Physical Activity and Postmenopausal Breast Cancer: Effect Modification by Breast Cancer Subtypes and Effective Periods in Life

Martina E. Schmidt,[1] Karen Steindorf,[1] Elke Mutschelknauss,[2] Tracy Slanger,[3] Silke Kropp,[3] Nadia Obi,[2] Dieter Flesch-Janys,[2] and Jenny Chang-Claude[3]

[1]Unit of Environmental Epidemiology, German Cancer Research Center, Heidelberg, Germany; [2]Institute for Medical Biometrics and Epidemiology, University Clinic Hamburg-Eppendorf, Hamburg, Germany; and [3]Department of Cancer Epidemiology, German Cancer Research Center, Heidelberg, Germany

Abstract

Physical activity (PA) has been inversely associated with postmenopausal breast cancer risk. However, it is unclear how and in which life periods PA may be effective to reduce breast cancer risk. Moreover, the evidence is still not judged as 'convincing' as there is some heterogeneity among study results. Most studies regarded breast cancer as a single disease, at best separated by menopausal status. Yet, breast cancers are heterogeneous and likely have different etiologies. Therefore, we analyzed the association of PA with different breast cancer subtypes in 3,414 postmenopausal cases and 6,569 controls from a case-control study on breast cancer conducted 2002-2005 in Germany (MARIE study). PA in the age periods 30-49 and 50+ years was assessed, including leisure-time PA (sports, cycling, walking) and non-recreational PA (occupational and household activities). There was a significant protective effect of leisure-time PA for ER+/PR+ carcinomas (adjusted odds ratio = 0.71, 95% confidence interval: 0.60, 0.85; trend P = 0.0001), but no effect for ER-/PR- carcinomas. Moreover, looking at physical activity pattern over time, the effect of PA after menopause on reducing breast cancer risk was more pronounced than the effect of PA before menopause. Overall, effects of PA were independent from adult weight gain, body mass index, and energy intake. These findings suggest that leisure-time PA after menopause may reduce postmenopausal breast cancer risk at least in part via hormonal pathways and not solely by changing body composition. Inactive postmenopausal women should be encouraged to become physically active even later in life. (Cancer Epidemiol Biomarkers Prev 2008;17(12):3402–10)

Introduction

Epidemiological evidence suggests a probable inverse association between physical activity (PA) and postmenopausal breast cancer risk (1, 2). However, the periods in life in which PA is effective and the mechanisms of action of PA on carcinogenesis are still unclear. Proposed mechanisms include alterations in steroid hormones, changes in body composition, immune modulation, free radical generation, and direct effects on the tumor. Since cancer is a complex process, multiple mechanisms may be operative. Type, intensity, and timing of PA may affect the mode of action of PA on the disease, possibly further depending on characteristics of the individual, stage of carcinogenesis, and tumor characteristics (3, 4). To date, most epidemiological research has regarded breast cancer as a single disease, at best separated by menopausal status. Yet, clinical, pathological, epidemiological, and molecular knowledge suggests that breast cancers are heterogeneous and may have different etiologies (5). Information on the association of PA with breast cancer according to hormone receptor status, histology, HER-2/neu status, or tumor grade (degree of differentiation) is scarce and inconsistent (6-12). Such detailed analyses might provide insight into the mode of action of PA. Therefore, we investigated the associations of PA performed in mid-life and post-menopausal with different breast cancer subtypes.

Materials and Methods

Study Population. The MARIE study is a large population-based case-control study of postmenopausal breast cancer carried out on women aged 50 to 75 years in 2002-2005 in two study regions in Germany. Study details have been published recently (13). Patients with histologically confirmed first primary invasive or in situ breast cancer were identified through frequent monitoring of hospital admissions, surgery schedules and pathology records of the 51 clinics serving our study regions. Per case who had given informed consent, two controls were randomly drawn from lists of residents provided by the population registries and frequency matched by birth year and study region to the cases. The study was approved by the ethics committees of both the University of Heidelberg and the University of Hamburg. All study participants gave written informed consent. Face-to-face interviews were conducted by trained interviewers using a standardized questionnaire to elicit information on demographics and all known and

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M.E. Schmidt and K. Steindorf contributed equally to this work.

Requests for reprints: Karen Steindorf, Unit of Environmental Epidemiology Deutsches Krebsforschungszentrum Im Neuenheimer Feld 280 69120 Heidelberg Germany. Phone: 49-6221-422351; Fax: 49-6221-422229. E-mail: k.steindorf@dkfz.de

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Table 1. Characteristics of postmenopausal cases and controls according to breast cancer subtypes, MARIE Study, Germany, 2002-2005

