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Associations between overall, healthful, and unhealthful low-fat dietary patterns and breast cancer risk in a Mediterranean cohort: The SUN project

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ABSTRACT

Objectives: Dietary patterns may have a greater influence on human health than individual foods or nutrients, and they are also of substantial interest in the field of breast cancer prevention. Beyond the adequate balance of macronutrients, evidence indicates that the quality of macronutrient sources may play an important role in health outcomes. We sought to examine the relationship between healthful and unhealthful low-fat dietary patterns in relation to breast cancer.

Methods: We used observational data from a Mediterranean cohort study (the Seguimiento Universidad de Navarra project). We prospectively followed 10 930 middle-aged women initially free of breast cancer during a median follow-up of 12.1 y. We calculated an overall, an unhealthful, and a healthful low-fat diet score, based on a previously validated 136-item food frequency questionnaire and grouped participants into tertiles. Incident breast cancer—overall and stratified by menopausal status—was the primary outcome. It was self-reported by participants and confirmed based on medical reports or consultation of the National Death Index. We used multivariable Cox regression models adjusted for potential confounders.

Results: During 123 297 person-years of follow-up, 150 cases of incident breast cancer were confirmed. No significant associations were observed for overall or premenopausal breast cancer. For postmenopausal women, we observed a significant association for moderate adherence to the unhealthful low-fat dietary score and postmenopausal breast cancer (comparing tertile 2 to tertile 1; hazard ratio = 2.18; 95% confidence interval, 1.15–4.13).

Conclusions: In conclusion, no clear associations were observed, although more research is needed to address the association between an unhealthful dietary pattern and postmenopausal breast cancer risk.

Introduction

Breast cancer is the most commonly diagnosed cancer among women worldwide. It represents one in four of all new cancer cases in women, and this number is expected to increase. It is also the leading cause of death among women globally, and it accounted for 626 679 deaths in 2018 [1].

Several factors are known to have an undeniable influence on breast cancer risk. Apart from genetic predisposition (which

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The present study was approved by the Institutional Review Board of the University of Navarra.

Voluntarily given informed consent through free fulfilment of the baseline questionnaire was gathered from all participants.

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accounts for <10% of breast cancer cases), lifestyle and hormonal factors have also been linked to breast cancer risk [2]. Nevertheless, some risk factors are potentially modifiable. In fact, the investigation into modifiable risk factors of breast cancer prevention has received increasing attention. One of these modifiable factors is diet. The role of several dietary factors in breast cancer causation is not completely understood, and only a few dietary factors, such as red and processed meat consumption, alcohol consumption, body fat, and adult weight gain, have convincing evidence related to breast cancer risk [3,4]. Indeed, diet-related factors contribute to 20% to 60% of cancers worldwide and to approximately one-third of deaths from cancer in Western countries [5]. Several studies have evaluated the role of dietary fat on breast cancer risk [6,7] with long-term controversies on health consequences. Regarding the association between a low-fat diet (LFD) and breast cancer risk, the strongest evidence comes from the Women's Health Initiative trial [8]. The intention of this trial was to address the effect of promoting a low-fat eating pattern (20% of total dietary energy from fat) together with increased consumption of vegetables, fruits, and cereals. After 8.1 y of follow-up, 655 (0.42%) women developed invasive breast cancer in the intervention group (n = 19 541) and 1072 (0.45%) women in the comparison group (n = 29 294) (hazard ratio [HR] = 0.91; 95% confidence interval (CI), 0.83−1.01) [9,10]. Specifically, breast cancer incidence was 9% lower for women in the dietary intervention group versus women in the comparison group, although this inverse association was not statistically significant. This could be for several reasons, including suboptimal study power, significant interaction between the HR for the intervention group versus the comparison group for baseline dietary fat consumption, and reduced follow-up time during the planned intervention [10]. On the contrary, a dietary pattern characterized by high-fat choices was associated with breast cancer in the European Prospective Investigation into Cancer and Nutrition (EPIC) cohort study [11]. Nonetheless, in the EPIC study, the investigators focused on variations in nutrient densities of fatty acid intake rather than on the quality of the macronutrients. Evidence has indicated that quality of foods and fat sources plays an important role in human diseases and health beyond the quantitative macronutrient composition of a healthy dietary pattern [12−14]. Thus, dietary fat quality has been suggested as related to the development of insulin resistance and metabolic syndrome, which are potential risk factors for breast cancer development [15−17]. Regarding LFDs, recent studies have identified the importance of distinguishing between healthy and less healthy LFDs [18]. In fact, in an updated systematic review and meta-analysis of observational studies [19], the investigators suggested an increased risk of breast cancer associated with a higher adherence to an a posteriori−defined Western dietary pattern and a reduced risk with a prudent dietary pattern, supporting the differences between an unhealthful and healthful dietary pattern on breast cancer risk.

