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# Leisure-time physical activity, sedentary behavior, and risk of breast cancer: Results from the SUN ('Seguimiento Universidad De Navarra') project

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ABSTRACT

Evidence is still limited on the influence of sedentary lifestyles on breast cancer (BC) risk. Also, prospective information on the combined effects of both sedentariness and leisure-time physical activity (LTPA) is scarce. We aimed to assess the association of higher sedentary behavior and LTPA (separately and in combination) with the risk of BC in a middle-aged cohort of university graduates. The SUN Project is a follow-up study initiated in 1999 with recruitment permanently open. Baseline assessments included a validated questionnaire on LTPA and sedentary habits. Subsequently, participants completed biennial follow-up questionnaires. Multivariable adjusted Cox models were used to estimate the hazard ratios (HR) for incident BC according to LTPA, TV-watching, the joint classification of both, and a combined 8-item multidimensional active lifestyle score. We included 10,812 women, with 11.8 years of median follow-up of. Among 115,802 women-years of follow-up, we confirmed 101 incident cases of BC. Women in the highest category of LTPA (>16.5 MET-h/week) showed a significantly lower risk of BC (HR = 0.55; 95% CI: 0.34–0.90) compared to women in the lowest category (≤6 MET/h-week). Women watching >2 h/d of TV sh owed a higher risk (HR = 1.67; 95% CI:1.03–2.72) than those who watched TV <1 h/d. Women in the highest category (6–8 points) of the multidimensional combined 8-item score showed a lower BC risk (HR = 0.35; 95% CI: 0.15–0.79) than those in the lowest category (<2 points) group. There was no significant supra-multiplicative interaction between TV-watching and LTPA. Both low LTPA and TV-watching >2 h/d may substantially increase BC risk, independently of each other.

## 1. Introduction

Breast cancer (BC) is the leading cause of cancer in women with more than 2 million incident cases and more than 600,000 deaths worldwide in 2018. Even though many advances have been made in the fields of BC treatment and prevention, it still causes more than 200,000 deaths a year in developed countries (Global Burden of Disease Cancer Collaboration, 2018). For Spanish women, BC is responsible for more than 30,000 incident cases and 6500 deaths annually (Ferlay et al., 2018). Thus, additional preventive strategies to tackle the current situation are needed.

Previous studies have suggested a potential preventive role of physical activity (PA) on some cancer types (e.g. colorectal, endometrial, and breast cancer) (Nunez et al., 2017). Published meta-analyses and systematic reviews focused on PA and BC risk have found a relative risk reduction for BC ranging from 10% to 20%, when comparing

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the incidence among women in the highest category of PA to women in the lowest category (McTiernan et al., 2018). According to menopausal status at BC diagnosis, in a meta-analysis of 38 prospective studies, premenopausal and postmenopausal women had very similar risk reductions when comparing the highest versus the lowest level of PA (Pizot et al., 2016). In another meta-analysis, authors found no association between PA and premenopausal BC risk (Neil-Sztramko et al., 2017).

In the Multi Case Control (MCC)-Spain study, authors found no association between household or recreational PA and BC risk in Spanish population (Huerta et al., 2019).

The available evidence on the association between sedentary habits and the risk of BC is also limited. In the last meta-analysis of the World Cancer Research Fund International (Chan et al., 2019), increased total sitting time was *not* associated with premenopausal BC, but it was with postmenopausal BC. Authors found a 7% relative increased risk per each additional 5 h/day of sitting time. In the abovementioned MCC-Spain study, sedentary time was associated with higher risk of postmenopausal BC (Huerta et al., 2019). Among surrogates of sedentary behaviors, TV viewing time has been proposed as the strongest predictor of adverse health outcomes (Hu et al., 2003). Available evidence suggests an increased risk for colorectal cancer associated with increasing TV time (Schmid and Leitzmann, 2014), although the evidence for BC is still limited.

One study of the European Prospective Investigation into Cancer and Nutrition (EPIC) Cohort used an index-based approach to study the association between higher levels of a healthy lifestyle index (including posited dietary components, high PA, avoidance of smoking, no alcohol consumption and low body-mass index) and BC risk (McKenzie et al., 2015). The authors found a significant 26% BC relative risk reduction in women with the highest index score, compared to women in the lowest adherence category. Nevertheless, this study did not consider sedentary time as part of the index.

Despite this, prospective information on the combined effects of both sedentariness and leisure-time physical activity (LTPA) is scarce.

Our objective was to analyze the association between higher LTPA, lower sedentary behavior, their combination and a higher adherence to an active-lifestyle score with BC risk in a middle-aged prospective cohort of university graduates.

## 2. Material and methods

### 2.1. Study population

The 'Seguimiento Universidad de Navarra' (University of Navarra Follow-up) (SUN) Project is a dynamic (recruitment continually open) and multi-purpose cohort study entirely composed of university graduates. Details of the design and methods of this cohort study have been described elsewhere (Carlos et al., 2018). For recruitment purposes, an invitation letter was sent to university graduates from Universidad de Navarra and several professional associations. This letter included the baseline questionnaire (Carlos et al., 2018). All graduates were eligible to participate in the study. The mean age at recruitment was 34.7 years (interquartile range: 26–42 years). Participants completed a 556-item baseline questionnaire and are contacted biennially thereafter and inquired about changes in lifestyles and incident diseases.