Characteristic	Cases*					Controls
	ER+/PR+	ER+/PR−	ER−/PR+	ER−/PR−	In situ	
	n (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)
Total	2,004 (100)	495 (100)	103 (100)	545 (100)	205 (100)	6,569 (100)
First degree history of breast cancer						
No	1,541 (76.9)	380 (76.8)	82 (79.6)	424 (77.8)	146 (71.2)	5,422 (82.5)
Yes	346 (17.3)	88 (17.8)	15 (14.6)	94 (17.2)	49 (23.9)	767 (11.7)
Unknown	117 (5.8)	27 (5.5)	6 (5.8)	27 (5.0)	10 (4.9)	380 (5.8)
Age at menarche						
<12	150 (7.5)	51 (10.3)	10 (9.7)	47 (8.6)	11 (5.4)	528 (8.0)
12-14	1,324 (66.1)	312 (63.0)	68 (66.0)	338 (62.0)	125 (61.0)	4,150 (63.2)
15-17	528 (26.3)	131 (26.5)	25 (24.3)	158 (29.0)	69 (33.7)	1,876 (28.6)
Unknown	2 (0.1)	1 (0.2)		2 (0.4)		15 (0.2)
Parity (gestation ≥ 28 wk)						
0	352 (17.6)	91 (18.4)	15 (14.6)	83 (15.2)	44 (21.5)	1,029 (15.7)
1	575 (28.7)	153 (30.9)	33 (32.0)	149 (27.3)	53 (25.9)	1,664 (25.3)
2	732 (36.5)	167 (33.7)	30 (29.1)	214 (39.3)	86 (42.0)	2,522 (38.4)
3+	345 (17.2)	84 (17.0)	25 (24.3)	99 (18.2)	22 (10.7)	1,354 (20.6)
Ever breastfeeding						
No	760 (37.9)	178 (36.0)	39 (37.9)	190 (34.9)	82 (40.0)	2,194 (33.4)
Yes	1,243 (62.0)	317 (64.0)	64 (62.1)	355 (65.1)	123 (60.0)	4,375 (66.6)
Unknown	1 (0.0)					
Type of menopause						
Natural	1,035 (51.6)	266 (53.7)	49 (47.6)	293 (53.8)	85 (41.5)	3,610 (55.0)
Induced †	145 (7.2)	37 (7.5)	12 (11.7)	30 (5.5)	22 (10.7)	500 (7.6)
Hysterectomy	455 (22.7)	104 (21.0)	23 (22.3)	128 (23.5)	59 (28.8)	1,477 (22.5)
Hormone therapy	339 (16.9)	80 (16.2)	13 (12.6)	83 (15.2)	36 (17.6)	880 (13.4)
Other	30 (1.5)	8 (1.6)	6 (5.8)	11 (2.0)	3 (1.5)	102 (1.6)
Mammograms						
No mammogram	232 (11.6)	39 (7.9)	14 (13.6)	82 (15.0)	7 (3.4)	723 (11.0)
1-4 mammograms	637 (31.8)	201 (40.6)	36 (35.0)	197 (36.1)	43 (21.0)	2,881 (43.9)
5-9 mammograms	507 (25.3)	119 (24.0)	21 (20.4)	134 (24.6)	65 (31.7)	1,555 (23.7)
10+ mammograms	610 (30.4)	131 (26.5)	32 (31.1)	126 (23.1)	89 (43.4)	1,356 (20.6)
Unknown	18 (0.8)	5 (1.0)		6 (1.1)	1 (0.5)	54 (0.8)
Ever benign breast disease ‡						
No	1,184 (59.1)	296 (59.8)	57 (55.3)	316 (58.0)	91 (44.4)	4,323 (65.8)
Yes	818 (40.8)	198 (40.0)	45 (43.7)	229 (42.0)	112 (54.6)	2,226 (33.9)
Unknown	3 (0.1)	1 (0.2)	1 (1.0)		2 (1.0)	20 (0.3)
Hormone therapy use						
Never	619 (30.9)	170 (34.3)	35 (34.0)	207 (38.0)	46 (22.4)	2,650 (40.3)
Current or within last 6 mo	991 (49.5)	218 (44.0)	48 (46.6)	188 (34.5)	111 (54.1)	2,179 (33.2)
Recency: 7-12 mo	52 (2.6)	10 (2.0)	1 (1.0)	17 (3.1)	8 (3.9)	133 (2.0)
1-< 3 y	125 (6.2)	39 (7.9)	3 (2.9)	47 (8.6)	17 (8.3)	539 (8.2)
3-< 5 y	63 (3.1)	18 (3.6)	4 (3.9)	23 (4.2)	5 (2.4)	262 (4.0)
5-< 10 y	78 (3.9)	27 (5.5)	5 (4.9)	37 (6.8)	10 (4.9)	373 (5.7)
10-< 15 y	28 (1.4)	6 (1.2)	1 (1.0)	13 (2.4)	3 (1.5)	197 (3.0)
15+ y	32 (1.6)	3 (0.6)	3 (2.9)	12 (2.2)	4 (2.0)	181 (2.8)
Occupational status						
Blue collar worker	258 (12.9)	63 (12.7)	17 (16.5)	81 (14.9)	17 (8.3)	791 (12.0)
Simple employee	470 (23.4)	124 (25.1)	17 (16.5)	127 (23.3)	52 (25.4)	1,610 (24.5)
Medium employee	771 (38.5)	183 (37.0)	42 (40.8)	214 (39.3)	86 (42.0)	2,575 (39.2)
Higher employee	404 (20.1)	104 (21.0)	22 (21.4)	106 (19.4)	41 (20.0)	1,299 (19.8)
Leading position	91 (4.5)	17 (3.4)	4 (3.9)	17 (3.1)	9 (4.4)	270 (4.1)
Unkonwn	10 (0.5)	4 (0.8)	1 (1.0)	0 (0.0)		24 (0.4)
Education						
Low	1,166 (58.2)	280 (56.6)	60 (58.3)	320 (58.7)	108 (52.7)	3,843 (58.5)
Medium	549 (27.4)	142 (28.7)	30 (29.1)	149 (27.3)	58 (28.3)	1,840 (28.0)
High	289 (14.4)	73 (14.7)	13 (12.6)	76 (13.9)	39 (19.0)	886 (13.5)
Smoking						
Never	1,053 (52.5)	280 (56.6)	61 (59.2)	315 (57.8)	117 (57.1)	3,468 (52.8)
Ex-smoker	569 (28.4)	119 (24.0)	24 (23.3)	131 (24.0)	56 (27.3)	1,888 (28.7)
Current smoker	382 (19.1)	96 (19.4)	18 (17.5)	99 (18.2)	32 (15.6)	1,210 (18.4)
Unknown						3 (0.0)
	median (Q1, Q3)	median (Q1, Q3)	median (Q1, Q3)	median (Q1, Q3)	median (Q1, Q3)	median (Q1, Q3)
Age years	63.6 (59.5, 67.4)	63.3 (59.2, 67.8)	63.0 (57.9, 66.9)	62.6 (58.4, 66.8)	63.3 (58.9, 66.6)	63.3 (59.0, 67.2)
Body mass index [kg/m^2]	25.5 (23.0, 28.7)	25.2 (22.6, 27.9)	25.2 (23.1, 27.8)	24.8 (22.4, 28.4)	24.4 (22.3, 27.5)	25.5 (22.9, 28.7)
Adult weight gain [kg]	12 (6, 19)	11 (6, 18)	11.5 (6, 17)	11 (5, 17)	10.5 (6, 17)	12 (6, 19)