Therefore, our aim was to assess the relationship between an overall, a healthful, and an unhealthful LFD pattern and risk of breast cancer incidence and also according to menopausal status (based on *a priori* hypothesis−oriented LFD score proposed by Shan et al. [18]) in a Mediterranean cohort, the Seguimiento Universidad de Navarra [SUN] project.

Materials and methods

Study population

This research was carried out within the SUN project [20], which is a Mediterranean dynamic, prospective, follow-up cohort study aimed at identifying dietary and non-dietary determinants of chronic diseases. The cohort began in 1999 and it is permanently open. More details have been published elsewhere [21]. Once the participants complete the first questionnaire, they become part of the cohort. Subsequently, biennial follow-up questionnaires are sent to update information. For participants whose information is lost during the follow-up, the National Death Index is periodically consulted to confirm vital status and, eventually, their cause of death. Our analysis included women who had completed and returned the self-reported semiquantitative food frequency questionnaire (FFQ) by December 2019. By then, 22,894 participants were recruited. To ensure a follow-up time of ≥2 y, we included only those participants who were recruited before March 2017. Of 13,833 eligible women, we excluded 113 participants with self-reported history of breast cancer at baseline, 259 women who reported menopause before 35 y, and 476 women with implausible total energy intake (<500 and >3500 kcal). [22]. Our final sample for the present analysis of different LFD scores and incidence of breast cancer included 10,930 women (Fig. 1). The present study was in line with the guidelines stated in the Declaration of Helsinki; all procedures involving participants were approved by the Institutional Review Board of the University of Navarra (August 30, 2001), and free fulfilment of the baseline questionnaire was considered as voluntarily given informed consent (protocol code 010830).

Assessment of LFD scores

Diet was assessed at baseline and after 10 y using a previously validated 136-item FFQ [23] whose reproducibility was specifically assessed in this cohort [24]. From each macronutrient, percent of energy was used instead of absolute intake to reduce bias and to represent dietary composition. We divided the participants into 11 strata according to their percentage of energy from fat, protein, and carbohydrates. For carbohydrates and protein, individuals in the highest category received 10 points and those in the lowest received 0 points. For total fat, we used reverse scoring:individuals in the lowest category received 10 points and those in the highest received 0 points. The points for the 3 above-mentioned macronutrients were then summed to build an overall LFD score, which ranged from 0 to 30 points. Therefore, the higher the score, the higher the adherence to the LFD. Two additional LFD scores were created to distinguish between unhealthful and healthful LFDs based on the quality of dietary fats rather than only considering the quantitative component. An unhealthful LFD score was calculated considering the percentage of energy from low-quality carbohydrates, animal protein, and unsaturated fat (reverse scoring); on the contrary, a healthful LFD score was calculated according to the percentage of energy from saturated fat (reverse scoring), high-quality carbohydrates, and plant protein (Supplementary Tables 1 and 2). Subsequently, we classified adherence to LFD scores in tertiles for the overall sample and according to menopausal status. The lowest category of each diet score was chosen as the reference category. Furthermore, to minimize within-person variation and reduce measurement error in exposures, we calculated the cumulative average of the three scores by averaging repeated measures after 10 years of follow-up.

Ascertainment of breast cancer

The main outcome for the present analysis was incidence of breast cancer. Prevalent breast cancer cases were excluded from our analyses. During the follow-up, participants were inquired about any incident cases of breast cancer and date of diagnosis, and medical records were requested to confirm the diagnosis. These participants were asked for a copy of their medical records. Then, a blinded trained oncologist confirmed the cases based on the medical records. Only confirmed cases that met the criteria were included in the analysis. Moreover, fatal breast cancer cases were reported to the research team by participant's next of kin, work associates, or postal authorities. For participants lost during the follow-up or with unidentified causes of death, the National Death Index was consulted.

Ascertainment of covariates

At baseline, information from demographic and lifestyle factors, including age, sex, educational level, smoking, physical activity, alcohol intake, dietary intakes, body weight, height, and health status, such as use and time of hormone replacement therapy, menopausal status, or family history of breast cancer, was collected and updated throughout follow-up [25,26]. Age at menopause was updated in the questionnaire after 18 y of follow-up. For those women with no available information on age at menopause, we used the 75th percentile of the age of menopause—52 y in our sample—as the cutoff point [27].

