 (0.77-0.97)	0.91 (0.81-1.02)
P_{trend}			0.07	0.45
Flight stairs (n/d)				
0	619	182,866	1.00 (reference)	1.00 (reference)
[1-4]	1,870	555,279	1.01 (0.92-1.10)	0.99 (0.90-1.08)
≥5	884	259,327	1.02 (0.92-1.13)	1.00 (0.90-1.12)
P_{trend}			0.64	0.84
Light household activity (h/wk)				
0	83	23,525	1.00 (reference)	1.00 (reference)
[1-4]	2,325	665,983	0.99 (0.80-1.24)	1.02 (0.82-1.28)
[5-13]	672	210,378	0.88 (0.70-1.11)	0.95 (0.75-1.20)
≥14	101	38,482	0.70 (0.52-0.94)	0.82 (0.61-1.11)
P_{trend}			<0.0001	<0.05
Heavy household activity (h/wk)				
0	674	193,248	1.00 (reference)	1.00 (reference)
[1-2]	1,490	446,671	0.94 (0.86-1.03)	0.98 (0.89-1.07)
[3-4]	537	169,267	0.88 (0.79-0.99)	0.94 (0.84-1.06)
≥5	174	55,313	0.87 (0.73-1.02)	0.97 (0.81-1.15)
P_{trend}			<0.05	0.47
Moderate recreational activity (hrs/week)				
Inactive†	668	175,292	1.00 (reference)	1.00 (reference)
0	56	19,010	0.82 (0.62-1.07)	0.80 (0.60-1.05)
[1-4]	2,031	616,798	0.87 (0.80-0.95)	0.87 (0.79-0.94)
[5-13]	253	77,703	0.81 (0.70-0.94)	0.86 (0.74-0.99)
≥14	39	12,009	0.82 (0.59-1.13)	0.89 (0.65-1.24)
P_{trend}			<0.01	<0.01
Vigorous recreational activity (h/wk)				
Inactive†	668	175,292	1.00 (reference)	1.00 (reference)
0	1,097	319,096	0.91 (0.88-1.00)	0.90 (0.81-0.99)
[1-2]	845	258,953	0.87 (0.79-0.96)	0.88 (0.79-0.97)
[3-4]	238	78,163	0.80 (0.69-0.92)	0.82 (0.71-0.95)
≥5	93	38,082	0.61 (0.49-0.76)	0.62 (0.49-0.78)
P_{trend}			<0.0001	<0.0001
Total recreational activity (MET-h/wk)				
Inactive†	653	171,415	1.00 (reference)	1.00 (reference)
<16.0	342	109,705	0.84 (0.74-0.96)	0.82 (0.71-0.93)
[16.0-22.3]	532	147,371	0.95 (0.85-1.07)	0.94 (0.84-1.06)
[22.3-33.8]	644	196,880	0.87 (0.78-0.97)	0.88 (0.79-0.98)
≥33.8	466	152,207	0.78 (0.69-0.88)	0.81 (0.72-0.92)
P_{trend}			<0.001	<0.01
Total physical activity (MET-h/wk)				
<28.3	607	172,963	1.00 (reference)	1.00 (reference)
[28.3-41.8]	606	168,853	1.02 (0.91-1.15)	1.05 (0.93-1.17)
[41.8-57.8]	542	171,208	0.90 (0.80-1.01)	0.94 (0.83-1.05)
≥57.8	529	171,363	0.85 (0.75-0.95)	0.90 (0.80-1.02)
P_{trend}			<0.001	<0.05

*Adjusted for BMI, menopausal status, HRT use, age at menarche, age at first full-term pregnancy, parity, marital status, use of oral contraceptives, first-degree family history of breast, personal history of benign breast disease, and employed (yes/no).
†Women that reported no moderate nor vigorous recreational activity were considered as ''inactive.''