(*Continued on the following page*)

Table 1. Characteristics of postmenopausal cases and controls according to breast cancer subtypes, MARIE Study, Germany, 2002-2005 (Cont'd)

Characteristic	Cases*					Controls
	ER+/PR+	ER+/PR−	ER−/PR+	ER−/PR−	In situ	
	median (Q1, Q3)	median (Q1, Q3)	median (Q1, Q3)	median (Q1, Q3)	median (Q1, Q3)	median (Q1, Q3)
Age at first pregnancy ≥ 28 wk§	24 (21, 27)	24 (21, 28)	24 (21, 27)	24 (21, 27)	24 (22, 28)	24 (21, 27)
Alcohol [g/day]	3.66 (0.91, 10.44)	3.83 (0.90, 10.79)	4.14 (0.71, 9.52)	2.92 (0.56, 7.71)	4.65 (1.43, 10.0)	3.60 (0.89, 10.47)

*Information on receptor status was available only for invasive carcinomas.
† Induced menopausal status including bilateral oophorectomy/chemotherapy/radiation.
‡ Benign breast disease included 'with or without biopsy'.
§ Parous women only.

suspected risk factors of breast cancer, particularly lifetime hormone therapy (HT) exposure. A total of 3,919 (65.6%) cases and 7,421 (43.4%) controls participated. Women were defined as postmenopausal if they reported a natural menopause 12 months before the reference date, a bilateral oophorectomy, or cessation of menses due to radiation or chemotherapy. Those above age 55 years whose menopausal status was unclear because of hysterectomy or hormone use were also considered as postmenopausal but assigned an unknown age at menopause. Our analyses were restricted to postmenopausal women (3,414 cases, 6,569 controls).

Hormone Receptor Information. Information on hormone receptor status was obtained from pathology reports from the respective hospitals. To assess hormone receptor status, pathologists largely (≥ 99%) used an 12 point immunoreactive score for immunohistochemical estrogen or progesterone receptor detection (ER-ICA, PR-ICA) with scores ≥ 3 considered as receptor positive. For few single cases (<1%) DCC or EIA were used.

Assessment of Physical Activity. Physical activity was assessed for the age periods 30-49 and 50+ years using a detailed interview-administered validated questionnaire (14). It first asked for occupational PA, i.e. number of years and hours per week employed during the considered age period, and whether tasks were sedentary, moderate, or physically strenuous. Next, splitting a typical week into weekdays and weekend, the total number of hours per week spent doing household tasks (including gardening and child care) was recorded. Similarly, the number of hours per week spent walking and the number of hours per week spent cycling were recorded. Finally, participants were asked to list up to three sports performed during the selected age periods, including sport type, duration, and frequency. A metabolic equivalent (MET) value was assigned to each reported activity according to the Compendium of Physical Activities (15, 16), i.e. MET values 3, 4 and 6 for household activity, walking and cycling, and MET values 1.5, 3, and 6 for sedentary, moderate, and physically strenuous occupational activity, respectively. Leisure-time PA in MET-hours per week was calculated by summing the average hours per week spent walking, cycling, and engaged in sports, weighted by the appropriate MET values. Likewise, non-recreational PA was obtained from occupational PA and household activity. Total PA values were calculated as the sum of leisure-time and non-recreational PA. These PA variables were generated for each age period separately, as well as over the whole period since age 30 years. On average, household activities contributed most to total MET-hours per week, followed by occupational PA and walking. Cycling and sports added fewer MET-hours to total PA, because about one third of women were not engaged in these activities.

Statistical Methods. Associations between PA variables and breast cancer risk overall were assessed with conditional logistic regression models stratified by the matching variables region and year of birth. Activity variables were categorized according to the quintiles of the control group. All analyses were conducted using SAS (version 9.1). The association between PA and breast cancer subtypes was modeled using polytomous logistic regression with the control group as the reference population and region and year of birth as covariates. Subtypes of invasive breast cancers were defined according to estrogen and progesterone receptor (ER, PR) status, histological types, HER-2/neu status, and tumor grade. As potential confounders we investigated the following variables: First degree family history of breast cancer, age at menarche, number of full-term pregnancies, age at first pregnancy (categorical, combined with "no pregnancy"), ever breastfeeding, duration of breastfeeding, ever benign breast disease, number of mammograms before diagnosis/reference date, age at menopause, type of menopause (natural, induced, hysterectomy, hormone therapy, other), HT use (categories: never, current, or recency of use: 7-12 months, 1-3, 3-5, 5-10, 10-15, 15+ years), occupational status, education, smoking (never, ex-smoker, current), alcohol, body mass index (BMI), and adult weight gain. None of these variables altered the point estimates for the PA variables substantially. In the final models we included those covariates that showed a significant effect on postmenopausal breast cancer. Linear trends were tested by entering PA as a continuous variable into the models. In addition, to further examine non-linear relations, we used the method of fractional polynomials (17). The continuous activity variable was entered in the multivariate logistic regression model via a set of defined transformations $\{x^{-2}, x^{-1}, x^{-0.5}, x^{0.5}, x^{1}, x^{2}, x^{3}, \log(x)\}$, allowing a maximum of two terms in the model. The best-fitting function was selected on the basis of the -2 log likelihood of the respective model. Case-case

comparisons based on this functional form were performed to evaluate heterogeneity between cancer subgroups (P_{diff}).

