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EPIDEMIOLOGY

Domain-specific patterns of physical activity and risk of breast cancer sub-types in the MCC-Spain study

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Abstract

Purpose Literature on the separate effects of physical activities (PA) on risk of breast cancer (BC) sub-types is heterogeneous. We investigated domain-specific associations between PA and BC risk by menopausal status and molecular subtype.

Methods 1389 histologically confirmed invasive BC cases and 1712 controls from the MCC-Spain study were included (age: 20–85 years). Questionnaire information on PA at work, at home, and during leisure time, including recreational PA and sedentary time, and data on reproductive history, anthropometry, family history of BC, diet, and lifestyles were obtained through face-to-face interviews. Information on the expression of oestrogen (ER), progesterone (PR), and HER2 receptors was available for > 95% of the cases. Mixed-effects multivariable logistic regression models were used to estimate odds ratios (OR) of BC sub-types.

Results Occupational PA (OPA) intensity was associated with higher BC risk. Associations were stronger for pre-menopausal ($OR_{\text{active/very active vs. sedentary job}}$ 1.89; 95% confidence interval (CI) 1.22, 2.91) and ER+/PR+, HER2− tumours (OR 1.80; 95% CI 1.28, 2.53). Sedentary time was associated with higher risk of post-menopausal BC ($OR_{\text{6–9 vs. <3 h/day}}$ 1.69; 95% CI 1.22, 2.32). Moderate-to-high-intensity household (HPA) and recreational PA (RPA) were inversely associated with BC occurrence in pre- and post-menopausal women, with estimated 14–33% lower risks (*P* for trend < 0.001) above 1000 MET·min/week.

Conclusions Higher levels of HPA and RPA were associated with lower risk of BC, with heterogeneity by molecular type, whereas sitting time was a consistent independent risk factor of BC risk. The positive association found for OPA with ER+/PR+ BC deserves further investigation.

Keywords Physical activity · MCC-Spain · Case–control study · Breast cancer · Hormone receptors

Introduction

Previous literature on the potential effect of domain-specific physical activities on breast cancer (BC) risk is heterogeneous [1-3]. Being the most common female cancer worldwide with over 2 million cases diagnosed in 2018 [4], fully elucidating the specific roles that distinct types and patterns of physical activities could have for preventing BC in different sub-populations may have important public health implications. But the evidence is yet inconclusive over an association which is nevertheless complex [5]. On the one hand, tumours of the breast show large cellular, genetic, and molecular heterogeneity [6, 7]. Such variability is the basis for the current clinical classification based on the expression of oestrogen and progesterone receptors (ER and PR), and the human epidermal growth factor receptor (HER2/ERBB2), which allows for targeted therapeutical approaches. On the other hand, physical activity does not refer to any singular event but to a plethora of daily movement patterns that differ in timing, setting, and amount [1], the effects of which could therefore vary by type, intensity,

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and duration. Furthermore, factors such as age, reproductive history, socio-economic status, occupational and environmental exposures, obesity, dietary habits, or alcohol intake, can severely confound the epidemiological observations [5, 8].

The updated WCRF comprehensive review of previous case–control and prospective studies judges as *probable* the evidence for a preventive role for physical activity against pre-menopausal BC (high-intensity recreational activities) and post-menopausal BC [5]. Previous meta-analyses of prospective studies have estimated the lower risks of BC associated with higher levels of PA, with risk reductions ranging between 3 and 20% [1–3, 9]. On the other hand, a large-scale individual-data meta-analysis involving one and a half million adults from 12 European and US prospective studies showed modest reductions of around 10% in BC risk (pre- and post-menopausal combined) when comparing people with very high levels of leisure-time PA (90th percentile) versus those with very low levels (10th percentile) [10]. Importantly, most of the evidence in support of an inverse association between PA and BC is focused on leisure-time (recreational) PA, whereas other domains such as household or occupational PA have been less studied [1, 2], even when these may account for a large proportion of total PA in the population. The gap in domain-specific PA analyses is more pronounced in recent literature studying BC risk factor profiles by ER, PR, and HER2 status, the results of which, conflicting and inconclusive, have been exclusively based on RPA [11–13].

Given the heterogeneity implicit in the study of physical activity and breast cancer, our objective was to perform a stratified analysis of the association of different PA domains on BC risk according to type and menopausal status, within the MCC-Spain study, a well-designed case–control study with accurate information on the molecular phenotype of breast tumours, detailed information on physical activity domains, intensity, and frequency, and ability to adjust for major confounders.

Methods

Study sample

MCC-Spain is a multicase–control study designed to elucidate the role of environmental factors on risk of common cancers in Spain. It was conducted from September 2008 to December 2013, and included a total of 1738 breast cancer cases and 1910 population controls (response rate: 71%) between 20 and 85 years old. Participants were recruited in 10 Spanish regions (Asturias, Barcelona, Cantabria, Girona, Gipuzkoa, Huelva, León, Madrid, Navarra, and Valencia). A detailed description of methods and sample characteristics has been published elsewhere [14].

Eligible patients for the current analysis were malignant BC cases with histological confirmation (International Classification of Diseases 10th Revision (ICD-10) [15] code C50), without prior history of the disease, and diagnosed between 2008 and 2013 in the selected hospitals. Case identification was performed by active search through periodical visits to relevant hospital departments (*i.e.* gynaecology, oncology, general surgery, radiotherapy, and pathology departments). Cases were invited to participate as soon as possible after diagnosis. Adequate population controls were randomly selected from the general practitioners lists in the same hospitals' catchment areas where cases were recruited, and were frequency matched to cases by age, sex, and region. Pathological data on ER, PR, and HER2 expression were available for 98.6%, 98.2%, and 96.0% of BC cases, respectively. The most frequent histological tumour types were invasive ductal carcinoma ($n = 1286$, 84.8%), and invasive lobular carcinoma ($n = 114$, 7.5%), while all other types together (medullary, colloid, papillary, tubular, and mixed carcinomas) accounted for less than 8% of the cases.

All participants signed an informed consent form and the study protocol was approved by the local Ethics Committees of all participating institutions.