Recruitment started in December 1999. Up to 2018, 22,790 participants answered the baseline questionnaire [Fig. 1]. We excluded men, participants who answered the baseline questionnaire after October 1st, 2015 -to ensure a follow-up period of at least 2 years-, participants lost to follow-up (overall retention 90%), women who reported a previous BC in the baseline questionnaire, participants with total daily energy intake lower than 500 kcal/d or higher than 3500 kcal/d (Willett, 2013) -as a surrogate of the adequate understanding of the questionnaire and of the quality of the gathered information-, participants because of age at menopause younger than 35 years -due to an eventual special hormonal status, considering the biologic link between hormonal exposure and BC risk-. Thus, 10,812 women were included in our analyses. The study was approved by the Institutional Review Board of the University of Navarra.

### 2.2. Physical activity and sedentary behavior assessment

In the baseline questionnaire, participants were asked to complete a PA questionnaire collecting information about 17 activities carried out during the previous year. To quantify the volume of activity during leisure time, an activity metabolic equivalent (MET) index was computed by assigning a multiple of resting metabolic rate (MET score) to each activity (Ainsworth et al., 2000), and the time spent in each of the activities was multiplied by the MET score specific to each activity, and then summed over all activities to obtain a value of overall weekly MET-hours. Finally, the continuous variable was categorized into three groups (0–6, >6–16.5 and >16.5 MET-h/week). The selected cut-off points have an equivalence in walking time per week that can be

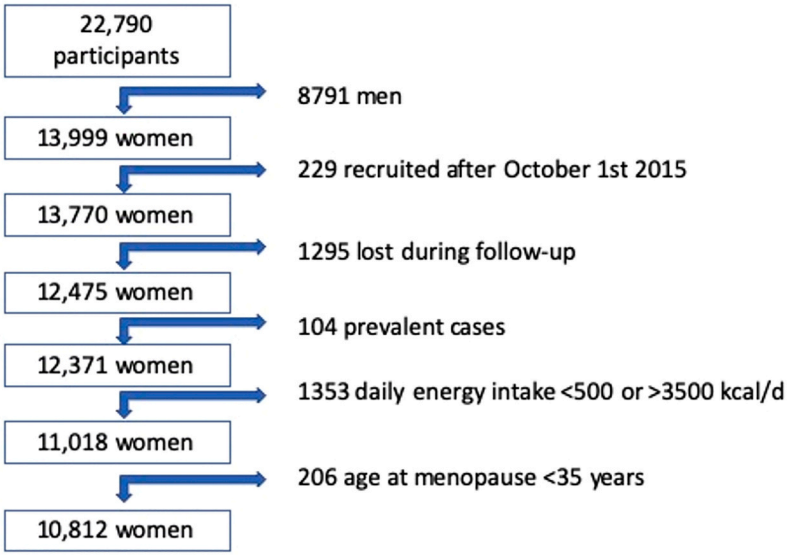


**Fig. 1.** Flow chart of participants in the SUN Project, 1999–2018.

easily translated into an intervention on women's leisure-time activity. The 6 MET-h/week cut-off point was selected because it approximately represents an equivalent physical activity of 30 min/day of walking during five days in a week. The 16.5 MET-h/week was selected as a value above the cohort median (16.1 MET-h/week), representing approximately an equivalent physical activity of 1 h/day of walking every day.

LTPA estimated with the questionnaire was previously validated by our group using a triaxial accelerometer as the gold standard (Martínez-González et al., 2005). Physical activity during leisure time (MET-hours/week) derived from the questionnaire moderately correlated with kilocalories per day assessed through the accelerometer (Spearman's rho = 0.507, 95% confidence interval (CI) 0.232, 0.707, $P < 0.001$).

For sedentary behavior assessment, we first analyzed the total amount of hours/day spent sitting by the participants. Also, information on hours per week spent by the subjects watching television during the week and for a typical day during the weekend was collected at baseline. A weighted mean ((5 x typical weekday +2 x typical weekend)/7) was calculated. For the present analysis, the continuous variable hours/day of TV-watching was categorized into three groups (<1, 1–2 and > 2 h/day). We also collected the time spent sitting while driving car and using the computer (hours/day). These variables were included in the multivariable adjusted model as potential confounders.

We also estimated an 8-item total active lifestyle score using additional information on PA and sedentary lifestyles collected in the baseline questionnaire (Alvarez-Alvarez et al., 2018) (Supplementary Table 1). Participants were subsequently categorized into 4 groups: low (<2), medium-low (2–3), medium-high (4–5) and high (6–8). A moderate correlation (r (Pearson) = 0.56) between LTPA in METs/min-week and this 8-item score of active lifestyles was found in the entire cohort (Alvarez-Alvarez et al., 2017).

### 2.3. Breast cancer ascertainment

The diagnosis of BC was initially self-reported in the follow-up questionnaires. Patients who had referred a diagnosis of BC were asked to provide a copy of medical reports and cases were then confirmed by an expert who was blinded to the exposure. We also included as confirmed BC cases, deaths due to BC that had been identified through consultation of the National Death Index. Alternatively, we included both confirmed plus only self-reported cases (though not confirmed, mostly because the reports were pending) as 'probable BC cases'.