Results

Table 1 presents the population characteristics. Cases and controls both had a median age of 63 years at diagnosis or reference date, respectively. Compared to controls, cases were more likely to have a family history of breast cancer, previous benign breast tumors, had hormone therapy, tended to have a higher number of mammograms (before diagnosis), a lower number of pregnancies, and to have breastfed less. Occupational status and educational level did not differ substantially between cases and controls. Distributions of cancer characteristics are described in Table 2. The majority of invasive carcinoma were ER+/PR+ (62.5%), ductal invasive (68.2%), identified as HER-2/neu negative (71.6%), and of grade 2 (52.7%). Compared to ER+/PR+ carcinomas, ER-/PR- carcinomas were more frequently ductal invasive (86.6% vs. 65.2%), HER-2/neu positive (32.3% vs. 13.8%), and of grade 3 (70.8% vs. 17.7%).

Median MET*h/wk of total physical activity over both age periods (i.e. since age 30 years) were 193.7 for cases and 196.6 for controls. Quintile cutpoints derived from controls were 148.0, 180.2, 213.6, and 260.5 MET*h/wk.

Regarding PA since age 30 years, only leisure-time PA showed a protective effect: breast cancer risk decreased with increasing leisure-time PA, and although the linear trend was not statistically significant, women in the highest quintile were at a significantly reduced risk relative to those in the lowest quintile (Table 3). For activity since age 50 years, effects were more pronounced, with an odds ratio (OR) of 0.90 (95% confidence interval (CI): 0.79, 1.04; linear trend $P = 0.027$) for the highest vs. lowest quintile of total PA (>233.3 vs. ≤122.3 MET*h/wk) and an even stronger protective effect for leisure-time PA (OR = 0.81; 95% CI: 0.70, 0.93 for the highest (>76.5) vs. lowest (≤36.0) quintile; linear trend $P = 0.017$). Non-recreational activity showed no strong protective effect and no significant trend, neither as a single activity variable in a logistic model nor when adjusted for leisure-time activity (data not shown). More specifically, leisure-time and total PA was inversely associated with invasive carcinomas but not with carcinomas in situ. Table 4 presents effects of leisure-time PA since age 50 years on in situ carcinomas and different breast cancer subtypes. In general, linear and non-linear models yielded similar results. Comparing invasive and in situ carcinomas resulted in $P_{diff} = 0.050$, based on only 205 in situ cases. Separating invasive tumors by receptor status, leisure-time PA since age 50 was inversely associated with the risk of ER+ as well as of PR+ carcinomas, but not with the risk of ER- or PR- carcinomas (Table 4). Considering ER/PR combined, the effect of leisure-time PA on ER+/PR+ differed significantly from the effects on ER+/PR- ($P_{diff} = 0.028$), ER-/PR+ ($P_{diff} = 0.024$), and ER-/PR- ($P_{diff} = 0.028$), with more active women having reduced risk for ER+/PR+ carcinomas compared to less active women (OR = 0.71; 95% CI: 0.60, 0.85 for the highest vs. lowest quintile; linear trend $P = 0.0001$), but no effects for the other receptor-types.

We further investigated associations between PA and breast cancer subtypes with respect to histology, HER-2/neu status, and tumor grade. As the distributions of these characteristics are not independent from the receptor status (Table 2), we performed these subtype analyses also restricted to receptor positive tumors (Table 4). Histological and HER2-neu subtypes might vary slightly with respect to the magnitude of the protective effect, but numbers of lobular and HER2-neu+ cases were low, and differences were not statistically significant. Regarding grade, the protective effect of PA appeared to be limited to low-grade tumors. Yet, when considering ER+/PR+ carcinomas only, there were no significant differences in risk reductions between the different grades. Considering ER-/PR- carcinoma only, no clear associations with any breast cancer subtype were found, but sample sizes were generally small (data not shown).

Table 2. Characteristics of invasive breast carcinoma, MARIE Study, Germany, 2002-2005

