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Interaction of sedentary behaviour and educational level in breast cancer risk

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Abstract

Objective

This cross-sectional study aims to analyse the relationship between sedentary behaviour and breast cancer (BC) risk from a social perspective.

Methods

Women aged 45–70 who participated in the Valencia Region Breast Cancer Screening Programme (2018–2019) were included, with a total of 121,359 women analysed, including 506 with cancer and 120,853 without cancer. The response variable was BC (screen-detected) and the main explanatory variable was sedentary behaviour ($\leq$2 / >2-$\leq$3 / >3-$\leq$5 / >5 hours/day, h/d). Nested logistic regression models (M) were estimated: M1: sedentary behaviour adjusted for age and family history of BC; M2: M1 + hormonal/reproductive variables (menopausal status, number of pregnancies, hormone replacement therapy; in addition, months of breastfeeding was added for a subsample of women with one or more live births); M3: M2 + lifestyle variables (body mass index, smoking habits); M4: M3 + socioeconomic variables (educational level, occupation); Final model: M4 + gender variables (childcare responsibilities, family size). Interaction between sedentary behaviour and educational level was analysed in the Final model. Moreover, for the whole sample, postmenopausal women and HR+ BC, the Final model was stratified by educational level.

Results

Sedentary behaviour was associated with an increased risk of BC with a nearly statistically significant effect in the Final model (>2-$\leq$3 h/d: OR = 1.22 (0.93–1.61); >3-$\leq$5 h/d: OR = 1.14 (0.86–1.52); >5: OR = 1.19 (0.89–1.60)). For women with a low educational level, sitting more than 2 h/d was associated with an increased risk of BC in the whole sample (>2-$\leq$3 h/d OR = 1.93 (1.19–3.21); in postmenopausal women (>2-$\leq$3 h/d, OR = 2.12 (1.18–

2.96), >5h/d OR = 1.75 (1.01–3.11)) and in HR+ BC (>2-≤3h/d, OR = 2.15 (1.22–3.99)). Similar results were observed for women with one or more live births.

Conclusions

Sitting >2 h/d is associated with BC risk in women with low educational level, especially in postmenopausal women and those with live births.

Introduction

Breast cancer (BC) is a significant public health problem worldwide [1]. In Spain, it is the most common type of cancer in women and causes the highest number of cancer deaths in this same population group [2].

The high incidence and mortality rate of BC demonstrate the need to investigate its risk factors. Only 5–10% of cancers are caused by genetic factors, and the remaining 90–95% are due to social, lifestyle and environmental aspects [3]. Several studies show that a diet rich in processed meat [4], alcohol consumption [5], smoking [6], and physical inactivity [7] are modifiable BC risk factors.

Most studies that analyse the relationship between BC and physical activity have focused on physical inactivity defined as the failure to meet World Health Organization (WHO) recommendations [8]. However, there is currently little consensus on the relationship between sedentary behaviour that is defined as any activity with an energy expenditure of less than 1.5 metabolic equivalents (METs) such as watching television, or driving [9], and BC. Some studies show a positive relationship between sedentary behaviour and BC risk [10–13], while other studies find no such association [14, 15].

Sedentary behaviour may influence the risk of BC through inflammatory, metabolic, and hormonal processes. It has been observed that sedentary behaviour leads to increased blood insulin level, which is associated with an increase of BC risk [9, 16, 17]. In addition, it has been proven that the bioavailability of free oestrogens (oestradiol, free oestradiol, and oestrone), which are released by adipose tissue in postmenopausal women [17], can induce cellular proliferation and stimulate tumour growth [16, 17]. Considering this, sedentary behaviour has been shown to increase both triglycerides and cholesterol in the blood [9], which may increase adipose tissue in women and consequently, the release of these free oestrogens.