Assessment of physical activity

A structured physical activity questionnaire was administered face-to-face by trained personnel covering PA at work, at home, and during leisure time. Occupational activity was self-reported as sedentary (almost exclusively sitting), low active (some physical demand, such as standing occupations, or walking short distances), moderately active (manual work without manual handling of loads), quite active (physically demanding), or very active (vigorous occupations involving heavy energy expenditure). For leisure-time PA, detailed information was gathered on regular recreational activities in an open-ended manner, recording the type, frequency (in hours per week), and age at starting and quitting of activities carried out for at least 6 months throughout life. The questionnaire also inquired about the number of weekly time dedicated to household activities of light intensity (e.g. cooking, washing dishes, ironing) and the total time (hours/week) spent in high-intensity household activities (e.g. scrubbing floors, washing windows, playing with children). Finally, participants were asked to report the total h/day spent sitting during leisure time (including transportation) within the last year, separately for weekdays and the weekend.

Metabolic equivalent (MET) values were assigned to each recreational PA item according to Ainsworth Compendium of Physical Activities [16], with 1 MET representing

the rate of energy expenditure at resting state (defined as 1 kcal kg^{-1} h^{-1}). Weekly volume of recreational physical activity (in MET·min/week) was then computed for each participant as the sum of total time dedicated to each activity per week weighted by its corresponding MET value. Volume of household activities was computed likewise by assigning MET values of 2.8 and 3.5 to the categories of 'light', and 'higher intensity' household activities, respectively. Sedentary time was obtained as the weighted mean of total hours/day spent sitting during weekdays and the weekend throughout the last year.

In order to minimise a potential reverse causation bias, occupational and recreational physical activity variables were defined to cover a 10-year exposure window up to the year previous to study entry (years −11 to −1, with recruitment date being time 0). For occupational activity, participants were assigned the intensity category of their longest-lasting job within the exposure time frame, or the most recent, in case of a tie. When the sum of working years was less than five for the whole 10-year period the participant was recoded as 'not working'.

Lifestyle and anthropometric data

The questionnaire further included questions on socio-demographic data, height, weight (of the previous year), family and personal medical history, drug use, menopausal status, reproductive history, ever use of oral contraceptives or hormonal replacement therapy, smoking (1-year previous to cancer diagnosis −or recruitment, in controls), and lifestyle habits. A socio-economic status score was developed as a combination of education, occupational social class, and self-reported parental socio-economic position. Diet of the previous year was assessed by means of a self-administered, validated, semi-quantitative food frequency questionnaire (FFQ) adapted for the MCC [17]. Waist and hip circumferences were measured with an inelastic tape following standard procedures.

Exclusion criteria, classification of the exposure, and statistical analyses

We excluded 208 non-invasive breast cancer cases and 339 participants with missing data on physical activity or sedentary time (including 141 invasive BC cases, 9.2%), leaving a final sample of 1389 invasive BC cases and 1712 controls. Missing data in covariates were replaced by single imputation (anthropometric variables), or by adding a 'missing' indicator category (categorical variables). As 438 participants included in the analysis did not fill in the FFQ, dietary variables were categorised into quartiles, further adding a 'missing' category as appropriate. For the current analysis, BC tumours were subclassified as luminal A-like (ER+ or PR+, with HER2−), positive for human epidermal growth factor receptor (HER2+, regardless of ER or PR expression), and triple negative (ER−, PR−, and HER2−) [18].

Physical activity variables were analysed according to specific domains: work, household and recreational PA, and sedentary time. Household PA (HPA) was classified in 4 categories, as '[0–500)', '[500–1000)', '[1000–2000)', and '≥2000 MET·min/week'. For the recreational domain, where it was possible to define a 'non-exposed' group, PA categories were chosen as 'none', '(0–500)', '[500–1000)', '≥1000 MET·min/week'. The same categorisation applied to HPA and RPA variables split by intensity level. Leisure-time sitting time was categorised into 4 groups, per 3 h/day increments.

Descriptive statistics performed were based on median values and inter-quartile ranges, for continuous variables, and frequencies for categorical ones. Statistical differences between cases and controls were tested using Mann–Whitney U or χ^2 tests.

Odds ratios (OR) and 95% confidence intervals (CI) of an invasive BC outcome by levels of physical activity were estimated using unconditional mixed-effects logistic regression models, with random intercepts by study centre. The reference group was defined as the lowest category for physical activity variables, and the group spending < 3 h/day sitting for sedentary time. We selected a common set of potential confounders based on a priori knowledge and on their specific effect in the models evaluated ($P < 0.1$). Final multivariate models were adjusted for age, socio-economic status (low, medium, high), family history of breast cancer (no, yes, unknown), age at menarche (≤12 years, 13–14 years, >14 years, unknown), age at first pregnancy (≤25 years, 26–30 years, >30 years, nulliparous, unknown), post-menopausal status (no, yes, unknown), ever use of oral contraceptives (no, yes, unknown), ever use of hormonal replacement therapy (no, yes, unknown), smoking (never, former, current, unknown), and daily intake of total energy (kcal/day), red meats (g/day), vegetables (g/day), and past alcohol consumption (at participant's 30–40 years old), in daily units of 10 g (none, ≤2 units/day, >2 units/day, unknown). Other variables such as body mass index (kg/m^2), waist circumference (cm), number of children, or fruit consumption (g/day) were also explored in specific models. Tests for trend were based on the regression coefficient of the physical activity variable, entered as continuous. For occupational activity, the trend was estimated by introducing the five-category variable as an ordinal predictor in the model, excluding non-workers. The potential interaction of PA domains with menopausal status or molecular profiles of the tumours was assessed by means of likelihood-ratio tests.

The shape of the association between PA and BC risk was explored by using a restricted cubic spline transformation of the exposure variables, with knots at the 5th, 35th, 65th,

and 95th percentiles. The results of the multivariable logistic regression models including the spline terms were plotted after running the *xblc* programme for STATA [19].

All statistical analyses were performed with STATA/SE 14.2. P values < 0.05 were considered statistically significant.