	All	ER+/PR+	ER+/PR−	ER−/PR+	ER−/PR−	Unknown
	n (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)
All invasive carcinomas	3,209 (100)	2,004 (100)	495 (100)	103 (100)	545 (100)	62 (100)
Row-%	100	62.45	15.43	3.21	16.98	1.93
Histology						
Ductal invasive	2,188 (68.18)	1,307 (65.22)	314 (63.43)	61 (59.22)	472 (86.61)	34 (54.84)
Lobular invasive	665 (20.72)	464 (23.15)	123 (24.85)	28 (27.18)	36 (6.61)	14 (22.58)
Other types	70 (2.18)	34 (1.70)	13 (2.63)	2 (1.94)	16 (2.94)	5 (8.06)
Ductal invasive + lobular	152 (4.74)	110 (5.49)	25 (5.05)	4 (3.88)	9 (1.65)	0 (6.45)
Mixed types	23 (0.72)	13 (0.65)	4 (0.81)	1 (0.97)	5 (0.92)	4 (0.00)
Tubular	97 (3.02)	70 (3.49)	15 (3.03)	7 (6.80)	2 (0.37)	3 (4.84)
Unknown	14 (0.44)	6 (0.30)	1 (0.20)	0 (0.00)	5 (0.92)	2 (3.23)
Her-2/neu status						
Negative	2,296 (71.55)	1,534 (76.55)	351 (70.91)	78 (75.73)	323 (59.27)	10 (16.13)
Positive	586 (18.26)	276 (13.77)	112 (22.63)	16 (15.53)	176 (32.29)	6 (9.68)
Unknown	327 (10.19)	194 (9.68)	32 (6.46)	9 (8.74)	46 (8.44)	46 (74.19)
Tumor grades						
1	604 (18.82)	447 (22.31)	107 (21.62)	16 (15.53)	20 (3.67)	14 (22.58)
2	1,691 (52.70)	1,190 (59.38)	283 (57.17)	52 (50.49)	133 (24.40)	33 (53.23)
3	890 (27.73)	355 (17.71)	104 (21.01)	35 (33.98)	386 (70.83)	10 (16.13)
unknown	24 (0.75)	12 (0.60)	1 (0.20)	0 (0.00)	6 (1.10)	5 (8.06)

Table 3. Effect of different physical activity types in different age periods on overall breast cancer risk: adjusted odds ratios and 95% confidence intervals, MARIE Study, Germany, 2002-2005

	1st quintile	2nd quintile	3rd quintile	4th quintile	5th quintile	Trend* *P*
Average PA over both periods (since age 30 y)						
Total PA	1 [Reference]	1.01 (0.88, 1.15)	1.02 (0.89, 1.17)	1.02 (0.89, 1.17)	0.97 (0.84, 1.11)	0.1801
Leisure-time PA	1 [Reference]	0.95 (0.83, 1.09)	0.88 (0.77, 1.01)	0.88 (0.76, 1.00)	0.85 (0.74, 0.98)	0.1453
Non-recreational PA	1 [Reference]	0.91 (0.80, 1.04)	1.00 (0.87, 1.14)	1.00 (0.87, 1.14)	0.92 (0.80, 1.06)	0.4828
Average PA during age 30 - 49 y						
Total PA	1 [Reference]	0.94 (0.82, 1.07)	1.05 (0.92, 1.21)	0.94 (0.82, 1.08)	0.97 (0.84, 1.11)	0.5496
Leisure-time PA	1 [Reference]	0.97 (0.85, 1.11)	0.90 (0.79, 1.03)	0.86 (0.75, 0.98)	0.91 (0.80, 1.04)	0.5199
Non-recreational PA	1 [Reference]	0.95 (0.83, 1.09)	1.08 (0.94, 1.23)	0.99 (0.86, 1.14)	0.97 (0.84, 1.12)	0.7389
Average PA since age 50 y						
Total PA	1 [Reference]	1.01 (0.88, 1.15)	1.03 (0.90, 1.17)	0.98 (0.86, 1.13)	0.90 (0.79, 1.04)	0.0273
Leisure-time PA	1 [Reference]	0.97 (0.85, 1.10)	0.90 (0.79, 1.03)	0.93 (0.81, 1.07)	0.81 (0.70, 0.93)	0.0171
Non-recreational PA	1 [Reference]	0.85 (0.74, 0.97)	0.95 (0.83, 1.08)	0.97 (0.84, 1.10)	0.90 (0.79, 1.04)	0.2745

NOTE: Separate conditional logistic regression models were performed for each PA variable stratified by region and year of birth, and adjusted for family history of breast cancer, number of pregnancies, breastfeeding, previous benign breast diseases, number of mammograms before diagnosis/reference date, type of menopause, and hormone therapy use.
*PA variable entered as continuous linear term into the model.

There was no confounding by adult weight gain, BMI, and energy intake (kcal/day; assessed by a detailed food frequency questionnaire). Thus, effects of leisure-time PA on ER+/PR+ carcinomas appeared to be independent from the effects of these variables (data not shown).

To investigate the effect of activity in different age periods, we classified for both assessed age periods the

Table 4. Effect of average leisure-time PA since age 50 years on different breast cancer subtypes: adjusted odds ratios and 95% confidence intervals, MARIE Study, Germany, 2002-2005