There is strong evidence that postmenopausal status [18, 19], nulliparity [20, 21], increased age at first birth [22] and the use of hormone replacement therapy (HRT) [23] are common BC risk factors. It is also widely known that breastfeeding plays a protective role against this type of cancer, with the longer breastfeeding lasts, the greater the reduction in risk [10]. There is no consensus regarding the relationship between sedentary behaviour and BC risk according to menopausal status. Some studies observed that sedentary behaviour has a more significant impact on BC risk in postmenopausal women [18, 19], while others do not observe this difference [5, 12]. The same is true in the impact according to different hormone receptor subtype [11], with some studies observing that sedentary behaviour has a higher impact on hormone receptor-positive (HR+) BC [19].

It is known that smoking and high body mass index (BMI) increase the risk of BC [24–26]. The impact of these factors on BC when combined with sedentary behaviour is currently unknown. Although there is no consensus regarding the direction of the relationship between

sedentary behaviour and BMI, as sedentary behaviour may entail an increase in BMI and the amount of adipose tissue, in combination they may both increase BC risk.

Likewise, we know that women with a high educational level are more likely to develop BC [27–29]. This may be due to the presence of hormonal and reproductive risk factors for BC associated with this group, such as nulliparity and HRT use [30, 31]. Moreover, it has been observed that women with high educational level have a higher risk of sedentary behaviour than those with a low educational level [32]. Although the influence of educational level on BC risk and sedentary behaviour has been observed, to the authors' knowledge, there are no studies that analyse the relationship between sedentary behaviour and BC while considering this social determinant. As regards occupation, there is currently little consensus on its relationship with BC. While some studies show that non-manual occupations increase BC risk [33, 34], others find no such association [14]. Moreover, there are currently no studies that include gender factors, such as women's family caregiving responsibilities, in BC risk analysis.

Due to these controversial results regarding the association between sedentary behaviour and BC and the lack of studies including the influence of social and gender determinants on this association, the objective of this study is to analyse the relationship between sedentary behaviour and BC from a social perspective.

Materials and methods

Study population

This cross-sectional study includes all women aged between 45 and 70 who participated in the population-based Valencia Region Breast Cancer Screening Programme (VR-BCSP) (Spain) between November 2018 and October 2019 (N = 289,315). The sample analysed were women who had concluded the screening process and for whom there was data on sedentary behaviour available (n = 121,359). A total of 506 women with screen-detected BC and 120,853 women without cancer were analysed.

Information collection

The data analysed were obtained from the VR-BCSP information system. This system provides information on the results of the screening process and, in the event of a BC diagnosis, on tumour characteristics. It also includes socioeconomic and lifestyle data. This information is collected through an epidemiological questionnaire that is conducted face to face with women when they attend their biennial programme appointment and before a possible BC diagnosis. Information on sedentary behaviour was collected using the short version of the International Physical Activity Questionnaire (IPAQ-short), which is part of the epidemiological questionnaire. This IPAQ-Short questionnaire has been internationally validated for collecting information on physical activity and sedentary behaviour [35].

In addition, the information system includes the Segmented, Integrated, and Geographic Population Analysis Code, which is obtained by linking data with the Population Information System of the Valencia Region Government's Department of Universal and Public Health. This code collects individual information on variables related to socioeconomic and gender characteristics for the entire population with the right to healthcare coverage, including family size or educational level.

Ethics considerations

This study was approved by the Research Ethics Committee of the General Directorate of Public Health and the Advanced Public Health Research Centre (CEI DGSP-CSISP) on 9 January

2,020 (reference no.: 20200109/04). Taking into account the project design and its large sample size, the ethics committee approved carrying out the study without requiring that individual consent be provided by each subject, in accordance with the regulations of the current version of the Declaration of Helsinki (October 2008, Seoul). The personal data included in this study was pseudonymised to guarantee confidentiality, privacy, and security. The project was carried out in accordance with the principles of the Declaration of Helsinki and Spanish confidentiality legislation (Spanish Organic Law 3/2018, of 5 December, on Personal Data Protection and Guaranteeing Digital Rights).