Results

Baseline characteristics showed differences between cases and controls (Table 1). Women who developed a BC were 3 years younger on average, were more likely current smokers, and most of them had excess body weight. Due to the age difference, cases were less frequently post-menopausal. As expected, a larger proportion of cases had had a relative affected by BC (24% vs. 14%). BC cases had higher intake of energy and red meat, but there was no difference in alcohol consumption between cases and controls. As for PA, cases had active jobs more frequently (19% vs. 14%), with similar engagement in household chores, despite a slightly higher proportion of reporters (98.2% vs. 97.1%). On the other hand, cases used to practise recreational PA (RPA) less frequently (57.2% vs. 60.7%) than controls, although median volumes of RPA were similar between cases and controls who reported regular RPA.

The association of the different PA variables with BC risk was explored in five logistic regression models (Table 2), which sequentially included socio-demographic, reproductive, and lifestyle covariates, plus models testing the independent effect of each PA variable and the potential mediating role of excess body weight. Occupational PA and sitting

Table 1 Descriptive characteristics of breast cancer cases and controls. MCC-Spain study

	Controls ($n=1712$)		Cases ($n=1389$)		P cases vs. controls[a]
Age	58.7	(21.7)	55.4	(18.1)	<0,001
Low socio-economic status	516	30.1%	437	31.5%	0.207
Current smoker[b]	363	21.2%	344	24.8%	0.049
Overweight or obese[c]	816	47.7%	717	51.6%	0.028
Family history of breast cancer	247	14.4%	337	24.3%	<0.001
Ever use of oral contraceptives	842	49.2%	655	47.2%	0.095
Ever use of hormonal replacement therapy	123	7.2%	90	6.5%	0.315
Post-menopausal	1191	69.6%	870	62.6%	<0.001
Energy intake (kcal/day)	1685	(655.0)	1770	(678.5)	<0.001
Past alcohol consumption (g/day)	1.7	(7.7)	1.6	(7.9)	0.487
Red meat intake (g/day)	47.2	(38.9)	53.8	(40.3)	<0.001
Vegetable intake (g/day)	180.2	(127.7)	171.6	(129.3)	0.196
Physical activity at work					<0.001
Sedentary or low active	558	32.6%	461	33.2%	
Active or very active	245	14.3%	266	19.2%	
Not working	909	53.1%	662	47.7%	
Household physical activity					
No	50	2.9%	25	1.8%	0.043
Yes (MET-min/week)	3528	(3318)	3192	(3612)	0.087
Recreational physical activity					
No	673	39.3%	595	42.8%	0.047
Yes (MET-min/week)	1008	(1290)	1008	(1068)	0.522
Time spent sitting (h/day)	5	(4.9)	5	(4.3)	0.569
Tumour type					
ER+/PR+	-		986	(73.8)	
HER2+	-		237	(17.7)	
Triple negative	-		113	(8.5)	

Values are medians and inter-quartile ranges for continuous variables, or numbers and percentages for categorical ones

[a]P values from Mann–Whitney U or χ^2 tests for the comparison of continuous and categorical variables, respectively, between cases and controls

[b]Smoking status in the previous year

[c]Body mass index calculated from self-reported weight in the previous year

Table 2 Odds ratios (95% CI) of breast cancer according to levels of physical activity (PA) domains among participants in the MCC-Spain study ($N = 3425$)

	Controls/cases	Model 1		Model 2		Model 3		Model 4		Model 5	
		OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
Occupation											
Sedentary	193/130	1		1		1		1		1	
Low or moderately active	365/331	1.28	(0.97, 1.68)	1.29	(0.98, 1.70)	1.30	(0.98, 1.72)	1.34	(1.01, 1.78)	1.34	(1.01, 1.79)
Active or very active	245/266	1.49	(1.11, 2.00)	1.57	(1.17, 2.11)	1.55	(1.15, 2.08)	1.67	(1.23, 2.28)	1.64	(1.20, 2.24)
Not working	909/662	1.18	(0.90, 1.54)	1.22	(0.93, 1.60)	1.24	(0.94, 1.63)	1.30	(0.98, 1.72)	1.28	(0.97, 1.69)
P for trend		0.001		0.002		0.002		0.003		0.004	
Household PA (MET-min/week)											
< 500	74/59	1		1		1		1		1	
500–999	111/103	1.11	(0.71, 1.73)	1.09	(0.70, 1.70)	1.10	(0.70, 1.73)	1.09	(0.69, 1.71)	1.11	(0.70, 1.75)
1000–1999	285/250	1.10	(0.74, 1.62)	1.10	(0.74, 1.62)	1.11	(0.75, 1.65)	1.06	(0.71, 1.59)	1.08	(0.72, 1.61)
≥ 2000	1242/977	0.96	(0.67, 1.37)	0.96	(0.67, 1.39)	0.96	(0.66, 1.39)	0.93	(0.64, 1.35)	0.95	(0.65, 1.38)
P for trend		0.463		0.534		0.446		0.511		0.596	
Recreational PA (MET-min/week)											
None	673/595	1		1		1		1		1	
0.1–500	280/212	0.86	(0.70, 1.07)	0.87	(0.70, 1.08)	0.88	(0.71, 1.10)	0.89	(0.71, 1.11)	0.91	(0.73, 1.13)
500–999	238/183	0.88	(0.70, 1.11)	0.89	(0.71, 1.12)	0.92	(0.73, 1.16)	0.92	(0.73, 1.16)	0.94	(0.74, 1.19)
≥ 1000	521/399	0.91	(0.77, 1.09)	0.91	(0.76, 1.09)	0.93	(0.78, 1.12)	0.95	(0.79, 1.15)	0.98	(0.82, 1.18)
P for trend		0.178		0.171		0.283		0.412		0.601	
Sitting time (h/day)											
< 3	284/197	1		1		1		1		1	
3–5.9	759/633	1.29	(1.04, 1.59)	1.28	(1.03, 1.59)	1.26	(1.01, 1.57)	1.29	(1.04, 1.61)	1.27	(1.02, 1.58)
6–8.9	372/340	1.43	(1.13, 1.82)	1.40	(1.10, 1.78)	1.39	(1.08, 1.77)	1.49	(1.16, 1.92)	1.44	(1.12, 1.85)
≥ 9	297/219	1.15	(0.88, 1.49)	1.12	(0.86, 1.46)	1.07	(0.82, 1.40)	1.13	(0.86, 1.48)	1.08	(0.82, 1.42)
P for trend		0.346		0.258		0.132		0.200		0.127	