Statistical analysis

For the main analysis, participants were divided into tertiles according to their adherence to different LFD scores, as previously described. Baseline characteristics are summarized as means and SDs from percentages of energy according to tertiles of adherence to LFD scores. We used Cox proportional hazard regression models to estimate HRs and 95% CIs for overall breast cancer (n = 10 930 women), premenopausal breast cancer (n = 9 971 women), and postmenopausal breast cancer (n = 3

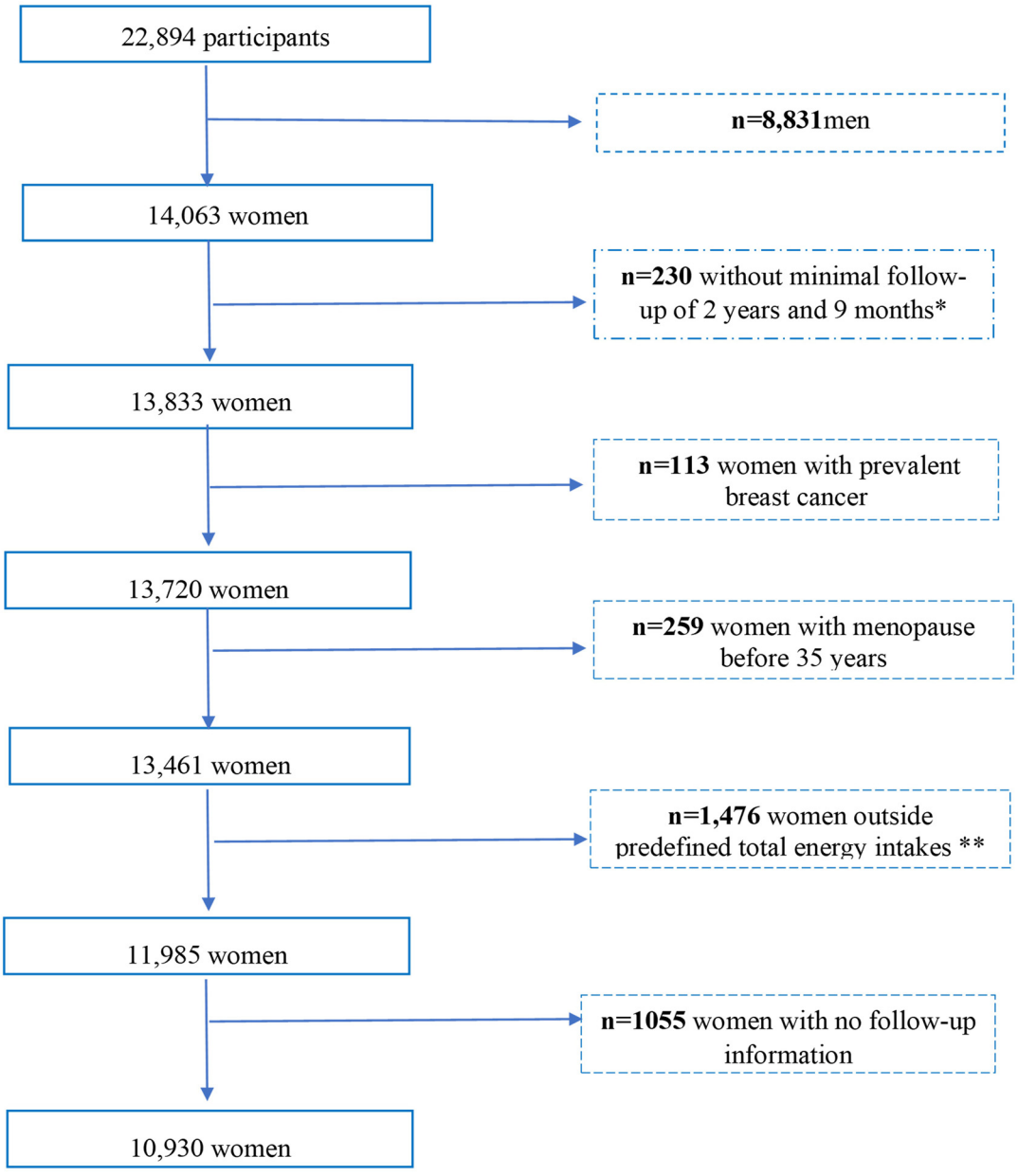

Fig. 1. Flowchart representing the inclusion and exclusion criteria for the selection of participants of the Seguimiento Universidad de Navarra (SUN) project, included in this analysis. SUN Project, 1999–2019. * To ensure a 2-y and 9-months follow-up. ** Energy limits proposed by Willett (2013): 500–3500 kcal/d.

299 women). The lowest tertile of adherence to each dietary pattern was considered the reference category.