Breast cancer subtypes	Cases*	Average leisure-time PA since age 50					Trend† *P*
	n	1st quintile	2nd quintile	3rd quintile	4th quintile	5th quintile	
In situ	205	1 [Reference]	1.11 (0.69, 1.81)	1.12 (0.69, 1.82)	1.40 (0.88, 2.22)	1.31 (0.82, 2.10)	0.3458
Invasive	3,209	1 [Reference]	0.96 (0.84, 1.10)	0.89 (0.78, 1.03)	0.91 (0.80, 1.05)	0.78 (0.68, 0.90)	0.0071
ER+	2,505	1 [Reference]	0.94 (0.81, 1.09)	0.88 (0.76, 1.03)	0.89 (0.76, 1.03)	0.76 (0.65, 0.89)	0.0035
ER−	650	1 [Reference]	1.03 (0.80, 1.33)	0.97 (0.75, 1.26)	1.09 (0.84, 1.40)	0.93 (0.71, 1.21)	0.7098
PR+	2,113	1 [Reference]	0.92 (0.79, 1.07)	0.85 (0.73, 1.00)	0.81 (0.69, 0.95)	0.72 (0.61, 0.84)	0.0004
PR−	1,041	1 [Reference]	1.03 (0.84, 1.27)	1.00 (0.81, 1.24)	1.19 (0.97, 1.46)	0.96 (0.77, 1.20)	0.5704
ER+/PR+	2,004	1 [Reference]	0.94 (0.81, 1.10)	0.87 (0.74, 1.02)	0.81 (0.69, 0.95)	0.71 (0.60, 0.85)	0.0001
ER+/PR−	495	1 [Reference]	0.92 (0.68, 1.25)	0.97 (0.72, 1.31)	1.27 (0.95, 1.69)	1.00 (0.74, 1.36)	0.2701
ER−/PR+	103	1 [Reference]	0.62 (0.32, 1.18)	0.74 (0.40, 1.39)	0.99 (0.55, 1.77)	0.91 (0.49, 1.67)	0.1563
ER−/PR−	545	1 [Reference]	1.14 (0.86, 1.49)	1.03 (0.77, 1.36)	1.12 (0.85, 1.48)	0.93 (0.69, 1.25)	0.8217
Ductal	2,188	1 [Reference]	1.01 (0.87, 1.18)	0.91 (0.77, 1.06)	0.92 (0.79, 1.07)	0.79 (0.67, 0.93)	0.0185
Lobular	665	1 [Reference]	0.78 (0.61, 1.00)	0.81 (0.63, 1.04)	0.76 (0.59, 0.98)	0.78 (0.60, 1.01)	0.2163
HER-2/neu -	2,296	1 [Reference]	1.02 (0.88, 1.19)	0.96 (0.82, 1.12)	0.97 (0.83, 1.14)	0.84 (0.72, 0.99)	0.1072
HER-2/neu +	586	1 [Reference]	0.96 (0.74, 1.25)	0.82 (0.63, 1.08)	0.85 (0.65, 1.11)	0.74 (0.56, 0.98)	0.0864
Grade 1	604	1 [Reference]	0.91 (0.69, 1.19)	0.93 (0.71, 1.22)	0.99 (0.75, 1.29)	0.77 (0.58, 1.02)	0.1426
Grade 2	1,691	1 [Reference]	0.91 (0.77, 1.08)	0.85 (0.72, 1.01)	0.90 (0.76, 1.07)	0.72 (0.60, 0.87)	0.0023
Grade 3	890	1 [Reference]	1.09 (0.88, 1.36)	0.96 (0.77, 1.21)	0.91 (0.72, 1.14)	0.91 (0.72, 1.15)	0.9540
ER+/PR+ & ductal	1,307	1 [Reference]	0.98 (0.81, 1.17)	0.83 (0.69, 1.01)	0.77 (0.63, 0.93)	0.69 (0.57, 0.85)	0.0007
ER+/PR+ & lobular	464	1 [Reference]	0.81 (0.60, 1.09)	0.88 (0.66, 1.19)	0.76 (0.56, 1.03)	0.79 (0.58, 1.08)	0.1367
ER+/PR+ & HER-2/neu -	1,534	1 [Reference]	0.96 (0.81, 1.15)	0.91 (0.76, 1.09)	0.85 (0.71, 1.02)	0.76 (0.63, 0.92)	0.0069
ER+/PR+ & HER-2/neu +	276	1 [Reference]	1.17 (0.82, 1.68)	0.95 (0.65, 1.39)	0.71 (0.47, 1.06)	0.70 (0.46, 1.05)	0.0161
ER+/PR+ & grade 1	447	1 [Reference]	0.87 (0.64, 1.19)	0.94 (0.69, 1.28)	0.90 (0.66, 1.23)	0.72 (0.52, 1.00)	0.0229
ER+/PR+ & grade 2	1,190	1 [Reference]	0.95 (0.79, 1.16)	0.89 (0.73, 1.09)	0.86 (0.70, 1.04)	0.71 (0.58, 0.88)	0.0028
ER+/PR+ & grade 3	355	1 [Reference]	0.96 (0.70, 1.31)	0.75 (0.53, 1.05)	0.57 (0.40, 0.82)	0.72 (0.51, 1.01)	0.1427

NOTE: For each breast cancer characteristic a separate polytomous logistic regression was performed, adjusted for region, year of birth, family history of breast cancer, number of pregnancies, breastfeeding, previous benign breast diseases, number of mammograms before diagnosis/reference date, type of menopause, and hormone therapy use.
*Controls: n = 6,569.
† PA variable entered as continuous linear term into the model.

women as low, moderately, or highly active according to the leisure-time PA tertiles of the controls (tertile cutpoints for age 30-49: 33 and 60 MET*h/wk; for age 50+: 31 and 58 MET*h/wk). Table 5 presents the results for ER+/PR+ carcinoma. Women with high leisure-time activity since age 50 years had reduced risk irrespective of their activity levels at age 30-49 years. In contrast, women who were less active since age 50 years had only modest or no risk reductions even when they were highly active during age 30-49 years.

For total PA and for non-recreational PA less clear associations with breast cancer subtypes could be found.

Discussion

We found an inverse association between physical activity and postmenopausal breast cancer risk, which was most pronounced for leisure-time PA. The protective effect was restricted to hormone receptor positive invasive carcinomas. PA after age 50 years appeared to be more effective at preventing postmenopausal ER+/PR+ carcinomas than PA in earlier adulthood. Further, the effect of PA on breast cancer subtypes was independent from the effect of adult weight gain, BMI, and energy intake. This study found no protective effect of PA for carcinoma in situ. After separating invasive carcinomas by histology, HER-2/neu status, or grade no substantial effect modification was seen. The magnitude of the protective effect might vary slightly but not significantly among histological and HER2-neu subtypes.