Study variables

The response variable is screen-detected BC (yes/no). In the context of the VR-BCSP, BC is defined as any tumour considered to be a breast carcinoma following a positive screening exam (mammogram) that is confirmed by pathological anatomy. Lobular carcinoma in situ is excluded from this definition. In terms of phenotype, BC is classified as HR+ (oestrogen receptor-positive, and/or progesterone receptor-positive and HER2 negative), Human Epidermal growth factor Receptor 2 (HER2+) (HER2+ regardless of ER or PR expression), or triple negative (TN) (oestrogen receptor-negative, progesterone receptor-negative and HER2 negative).

The main explanatory variable is sedentary behaviour, which was determined by the question "During the last 7 days, how much time did you spend sitting on a week day?" from the IPAQ-short questionnaire (available on https://sites.google.com/view/ipaq?pli=1). In accordance with the questionnaire protocol, the variable is classified based on the interquartile ranges of the sitting time: ≤ 2 / >2-≤ 3 / >3-≤ 5 / >5 hours/day sitting.

Based on scientific evidence, the following variables were considered:

Adjustment: age (continuous variable) and family history of BC (yes/no). The "yes" category of the family history variable includes: very strong (first-degree relative with BC in premenopausal years or bilateral cancer), strong (first-degree relative with BC in postmenopausal years or unilateral cancer), and minor (second-degree or more distant relative).

Hormonal/reproductive: menopausal status (premenopausal/postmenopausal), months of breastfeeding (0/<6/≥ 6), number of pregnancies (0/1/≥ 2), and HRT use (yes/no). The number of pregnancies variable refers to all the pregnancies that the women have had regardless of duration and outcome.

Lifestyle: BMI (as a continuous variable) calculated based on self-reported weight (Kg) divided by self-reported height squared (m^2) and smoking habits (non-smoker/former /current).

Socioeconomic: educational level (low/medium-high) and occupation (non-manual/manual/ not working/homemaker). The "low" educational level includes illiterate, no schooling, and primary education only, and the "medium-high" category comprises secondary education, post-secondary non tertiary and tertiary education.

Gender: childcare responsibilities (yes/no) and family size (FS) (small/medium-large). A small FS is a family unit of <3 people, including women who live alone.

Statistical analysis

The relationship between BC and sedentary behaviour and the set of explanatory variables was assessed by performing a bivariate analysis through a chi-square or Mann-Whitney U test.

Next, nested logistic regression models (M) were estimated to analyse the relationship between BC risk and sedentary behaviour considering other explanatory variables. The models

analysed were: M1: BC risk associated with sedentary behaviour adjusted for age and family history of BC; M2: M1 and hormonal/reproductive variables; M3: M2 and lifestyle variables; M4: M3 and socioeconomic variables; and then, the Final model: M4 and gender variables.

Multivariate logistic regression models were used to explore the possible relationship between sedentary behaviour and BC risk. Moreover, to analyse the interaction between sedentary behaviour and educational level (as categorical variables), this interaction was added to the Final model, which includes all the explanatory variables. This interaction has been explored for the whole sample and according to menopausal status and for the BC phenotypes: HR+ (HR+ vs. no cancer) and HER2+ (HER2+ vs. no cancer). The TN phenotype was not included in the analysis as the sample size was insufficient (TN = 20). For the models where the interaction was statistically significant, stratification by educational level has been analysed.

In order to include the months of breastfeeding variable in the analysis, the same statistical analysis explained above were conducted for a subsample of women with one or more live births (n = 108,121).

The models results are presented in terms of odds ratio (OR) and 95% confidence interval (CI), considering a significance level of less than 0.05. The statistical programme R v4.1.1 was used.

Results

According to the results of the descriptive analysis (Table 1), >2-≤3 h/d of sitting is the most frequent sedentary behaviour category in both women with BC and without BC (29.45% and 26.58% respectively, p = 0.197). A statistically significant association can be seen between BC and increasing age (p<0.001), having a family history of BC (p = 0.047), number of pregnancies (p = 0.002), months of breastfeeding (p = 0.026), higher BMI (p<0.001), smoking habits (p = 0.021), childcare responsibilities (p = 0.005) and FS (p = 0.005).