We calculated person-years of follow-up from the date of the return of the baseline questionnaire until breast cancer diagnosis for cases and death or from date of return of the last questionnaire for non-cases. All Cox models were stratified for age (decades) and recruitment period. We used multivariable adjusted models to control for potential confounders. Model 1 was adjusted for height (continuous), years at university (continuous), family history of breast cancer (, none, age <45 years or age ≥45 years), smoking status (never smoker, former smoker, and current smoker), lifetime tobacco exposure (pack-years), physical activity (Metabolic equivalent task (MET), h/wk, continuous), TV watching (h/d, continuous), alcohol intake (g/d, continuous), body mass index (BMI) (<25, ≥25 and <30, or ≥30 kg/m^2), age of menarche (<10, 10–11, 12–13, and ≥14 years), age at menopause (<50 and ≥50 years), history of pregnancy (age <25 years and nulliparous, age ≥25 years and nulliparous, first pregnancy at age ≤25 years and <30 years old, and first pregnancy at age ≥30 years old), months of breastfeeding (continuous), use of hormone replacement therapy (yes or no), coffee consumption (<1 or ≥1 cups/d), energy intake (Kcal/d, continuous), and oral contraceptives (yes or no). The 2-year questionnaire included a non-specific question about habitual medication use during the previous 2 years. Repeated measurements were adjusted for the same variables as multivariable adjusted model, discussed previously, using cumulative averages for all dietary variables using updated data from the FFQ after 10 years of follow-up by cumulative average method.

We further applied stratification analysis for associations between LFD scores and breast cancer incidence according to menopausal status. For the assessment of premenopausal breast cancer as the outcome, women who reported being menopausal before baseline assessment were excluded, and we censored follow-up time at the age of 52 years or at the self-reported age of menopause, whichever occurred first. When assessing postmenopausal breast cancer, women were considered at risk only after having turned 52 years old or after their self-reported age of menopause, whichever occurred last. For initially premenopausal women who turned postmenopausal during follow-up, we calculated time since recruitment as the difference between the self-reported date of menopause and the date of completion of the baseline assessment. Analyses for premenopausal breast cancer were right-censored when women turned 52 years old and analyses for postmenopausal breast cancer were left-censored at the age of 52 years. Among premenopausal women, we did not adjust for age at menopause and use of hormone replacement therapy. For the analyses on postmenopausal breast cancer, we also

adjusted for the time between recruitment and menopause, but we no longer adjusted for oral contraceptives.

We also conducted tests of linear trend to evaluate dose-response relationships, assigning to each category of the adherence to the different LFD score its tertile-specific median and using the resulting variable as continuous in the previously discussed models. Furthermore, to address the dose-response relationship between each score and the main outcome, restricted cubic splines models were used controlling for all the previously discussed covariates. We also tested the interaction between the unhealthful LFD score and BMI (<25 or ≥ 25 kg/m^2).

Analyses were performed using STATA/SE version 16.1 (StataCorp, College Station, TX, USA); we used two-sided *P* values, and the statistical significance threshold was set a priori at 0.05.

Results

Participant characteristics

All variables considered were adjusted for age by the inverse probability weighting method (Supplementary Table 3). We also considered their baseline characteristics without adjusting for the inverse probability weighting (Table 1). Briefly, a total of 10 930 women met the inclusion criteria for the present analysis with a mean [SD] age, 35.2 [10.6] y. At baseline, the overall LFD score ranged from 0 to 12 points for the lowest tertile and 19 to 30 points for the highest tertile. Moreover, the unhealthful LFD score ranged from 0 to 13 points for the lowest tertile and from 18 to 30 points for the highest tertile. The healthful LFD score ranged from 0 to 11 points for the lowest category and from 20 to 30 points for the highest.

Baseline characteristics of participants by categories of the three LFD scores are listed in Table 1. Participants with a higher overall LFD score and healthful LFD score were older, more physically active, had a lower consumption of alcohol, were more likely to be never smokers and former smokers, and had a higher proportion of hormone replacement therapy use. Furthermore, there was a higher proportion of women with earlier age of menarche (10–11 years). Moreover, these participants had lower total energy, saturated fat, and polyunsaturated fat intakes but higher carbohydrate and protein intakes. On the other hand, women with a higher unhealthful LFD score were older, had a higher BMI, were more physically active, had lower consumption of alcohol intake, had lower energy intake mainly from high-quality carbohydrates intake, and had lower fat intake.

Low-fat diet scores and risk of overall breast cancer

Among 123 312 person-years of follow-up, we identified 150 confirmed breast cancer cases between 1999 and 2019. The median follow-up time was 12.1 years (SD:4.6years). Associations between an overall, healthful, or unhealthful LFD and incidence of breast cancer are listed in Table 2. Neither the overall LFD, the unhealthful LFD, nor the healthful LFD score was associated with risk of overall breast cancer. Thus, in the fully adjusted model, a higher overall LFD score was not associated with the risk of breast cancer (HRtertile [T] 3 versus T1 = 1.03; 95% CI, 0.66–1.61; *P* for trend = 0.923). Similar results were observed for repeated measurements after 10 y of follow-up (T3 versus T1 = 0.93; 95% CI, 0.63–1.38; *P* for trend = 0.923). Estimated HRs were close to the null regarding the unhealthful (T3 versus T1 = 1.24; 95% CI, 0.78–1.95; *P* for trend = 0.294) and the healthful LFD scores (T3 versus T1 = 1.09; 95% CI, 0.69–1.71; *P* for trend = 0.959). We did not find any statistically significant result considering repeated measurements after 10 y of follow-up. Restricted cubic splines suggested no deviation from linearity