To date, this is the largest case-control study with comprehensive assessment of physical activities for two different age periods, assessing risk of breast cancer subtypes. All known or suspected confounders were recorded, with special emphasis on HT use. Limitations of our study also need to be considered. Despite great efforts, response rates were low, potentially introducing selection bias. Information collected by short questionnaire from subjects who refused full participation indicated that full participants were better educated. However, we found no strong association between education or occupational status and leisure-time PA. Moreover, it is unlikely that the effect modification by the breast cancer subtypes would have been substantially affected by a potential selection of cases. As with all case-control studies, recall bias is a potential threat. Since at that time interviews had been performed, PA was not a major topic for breast cancer patients in our study regions, differential recall of activity among cases and controls is unlikely. However, despite recall aids in the interviews, it cannot be ruled out completely that PA in the past (30-49 years) was less well recalled than PA in more recent years (age 50+), potentially leading to the weaker association between PA in mid-life and breast cancer risk. Furthermore, our questionnaire had some limitations in assessing non-recreational activity (occupational and household tasks). Household tasks comprise many different, often unstructured and intermittent activities, but for the sake of interview duration the questionnaire did not assess the types of household tasks (which included gardening and child care). Thus, activities of very different intensities such as dusting or heavy gardening were assigned the same MET value. In addition, the considered age periods were relatively wide, but the questionnaire was inappropriate to catch changing household activity patterns, e.g. when switching from full-time employment to maternal leave within the considered age periods. Hence, non-recreational activity may have been assessed with considerable measurement error. In contrast, sports were assessed more precise by specifying the number of years, duration, frequency, and type of sports. Walking and cycling was assessed similar to household activity, but these activities are well-defined and general walking and cycling pattern may be more constant over time. These might be reasons for our finding that including non-recreational activity in the analysis resulted in a weaker association with breast cancer than considering leisure-time activity only. However, most previous studies on physical activity and breast cancer considered leisure-time activity only, and several of them found an association (1). It is still unclear whether the more intense, less interrupted, and often longer lasting leisure-time activities may have different biological effects in the body than typical household activities. Finally, analyzing various breast cancer subgroups and considering different activity types from different age periods leads to multiple comparisons. We did not adjust for multiple comparisons, as this is not a confirmatory but rather an explorative analysis to gain hints on mode of actions of PA on different breast cancer subtypes. Our findings of effect modification by hormone receptor status need to be confirmed in other studies. Future research should take into account that various breast cancer subtypes with potentially different etiologies exist.

Table 5. Effect of different activity patterns on ER+/PR+ carcinomas, MARIE study, Germany, 2002-2005

		Leisure-time PA since age 50 y (tertiles)*								
		Low activity			Moderate activity			High activity		
		Cases	Controls	OR (95% CI)	Cases	Controls	OR (95% CI)	Cases	Controls	OR (95% CI)
Leisure-time PA during age 30-49 y (tertiles)†	Low activity	500	1,510	1 [Reference]	164	498	0.92 (0.75, 1.14)	44	155	0.79 (0.55, 1.13)
	Moderate activity	146	478	0.86 (0.70, 1.08)	385	1,221	0.89 (0.76, 1.05)	154	516	0.79 (0.64, 0.98)
	High activity	57	182	0.91 (0.66, 1.26)	141	461	0.86 (0.69, 1.07)	413	1,548	0.75 (0.64, 0.88)

*Cut-offs for tertiles: 33 MET*h/wk, 60 MET*h/wk.
†Cut-offs for tertiles: 31 MET*h/wk, 58 MET*h/wk.

Few studies (6-12) have analyzed the effect of PA on breast cancer subtypes with respect to ER or ER/PR status, and results are inconsistent. While we found risk reductions only for ER+/PR+ carcinomas, other studies found protective effects of exercise for ER+/PR+ as well as for ER-/PR- breast cancers (6), for ER+ and ER- carcinomas (10), or for ER+ cases and cases overall (8). In the US Womens Health Study (12), recent recreational PA showed a clear significant protective effect on overall postmenopausal breast cancer risk, but no effect was seen when only ER+/PR+ carcinomas (n = 157) were considered. Other studies found most marked reductions for ER+/PR-, and borderline or non-significant reductions for ER+/PR+ and ER-/PR- carcinomas (7, 9). However, in one of these studies (9) activity categories were based on only two questions where 'high activity' reflected extreme activity, and in the latter study (7), 34% of cases had unknown ER/PR status, for which a strong and significant inverse association with recreational PA was seen. In contrast, the California Teachers Study (11) found clear reductions of ER-/PR- cancer risk but not of ER+/PR+ or ER+/PR- risks. However, in that study moderate and strenuous recreational activities were analyzed separately, and walking or cycling for locomotion were not assessed. Thus the effect of overall recreational activity on ER+/PR+ risk is unclear. Their finding of a risk reduction for ER-/PR- carcinoma seems to be in contrast to our findings. Yet, clear reductions were only seen with at least 3.5h exercise per week, which in our population was rarely reached. Our highest quintile of leisure-time activity since age 50 could be reached, for example, already with a combination of 2h walking and 0.5h cycling for locomotion daily without any additional sports. In all of the above mentioned studies including our own, ER and PR status were analyzed only as dichotomous variables. However, receptor status is in fact a quantitative characteristic with extreme variation. Several methods of evaluating hormone receptor status exist, and there is much debate about the correct cutoff point for distinguishing ER+ from ER- or PR+ from PR- tumors (18). Particularly in older studies, assessment of ER and PR status were not standardized. Thus, there may have been considerable misclassification of hormone receptor status, which could have biased some previous study results towards a finding of no difference between receptor groups.