### 2.4. Covariate assessment

Information about sociodemographic, lifestyle and medical variables was obtained from the baseline questionnaire. The questionnaire included information on age of menopause, age of menarche, use of hormone replacement therapy and its duration, pregnancies, time of breast-feeding, previous diagnosis of benign breast diseases (e.g. fibrocystic mammary disease) or breast biopsy, and baseline chronic diseases. Participants also completed a 136-item food-frequency questionnaire at baseline. The FFQ was previously validated (Martin-Moreno et al., 1993) and our group has also assessed its reproducibility within the SUN Project (de la Fuente-Arrillaga et al., 2010). Missing values at baseline were imputed using multivariable linear regression models for continuous variables and multivariable logistic or multinomial regression models for categorical variables. Imputations represented <5% of missing covariates.

For those participants who were premenopausal at baseline, menopausal status – including age at menopause – was updated in the 16-years follow-up questionnaire. For those women with no available information on age at menopause, we used as cutoff point the 75th percentile of the age of menopause (52 years in our sample) (Shivappa et al., 2015).

### 2.5. Statistical analysis

Quantitative baseline characteristics of participants were summarized with means and standard deviations, and qualitative traits with proportions across the four groups of the active lifestyle score. To assess the risk of BC, we fitted Cox regression models. We estimated Hazard ratios (HR) and their 95% CI for categories of PA (0–6, 6.1–16.5 and > 16.5 MET-h/week), categories of TV-watching (<1, 1–2 and > 2 h/day), and the four groups of the active lifestyle score. To ascertain the joint effect of low LTPA and sedentary behavior, participants with the lowest baseline LTPA levels (<<6 MET-h/week) and with the highest category of TV-watching (>2 h/d) were considered as the reference category, and they were compared with the other three categories created by combining both exposures. We studied supra-multiplicative interaction between LTPA levels and TV-watching categories using the likelihood-ratio test for assessing the statistical significance of a product-term (1 degree of freedom).

Age was the underlying time variable and we stratified our analyses by recruitment period (1999–2003, 2004–2008, and 2009–2015) and age (decades). The follow-up time was considered from time to study entry – date of completion of basal questionnaire – until the date of BC diagnosis for both confirmed and probable cases, and date of death for deceased participants or last contact for non-cases alive at the end of follow-up. We adjusted a multivariable model including as potential confounders height, family history of BC (3 categories), smoking habit (3 categories), lifetime tobacco exposure (pack-years), age of menarche (3 categories), menopausal status, obstetric history (5 categories, see Table 1), lifetime breast-feeding, hormone replacement therapy, years of university studies, body-mass index (kg/m$^2$), alcohol consumption, adherence to the traditional Mediterranean diet (Trichopoulou et al., 2003), consumption of sugar-sweetened beverages (servings/day) (Romanos-Nanclares et al., 2019) and total energy intake (kcal/day). For the sedentary behavior analysis, assessed as hours of TV-watching per day, we additionally adjusted for physical activity (MET-h/week) and time spent sitting during activities such as car driving or sitting in front of the computer. A linear trend test was estimated for the LTPA, TV-watching and the PA score using the median of each category as a continuous variable. As sensitivity analyses, we repeated our analyses for probable BC risk, without excluding participants with abnormal daily energy intake, age of menopause younger than 35 years and including previous diagnosis of benign breast diseases as covariates. We also repeated our analyses assuming age at menopause to be at 50 years and assuming age at menopause to be at 55 years of age.

Analyses were performed using STATA/SE version 15.0 (StataCorp), we used two-sided $p$-values and $p$ values below 0.05 were deemed statistically significant.

## 3. Results

For the final analysis, 10,812 women were included (median follow-up of 11.8 years, range: 1.6–18.4 years). Mean baseline age of our participants was 34.7 years (SD: 10.6 years). The overall mean LTPA at baseline was 20.2 MET-h/week (SD: 18 MET-h/week). Most participants were included in the medium categories of the active lifestyle score accounting for almost 75% of the women included in the analysis. Only 10.8% showed a score < 2 points and 13.2% a PA Score 6–8 points.

Participants with higher adherence to the active lifestyle score had a lower mean baseline BMI, showed a higher adherence to the Mediterranean diet score, and were less likely to smoke, compared with the other three categories (Table 1). As expected, values of mean baseline physical activity in MET-h/week increased through the different categories of the score.

During a total follow-up of 115,802 women-years, 190 probable incident cases of BC were identified, out of which 101 were confirmed. The mean age at BC diagnosis was 48.7 years (SD 8.3 years) for confirmed cases, and 48.0 years (SD 9.1) for probable cases. Overall,

**Table 1**
Baseline characteristics of female participants in the SUN Project, according to the active lifestyle score, $N = 10{,}812$.