Model 1: Mixed-effects logistic regression model adjusted by age and socio-economic status, with random intercepts by study centre

Model 2: As model 1, plus adjustment by family history of breast cancer, age at menarche, age at first pregnancy, menopausal status, ever use of oral contraceptives, and ever use of hormonal replacement therapy

Model 3: As model 2, plus adjustment by smoking and intake of energy, red meat, vegetables, and alcohol

Model 4: as model 3, mutually adjusted by all PA variables in the table

Model 5: as model 4, further adjusted by body mass index and central obesity

OR odds ratio, *CI* confidence interval

time showed the strongest effects, with little variation across models. Women with active or very active jobs had 55% higher risk of BC as compared to women with sedentary occupations (OR 1.55; 95% CI 1.15, 2.08). Occupational PA was significantly associated with ER+/PR+, and with HER2− tumours (ORs 1.54–1.72 for the 'active/very active' vs. 'sedentary' categories; $P < 0.01$; Table S1). On the other hand, BC was more frequent among women who spent 6–9 h per day sitting than among those who sit for less than 3 h/day on average (OR 1.39; 1.08, 1.77). These associations were stronger among pre-menopausal women (Table 3), and luminal A-like cancers (ER+/PR+, HER2−). As for intensity, a strong significant inverse trend with BC risk was found for HPA of high intensity ($P = 0.018$) among pre-menopausal women, whereas moderate-intensity RPA was also associated with lower BC risk (Table 4). When stratifying by receptor status, an inverse statistically significant association was revealed for recreational PA against HER2+ tumours (50% lower chance of HER2+ BC for ≥ 1000 MET·min/week vs. none; $P < 0.001$) (Table 5) and also for ER− (OR 0.60; 0.40, 0.91; $P = 0.046$) and PR− (OR 0.65; 0.47, 0.90; $P = 0.017$) tumour types (Table S1). Finally, sitting time did not show any specific differential pattern by molecular type of the tumour, with point estimates suggesting increased risk of BC for sedentary behaviours (despite non-statistically significant linear trends). A restricted cubic spline modelling of moderate-to-vigorous leisure-time PA (MVLTPA) and sitting time illustrated the non-linearity of these associations

Table 3 Odds ratios (95% CI) of breast cancer by menopausal status according to levels of physical activity (PA) domains in the MCC-Spain study

	Pre-menopausal			Post-menopausal		
	Controls/cases	OR	95% CI	Controls/cases	OR	95% CI
Occupation						
Sedentary	98/80	1		95/50	1	
Low or moderately active	176/167	1.07	(0.73, 1.57)	189/164	1.56	(1.03, 2.38)
Active or very active	104/120	1.30	(0.84, 2.00)	141/146	1.89	(1.22, 2.91)
Not working	143/151	1.17	(0.78, 1.75)	766/510	1.46	(0.98, 2.17)
P for trend		0.126			0.005	
			P for interaction = 0.378			
Household PA (MET-min/week)						
< 500	26/23	1		48/36	1	
500–999	42/49	1.21	(0.58, 2.52)	69/54	0.99	(0.56, 1.78)
1000–1999	101/117	1.25	(0.65, 2.40)	184/133	0.91	(0.55, 1.52)
≥ 2000	352/329	0.91	(0.49, 1.69)	890/647	0.87	(0.55, 1.38)
P for trend		0.274			0.682	
			P for interaction = 0.622			
Recreational PA (MET-min/week)						
None	230/235	1		443/360	1	
0.1–500	98/98	1.10	(0.77, 1.57)	182/114	0.77	(0.58, 1.02)
500–999	71/70	0.95	(0.64, 1.43)	167/113	0.87	(0.66, 1.17)
≥ 1000	122/115	0.94	(0.67, 1.32)	399/283	0.90	(0.72, 1.11)
P for trend		0.454			0.367	
			P for interaction = 0.494			
Sitting time (h/day)						
< 3	104/99	1		180/98	1	
3–5.9	216/219	1.06	(0.75, 1.51)	543/413	1.39	(1.04, 1.86)
6–8.9	125/122	1.07	(0.72, 1.61)	247/218	1.69	(1.22, 2.32)
≥ 9	76/78	1.10	(0.70, 1.71)	221/141	1.14	(0.81, 1.61)
P for trend		0.435			0.203	
			P for interaction = 0.208			

Mixed-effects logistic regression models adjusted by age, socio-economic status, family history of breast cancer, age at menarche, age at first pregnancy, menopausal status, ever use of oral contraceptives, ever use of hormonal replacement therapy, smoking and intake of energy, red meat, vegetables, and alcohol, with random intercepts by study centre

OR odds ratio, *CI* confidence interval

Table 4 Odds ratios (95% CI) of breast cancer according to intensity levels of recreational and household physical activity, by menopausal status in the MCC-Spain study ($N = 3425$)