The nested logistic regression models (Table 2) show that sedentary behaviour is positively associated with BC risk. In Model 1, which includes age and family history of BC as adjustment variables, sitting >2-≤3h/d shows a statistically significant relationship (OR = 1.29 (1.01–1.66), p-value = 0.044), being the rest of categories nearly significant (>3-≤5 h/d: OR = 1.18 (0.91–1.53), p-value = 0.206; >5 h/d: OR = 1.21 (0.93–1.57), p-value = 0.156). When including hormonal/reproductive (M2), lifestyle (M3), socioeconomic (M4), and gender (Final model) variables, similar results are observed. In the Final model, the OR for sitting >2-≤3 h/d is 1.22 (CI = 0.93–1.61, p-value = 0.161); for >3-≤5 h/d is 1.14 (CI = 0.86–1.52, p-value = 0.360) and for >5 h/d is 1.19 (CI = 0.89–1.60, p-value = 0.231).

When studying the interaction between sedentary behaviour and educational level added in the Final model, a statistically significant relationship is observed for the whole sample (p-int = 0.015), in postmenopausal women (p-int = 0.005) and in HR+ BC (p-int = 0.013) (results not shown in table). This is also observed for the subsample of women with one or more live births (whole subsample: p-int = 0.048; postmenopausal women: p-int = 0.013; HR+ BC: p-int = 0.049) (results not shown in table).

Stratifying by educational level, the results for the whole sample show that women with low educational level who spent >2-≤3 h/d sitting are at a higher BC risk (OR = 1.93 (1.19–3.21), p-value = 0.008) with statistically significant differences (Table 3). This relationship is also found in women with low educational level who spend >3-≤5 h/d (OR = 1.51 (0.92–2.54), p-value = 0.113) and >5 h/d sitting (OR = 1.66 (0.98–2.86), p-value = 0.061) with a nearly statistical significance (Table 3). These results are not observed in women with high educational level. Additional information of other explanatory variables results is provided in S1 Table.

Table 1. Characteristics of women with and without breast cancer from the sample.

	Cancer	No cancer	p value
	n (%)	n (%)	
	506	120,853	
Sedentary behaviour (h/d sitting)			
≤2	109 (21.54)	30,666 (25.37)	0.197
>2-≤3	149 (29.45)	32,126 (26.58)	
>3-≤5	126 (24.90)	28,909 (23.92)	
>5	122 (24.11)	29,152 (24.12)	
Age (years)[a] median (min-max)	57.5 (45–70)	56.0 (45–70)	<0.001
Family history of BC			
No	356 (70.50)	89,582 (74.36)	0.047
Yes	149 (29.50)	30,888 (25.64)	
Hormonal/Reproductive variables			
Menopausal status			
Premenopausal	140 (28.40)	36,635 (31.23)	0.175
Postmenopausal	353(71.60)	80,668 (68.77)	
Number of pregnancies			
≥2	333 (66.07)	88,037 (72.97)	0.002
1	102 (20.24)	19,649 (16.29)	
None	69 (13.69)	12,959 (10.74)	
Months of breastfeeding[b]			
≥6	183 (43.57)	50,618 (48.90)	0.026
<6	115 (27.38)	28,654 (27.68)	
0	122 (29.05)	24,237 (23.42)	
HRT			
No	465 (91.90)	112,933 (93.45)	0.160
Yes	41 (8.10)	7,920 (6.55)	
Lifestyle variables			
BMI[a] median (min-max)	2,711 (16.85–47.26)	2,635 (14.17–57.78)	<0.001
Smoking habits			
Non-smoker	238 (47.04)	62,362 (51.60)	0.021
Current	133 (26.28)	32,225 (26.66)	
Former	135 (26.68)	26,266 (21.73)	
Gender variables			
Childcare responsibilities			
No	100 (19.92)	30,269 (25.40)	0.005
Yes	402 (80.08)	88,888 (74.60)	
FS			
Small	213 (42.43)	43,315 (36.35)	0.005
Medium-Large	289 (57.57)	75,842 (63.65)	
Socioeconomic variables			
Educational level			
Low	164 (35.04)	34,814 (31.37)	0.097
Medium-High	304 (64.96)	76,153 (68.63)	
Occupation			

(Continued)