| Variable | Active lifestyle score | | | | p value† |
|---|---|---|---|---|---|
| | <2 | 2–3 | 4–5 | 6–8 | |
| n (%)* | 1166 (10.8) | 4208 (38.9) | 4016 (37.1) | 1422 (13.2) | |
| Age (years) | 34.4 (10.2) | 34.5 (10.4) | 34.6 (10.7) | 35.8 (10.9) | <0.01 |
| Body mass index (kg/m$^2$) | 23 (3.6) | 22.4 (3.2) | 22 (2.8) | 21.5 (2.4) | <0.01 |
| Height (cm) | 163 (6) | 163 (6) | 164 (6) | 164 (6) | <0.01 |
| Physical activity (MET-h/week) | 6.2 (4.6) | 12.3 (10.4) | 25.6 (18.1) | 40.2 (24.5) | <0.01 |
| Time spent sitting (h/d) | 6.7 (2.0) | 5.5 (2.4) | 4.9 (2.4) | 3.9 (2.1) | <0.01 |
| TV viewing time (h/d) | 2.3 (1.2) | 1.7 (1.2) | 1.5 (1.1) | 1.1 (0.8) | <0.01 |
| Total energy intake (kcal/d) | 2250 (588) | 2292 (566) | 2300 (575) | 2339 (573) | <0.01 |
| Alcohol intake (g/d) | 3.7 (5.8) | 3.9 (5.7) | 4.2 (6.0) | 4.3 (6.0) | <0.01 |
| Age of menarche (years) | 12.6 (1.4) | 12.6 (1.4) | 12.7 (1.4) | 12.7 (1.4) | 0.11 |
| Age of menarche (%) | 0.7 | | | | |
| <10 years | 96.2 | 1.4 | 1.1 | 0.8 | 0.07 |
| 10–16 years | 3.1 | 96.4 | 96.4 | 95.9 | |
| >16 years | | 2.2 | 2.5 | 3.3 | |
| Obstetric history (including age at first pregnancy) (%) | | | | | |
| Age < 25 years & nulliparous | 15.6 | 17.9 | 19.8 | 18.6 | 0.02 |
| Age ≥ 25 years & nulliparous | 50.1 | 48.9 | 47.9 | 47.0 | |
| First pregnancy <25 years | 5.0 | 4.1 | 4.9 | 5.4 | |
| First pregnancy 25–30 years | 13.3 | 14.8 | 14.0 | 15.5 | |
| First pregnancy ≥30 years | 16.0 | 14.3 | 13.4 | 13.4 | |
| Lifetime breast-feeding (months) | 2.0 (4.4) | 2.2 (4.7) | 2.5 (5.4) | 2.6 (5.3) | <0.01 |
| Adherence to Mediterranean diet score | 3.7 (1.6) | 3.9 (1.7) | 4.1 (1.7) | 4.4 (1.7) | <0.01 |
| Time of university education (years) | 4.9 (1.2) | 4.8 (1.3) | 4.8 (1.4) | 4.8 (1.4) | 0.94 |
| Diabetes (%) | 0.7 | 1.1 | 1.2 | 1.1 | 0.56 |
| Menopause (%) | 10.9 | 10.1 | 11.9 | 13.2 | 0.01 |
| Age of menopause (years) | 51.1 (2.6) | 51.4 (2.3) | 51.5 (2.5) | 51.7 (1.8) | 0.58 |
| Use of hormone-replacement therapy (%) | 5.0 | 4.0 | 4.9 | 5.2 | 0.12 |
| Time of hormone-replacement therapy (months) | 1.4 (2.4) | 1.2 (2.4) | 1.3 (2.3) | 1.2 (2.3) | 0.55 |
| Smoking (%) | | | | | |
| Never smoker | 46.1 | 51.2 | 54.3 | 54.1 | <0.01 |
| Current smoker | 33.3 | 29.4 | 24.5 | 23.1 | |
| Former smoker | 20.7 | 19.4 | 21.2 | 22.8 | |
| Lifetime tobacco exposure (pack-years) | 4.2 (7.3) | 4.0 (7.6) | 3.5 (7.4) | 3.5 (7.0) | <0.01 |
| Family history of BC (%) | | | | | |
| None | 90.6 | 89.6 | 88.8 | 89.7 | 0.02 |
| Before the age of 45 years | 8.8 | 8.3 | 8.9 | 8.0 | |
| After the age of 45 years | 0.6 | 2.0 | 2.2 | 2.2 | |

* Values represent means (standard deviations), unless otherwise stated.
† ANOVA test for means comparisons and Chi-Squared test for proportions comparisons.

women in the highest LTPA category showed a significantly lower risk of BC compared to women in the lowest category [Table 2]. According to menopausal status, women who performed >16.5 MET-h/week of LTPA had a borderline lower risk of premenopausal BC when compared to women who performed LTPA below 6 MET-h/week. The risk of postmenopausal BC decreased in both the medium and high PA categories, although results were not statistically significant.

**Table 2**
Hazard ratio (95% CI) of overall breast cancer -confirmed cases- and by menopausal status according to leisure-time physical activity categories in the SUN Project.

| | Physical activity (MET-h/week categories) | | | |
|---|---|---|---|---|
| | Low (0–6) | Medium (6.1–16.5) | High (>16.5) | p for trend |
| Overall | | | | |
| Cases/women-years | 31/ 23,590 | 32/ 39,632 | 38/ 52,580 | |
| Age adjusted | 1 (ref.) | 0.64 (0.39–1.05) | 0.57 (0.35–0.92) | 0.05 |
| Multivar. Adjusted* | 1 (ref.) | 0.62 (0.37–1.01) | 0.55 (0.34–0.90) | 0.05 |
| Premenopausal† | | | | |
| Cases/women-years | 18/ 20,013 | 17/33,078 | 22/43,715 | |
| Age adjusted | 1 (ref.) | 0.61 (0.31–1.19) | 0.58 (0.31–1.08) | 0.16 |
| Multivar. Adjusted* | 1 (ref.) | 0.61 (0.31–1.20) | 0.53 (0.28–1.01) | 0.11 |
| Postmenopausal† | | | | |
| Cases/women-years | 10/3873 | 13/7056 | 11/49,378 | |
| Age adjusted | 1 (ref.) | 0.71 (0.31–1.63) | 0.45 (0.19–1.07) | 0.07 |
| Multivar. Adjusted* | 1 (ref.) | 0.69 (0.30–1.59) | 0.48 (0.20–1.17) | 0.13 |