	Overall			Pre-menopausal			Post-menopausal		
	Controls/cases	OR	95% CI	Controls/cases	OR	95% CI	Controls/cases	OR	95% CI
Moderate-intensity household PA (MET-min/week)									
< 500	118/109	1		49/53	1		69/56	1	
500–999	173/150	0.96	(0.68, 1.37)	69/67	0.88	(0.51, 1.51)	104/83	1.00	(0.62, 1.61)
1000–1999	362/301	0.93	(0.68, 1.27)	132/138	0.89	(0.55, 1.44)	230/163	0.85	(0.56, 1.31)
≥ 2000	1059/829	0.88	(0.66, 1.18)	271/260	0.76	(0.48, 1.21)	788/568	0.87	(0.59, 1.28)
P for trend		0.903			0.411			0.974	
				P for interaction = 0.917					
High-intensity household PA (MET-min/week)									
< 500	765/696	1		204/259	1		561/437	1	
500–999	309/244	0.85	(0.69, 1.04)	102/96	0.73	(0.52, 1.04)	207/148	0.88	(0.68, 1.14)
1000–1999	382/233	0.62	(0.51, 0.76)	123/87	0.50	(0.35, 0.71)	259/146	0.68	(0.52, 0.87)
≥ 2000	256/216	0.87	(0.70, 1.09)	92/76	0.64	(0.44, 0.95)	164/139	0.98	(0.74, 1.30)
P for trend		0.081			0.018			0.438	
				P for interaction = 0.458					
Moderate-intensity recreational PA (MET-min/week)									
None	1058/946	1		304/337	1		754/609	1	
0.1–500	285/210	0.82	(0.66, 1.01)	98/96	0.94	(0.67, 1.32)	187/114	0.75	(0.57, 0.98)
500–999	170/118	0.79	(0.61, 1.03)	60/43	0.71	(0.45, 1.10)	110/75	0.86	(0.62, 1.19)
≥ 1000	194/112	0.67	(0.52, 0.87)	58/42	0.71	(0.45, 1.11)	136/69	0.64	(0.46, 0.88)
P for trend		0.001			0.034			0.009	
				P for interaction = 0.763					
High-intensity recreational PA (MET-min/week)									
None	1654/1344	1		487/491	1		1167/852	1	
0.1–500	21/15	0.77	(0.38, 1.54)	13/12	1.01	(0.43, 2.39)	8/3	0.53	(0.14, 2.07)
500–999	17/14	1.02	(0.49, 2.14)	8/6	0.73	(0.24, 2.25)	9/8	1.19	(0.43, 3.26)
≥ 1000	20/16	0.86	(0.43, 1.70)	13/9	0.70	(0.28, 1.71)	7/7	1.12	(0.37, 3.36)
P for trend		< 0.001			0.433			< 0.001	
				P for interaction = 0.902					

Mixed-effects logistic regression models adjusted by age, socio-economic status, family history of breast cancer, age at menarche, age at first pregnancy, menopausal status (overall models), ever use of oral contraceptives, ever use of hormonal replacement therapy, smoking and intake of energy, red meat, vegetables, and alcohol, with random intercepts by study centre

OR odds ratio, *CI* confidence interval

(Fig. 1), with the lowest risk estimates found at MVLTPA values between 2000 and 3000 MET·min/week, and a peak at 5–6 h of regular daily sitting time.

Discussion

Our analysis shows that distinct types of physical activities were differently associated with overall breast cancer risk in the MCC-Spain study, with opposing effects for occupational PA (pointing to higher BC risk) and household or recreational PA (pointing to lower risk). Besides, the effects of OPA and RPA also differed by menopausal status and molecular profile of the tumours. On the other hand, a sedentary behaviour was associated with increased premenopausal BC risk, regardless of molecular characteristics of the tumour. The heterogeneity in PA types and patterns and in BC sub-types warranted a detailed stratified analysis by PA domains and tumour type.

Occupational PA was associated with a 55% increased risk of BC overall, after accounting for socio-demographic, reproductive, and lifestyle characteristics. When further adjusting by obesity, point estimates were even higher, suggesting that the independent effects of occupational exposures on BC risk could be larger after discounting the potential benefits of active jobs in controlling adiposity. In our study, active workers were more likely to have rotating or night-shift works (28.8% vs. 12.1% for 'active/very active'

Table 5 Odds ratios (95% CI) of breast cancers defined by hormone receptor status according to levels of physical activity (PA) domains in the MCC-Spain study

	ER+/PR+, HER2−			HER2+			Triple negative		
	Cases	OR	95% CI	Cases	OR	95% CI	Cases	OR	95% CI
Occupation									
Sedentary	81	1		29	1		12	1	
Low or moderately active	236	1.51	(1.10, 2.08)	61	1.01	(0.61, 1.67)	21	0.87	(0.40, 1.87)
Active or very active	190	1.80	(1.28, 2.53)	47	1.15	(0.67, 1.97)	22	1.28	(0.59, 2.79)
Not working	479	1.43	(1.04, 1.95)	100	0.80	(0.49, 1.32)	58	1.17	(0.57, 2.40)
P for trend		0.001			0.740			0.519	
Household PA (MET-min/week)									
< 500	42	1		9	1		4	1	
500–999	71	1.02	(0.62, 1.68)	19	1.31	(0.55, 3.14)	7	1.02	(0.28, 3.78)
1000–1999	173	1.06	(0.68, 1.64)	44	1.26	(0.57, 2.76)	22	1.52	(0.49, 4.70)
≥ 2000	700	0.93	(0.62, 1.39)	165	1.06	(0.51, 2.22)	80	1.12	(0.38, 3.24)
P for trend		0.534			0.553			0.058	
Recreational PA (MET-min/week)									
None	398	1		125	1		54	1	
0.1–500	147	0.90	(0.70, 1.15)	38	0.75	(0.50, 1.12)	13	0.63	(0.33, 1.19)
500–999	131	0.97	(0.75, 1.25)	28	0.64	(0.41, 1.01)	19	1.04	(0.59, 1.84)
≥ 1000	310	1.09	(0.89, 1.33)	46	0.50	(0.34, 0.73)	27	0.75	(0.45, 1.25)
P for trend		0.560			< 0.001			0.441	
Sitting time (h/day)									
< 3	140	1		39	1		15	1	
3–5.9	446	1.26	(0.99, 1.61)	108	1.10	(0.74, 1.65)	57	1.87	(1.01, 3.48)
6–8.9	242	1.38	(1.05, 1.81)	55	1.16	(0.73, 1.82)	25	1.66	(0.83, 3.32)
≥ 9	158	1.07	(0.80, 1.45)	35	0.86	(0.52, 1.43)	16	1.14	(0.53, 2.46)
P for trend		0.132			0.533			0.414	

Mixed-effects logistic regression models adjusted by age, socio-economic status, family history of breast cancer, age at menarche, age at first pregnancy, menopausal status, ever use of oral contraceptives, ever use of hormonal replacement therapy, smoking and intake of energy, red meat, vegetables, and alcohol, with random intercepts by study centre