Low-fat diet scores and premenopausal breast cancer

When we stratified the analyses by menopausal status, none of the scores was associated with the risk of premenopausal breast cancer in the multivariable adjusted model (HR T3 versus T1 = 0.89; 95% CI, 0.53–1.49; *P* for trend = 0.649, for overall LFD), (HR T3 versus T1 = 0.97; 95% CI, 0.58–1.61; *P* for trend = 0.850, for unhealthful LFD), (HR T3 versus T1 = 1.05; 95% CI, 0.61–1.81; *P* for trend = 0.831, for healthful LFD) (Table 3). Similar results were observed when we performed repeated measurements after 10 y of follow-up. Restricted cubic splines suggested no deviation from linearity

Low-fat diet scores and postmenopausal breast cancer

We found a significant association between a moderate adherence (T2) to an unhealthful LFD score (median = 17 [14–17]) and postmenopausal breast cancer risk in both age-adjusted (T2 versus T1 = 2.19.; 95% CI, 1.16–4.13) and multivariable adjusted models (T2 versus T1 = 2.18; 95% CI, 1.15–4.13) (Table 4). These results were no longer significant when we carried out repeated measurements considering data aftr 10 years of follow up . Restricted cubic splines suggested no deviation from linearity .

Discussion

In this Mediterranean cohort study, we aimed to apply a previously defined *a priori* LFD score with a healthful and an unhealthful version, proposed by Shan et al. [18], to breast cancer risk. Our results found no clear association between these dietary patterns and breast cancer risk, although a significant association between moderate adherence to the unhealthful LFD and postmenopausal breast cancer risk was observed. However, this association must be considered with caution because of the lower cases of postmenopausal breast cancer and the non-significant association with repreated measurements.

Shan et al. [18] proposed differentiating between a healthful and an unhealthful LFD when addressing the potential association between adherence to an LFD and disease outcomes. They highlighted the importance of considering the quality of fat and carbohydrate sources consumed in LFDs, which may also be crucial for breast cancer prevention. To the best of our knowledge, only one prospective study [18] has used healthful and unhealthful LFDs, which were assessed in relation to mortality among US adults. The investigators found that unhealthful LFD scores were directly associated with the risk of total mortality, whereas healthy LFD scores were associated with lower total mortality. Even though dietary guidelines have focused on recommending an LFD for prevention of chronic diseases [28], inconsistent associations have been reported between total fat consumption and health outcomes [29–32].

The strongest evidence on the association between an LFD and breast cancer risk comes from the Women's Health Initiative [8–10]. Briefly, women were randomly assigned to a dietary modification intervention group (40% [*n* = 19 541]) or a comparison group (60% [*n* = 29 294]). The intervention was designed to promote dietary change with the goals of reducing intake of total fat to 20% of energy and increasing consumption of vegetables and fruit to ≥5 servings per day and grains to ≥6 servings per day. Despite null results for overall breast cancer, the investigators observed a significant reduction in triple-negative tumors, which are especially aggressive. It is important to mention that the intervention in the Women's Health Initiative trial aimed to increase the adherence to an LFD rich in vegetables, fruit, and grains (i.e., a

Table 1
Baseline characteristics of participants according to categories of the overall, unhealthful, and healthful low-fat dietary patterns: the Seguimiento Universidad de Navarra cohort: 1999–2019