* Adjusted for height (cm), family history of breast cancer (no history, before 45 years, after 45 years), smoking habit (never, former or current smoker), lifetime tobacco exposure (pack-years) age at menarche (<10 years, 10–16 years or > 16 years), obstetric history (5 categories), lifetime breast-feeding (months), years of university studies, Mediterranean diet adherence score (0–8), alcohol consumption (g/d), total daily energy intake (tertiles of kcal/d), body-mass index (kg/m$^2$), consumption of sugar-sweetened beverages (drinks/day) and TV-watching (h/d). Only for postmenopausal women: Hormone replacement therapy (yes/no), duration of hormone replacement therapy (months), age at menopause (<50 years, 50–55 years or > 55 years), and time in study (years). Age as underlying time variable. Stratified analyses by recruitment period and age (decades).
† Censoring at the age of 52 years.

The median time spent sitting was 5.2 h/day. We found a borderline higher risk for BC associated with an increasing amount of h/day spent sitting (HR = 1.07; 95% CI: 0.98–1.17). For TV-watching, women who spent >2 h/d had a significantly higher risk of BC compared to women with less than 1 h/d of TV watching [Table 3]. The estimated risk was even stronger for premenopausal BC. No differences in the risk of postmenopausal BC were found according to categories of TV-watching.

When we considered the joint exposure to both levels of LTPA and TV-watching (Fig. 2), those women who spent at least 2 h/d watching TV showed a higher risk of BC, independently of their reported level of LTPA. We found no interaction between the levels of LTPA and TV-watching in the subsequent risk of BC (p for interaction = 0.98). Results were consistent for premenopausal BC with an increased risk for women spending at least 2 h/d TV-watching despite their level of physical activity; women in the ≤6MET-h/week category showed the highest risk (HR = 4.77; 95% CI = 1.93–11.83 compared to women with >6 MET-h/week). For postmenopausal BC risk, no differences were found in the joint exposure analysis (data not shown).

According to the 8-item active lifestyle score [Table 4], engaging in higher levels of active lifestyle was associated with a reduced risk of overall BC. Women in the medium-low and medium-high categories had a non-significant reduction in overall BC risk. According to menopausal status, we observed a trend to risk reduction for both pre- and postmenopausal BC for women with higher levels of active lifestyle score, although the results did not reach the statistical threshold.

**Table 3**
Hazard ratio (95% CI) of overall breast cancer -confirmed cases- and by menopausal status according to categories of TV-watching in the SUN Project.

| | Hours/day of TV-watching | | | |
|---|---|---|---|---|
| | <1 h | 1–2 h | >2 h | p for trend |
| Overall | | | | |
| Cases/women-years | 30/ 35,469 | 30/ 44,842 | 41/ 35,491 | |
| Age adjusted | 1 (ref.) | 0.88 (0.53–1.45) | 1.49 (0.93–2.38) | 0.07 |
| Multivar. Adjusted* | 1 (ref.) | 0.92 (0.55–1.54) | 1.67 (1.03–2.72) | 0.02 |
| Premenopausal† | | | | |
| Cases/women-years | 15/ 30,297 | 15/35,402 | 27/31,106 | |
| Age adjusted | 1 (ref.) | 0.95 (0.46–1.95) | 1.91 (1.02–3.60) | 0.02 |
| Multivar. Adjusted* | 1 (ref.) | 1.08 (0.52–2.22) | 2.22 (1.15–4.28) | 0.01 |
| Postmenopausal† | | | | |
| Cases/women-years | 12/6835 | 12/6813 | 10/6659 | |
| Age adjusted | 1 (ref.) | 1.02 (0.46–2.27) | 0.90 (0.39–2.08) | 0.79 |
| Multivar. adjusted* | 1 (ref.) | 1.14 (0.50–2.62) | 1.07 (0.45–2.60) | 0.87 |

* Adjusted for height (cm), family history of breast cancer (no history, before 45 years, after 45 years), smoking habit (never, former or current smoker), lifetime tobacco exposure (pack-years), age at menarche (<10 years, 10–16 years or > 16 years), obstetric history (5 categories), lifetime breast-feeding (months), years of university studies, Mediterranean diet adherence score (0–8), physical activity in MET-h/week (quartiles), alcohol consumption (g/d), total daily energy intake (tertiles of kcal/d), body-mass index (kg/m$^2$), consumption of sugar-sweetened beverages (drinks/day), and time spent sitting car driving and with computer (h/d). Only for postmenopausal women: Hormone replacement therapy (yes/no), duration of hormone replacement therapy (months), age at menopause (<50 years, 50–55 years or > 55 years) and time in study (years). Age as underlying time variable. Stratified analyses by recruitment period and age (decades).

† Censoring at the age of 52 years.