Table 1. (Continued)

Manual	132 (28.70)	34,670 (31.41)	0.271
Non-manual	107 (23.26)	27,501 (24.92)	
Not working	50 (10.87)	11,654 (10.56)	
Homemakers	171 (37.17)	36,539 (33.11)	
Tumour characteristics[c]			
HR+	323 (81.57)	-	
HER2+	53 (13.38)	-	
TN	20 (5.05)	-	

[a]Mann-Whitney U test

[b]For the subsample of women with one or more live births

[c] % calculated from the total cases with information on their phenotype (n = 396)

Abbreviations: h/d (hours per day); BC (breast cancer); HRT (Hormone Replacement Therapy); BMI (Body Mass Index); FS (Family Size); HR+ (oestrogen receptor-positive, and/or progesterone receptor-positive and HER2 negative), HER2+ (HER2+ regardless of ER or PR expression), TN (Triple Negative -oestrogen receptor-negative, progesterone receptor-negative and HER2 negative-)

In postmenopausal women, those with low educational level who spend more than 2 h/d sitting showed an increased BC risk with statistically significant differences ($>2\text{-}\leq3$ h/d: OR = 2.12 (1.28–3.62), p-value = 0.004, >5 h/d: OR = 1.75 (1.01–3.11), p-value = 0.049). In HR+ BC, this association was observed only in those with a low educational level who spent $>2\text{-}\leq3$ h/d sitting OR = 2.15 (1.22–3.99), p-value = 0.011 (Table 3).

Table 2. Relationship between sedentary behaviour and breast cancer risk adjusting for additional explanatory variables. Nested logistic regression models (M) for the whole sample.

	Sedentary behaviour (h/d sitting)	OR (CI)	p value
Model 1: sedentary behaviour + age and family history of BC	≤2	1	
	$>2\text{-}\leq3$	1.29 (1.01–1.66)	0.044
	$>3\text{-}\leq5$	1.18 (0.91–1.53)	0.206
	>5	1.21 (0.93–1.57)	0.156
Model 2: M1 + hormonal/reproductive variables (menopausal status, number of pregnancies, HRT)	≤2	1	
	$>2\text{-}\leq3$	1.26 (0.98–1.62)	0.071
	$>3\text{-}\leq5$	1.17 (0.90–1.52)	0.025
	>5	1.13 (0.87–1.48)	0.349
Model 3: M2 + lifestyle-related variables (BMI, smoking habits)	≤2	1	
	$>2\text{-}\leq3$	1.27 (0.99–1.65)	0.064
	$>3\text{-}\leq5$	1.18 (0.90–1.54)	0.228
	>5	1.13 (0.87–1.48)	0.367
Model 4: M3 + socioeconomic variables (educational level, occupation)	≤2	1	
	$>2\text{-}\leq3$	1.24 (0.94–1.64)	0.130
	$>3\text{-}\leq5$	1.14 (0.86–1.52)	0.359
	>5	1.19 (0.89–1.60)	0.229
Final model: M4 + gender-related variables (childcare responsibilities, FS)	≤2	1	
	$>2\text{-}\leq3$	1.22 (0.93–1.61)	0.161
	$>3\text{-}\leq5$	1.14 (0.86–1.52)	0.360
	>5	1.19 (0.89–1.60)	0.231

Abbreviations: h/d (hours per day); BC (breast cancer); HRT (Hormone Replacement Therapy); BMI (Body Mass Index); FS (Family Size)

Table 3. Relationship between sedentary behaviour and breast cancer risk stratified by educational level: Final Model for the whole sample, postmenopausal women and HR+ breast cancer (HR+ vs. no cancer).