OR odds ratio, *CI* confidence interval

versus 'sedentary' workers). Chronodisruptive shift working is now recognised as a probable human carcinogen [20], and a previous report from the MCC-Spain study showed that night-shift workers were at 18% higher risk of BC than day workers [21]. However, adjusting our models by having ever worked on a night shift had virtually no impact on the risk estimates for active workers, suggesting that chronodisruption would not be the principal mediating factor explaining the association with OPA. The fact that OPA was only related with ER+/PR+ BC would rather suggest that PA at work might be confounded by occupational risk exposures probably related to endocrine disruptive mechanisms that would trigger cell proliferation through the agonist activation of hormonal pathways. Among women with ER+/PR+ tumours, certain occupations were over-represented among cases, including jobs implying potential exposition to chemical hazards (such as laundry workers or cleaning staff), but also others without a clear environmental exposure to disruptive chemicals (such as waitresses or cooks). An in-depth analysis of occupational risks and BC risk is warranted not only to better understand the inter-dependent effects of physical activity and occupational exposures, but also to mitigate the gender bias in the epidemiologic literature regarding the paucity of investigation of job-related breast cancer hazards [22, 23]. Regardless of the speculative mechanisms that would account for an increased risk of breast cancer among active workers, our findings contrast with some [2, 3] (but not all [1]) previous studies showing reduced BC risk among women with higher OPA. It is unclear whether a publication bias could exist pertaining to negative results of physical activity, as accruing evidence has started to unveil deleterious health effects of occupational PA [24, 25], an important yet so far a poorly studied issue. Although previous studies reporting adverse health outcomes of OPA have mainly focused on cardiovascular diseases [26, 27], our results would suggest that physically

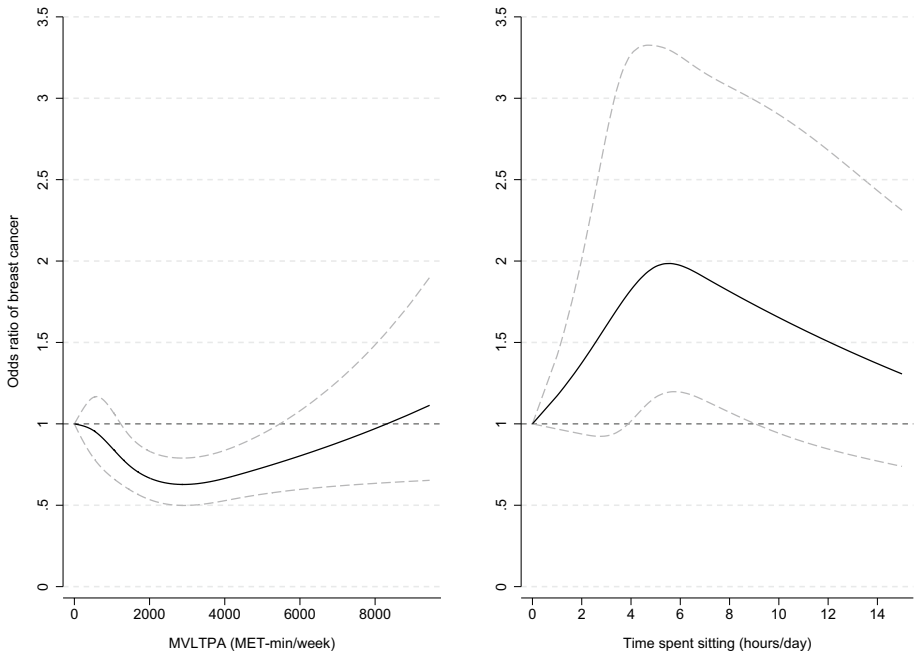

Fig. 1 Multivariable restricted cubic spline modelling of overall breast cancer risk according to moderate-to-vigorous leisure-time physical activity (MVLTPA) and sitting time in the MCC-Spain study

demanding occupations might also be detrimental to health by increasing cancer risk.

Neither household nor recreational PA were significantly associated with BC risk overall. However, a lower risk of BC was observed at higher levels of HPA of moderate-to-high intensity, which was stronger among pre-menopausal women, with an estimated 36% lower risk of BC for the comparison of extreme categories. At least a moderate-intensity level was also required to bring to light a protective effect of RPA: women who exceeded 1000 MET·h/week were at 33% (13% to 48%) lower risk of BC overall than those not engaging in RPA, with the inverse trend being statistically significant both in pre-menopausal and post-menopausal women. For high-intensity RPA, trend *P* values were also significant, but the scarce number of cases available did not allow to obtain precise estimates in stratified analyses. These results agree with previous meta-analyses consistently showing the highest reductions in BC risk for vigorous recreational PA [1, 3, 5].

In general, the effects of physical activity are more easily discernible when major BC risk factors are not present, i.e. among non-obese, post-menopausal women, without family history of the disease, and for tumours not expressing oestrogen or progesterone receptors [1, 3]. Our results confirm previous studies linking RPA with hormone negative (ER−/PR−) breast cancers, but also revealed a strongly significant association with HER2+ tumours. These cancers were less frequent among women doing more than the recommended 500 MET·min/week of RPA [28] than among women not engaging in RPA at all (*P* for linear trend < 0.001) and half as frequent at levels above 1000 MET·min/week of RPA (between 27 and 66% lower risk). At this point, results in literature are conflicting. A link of borderline statistical significance between RPA and HER2+ BC tumours has been reported in a previous Spanish study [11] with 698 middle-age women. The larger number of cases of the present study may have allowed for more precise estimates of HER2+ BC risk. However, Ma et al. found that higher RPA reduced the risk of ER+/PR+, HER2− (luminal A) breast cancers, but not HER2+ tumours, in participants from the Women's CARE Study [29]. Similarly, a Norwegian study also reported an inverse association for ER+/PR+, HER2− ($P < 0.01$), but also an inverse trend ($P = 0.1$) for ER− PR− HER2+ tumours [13]. While specific mechanisms of action for PA against HER2+ tumours have not been identified, the relationship between RPA and BC risk by HER2 status warrants further investigation, given the heterogeneity and scarcity of the data available.