**Table 4**
Hazard ratio (95% CI) of overall breast cancer -confirmed cases- and by menopausal status according to active lifestyle score categories in the SUN Project.

| | Physical activity score | | | | |
|---|---|---|---|---|---|
| | Low (<2) | Medium-low (2–3) | Medium-high (4–5) | High (6–8) | p for trend |
| Overall | | | | | |
| Cases/women-years | 17/ 12,766 | 37/ 45,425 | 38/ 42,624 | 9/14986 | |
| Age adjusted | 1 (ref.) | 0.62 (0.35–1.10) | 0.66 (0.37–1.17) | 0.39 (0.17–0.87) | 0.03 |
| Multivar. Adjusted* | 1 (ref.) | 0.58 (0.32–1.02) | 0.59 (0.33–1.06) | 0.35 (0.15–0.79) | 0.01 |
| Premenopausal† | | | | | |
| Cases/women-years | 8/ 10,745 | 22/38,655 | 22/35,368 | 5/12,037 | |
| Age adjusted | 1 (ref.) | 0.73 (0.32–1.63) | 0.77 (0.34–1.73) | 0.44 (0.14–1.34) | 0.18 |
| Multivar. Adjusted* | 1 (ref.) | 0.71 (0.31–1.61) | 0.68 (0.30–1.57) | 0.37 (0.12–1.18) | 0.09 |
| Postmenopausal† | | | | | |
| Cases/women-years | 8/ 2126 | 11/7385 | 12/7603 | 3/3193 | |
| Age adjusted | 1 (ref.) | 0.44 (0.18–1.10) | 0.45 (0.18–1.10) | 0.27 (0.07–1.02) | 0.04 |
| Multivar. adjusted* | 1 (ref.) | 0.40 (0.15–1.04) | 0.40 (0.16–1.04) | 0.27 (0.07–1.05) | 0.04 |

* Adjusted for height (cm), family history of breast cancer (no history, before 45 years, after 45 years), smoking habit (never, former or current smoker), lifetime tobacco exposure (pack-years), age at menarche (<10 years, 10–16 yearas or > 16 years), obstetric history (5 categories), lifetime breast-feeding (months), years of university studies, Mediterranean diet adherence score (0–8), alcohol consumption (g/d), total daily energy intake (tertiles of kcal/d), consumption of sugar-sweetened beverages (drinks/day), and body-mass index (kg/m$^2$). Only for postmenopausal women: Hormone replacement therapy (yes/no), duration of hormone replacement therapy (months), age at menopause (<50 years, 50–55 years or > 55 years), and time in study. Age as underlying time variable. Stratified analyses by recruitment period and age (decades).

† Censoring at the age of 52 years.

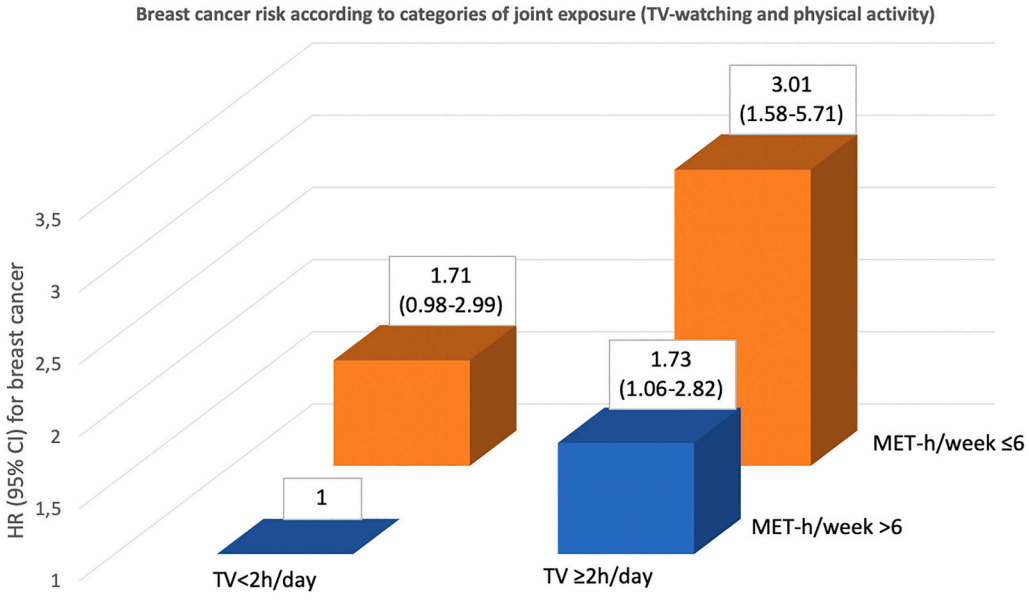


**Fig. 2.** Hazard ratio (95% CI) of overall breast cancer -confirmed cases- according to a joint classification of TV-watching and physical activity in the SUN Project.
Adjusted for height (cm), family history of breast cancer (no history, before 45 years, after 45 years), smoking habit (never, former or current smoker), lifetime tobacco exposure (pack-years), age at menarche (<10 years, 10–16 years or > 16 years), obstetric history (5 categories), lifetime breast-feeding (months), years of university studies, Mediterranean Diet Adherence Score (0–8), alcohol consumption (g/d), total daily energy intake (tertiles of kcal/d), consumption of sugar-sweetened beverages (drinks/day) and Body-Mass Index (kg/m$^2$). Only for postmenopausal women: hormone replacement therapy (yes/no), duration of hormone replacement therapy (months), age at menopause (<50 years, 50–55 years or > 55 years), and time in study (years). Age as underlying time variable. Stratified analyses by recruitment period and age (decades).