				Educational level	
	Sedentary behaviour (h/d sitting)	Low OR (CI)	p value	Medium-High OR (CI)	p value
Whole sample[a]					
	≤2	1		1	
	>2-≤3	1.93 (1.19–3.21)	0.008	0.96 (0.68–1.35)	0.803
	>3-≤5	1.51 (0.92–2.54)	0.113	1.00 (0.70–1.43)	0.986
	>5	1.66 (0.98–2.86)	0.061	1.01 (0.71–1.44)	0.952
Postmenopausal women [b]					
	≤2	1		1	
	>2-≤3	2.12 (1.28–3.62)	0.004	0.84 (0.55–1.29)	0.434
	>3-≤5	1.63 (0.97–2.83)	0.070	0.90 (0.59–1.39)	0.640
	>5	1.75 (1.01–3.11)	0.049	0.84 (0.54–1.31)	0.435
HR+ BC[c]					
	≤2	1		1	
	>2-≤3	2.15 (1.22–3.99)	0.011	0.89 (0.58–1.36)	0.601
	>3-≤5	1.45 (0.79–2.75)	0.242	0.89 (0.57–1.37)	0.587
	>5	1.60 (0.84–3.12)	0.156	0.74 (0.47–1.17)	0.206

[a]Final model variables: sedentary behaviour, age, family history of breast cancer, menopausal status, number of pregnancies, hormonal replacement therapy, body mass index, smoking habit, occupation, childcare responsibilities, family size

[b]Final model variables: sedentary behaviour, age, family history of breast cancer, number of pregnancies, hormonal replacement therapy, body mass index, smoking habit, occupation, childcare responsibilities, family size

[c]Final model considering tumour phenotype (HR+ vs. no cancer) variables: sedentary behaviour, age, family history of breast cancer, menopausal status, number of pregnancies, hormonal replacement therapy, body mass index, smoking habit, occupation, childcare responsibilities, family size

Abbreviations: h/d (hours per day); BC (breast cancer); HR+ (oestrogen receptor-positive, and/or progesterone receptor-positive and HER2 negative)

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In the subsample of women with one or more live births, for those with low educational level, all sedentary behaviour categories of more than 2h/d sitting are statistically significantly associated with a higher risk of BC (>2-≤3 h/d: OR = 1.99 (1.20–3.43), p-value = 0.010, >3-≤5 h/d: OR = 1.67 (1.00–2.90), p-value = 0.057, >5 h/d: OR = 1.77 (1.02–3.14), p-value = 0.045) (Table 4). Additional information of other explanatory variables results is provided in S2 Table. This statistically significantly relationship was also observed in postmenopausal women for all sedentary behaviour categories (>2-≤3 h/d: OR = 2.22 (1.30–3.96), p-value = 0.005, >3-≤5 h/d: OR = 1.85 (1.07–3.32), p-value = 0.032, >5 h/d: OR = 1.30 (1.06–3.50), p-value = 0.001) and in HR+ BC, only for >2- ≤3 h/d category (OR = 2.10 (1.16–3.99), p-value = 0.017) (Table 4).

Discussion

According to the results, sedentary behaviour is associated with an increased risk of BC when sitting for more than 2 hours per day. This relationship was only found among women with a low educational level, being also observed in postmenopausal women, in HR+ BC and in women with one or more live births.

In this study, the relationship between sedentary behaviour and BC risk has been observed taking into account evidence-based BC risk factors such as age, family history of BC, hormonal and reproductive characteristics, lifestyle behaviours and socioeconomic and gender determinants. Currently, there is limited consensus regarding this relationship. While some studies,

Table 4. Relationship between sedentary behaviour and breast cancer risk in the subsample of women with one or more live births. Final model stratifying by educational level in the whole subsample, in postmenopausal women and considering HR+ breast cancer.

				Educational level	
	Sedentary behaviour (h/d sitting)	Low OR (CI)	p value	Medium-High OR (CI)	p value
Whole subsample[a]					
	≤2	1		1	
	>2-≤3	1.99 (1.20–3.43)	0.010	1.06 (0.73–1.53)	0.771
	>3-≤5	1.67 (1.00–2.90)	0.057	1.01 (0.69–1.50)	0.950
	>5	1.77 (1.02–3.14)	0.045	0.95 (0.63–1.41)	0.781
Postmenopausal women[b]					
	≤2	1		1	
	>2-≤3	2.22 (1.30–3.96)	0.005	0.95 (0.60–1.49)	0.815
	>3-≤5	1.85 (1.07–3.32)	0.032	0.88 (0.55–1.41)	0.596
	>5	1.90 (1.06–3.50)	0.001	0.81 (0.49–1.33)	0.410
HR+ BC[c]					
	≤2	1		1	
	>2-≤3	2.10 (1.16–3.99)	0.017	1.03 (0.66–1.63)	0.883
	>3-≤5	1.53 (0.82–2.95)	0.189	0.91 (0.56–1.48)	0.711
	>5	1.61 (0.83–3.19)	0.165	0.74 (0.44–1.23)	0.240