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Table 4. RR estimates of breast cancer associated with indices of physical activity, according different risk factors, cohort E3N, France, 1990 and 2002

Variable	Cases	Total person-years	Multivariate* RR	$P_{interaction}$	Cases	Total person-years	Multivariate* RR	$P_{interaction}$
	BMI ≥ 25 kg/m^2				Family history of breast cancer			
Walking (m/d)								
<500	212	62,079	1.00 (reference)	0.90	215	40,732	1.00 (reference)	0.47
[500-2,000]	288	80,274	1.02 (0.86-1.22)		336	57,310	1.14 (0.96-1.36)	
≥2,000	53	17,211	0.91 (0.67-1.22)		77	14,991	0.99 (0.75-1.29)	
P_{trend}			0.72				0.69	
Flight stairs (n/d)								
0	126	32,587	1.00 (reference)	0.96	118	20,388	1.00 (reference)	0.41
[1-4]	289	91,265	0.84 (0.68-1.04)		361	64,088	1.01 (0.81-1.25)	
≥5	147	38,211	1.02 (0.80-1.30)		156	30,074	0.95 (0.74-1.21)	
P_{trend}			0.72				0.65	
Light household activity (h/wk)								
0	12	3,358	1.00 (reference)	0.89	20	2,744	1.00 (reference)	0.91
[1-4]	338	101,603	1.00 (0.56-1.79)		424	76,325	0.78 (0.50-1.23)	
[5-13]	142	38,043	1.11 (0.61-2.00)		129	24,271	0.74 (0.46-1.20)	
≥14	22	8,885	0.71 (0.35-1.46)		20	3,994	0.70 (0.37-1.33)	
P_{trend}			0.71				0.27	
Vigorous household activity (h/wk)								
0	100	27,732	1.00 (reference)	0.97	135	22,578	1.00 (reference)	0.55
[1-2]	238	72,527	0.91 (0.72-1.15)		286	50,891	0.93 (0.75-1.15)	
[3-4]	114	30,371	1.04 (0.79-1.36)		96	18,874	0.87 (0.66-1.13)	
≥5	38	12,585	0.86 (0.58-1.25)		35	6,462	0.89 (0.60-1.32)	
P_{trend}			0.78				0.30	
Moderate recreational activity (h/wk)								
Inactive†	144	39,552	1.00 (reference)	0.70	140	19,996	1.00 (reference)	0.73
0	6	2,236	0.73 (0.32-1.65)		10	2,177	0.69 (0.36-1.31)	
[1-4]	320	91,785	0.94 (0.77-1.15)		353	70,348	0.72 (0.59-0.89)	
[5-13]	38	11,878	0.81 (0.56-1.17)		48	8,826	0.79 (0.56-1.10)	
≥14	6	1,740	0.88 (0.38-2.00)		12	1,444	1.23 (0.68-2.23)	
P_{trend}			0.37				0.18	
Vigorous recreational activity (h/wk)								
Inactive†	144	39,552	1.00 (reference)	0.35	140	19,996	1.00 (reference)	0.24
0	197	53,042	1.00 (0.80-1.24)		207	37,012	0.81 (0.65-1.01)	
[1-2]	124	36,391	0.95 (0.74-1.21)		151	28,976	0.76 (0.60-0.97)	
[3-4]	18	9,289	0.50 (0.30-0.82)		42	8,821	0.68 (0.48-0.97)	
≥5	13	4,686	0.71 (0.40-1.27)		17	4,669	0.51 (0.30-0.87)	
P_{trend}			<0.01				<0.01	
Total recreational activity (MET-h/wk)								
Inactive†	142	38,631	1.00 (reference)	0.93	136	19,596	1.00 (reference)	0.69
<16.0	57	18,478	0.83 (0.61-1.13)		64	13,027	0.70 (0.51-0.95)	
[16.0-22.3]	97	23,785	1.10 (0.84-1.42)		95	16,853	0.83 (0.64-1.09)	
[22.3-33.8]	106	28,491	1.03 (0.79-1.32)		106	21,823	0.73 (0.56-0.94)	
≥33.8	56	20,627	0.71 (0.51-0.97)		92	17,292	0.77 (0.59-1.02)	
P_{trend}			0.16				0.09	
Total physical activity (MET-h/wk)								
<28.3	108	32,154	1.00 (reference)	0.94	131	20,383	1.00 (reference)	0.36
[28.3-41.8]	117	27,901	1.27 (0.97-1.65)		114	19,130	0.95 (0.73-1.22)	
[41.8-57.8]	93	28,030	0.99 (0.74-1.31)		91	19,715	0.75 (0.57-0.98)	
≥57.8	85	26,971	0.91 (0.68-1.22)		107	18,726	0.90 (0.69-1.17)	
P_{trend}			0.27				0.13	