Results barely changed when we included both confirmed and probable BC cases in the analysis. The risk for BC remained higher for women spending >2 h/d TV-watching, although statistical significance was borderline (HR = 1.37; 95% CI = 0.96–1.95). For the joint classification of TV-watching and LTPA the estimated risk was attenuated [Supplementary Tables 2–5]. Sensitivity analyses confirmed the robustness of our findings [Supplementary Figs. 1–3].

## 4. Discussion

In this Mediterranean cohort we found a lower risk of BC for women who engaged in higher levels of LTPA (>16.5 MET-h/week) compared to women in the lower categories of active lifestyle (<6 MET-h/week). We found a detrimental effect of TV watching with an increased risk of BC for women who reported >2 h/day of TV watching. According to our results, the detrimental effect of TV-watching over BC risk was independent from PA level (< or ≥ 6 MET-h/week).

The influence of physical activity on BC risk has been long studied. We identified three recent meta-analyses/systematic reviews that focused on PA and BC risk (McTiernan et al., 2018; Pizot et al., 2016; Neil-Sztramko et al., 2017). In most studies, PA was self-reported, and different PA questionnaires were used. The Breast Cancer Report published in 2017 by the American Institute for Cancer Research concluded that the evidence suggesting that total PA decreases the risk of premenopausal BC is limited and that total PA probably protects against postmenopausal BC (World Cancer Research Fund/American Institute for Cancer Research, 2017). Some published works examined the associations by type of activity, and they reported similar risk reductions for both nonoccupational and occupational PA (Pizot et al., 2016). In our cohort, a significant reduction in BC risk was observed for women engaging the higher levels of LTPA. A trend towards a protective effect was observed for both pre- and postmenopausal BC cases, although it did not reach statistical significance. This could be partially explained by the limited number of BC cases registered in our cohort and more mature data on follow-up are highly awaited. It must be taken into account that a high proportion of university graduates generally end up into sedentary works. In these population, the protective benefits of LTPA could be greater than in the general population.

In our cohort, longer TV-watching as a marker of sedentariness was associated with a higher risk of BC. There is limited evidence for the association between sedentary behaviors and a higher risk of BC. Commonly, time spent in sedentary behaviors is assessed by inquiring about the total amount of time per day (h/day) spent sitting (driving, at work, watching television or using a computer at home). In our study, the choice of TV viewing time as a measure of sedentary behavior was made on the basis of a potential intervention. It may be easier to modify leisure-time activities rather than total sitting time, as it can be highly influenced by the time sitting during working hours. Furthermore, total daily sitting time might be highly influenced by hours of occupational sitting and university graduates tend to have a sedentary work (McCrady and Levine, 2009). Our cohort would be relatively homogeneous in this aspect. In a large, population-based prospective cohort study, occupational sedentariness was an independent risk factor for increased premenopausal BC (Johnsson et al., 2017). In an accelerometer-based case-control study examining PA in women with BC, the risk of BC was relatively increased by 81% (95% CI 1.26–2.60) in women with the longest amount of time spent sitting (Dallal et al., 2012). Sedentary behavior was also associated with BC risk in the Black Women's Health Study. In that prospective cohort of African American women, higher total time spent sitting at baseline (≥10 vs. <5 h/day) was associated with a 27% relative higher risk of BC (Nomura et al., 2016).

Sedentariness is defined as activities done in sitting or reclining posture with an energy expenditure typically in the range of 1.0 to 1.5 multiples of the basal metabolic rate (Ainsworth et al., 2000). In the present study, we focused our analysis in TV-watching as an estimate of leisure-time sedentary behavior. Nevertheless, in the multivariable adjusted model we included the time spent sitting while driving and using the computer, as these factors may influence the total daily time spent sitting (Owen et al., 2010a). After adjusting for these factors, the risk of BC remained higher for women with >2 h/d of TV-watching. Similarly, for colorectal cancer, sedentary behavior was associated with a 54% (95% CI 1.19–1.98) relatively increased risk of colon cancer for time spent TV-watching (Schmid and Leitzmann, 2014). Furthermore, it has been found that sedentary behavior increases the risk of advanced colon adenomas, suggesting that sedentary behavior is an early contributor to oncogenesis (Cao et al., 2015).

The concept of sedentariness has been long used to describe the lack of exercise. However, epidemiologic evidence suggests that the metabolic and long-term health consequences of daily sedentary behavior (too much sitting) are distinct from those associated with a lack of activity (too little exercise) (Owen et al., 2010b). An increase of sedentary behaviors far from the Mediterranean lifestyle is happening despite its health impact. In a representative sample of more than 400 Spanish children and adolescents (38% females), authors found that almost 50% during weekdays and 84% during weekends did not meet the recommendation of using screens less than 2 h per day (Mielgo-Ayuso et al., 2017).

With our active lifestyle score analysis, we found that women in the highest adherence category had a significant reduction in the risk of BC, when compared with women in the lowest category. These results are consistent with previous studies despite the different score definitions. An index-based approach was used to analyze the association between adherence to American Cancer Society guidelines and BC incidence in the National Institutes of Health-American Association of Retired Persons (NIH-AARP) cohort. The index included PA and daily time spent watching television, among other lifestyle variables. Women in the highest quintile had a significantly lower risk of BC (Cifu and Arem, 2018). Participants in that study had a higher baseline BMI than ours. Similar approaches have been used in the EPIC Study but, as previously noticed, this latter study did not include sedentary time as part of the index (McKenzie et al., 2015).