Sedentary behaviour is a known independent risk factor for cancer, including colorectal, endometrium, and breast tumours [30]. In our study, BC cases (particularly, pre-menopausal) were significantly more sedentary than controls, independently of physical activity patterns and dietary and lifestyle risk factors. Tests for trend were not significant, however, because of an anomalous performance of the upper category (≥ 9 h/day of leisure-time sitting time), probably affected by reporting bias and/or reverse causation. In the Women's Health Initiative prospective study, sitting time correlated with increased oestrogen metabolites in post-menopausal women [31], a major determinant of this cancer [32] but was not independently associated with BC incidence [33]. However, a

case–control study of Polish women using accelerometers reported an 81% increased risk of breast cancer for the most sedentary group, independently of moderate-to-vigorous PA, both in pre- and post-menopausal women [34].

Proposed mechanisms for a protective role of PA against BC involve endocrine actions on sex-steroid and insulin signalling pathways, and long-term effects on the immune system and low-grade systemic inflammation [35–37]. Importantly, PA reduces plasma oestradiol concentrations and increases sex-hormone binding globulin (SHBG) [35] which is partly mediated by reductions in total body fat [38], thus limiting the proliferative actions of sex hormones over the cell cycle. However, because of the multifactorial aetiology of breast cancers, it is unlikely that any single factor is sufficient to drive the initiation and progression of malignant cells, but rather PA would act through the modulation of several combined endocrine, inflammatory, immune, and molecular mechanisms [35].

Limitations include the potential of recall bias, measurement error, or residual confounding. To minimise the effect of reverse causation due to eventual lifestyle changes incurred by the cases, data were collected excluding the last year whenever possible. However, we cannot totally discard that pre-diagnostic conditions could have partially affected the reporting of PA variables. Because of the multicase–control design, controls were matched to the whole pool of cancer cases, and the analysis of separate entities such as breast cancer does not benefit from the matching procedure. Consequently, all models included the matching factors (age and region) as covariates. The study has several strengths also, such as the molecular characterisation of the tumours (ER, PR, and HER2 status), the histological confirmation of all tumours, the large sample of population controls selected from the same healthcare areas of the cases, and extensive data available on potential confounders. Finally, physical activity was assessed with an exhaustive, open-ended, PA questionnaire that included specific questions on the main PA domains (work, household, and recreational) and sedentary time.

In conclusion, our results revealed a higher risk of premenopausal, luminal A-like, breast cancer among women with active or very active occupations as compared to sedentary workers. Household and recreational activities were inversely associated with overall BC risk at moderate-to-high intensity levels, supporting most previous literature. A strong inverse association of recreational physical activity with HER2+ tumours was found which deserves further study. Finally, sedentary behaviour during leisure time was a consistent risk factor for overall and pre-menopausal breast cancer.

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Data availability The datasets generated and analysed during the current study area available, with restrictions, from the MCC-Spain study coordinators, Manolis Kogevinas (manolis.kogevinas@isglobal.org) and Marina Pollán (mpollan@isciii.es), on reasonable request. The release of the database in whole or in part would require prior approval by the PI of each centre providing the data and by the Steering Committee of the MCC-Spain study (www.mccspain.org) for further information on how to establish a collaboration and gain access to MCC-Spain data.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

References

1. Friedenreich CM, Cust AE (2008) Physical activity and breast cancer risk: Impact of timing, type and dose of activity and population subgroup effects. Br J Sports Med 42:636–647. https://doi.org/10.1136/bjsm.2006.029132
2. Pizot C, Boniol M, Mullie P et al (2016) Physical activity, hormone replacement therapy and breast cancer risk: a meta-analysis of prospective studies. Eur J Cancer 52:138–154. https://doi.org/10.1016/j.ejca.2015.10.063
3. Wu Y, Zhang D, Kang S (2013) Physical activity and risk of breast cancer: a meta-analysis of prospective studies. Breast Cancer Res Treat 137:869–882. https://doi.org/10.1007/s10549-012-2396-7
4. International Agency for Research on Cancer (2018) Global Cancer Observatory. https://gco.iarc.fr. Accessed 14 Apr 2019.
5. World Cancer Research Fund, American Institute for Cancer Research (2018) Continuous Update Project Expert Report 2018. Diet, nutrition, physical activity and breast cancer. https://dietandcancerreport.org. Accessed 5 Dec 2018.
6. Ellsworth RE, Blackburn HL, Shriver CD et al (2017) Molecular heterogeneity in breast cancer: state of the science and