*Adjusted for BMI, menopausal status, HRT use, age at menarche, age at first full-term pregnancy, parity, marital status, use of oral contraceptives, first-degree family history of breast, personal history of benign breast disease, and employed (yes/no).
†Women that reported no moderate nor vigorous recreational activity were considered as ''inactive.''

recreational activities were considered as the common reference when we estimated the relative risks (RR) of breast cancer associated with moderate, vigorous, and total recreational activities. The confounding factors taken into consideration were body mass index [BMI = weight/height (kg/m^2)] at baseline divided into quartiles (cut points: 20.4, 22.0, and 24.0 kg/m^2), history of breast cancer in first-degree relatives (yes/no), age at menarche (cut points: 12, 13, and 14), age at first full-term pregnancy (cut points: 23, 26, and 30 years), parity (0, 1-3, and ≥4), history of benign breast disease (yes/no), marital status (if ever married or not), employment at enrollment (yes/no), and use of oral contraceptive (ever/never). Other confounding variables (years of education, tobacco use, and alcohol consumption) were first included in the analyses and then removed because they were not statistically linked to the risk of breast cancer and did not influence the other risk estimates. Because all results were very similar for premenopausal and postmenopausal breast cancer risks, only results for these two subgroups combined are presented. As menopausal status changed during follow-up for 45,573 women, it was included in Cox's models as a time-dependent variable. Adjustment for hormone replacement therapy (HRT) use was done in combination with menopausal status, using a variable defined according to HRT use, and to menopausal status as time-dependent variable.

Effect modification by BMI, family history of breast cancer, nulliparity, and HRT use was tested using heterogeneity tests in which we tested the equality of trends in risk of breast cancer with each type of physical activity in the two groups considered for their effect modification. For instance, we compared the trend in risk of breast cancer with vigorous recreational activity among women with and without family history of breast cancer.

Table 4. RR estimates of breast cancer associated with indices of physical activity, according different risk factors, cohort E3N, France, 1990 and 2002 (Cont'd)

Cases	Total person-years	Multivariate* RR	$P_{interaction}$	Cases	Total person-years	Multivariate* RR	$P_{interaction}$
Nulliparous women				HRT users			
136	36,589	1.00 (reference)	0.21	575	146,867	1.00 (reference)	0.54
256	60,446	1.15 (0.94-1.41)		855	213,832	0.99 (0.86-1.14)	
75	19,710	1.08 (0.82-1.44)		195	56,275	0.98 (0.84-1.14)	
		0.35				0.81	
75	21,834	1.00 (reference)	0.18	296	75,754	1.00 (reference)	0.49
282	67,096	1.21 (0.93-1.57)		918	234,854	1.02 (0.92-1.14)	
116	29,672	1.15 (0.86-1.55)		435	112,523	0.91 (0.77-1.07)	
		0.43				0.49	
15	5,237	1.00 (reference)	0.16	46	10,376	1.00 (reference)	0.32
371	88,813	1.49 (0.89-2.50)		1,126	285,298	0.93 (0.68-1.25)	
49	14,396	1.27 (0.70-2.28)		330	87,853	0.88 (0.64-1.21)	
6	2,003	1.12 (0.43-2.90)		54	15,124	0.89 (0.59-1.33)	
		0.82				0.30	
121	31,362	1.00 (reference)	0.54	333	83,058	1.00 (reference)	0.45
193	49,553	1.02 (0.81-1.28)		711	187,661	0.97 (0.85-1.11)	
50	13,294	1.02 (0.72-1.43)		263	70,392	0.97 (0.82-1.15)	
11	3,442	0.92 (0.49-1.73)		79	21,226	1.02 (0.79-1.31)	
		0.83				0.91	
101	22,996	1.00 (reference)	0.23	300	71,345	1.00 (reference)	0.65
4	2,478	0.39 (0.14-1.05)		26	7,714	0.83 (0.55-1.25)	
277	68,747	0.93 (0.74-1.18)		999	264,255	0.90 (0.79-1.03)	
47	9,890	1.15 (0.81-1.63)		132	34,178	0.90 (0.73-1.11)	
3	1,652	0.46 (0.14-1.45)		20	5,060	0.98 (0.62-1.54)	
		0.83				0.32	
101	22,996	1.00 (reference)	0.09	300	71,345	1.00 (reference)	0.45
149	36,382	0.94 (0.73-1.22)		533	137,972	0.91 (0.79-1.05)	
114	27,618	0.98 (0.74-1.28)		415	108,052	0.94 (0.80-1.09)	
31	9,197	0.81 (0.54-1.22)		123	33,014	0.91 (0.73-1.12)	
11	5,601	0.42 (0.22-0.82)		48	15,914	0.70 (0.51-0.96)	
		0.18					
99	22,431	1.00 (reference)	0.41	296	69,769	1.00 (reference)	0.67
33	10,660	0.69 (0.46-1.04)		168	46,437	0.85 (0.70-1.03)	
69	16,916	0.96 (0.70-1.31)		251	63,557	0.93 (0.78-1.10)	
92	21,349	1.01 (0.76-1.35)		312	81,891	0.92 (0.78-1.08)	
74	18,921	0.95 (0.70-1.29)		239	64,819	0.87 (0.73-1.04)	
		0.64				0.41	
96	25,906	1.00 (reference)	0.39	285	73,109	1.00 (reference)	0.64
85	18,775	1.24 (0.92-1.67)		289	70,072	1.11 (0.94-1.32)	
55	15,673	0.97 (0.69-1.35)		250	70,600	0.96 (0.81-1.15)	
66	16,497	1.17 (0.85-1.61)		271	70,702	1.01 (0.85-1.21)	
		0.46				0.70	