Physical activity and sedentariness have been suggested to modify the risk of BC through several mechanisms. An active lifestyle is linked to a decrease in body weight and body fatness, thereby changing concentrations of circulating hormones and improvement of insulin sensitivity and reduction of fasting insulin and C-peptide levels (McTiernan, 2008). In addition, physical activity may have immunomodulatory effects and promote both cancer cells surveillance and elimination (Friedenreich et al., 2010). Contrarily, hourly increments of change in TV-watching have been as well directly associated with BMI, waist circumference, fasting insulin and HOMA-IR (Wiseman et al., 2014). Conversely, standing and other light activities can improve muscle contraction, glucose regulation and endothelial function (Thosar et al., 2012). Individuals who have increased TV viewing time tend to have poor lifestyle behaviors, such as being more likely to smoke or eating a poor diet (Sisson et al., 2012). The association between prolonged TV time and vitamin D deficiency has also been hypothesized as a potential mechanistic pathway (Lynch, 2010).

The most important strengths of this study rely on the prospective nature of the SUN Project ensuring temporal sequence between exposure and outcome, its large sample size with a long follow-up and a good overall retention. Moreover, results were adjusted for a wide number of potential confounders. Lastly, self-reported cancer cases were confirmed via medical reports to ensure that the final diagnosis was a breast carcinoma. Indeed, this procedure might have led to an underreporting of actual breast cancer cases. Nevertheless, we believe that this underreporting is limited because the age-adjusted breast cancer incidence is aligned with the age-adjusted Spanish breast cancer incidence (Galceran et al., 2017). In fact, our age-adjusted BC incidence falls within the estimated 95% CI for the Spanish population despite the baseline characteristics of our participants, who are not representative of the general population.

Nevertheless, some limitations should be acknowledged. First, the small number of incident BC cases in the cohort may limit our statistical power. Second, women in our study were relatively young, which may partially explain the low incidence of BC, especially postmenopausal BC. The results obtained in the postmenopausal analysis must be interpreted cautiously. Nevertheless, the analysis on premenopausal BC might be very interesting as the evidence for premenopausal BC is far more limited than for postmenopausal women. Results for postmenopausal women should be confirmed in future studies. Third, although a higher socio-economic status has also been associated with a higher incidence of BC, we had no available information on socio-economic status apart from years of university studies that were included in the multivariable analysis. In any case, our sample was relatively homogenous because it was restricted to university graduates. This fact is very likely to have reduced the potential for residual confounding by educational or socioeconomic status. In addition, and although this restriction may limit the external validity of our study, it must be considered that a high proportion of the participants included are graduates in Health Sciences. As such, their understanding of the questionnaires and the quality of the reported information might be presumably high. Thus, our results may rely on high internal validity. Fourth, a potential limitation of our study was the self-reported exposure as participants may tend to misreport their LTPA. Nevertheless, this tool has been previously validated (Martínez-González et al., 2005) and it was appraised from different sources of information obtaining similarly significant results. In addition, the most likely direction of a potential measurement inaccuracy would be towards the null value. It should also be noted that we had not enough information to assess changes in LTPA throughout time as a risk factor for BC. In the SUN Project, leisure time activities are re-assessed in the 14-years follow-up questionnaire. However, published data suggest that we might not expect great variations in PA levels of participants throughout time (Ma et al., 2016). Fifth, the eight-item lifestyle score has not been formally validated, although previous publications from our group have shown a highly predictive potential for hard clinical endpoints using this score (Alvarez-Alvarez et al., 2018; Alvarez-Alvarez et al., 2017). Importantly, when we repeated our analyses considering only BC cases which had been blindly confirmed –with high specificity– by an oncologist, our results barely changed with respect to those including also probable cases. With perfect specificity, the non-differential sensitivity of disease misclassification would not bias the measure of association (Greenland and Lash, 2008).

In summary, in this Mediterranean cohort, women in the highest LTPA categories showed a significant decrease in BC risk. More than 2 h/day of TV-watching was associated with a higher risk of BC development. The harmful effect of TV-watching persisted despite the practice of >6 MET-h/week of PA. This study adds new evidence in favor of an active lifestyle for BC prevention.

## Author contributions

Conceptualization, E.T. and R.S.-B.; methodology, M.A.M.-G.; validation, R.S.-B. and I.G.; formal analysis, R.S.-B. and E.T.; resources, M.A.M.-G.; data curation, R.S.-B., A.R.-N.; writing—original draft preparation, R.S.-B. and E.T.; writing—review and editing, all authors; supervision, A.G. and E.T.; project administration, M.A.M.-G.; funding acquisition, M.A.M.-G. and E.T.. All authors have read and agreed to the published version of the manuscript.

## Credit author statement

All authors have read and agreed to the published version of the manuscript

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## Declaration of Competing Interest

The authors declare no conflict of interest. The funders had no role in the design of the study; in the collection, analyses, or interpretation of data; in the writing of the manuscript, or in the decision to publish the results.

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## Appendix A. Supplementary data

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