Our results suggest that in women who are physically active after menopause the risk of invasive postmenopausal breast cancer may be reduced at least in part via steroid hormonal pathways. Epidemiological studies have found direct associations between endogenous levels of steroid hormones and postmenopausal breast cancer (19, 20), especially ER+/PR+ cancer (21). In postmenopausal women, circulating estrogens are derived largely from aromatization of androstenedione to estrone in the adipose tissue. Additionally, postmenopausal breast cancers produce intratumoral estrogen. Estrogen activates estrogen receptor (ER) through genomic and non-genomic pathways, which leads to processes that promote the proliferation of breast cancer cells. ER can also be activated by signal crosstalk between estrogen and growth factors such as epidermal growth factor and insulin-like growth-factor-1 (22). Women who are physically active during postmenopausal years may have lower concentrations of serum estrone, estradiol, and androgens, which are precursors of estrogens, than inactive women, and levels of sex hormone binding globulin may be increased (23-27). In contrast to the reduction of ER+/PR+ carcinoma risk, we found no reduction of ER+/PR- carcinoma risk in physically active women, with all ORs around one. Thus, one may speculate that PR is important in the mode of action of PA on breast cancer. Evidence is increasing that progesterone plays a key role in the regulation of cell proliferation and differentiation in the mammary gland. A recent study demonstrated that, either in ER+ or ER- cell context, progestins induced proliferation and regulated proteases activity and metastasis through PR ability to activate c-Src dependent signaling pathways (28). The expression of PR is up-regulated by estrogen stimulation (29), hence PR expression might be affected by exercise via reduced estrogen levels. Further, there is some limited evidence, that exercise may decrease plasma levels of progesterone (30, 31).

To our knowledge this is the first study investigating the association of PA and breast cancer subtypes according to histological type. Evidence exists that lobular carcinomas tend to present higher numbers of hormone receptors and are more hormonally responsive than ductal carcinomas (32). This could be one reason for the observed (non-significant) slight differences in the magnitude of the protective effect regarding lobular and ductal hormone receptor positive carcinomas. However, larger numbers of lobular cases are needed, and the quantitative nature of ER and PR expression should be taken into account in future epidemiological studies. More recent molecular research found divergent complex pathways towards invasive breast cancer, which suggest that grade (degree of differentiation), more than any other clinico-pathological parameter, reflects the extent, complexity, and type of genomic aberrations (33). Our finding of no clear effect of PA on grade 3 carcinoma risk overall, but comparable effects on grade 1, 2, and 3 ER+/PR+ carcinoma risks, supports the view that hormone receptor status rather than different genetic alterations in low- and high-grade tumors might be relevant for a protective effect of PA on breast cancer.

For carcinoma in situ we found no protective effect of PA in either age period. However, ER/PR information of carcinoma in situ was not available. Hence, associations between PA and receptor positive carcinomas in situ could not be analyzed. Furthermore, the majority of in situ carcinomas are detected by mammograms, and the proportion of women with regular mammograms among in situ cases was higher than among controls or among cases with invasive carcinoma (81%, 53%, 61%, respectively). Women with regular mammograms are potentially more health conscious, and hence might tend to be physically more active. Thus a true effect of PA on carcinoma in situ might be biased towards null. However, even when we restricted the analyses to cases and controls with regular mammography, there was still no protective effect of PA on carcinoma in situ. Compatible with our results, a study with 1,689 in situ cases (34) found neither an association of lifetime recreational PA nor strenuous occupational PA with risk of breast carcinoma in situ, while recreational PA was associated with a reduced risk of invasive breast cancer.

In contrast, two studies (11, 35) found some associations between strenuous PA and carcinomas in situ.

Up to date it is unclear in which periods of life PA is most effective to reduce breast cancer risk (1). Women who are very active at younger ages tend to be among the more active group also at later ages, and inactive young women tend to be also rather inactive in later life. Thus, PA measures of different age periods are often highly correlated, and therefore, few studies were able to identify a time in life when PA had the greatest association with breast cancer risk. Due to our large sample size, we were able to investigate the effect of varying activity levels in midlife and postmenopausal years. Our results that show protective effects of leisure PA since age 50 years on ER+/PR+ carcinoma risk irrespective of the activity level at age 30-49 years, suggest that PA in later life may be more effective at preventing postmenopausal breast cancer than PA in earlier adulthood. Accordingly, a large case-control study (36) found the strongest breast cancer risk reduction for activity done later in life, particularly between menopause and the reference year. Compared to women who were in the lowest total PA tertiles before and after menopause (never-exercisers), late-life exercisers had a risk reduction similar to life-long exercisers, while early-life exercisers had no clear risk reduction. A large Swedish study (37) found that recent leisure-time activity was associated with a reduced risk of postmenopausal breast cancer in contrast to activity from age 18 to 30 or during childhood. In contrast, the Shanghai Breast Cancer Study (6) found similar risk reductions for early-life and late-life exercisers (any sports in either adolescence or the previous 10 years), but stronger risk reductions for life-long exercisers.

In summary, we found an inverse association of leisure-time PA (walking, cycling, sports) with hormone receptor positive invasive breast carcinoma risk in postmenopausal women. Our results suggest that the mechanism of action of PA on postmenopausal breast carcinogenesis might include at least in part steroid hormonal pathways. Hereby, PA seems to act not solely via changes in body composition. These results need to be confirmed by future research, which should take the heterogeneity of breast tumors into account. In addition, PA after menopause seemed to be more relevant than PA before menopause for the reduction of postmenopausal breast cancer risk. While for several other diseases evidence exists for a beneficial effect of physical activity through all ages, postmenopausal women who are nevertheless still inactive should be encouraged to become physically active even later in life.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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Martina E. Schmidt, Karen Steindorf, Elke Mutschelknauss, et al.

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