Results

Baseline characteristics of the study population according to total physical activity are presented in Table 1. Almost all correlations were significantly different from zero. Age at first full-term pregnancy, years of education, and being employed were negatively related to total physical activity (ρ = −0.10, −0.13, and −0.21, respectively).

Data on levels of habitual physical activity are presented in Table 2. Increased levels of total activity were highly related to increased levels of moderate and vigorous recreational activity (ρ = 0.58 and 0.64, respectively). This shows that total physical activity is probably more determined, in our cohort, by the intensity of the activity, estimating by the metabolic equivalent, than by the frequency.

We estimated the RRs of breast cancer associated with habitual levels of physical activity (Table 3). We observed a decrease in risk of breast cancer with increasing levels of light household activity (P_{trend} < 0.0001). This association was weaker when multivariate adjustment was considered (P_{trend} < 0.05). Women who reported ≥14 weekly hours of light household activity had a nonsignificant decreased risk (RR, 0.82; 0.61-1.11) of breast cancer compared with women who had no such activity. We observed a decrease in risk of breast cancer, with increasing levels of moderate (P_{trend} < 0.01) and vigorous (P_{trend} < 0.0001) recreational activities. Multivariate adjustment did not materially change the risk estimates. Women who reported five or more weekly hours of vigorous recreational activity had lower risk of breast cancer (multivariate RR, 0.62; 0.49-0.78) than women who reported neither moderate nor vigorous recreational activity. We observed a negative trend in risk of breast cancer associated with total recreational activity (P_{trend} < 0.01) and total physical activity (P_{trend} < 0.05). Women in the fourth quartile of total recreational activity had a multivariate RR of 0.81 (0.72-0.92) compared with women who reported neither moderate nor vigorous recreational activity. Further adjustment for other types of activity did not modify our results.

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To explore whether physical activity remains ''protective'' for women at high risk of breast cancer, we repeated our analyses stratifying on BMI, first-degree family history of breast cancer, nulliparity, and use of HRT. Because risk patterns associated with physical activity of women with BMI < 25 kg/m^2, without family history of breast cancer, parous women, or HRT nonusers were similar to the pattern of risk in the whole cohort, we present only risk estimates in subgroups of women at high risk of breast cancer. Possible effect modification for these factors was tested with tests for heterogeneity.

No significant effect modification was observed with any factor examined (BMI, family history of breast cancer, nulliparity, and HRT use).

We found no clear effect modification by BMI status (Table 4), although among overweight women, point estimates did not reach significance except for vigorous (P_{trend} < 0.01) and total recreational activity for which a RR of 0.71 (0.51-0.97) was observed for total recreational activity when comparing the most active women with women that reported neither moderate nor vigorous recreational activity.

No major evidence for effect modification by family history of breast cancer was observed (Table 4); 11.4% (n = 10,373) of the study population included in the analyses had such a family history. However, the protective effect of both vigorous and total recreational activity was of higher magnitude among women with family history of breast cancer than among women without such history (data not shown), although heterogeneity tests were not significant.