Characteristics	Overall low-fat diet score			Unhealthful low-fat diet score			Healthful low-fat diet score		
	T1	T2	T3	T1	T2	T3	T1	T2	T3
Participants, no.	4039	3357	3534	4,057	3,354	3,519	3,968	3,542	3,420
Median score (range)	9 (0–12)	15 (13–18)	22 (19–30)	11 (0–13)	16 (14–17)	20 (18–30)	7 (0–11)	15(12–19)	24 (20–30)
Age (y),	34.0 (9.9)	34.9 (10.4)	37 (11.3)	35.7 (10.9)	34.7 (10.3)	35.1 (10.5)	32.9 (9.3)	35.1 (10.1)	38.1 (11.8)
Body mass index (kg/m^2)	22.1 (3.1)	22.2 (3.0)	22.4 (3.1)	22.2 (3.1)	22.1 (3)	22.3 (3.1)	21.9 (3.0)	22.3 (3.1)	22.5 (3.1)
Physical activity (METs, h/wk)	17.2 (18.8)	18.4 (18.8)	21.0 (21.2)	19.1 (19.6)	19.1 (20.5)	18.1 (19.0)	16.3 (18.6)	18.2 (18.1)	22.3 (21.9)
Alcohol intake (g/d)	4.4 (6.1)	4.4 (6.5)	3.2 (4.8)	4.4 (6.2)	4.1 (5.9)	3.6 (5.4)	4.0 (5.7)	4.1 (5.9)	3.9 (6.1)
Years at university	4.8 (1.3)	4.9 (1.3)	4.8 (1.4)	4.8 (1.3)	4.8 (1.3)	4.9 (1.3)	4.8 (1.3)	4.9 (1.3)	4.8 (1.4)
Height (cm)	163.7 (6.1)	163.7 (6)	163.5 (6)	163.7 (6.1)	163.5 (6.0)	163.7 (6.0)	163.9 (6)	163.6 (6)	163.4 (6.1)
Smoking (%)									
Never	48.2	52.0	55.3	48.7	53.1	53.6	51	50.9	53.2
Current smoker	26.7	22.4	18.4	23.1	22.8	22.2	26.6	23.1	17.7
Former smoker	25.2	25.6	26.3	28.2	24.1	24.2	22.5	26	29
Lifetime tobacco exposure (pack-years)	4.4 (7)	4.1 (7.1)	4.2 (7.4)	4.6 (7.4)	3.9 (7)	4.1 (7.1)	3.9 (6.6)	4.3 (7.2)	4.6 (7.7)
H/d television watching	1.7 (1.3)	1.6 (1.2)	1.6 (1.2)	1.7 (1.3)	1.6 (1.2)	1.6 (1.2)	1.7 (1.3)	1.6 (1.2)	1.6 (1.2)
Age at menarche (%)									
Early	0.9	1.0	1.4	1.1	1.2	1.0	0.9	1.2	1.3
10–11 years	18.3	19.2	20.1	19.2	17.6	20.6	18	19.2	20.5
12–13 years	18.3	53.9	54.4	54.8	56.6	52.6	54.8	54.3	54.7
≥14 years	25.3	25.7	24.0	24.8	24.5	25.7	26.3	25.2	23.5
Obstetric history (%)									
Age <25 y and nulliparous	20.5	18.1	14.3	17.9	18.7	16.7	21.9	17	13.8
Age ≥ 25 y and nulliparous	47.4	48.6	51.3	48.2	48.3	50.8	47.8	48.8	50.8
First pregnancy ≤25 and >30 years old	18.7	18.8	19.9	19.9	19.3	18.2	17.5	19.5	20.6
First pregnancy ≥30 years old	13.3	14.4	14.3	14.1	13.7	14.2	12.7	14.6	14.8
Oral contraceptive use (%)									
No	97.5	97.7	97.5	97.7	97.6	97.3	97.4	97.6	97.7
Yes	2.5	2.3	2.5	2.3	2.4	2.7	2.6	2.4	2.2
Menopausal status at recruitment (%)									
Premenopausal (%)	94.7	92.9	88.5	91.6	92.6	92.4	95.9	93.7	86.2
Postmenopausal (%)	5.3	7.0	11.5	8.4	7.3	7.6	4.1	6.3	13.8
Age at menopause (%)*									
Postmenopausal <50 y	2.1	2.9	4.8	3.7	3.1	2.8	1.60	2.5	5.9
Postmenopausal ≥50 y	3.2	4.0	6.6	4.7	4.2	4.8	2.5	3.7	7.9
Family history of breast cancer (%)†									
None	89.3	88.9	89.8	89.1	89.1	89.8	89.3	89.5	89.2
Before age 45 years	1.9	1.8	1.6	2	1.8	1.6	1.9	1.6	1.9
After age 45 years	8.7	9.2	8.6	8.9	9	8.6	8.7	8.8	8.9
Hormone replacement therapy (%)‡									
No	96.7	95.5	93.4	94.9	96	95	97	95.9	92.6
Yes	3.2	4.5	6.6	5.1	4	5	2.3	4.1	7.4
Time of hormone replacement therapy (years)	0.1 (0.7)	0.1 (0.9)	0.2 (1.1)	0.2 (0.9)	0.1 (0.9)	0.2 (1)	0.1 (0.7)	0.1 (0.9)	0.3 (1.1)
Breastfeeding (mo)	2.2 (4.8)	2.3 (4.9)	2.5 (5.1)	2.3 (4.8)	2.3 (4.9)	2.4 (5.1)	2.1 (4.9)	2.4 (4.8)	2.5 (5.1)
Coffee consumption (servings/d), (%)									
<1	36.4	35	34.5	35.3	36.5	34.5	37.2	33.5	35.1
≥1	63.6	65	65.4	64.7	63.5	65.5	62.7	66.4	64.9
Consumption of fiber (g/d)	24.5 (9.7)	24.8 (10.9)	33.7 (14.1)	30.2 (13.5)	28.7(11.8)	26.9 (10.8)	21 (7.3)	27.9 (8.1)	38.3 (13.7)
Total energy intake (kcal/d)	2363 (578.7)	2312 (558.4)	2202 (569.4)	2344(586.0)	2307 (565.9)	2229 (559.6)	2341 (575.5)	2316 (550.6)	2221 (587.3)
Total carbohydrates, % of energy intake	37.5 (5.6)	43.6 (4.8)	49.5 (5.5)	40.2 (7.5)	43.5 (6.7)	46.6 (6.1)	38.7 (6.4)	43.5 (5.6)	48.3 (6.6)
High-quality carbohydrates	9.7 (4.7)	12.1 (5.7)	16.7 (8.0)	13.6 (7.7)	12.7 (6.7)	11.6 (5.6)	7.7 (3.1)	11.9 (4.0)	19.4 (7.0)
Low-quality carbohydrates	19.7 (7.0)	22.1 (7.8)	21.8 (8.8)	17.8 (7.0)	21.3 (7.3)	24.8 (7.8)	21.8 (7.3)	22.2 (7.9)	19.2 (8.4)
Total protein, % of total energy intake	17.6 (3.3)	18.5 (3.4)	19.3 (3.2)	17.2 (3.2)	18.6 (3.1)	19.6 (3.2)	18.3 (3.6)	18.3 (3.0)	18.6 (3.4)
Animal protein	13 (3.6)	13.1 (3.6)	13 (3.4)	11.9 (3.5)	13.2 (3.4)	14.1 (3.4)	14 (3.7)	12.9 (3.1)	12 (3.5)
Plant protein	4.7 (1)	5.4 (1)	6.3 (1.4)	5.3 (1.4)	5.4 (1.2)	5.6 (1.3)	4.4 (0.8)	5.4 (0.7)	6.7 (1.2)
Total fat, % of total energy intake	43.5 (4.3)	36.6 (2.2)	30.1 (4)	41.3 (6.5)	36.6 (5.2)	32.6 (4.9)	41.7 (5.5)	36.9 (4.8)	31.9 (5.6)
Saturated fat	14.5 (3.0)	12.5 (2.3)	10.1 (2.4)	13 (3.3)	12.7 (3.1)	11.6 (2.7)	15.1 (2.5)	12.3 (1.8)	9.5 (2)
Monounsaturated fat	19.4 (3.4)	15.6 (2.0)	12.6 (2.2)	18.9 (3.9)	15.5 (2.5)	13.2 (2.2)	18 (3.8)	16 (3.3)	13.9 (3.4)
Polyunsaturated fat	6 (1.7)	5.1 (1.3)	4.2 (1.1)	5.9 (1.8)	5.1 (1.3)	4.3 (1.1)	5.6 (1.7)	5.2 (1.5)	4.7 (1.4)
Adherence to the Mediterranean diet§	3.4 (1.7)	3.8 (1.6)	4.6 (1.6)	4.2(1.7)	3.8 (1.7)	3.7 (1.7)	2.7 (1.3)	4 (1.3)	5.3 (1.4)