[a] Final model with the variables: sedentary behaviour, age, family history of BC, menopausal status, number of pregnancies, months of breastfeeding, hormonal replacement therapy, body mass index, smoking habit, occupation, childcare responsibilities, family size

[b] Final model with the variables: sedentary behaviour, age, family history of BC, number of pregnancies, months of breastfeeding, hormonal replacement therapy, body mass index, smoking habit, occupation, childcare responsibilities, family size

[c] Final model considering tumour phenotype (HR+ vs. no cancer) with the variables: sedentary behaviour, age, family history of BC, menopausal status, number of pregnancies, months of breastfeeding, hormonal replacement therapy, body mass index, smoking habit, occupation, childcare responsibilities, family size

Abbreviations: h/d (hours per day); BC (breast cancer); HR+ (oestrogen receptor-positive, and/or progesterone receptor-positive and HER2 negative)

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such as Huerta et al. [19], find an association, others, like the study conducted by Nomura et al. [15], do not observe it.

The novelty of this study lies in the observation that sedentary behaviour is associated with BC risk when studied in interaction with educational level. The results indicate that sitting more than 2 h/d increases BC risk in women with a low educational level. In the subsample of women with one or more live births, where the breastfeeding months, a well-known protective factor against BC [10], have been taken into account, this relationship has been observed in all sedentary behaviour categories. This differential impact on BC risk based on educational level is observed in other risk behaviours. For example, Bjerkaas et al. [36] found that smoking habit increases BC risk only in women with low educational level. These results suggest a possible hypothesis: the differential impact of sedentary behaviour on BC risk according to educational level could be partly explained by the profile of health-related behaviours specific to each population group. On one hand, it is known that women with high educational level have higher risk of BC [27–29] and this has been explained by their major exposition to reproductive and hormonal risk factors. Well known BC risk factors, such as nulliparity, HRT use, and fewer months of breastfeeding [20–23], are more common in women with high educational level [30, 31]. This could explain why, in our study, sedentary behaviour is not associated with BC in women with high educational level. On the other hand, in women with a low educational level, who have a lower prevalence of reproductive and hormonal risk factors, sedentary behaviour is associated with BC risk. Further research is needed to accept, reject or reformulate this hypothesis.

Regarding women's menopausal status, studies such as those by Chan et al. [18] and Huerta et al. [19] observe that, sedentary behaviour has a greater impact on BC risk in postmenopausal women, in line with our results. In postmenopausal women, greater amounts of free oestrogens, which have previously been associated with a higher BC risk, are produced in adipose tissue [17, 37]. Thus, this could explain why sedentary behaviour, which in turn entails a higher BMI and a larger quantity of adipose tissue, are related to an increased risk of BC in postmenopausal women. Additionally, the results of the present study show that, for postmenopausal women, only those with low educational level sitting for more than 2 h/d are at a higher risk of BC, being this fact also observed in those women with one or more live births. This difference may, once again, be attributed to differences by educational level in the prevalence of hormonal and reproductive risk factors, along with the inherent hormonal changes caused by menopause.

Currently, there is still little consensus regarding the influence of sedentary behaviour on BC risk according to phenotype [11]. Our results suggest that sedentary behaviour has a greater impact on BC with hormonal receptors (HR+), which concurs with some of the current literature [19]. This association may be due to the impact of physical activity and sedentary behaviour on hormonal factors [17, 18]. Sedentary behaviour could increase the bioavailability of free oestrogens, which are known to play an important role in the development of HR+ phenotype BC [38]. Furthermore, screen-detected BC is influenced by hormonal factors, reflected in the higher diagnosis rate of HR+ tumours [39]. Therefore, the fact that the cancers included in this study are screen-detected could influence the results. But additionally, in this study's results, the impact of sedentary behaviour on the risk of HR+ BC is observed only in women with low educational level. Once again, this may indicate the differential risk of BC based on this social determinant.