The decrease in risk of breast cancer with increasing vigorous recreational activity was still observed among nulliparous women (P_{trend} < 0.05; Table 4). Moreover, among these women, the reduction of risk with vigorous recreational activity was of higher magnitude (RR, 0.42; 0.22-0.82 for the most active women compared with women that reported neither moderate nor vigorous recreational activity), although the test for heterogeneity was not statistically significant.

No effect modification by HRT use was seen on the association between postmenopausal breast cancer risk and levels of habitual physical activity (Table 4). Among HRT users, the RR of breast cancer with vigorous recreational activity was 0.70 (0.51-0.96) for the most active women compared with women that reported neither moderate nor vigorous recreational activity.

Discussion

Our results from a large prospective cohort of French women support a protective role of physical activity on breast cancer risk. The strongest associations were observed for vigorous recreational activity and, to a lesser extent, for moderate recreational activity. Moreover, the decrease in risk with increasing vigorous recreational activity was still observed among subgroups of women at higher risk of breast cancer: overweight women, women with family history of breast cancer, HRT users, and those who are nulliparous.

Strengths of the present study include the prospective design, the large size of the cohort, the high rate of follow-up, histologic confirmation of breast cancers, and the detailed information available on potential confounders and effect modifiers, including updated data on reproductive and anthropometric characteristics, menopausal status, and HRT use.

Assessing physical activity in epidemiologic studies is difficult because of the complex nature of this lifestyle exposure, the lack of available gold standards to validate exposure assessments, and the need to rely on self-reports in large epidemiologic studies. Moreover, the complexity of assessing physical activity implies that each method of assessment may introduce a misclassification bias in the analyses. The use of different methods of assessment may explain the heterogeneity of the results observed across previous studies of physical activity and breast cancer (10). We addressed some of the methodologic limitations of previous studies by assessing recreational and household activity, by recording frequency and duration of the activity and by applying a measure of the intensity of activity to each reported activity. Our method did have some limitations, including the measurement of current and not lifetime physical activity, the use of questions with prespecified categories, the application of an intensity value rather than direct rating by the study participants themselves of the intensity of their activity, and the lack of data on occupational activity. However, concerning this last point, because this cohort was primarily made up of teachers, their occupational activities would have been very homogeneous.

An additional limitation of our study is the lack of adjustment for energy intake. Because dietary intake was only assessed 3 years after the baseline assessment of physical activity used for this analysis, we did not have measures of diet and physical activity taken concurrently for the entire cohort. To examine the effect of energy adjustment, we conducted a separate sensitivity analysis, including women who answered the dietary questionnaire, in which we reran the models of the association between physical activity and breast cancer, between 1993 and 2002, with and without energy adjustment. Because the risk estimates were not materially altered and energy did not seem to be an important confounder for this population, we decided to present the results for the full set of cases that had been diagnosed in our cohort.

The majority of studies conducted thus far have shown a reduction in risk of breast cancer among the most physically active participants, as defined in the study populations, compared with the least active (2, 3). The most recent prospective cohort study from Norway, however, reported no association (11). The reduction in risk, in the previous studies showing a risk decrease, ranges from 10% to 70%. The definition of ''most active'' has varied considerably across studies making comparisons across studies challenging and defining clear public health recommendations on the level of physical activity needed for breast cancer risk reduction difficult. Our study further supports this association, with the additional precision that the largest risk reductions were found for recreational activity and specifically for vigorous recreational activity. Such a decrease in risk with recreational activity is supported by several past and recent studies (3, 12-16), whereas one recent study found a decrease in risk restricted to occupational activities among postmenopausal women (17). It remains unclear whether it is moderate or vigorous intensity activity that is needed for a reduction in breast cancer risk because previous studies have shown risk reductions with moderate (13, 16, 18, 19), others with vigorous intensity activity (12, 15, 20, 21), and finally some studies did not find any further risk reduction with intensity of activity (17, 22). The differences across these study results may be attributable to the manner in which the data were originally collected, hence making any generalizations on the association between intensity of physical activity and breast cancer risk difficult. Other studies that found no difference in risk of breast cancer according to intensity concluded that duration and frequency, rather than intensity, are major contributors of the risk variation (13, 14, 17). One possible explanation of our results may be that moderate activity is more difficult to recall and report than vigorous activity and that people tend to overestimate intensity when reporting moderate activities (23). This difference in ability to recall moderate from vigorous activities may generate more misclassification for moderate activity, resulting in nonstatistically significant results. Moreover, our results concerning vigorous activity may have

captured part of the relation between breast cancer risk and moderate recreational activity.