MET, metabolic equivalent task; T, tertile.
Values are expressed as the mean (SD) for quantitative variables and as percentage for categorical ones. Interquartile ranges are expressed for the group variable.
*Only for postmenopausal women.
†Information from mother, sisters, and both grandmothers were collected.
‡For women with no available information on age at menopause, we used the 75th percentile of the age of menopause (52 y in our sample).
§Score proposed by Trichopoulou et al. (2003) without alcohol component.

Table 2
Hazard ratio and 95 CIs of confirmed overall breast cancer cases, according to tertiles of the overall low-fat diet score, and a healthful and unhealthful low-fat diet scores considering among 10 930 women from the SUN cohort (1999–2019)

Overall breast cancer (n = 150)	T1 (ref.)	T2	T3	P for trend
Overall low-fat diet score				
n	4039	3357	3534	
Median (range)	9 (0–12)	15 (13–18)	22 (19–30)	
Incidence cases	56	48	46	
Person-years of follow-up	46 638	37 936	38 725	
Incidence rate/10 000 person-years	8.8	10.5	9.8	
Age-adjusted model	1 (ref.)	1.13 (0.73–1.74)	0.94 (0.60–1.47)	0.781
Multivariable adjusted model	1 (ref.)	1.14 (0.74–1.77)	1.03 (0.66–1.61)	0.887
Repeated measurements*	1 (ref.)	1.04 (0.71–1.54)	0.93 (0.63–1.38)	0.923
Unhealthful low-fat diet score				
n	4057	3354	3519	
Median (range)	11 (0–13)	16 (14–17)	20 (18–30)	
Incidence cases	55	51	44	
Person-years of follow-up	46 543	37 437	39 318	
Incidence rate/10 000 person-years	8.6	10.9	9.6	
Age-adjusted model	1 (ref.)	1.34 (0.86–2.07)	1.17 (0.75–1.82)	0.422
Multivariable adjusted model	1 (ref.)	1.36 (0.88–2.11)	1.24 (0.78–1.95)	0.294
Repeated measurements	1 (ref.)	1.12 (0.76–1.75)	1.09 (0.74–1.61)	0.677
Healthful low-fat diet score				
n	3968	3542	3420	
Median (range)	7 (0–11)	15 (12–19)	24 (20–30)	
Incidence cases	52	52	46	
Person-years of follow-up	46 368	40 461	36 468	
Incidence rate/10 000 person-years	7.9	10.6	10.6	
Age-adjusted model	1 (ref.)	1.14 (0.73–1.77)	0.99 (0.62–1.58)	0.960
Multivariable adjusted model	1 (ref.)	1.19 (0.77–1.84)	1.09 (0.69–1.71)	0.959
Repeated measurements	1 (ref.)	1.15 (0.78–1.69)	1.02 (0.68–1.54)	0.990