implications for patient care. Semin Cell Dev Biol 64:65–72. https://doi.org/10.1016/j.semcdb.2016.08.025
7. Rivenbark AG, O'Connor SM, Coleman WB (2013) Molecular and cellular heterogeneity in breast cancer: challenges for personalized medicine. Am J Pathol 183:1113–1124. https://doi.org/10.1016/j.ajpath.2013.08.002
8. Weiderpass E, Meo M, Vainio H (2003) Risk factors for breast cancer, including occupational exposures. Saf Health Work 2:1–8. https://doi.org/10.5491/shaw.2011.2.1.1
9. Chen X, Wang Q, Zhang Y et al (2019) Physical activity and risk of breast cancer: a meta-analysis of 38 cohort studies in 45 study reports. Value Heal 22:104–128. https://doi.org/10.1016/j.jval.2018.06.020
10. Moore SC, Lee I-M, Weiderpass E et al (2016) Association of leisure-time physical activity with risk of 26 types of cancer in 1.44 million adults. JAMA Intern Med 175:959–967. https://doi.org/10.1001/jamainternmed.2016.1548
11. Lope V, Martín M, Castelló A et al (2017) Physical activity and breast cancer risk by pathological subtype. Gynecol Oncol 144:577–585. https://doi.org/10.1016/j.ygyno.2016.12.014
12. Ma H, Xu X, Clague J et al (2016) Recreational physical activity and risk of triple negative breast cancer in the California Teachers Study. Breast Cancer Res 18:62. https://doi.org/10.1186/s13058-016-0723-3
13. Ellingjord-Dale M, Vos L, Hjerkind KV et al (2017) Alcohol, physical activity, smoking, and breast cancer subtypes in a large, nested case–control study from the Norwegian Breast Cancer Screening Program. Cancer Epidemiol Biomarkers Prev 26:1736–1744. https://doi.org/10.1158/1055-9965.EPI-17-0611
14. Castaño-Vinyals G, Aragonés N, Pérez-Gómez B et al (2015) Population-based multicase-control study in common tumors in Spain (MCC-Spain): rationale and study design. Gac Sanit 29:308–315. https://doi.org/10.1016/j.gaceta.2014.12.003
15. World Health Organization (2018) ICD-10: International Statistical classification of diseases and related health problems. Tenth Revision. WHO, Geneva
16. Ainsworth BE, Haskell WL, Herrmann SD, et al The Compendium of Physical Activities Tracking Guide. https://sites.google.com/site/compendiumofphysicalactivities. Accessed 7 July 2018.
17. de Batlle J, Gracia-Lavedan E, Romaguera D et al (2018) Meat intake, cooking methods and doneness and risk of colorectal tumours in the Spanish multicase-control study (MCC-Spain). Eur J Nutr 57:643–653. https://doi.org/10.1007/s00394-016-1350-6
18. Puig-Vives M, Sánchez MJ, Sánchez-Cantalejo J et al (2013) Distribution and prognosis of molecular breast cancer subtypes defined by immunohistochemical biomarkers in a Spanish population-based study. Gynecol Oncol 130:609–614. https://doi.org/10.1016/j.ygyno.2013.05.039
19. Orsini N, Greenland S (2011) A procedure to tabulate and plot results after flexible modeling of a quantitative covariate. Stata J 11:1–29
20. International Agency for Research on Cancer (2010) IARC monographs on the evaluation of carcinogenic risks to humans. Painting, firefighting, and shiftwork. IARC, Lyon
21. Papantoniou K, Castaño-Vinyals G, Espinosa A et al (2016) Breast cancer risk and night shift work in a case–control study in a Spanish population. Eur J Epidemiol 31:867–878. https://doi.org/10.1007/s10654-015-0073-y
22. Messing K, Östlin P (2006) Gender equality, work, and health: a review of the evidence. WHO, Geneva
23. Li J, Loerbroks A, Angerer P (2013) Physical activity and risk of cardiovascular disease. Curr Opin Cardiol 28:575–583. https://doi.org/10.1097/HCO.0b013e328364289c
24. Coenen P, Huysmans MA, Holtermann A et al (2018) Can socioeconomic health differences be explained by physical activity at work and during leisure time? Rationale and protocol of the active worker individual participant meta-analysis. BMJ Open 8:e023379. https://doi.org/10.1136/bmjopen-2018-023379
25. Holtermann A, Krause N, Van Der Beek AJ, Straker L (2018) The physical activity paradox: Six reasons why occupational physical activity (OPA) does not confer the cardiovascular health benefits that leisure time physical activity does. Br J Sports Med 52:149–150. https://doi.org/10.1136/bjsports-2017-097965
26. Li J, Loerbroks A, Angerer P (2013) Physical activity and risk of cardiovascular disease: what does the new epidemiological evidence show? Curr Opin Cardiol 28:575–583. https://doi.org/10.1097/HCO.0b013e328364289c
27. Hall C, Heck JE, Sandler DP, et al. (2018) Occupational and leisure-time physical activity differentially predict 6-year incidence of stroke and transient ischemic attack in women. Scand J Work Environ Health 45:0–13. https://doi.org/10.5271/sjweh.3787
28. World Health Organization (2010) Global recommendations on physical activity for health. WHO, Geneva
29. Ma H, Xu X, Ursin G et al (2015) Reduced risk of breast cancer associated with recreational physical activity varies by HER2 status. Cancer Med 4:1122–1135. https://doi.org/10.1002/cam4.465
30. Kerr J, Anderson C, Lippman SM (2017) Physical activity, sedentary behaviour, diet, and cancer: an update and emerging new evidence. Lancet Oncol 18:e457–e471. https://doi.org/10.1016/S1470-2045(17)30411-4
31. Oh H, Arem H, Matthews CE et al (2017) Sitting, physical activity, and serum oestrogen metabolism in postmenopausal women: the Women's Health Initiative Observational Study. Br J Cancer 117:1070–1078. https://doi.org/10.1038/bjc.2017.268
32. Key T, Appleby P, Barnes I, Reeves G (2002) Endogenous sex hormones and breast cancer in postmenopausal women: re-analysis of nine prospective studies. J Natl Cancer Inst 94:606–616
33. Nomura SJO, Dash C, Sheppard VB et al (2017) Sedentary time and postmenopausal breast cancer incidence. Cancer Causes Control 28:1405–1416. https://doi.org/10.1007/s10552-017-0968-x
34. Dallal CM, Brinton LA, Matthews CE et al (2012) Accelerometer-based measures of active and sedentary behavior in relation to breast cancer risk. Breast Cancer Res Treat 134:1279–1290. https://doi.org/10.1007/s10549-012-2129-y
35. Friedenreich CM, Woolcott CG, McTiernan A et al (2010) Alberta physical activity and breast cancer prevention trial: Sex hormone changes in a year-long exercise intervention among postmenopausal women. J Clin Oncol 28:1458–1466. https://doi.org/10.1200/JCO.2009.24.9557
36. Alegre MM, Knowles MH, Robison RA, O'Neill KL (2013) Mechanics behind breast cancer prevention—focus on obesity, exercise and dietary fat. Asian Pacific J Cancer Prev 14:2207–2212. https://doi.org/10.7314/APJCP.2013.14.4.2207
37. de Boer MC, Wörner EA, Verlaan D, van Leeuwen PAM (2017) The mechanisms and effects of physical activity on breast cancer. Clin Breast Cancer 17:272–278. https://doi.org/10.1016/j.clbc.2017.01.006
38. Friedenreich CM, Neilson HK, Woolcott CG et al (2011) Mediators and moderators of the effects of a year-long exercise intervention on endogenous sex hormones in postmenopausal women. Cancer Causes Control 22:1365–1373. https://doi.org/10.1007/s10552-011-9809-5

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