We investigated possible effect modifications by BMI, familial history of breast cancer, parity, and HRT use. Considering the influence of BMI on the association between physical activity and the risk of breast cancer, some studies showed a greater reduction of breast cancer risk among leanest women (13, 14, 22, 24-26). Others found a greater decrease in risk among heavier women, first when considering BMI and physical activity at age 18 (20) and second at baseline (27) in a cohort study of women ages ≥55 years. Some studies, like ours, found no effect modification by BMI (18, 28-32). The fact that our study population was lean with few overweight (16.5%, n = 14,968) and nearly no obese women (2.9%, n = 2,659) at enrollment may account for our lack of ability to show an effect modification by BMI.

To our knowledge, five studies investigated an effect modification by family history of breast cancer (18, 22, 33-35). Four were population-based case-control studies, and the study by Moore et al. (35) was a cohort study. Verloop et al. (22) found that the decrease in risk of breast cancer with increasing physical activity was restricted to women with a family history of breast cancer, whereas the opposite was observed by Carpenter et al. (33) and Patel et al. (34) and no effect in the studies by Friedenreich et al. (18) and by Moore et al. (35). In our study, no clear differences were seen according to family history of breast cancer.

No evidence of an effect modification by parity has been reported previously (36), but this effect has been investigated by few studies only (18, 22, 24, 26, 28, 35, 37-40). Two studies (28, 37) observed stronger effects of recreational physical activity among parous women than among nulliparous, whereas two others (22, 24) found a stronger decrease in risk with occupational and recreational activities among nulliparous women than among parous ones. Finally, four studies (35, 38-40) found no effect modification, and a last one (26) found an increase in risk of breast cancer with increasing occupational physical activity among nulliparous women, whereas no relation was seen among parous women.

Finally, the effect modification by HRT use has been investigated in several studies (13, 14, 18, 20, 26, 28, 35, 41). Five studies showed no interaction (13, 18, 20, 28, 35, 41). Patel et al. (14) suggested that the decrease in risk of breast cancer with increasing physical activity was stronger among HRT nonusers. Finally, Moradi et al. (26) only observed such a decrease among lean women who never used HRT.

Several biological mechanisms have been proposed to explain the inverse association between physical activity and breast cancer risk, including a reduction of the exposure to endogenous steroids, a control of weight gain throughout life, changes in insulin and insulin-like growth factor-I circulating levels, and an enhancement of natural immune mechanisms (2, 3, 5, 42). Participation in high-intensity, vigorous sports like ballet dancing or gymnastics particularly at the time of puberty or in early adulthood resulted in reversible abnormal luteal function and loss of the luteinizing hormone surge (43), which could have the effect of decreasing lifelong estrogen levels and thereby decreasing breast cancer risk. The effect of exercise in early life with a subsequent decreased risk of breast cancer has been supported by some studies (44). Overall, however, the majority of studies on physical activity and breast cancer have found a stronger effect of activity on postmenopausal rather than premenopausal breast cancer (45), suggesting that other mechanisms, particularly the prevention of postmenopausal weight gain, which is an established risk factor for breast cancer (46), may be of particular importance. Randomized controlled trials of exercise for breast cancer prevention are being conducted or have recently published results (47) that suggest that body composition and body fat may be important mechanisms within the causal pathway between physical activity and breast cancer risk (48), possibly having a greater effect than the endogenous estrogens (42) and androgens (49) and insulin-like growth factors (50). Additional research is clearly needed to delineate more clearly the underlying mechanisms and how these may be influenced by different types and levels of physical activity done at various time points in a woman's life.

In conclusion, our results suggest that a considerable decrease in risk of breast cancer could be achieved by practicing recreational activity particularly at a vigorous intensity. Of importance for public health recommendations is that the decrease in risk was also observed among women at high risk of breast cancer (i.e., overweight women, nulliparae, HRT users, and those with a family history of breast cancer).

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