Considering other factors related to BC, this study reinforces the role of increased age, family history, nulliparity, a high BMI, and smoking habits in BC risk [20, 21, 25, 26, 40], which is widely evidenced in current literature. This underscores the results obtained regarding the role of sedentary behaviour in BC risk, as even when accounting for other known BC risk factors, sedentary behaviour also seems to influence the occurrence of this disease.

This study analysed the cancers detected in women who participated in the VR-BCSP. Some studies have observed that women participating in screening programs tend to have healthier behaviours [41, 42]. On the other hand, other studies have shown that BC most frequently diagnosed in screening are HR+ [39]. These circumstances could influence the characteristics of our sample. Nevertheless, considering that the VR-BCSP is a population-based programme targeting all women aged 45–69 with a 73% participation rate [43], the results could be extrapolated to the general population.

One limitation of this study is that the relationship between sedentary behaviour and BC in women with TN cancer could not be analysed due to the scarce sample (n = 20). Despite this, the study provides relevant information regarding the relationship with HR+ cancers. Furthermore, another limitation is that it has not been possible to analyse "live births" variable as a breast cancer risk factor because this information was not available for the entire sample.

The study data was collected through a questionnaire, which could potentially entail social desirability bias. Women may have underestimated the amount of time they spend sitting each day. In addition, the IPAQ-Short questionnaire does not differentiate between the different types of sedentary activities. Nonetheless, the IPAQ-Short is internationally validated [33], therefore lending validity to the results.

Currently, there is no consensus on the cut-off for studying sedentary behaviour and its impact on BC risk. In this study, it has been observed that spending more than 2 hours per day sitting is associated with BC risk. Other studies also observe this relationship but at different

sedentary behaviour cut-offs. For example, Huerta et al. [19] show an association with more than 3 hours per day sitting, whereas Dellal et al. [12] observe it with a cut-off of more than 6 hours per day. This highlights the need to further explore this relationship.

This study's main strength is that it provides novel results regarding the relationship between sedentary behaviour and BC while also considering health-related and socioeconomic variables such as educational level. According to the authors' knowledge, it is one of just a few studies that consider these factors when analysing the relationship between sedentary behaviour and BC.

The European Commission Initiative on Breast Cancer (ECIBC) is currently defining a series of quality criteria that BC screening programmes must meet through the European Quality Assurance Scheme for Breast Cancer Services [44]. One of these quality criteria involves giving healthy lifestyle recommendations related to physical activity and diet during screening. Therefore, in line with ECIBC recommendations and based on the evidence revealed by this study, women who attend screening appointments should be provided with healthy lifestyle recommendations that highlight the risks of sedentary behaviour. Furthermore, the role played by sedentary behaviour in BC risk should also be considered in health promotion programmes and specific actions should be designed for women who are more likely to develop BC due to social and gender-related factors, in line with the principles of proportionate universalism.

Conclusion

This study has revealed that sedentary behaviour is positively associated with BC risk in women with low educational level, especially in postmenopausal women and those with one or more live births. These novel results suggest that a social equity perspective should be incorporated into breast cancer prevention research and public health policies.

Supporting information

S1 Table. Relationship between sedentary behaviour and breast cancer risk for the whole sample. Final statistical model stratified by educational level. h/d (hours per day); BC (breast cancer); HRT (Hormone Replacement Therapy); BMI (Body Mass Index); FS (Family Size). (DOCX)

S2 Table. Relationship between sedentary behaviour and breast cancer risk for the subsample of women with one or more live births. Final statistical model stratified by educational level. h/d (hours per day); BC (breast cancer); HRT (Hormone Replacement Therapy); BMI (Body Mass Index); FS (Family Size). (DOCX)

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