BMI, body mass index; CI, confidence interval; MET, metabolic equivalent task; SUN, Seguimiento Universidad de Navarra, T, tertile; ref, reference category.
Results from Cox regression models. All Cox models were stratified for age (decades) and recruitment period. Multivariable adjusted model for height (continuous) years at university (continuous), family history of breast cancer (none, age <45 years and age ≥45 years), smoking status (never smoker, former smoker, or current smoker), lifetime tobacco exposure (pack-years), physical activity (MET, h/wk), TV watching (h/d), alcohol intake (g/d, continuous), BMI (<25, ≥25 and <30, or ≥30 kg/m^2), age of menarche (<10, 10–11, 12–13, or ≥14 years), age at menopause (<50 or ≥50 years), history of pregnancy (age <25 y and nulliparous, age ≥25 y and nulliparous, first pregnancy at <25 and <30 y old, or first pregnancy at ≥30 y old), months of breastfeeding (continuous), use of hormone replacement therapy (yes or no), coffee consumption (<1 or ≥1), energy intake (Kcal/d), and oral contraceptives (yes or no).
The P value when we assigned the median value to each quartile and entered this as a continuous variable in the model.
*Repeated measurements were adjusted for the same variables as multivariable adjusted model, using cumulative averages for all dietary variables.

healthful LFD) [33]. On the contrary, there is not strong evidence of the potential harms of an unhealthful LFD. In this context, the quality of carbohydrates and the quality and types of fats that may still be consumed in an LFD may play a role on breast cancer risk. Evidence regarding the relationship between dietary fat intake and breast cancer risk is inconsistent, and future studies with longer follow-up are still needed. Evidence from a review of observational studies [34] observed no clear association between overall fat intake and breast cancer risk. On the other hand, and regarding subtypes of fat intake, investigators concluded that intake of animal and saturated fat has been associated with increased risk of breast cancer in previous studies [34]. Furthermore, conclusions from the EPIC cohort study [35] regarding dietary fat intake and breast cancer risk suggested a weak association between saturated fat intake and breast cancer risk, particularly among postmenopausal women. A recent review by Forouhi et al. [36] found that the type of fat was associated with human health in an independent manner from total fat intake, suggesting that the quality of fat—rather than the overall fat intake—may play a role in breast cancer risk, because dietary fats typically are mixtures of different types of fatty acids that may have a different effect on chronic diseases such as cancer.

In addition, when addressing the potential effects of decreasing dietary fat content, it is important to consider the quality of the macronutrients that replace those fats in an isocaloric diet. Unless caloric restriction is intended, fat intake will be replaced mainly by carbohydrates in an LFD. Therefore, it becomes relevant to consider the quality of the carbohydrates that are replacing those fats. A recent meta-analysis of prospective cohort studies [37] found that high dietary glycemic index diet was associated with a higher risk of breast cancer. Similarly, a meta-analysis of cohort studies [38] aimed to elucidated which sources of carbohydrate (dietary fiber, whole grain, sugar, and unidentified carbohydrates) may have different effects on breast cancer. In that study, overall dietary carbohydrate intake was associated with a lower risk of breast cancer incidence. On the other hand, higher dietary fiber intake was associated with a significant reduction in breast cancer incidence, especially among premenopausal women. Finally, they suggested a direct association between sugar consumption and breast cancer incidence. In another meta-analysis [39], both a dietary pattern with a high glycemic index or high glycemic load were associated with a higher risk of breast cancer. Therefore, the effect of an LFD pattern on longtime breast cancer risk may be driven not only by the quantity and quality of fat but also by the type of carbohydrates that replace those fats.

Our results must be interpreted with caution because of the lower number of cases of postmenopausal breast cancer and the absence of significant association with repeated measurements . However, there was a two-fold increase in the risk of breast cancer associated with a moderate adherence to an unhealthful LFD score, which represents not only poor-quality fats but also poor-quality carbohydrate choices. This may reflect an overall poor-quality dietary profile resembling a more westernized dietary pattern characterized by animal products, low-quality carbohydrates, and a low

Table 3
Hazard ratio and 95 CIs of confirmed premenopausal breast cancer according to tertiles of the overall low-fat diet score, and healthful and unhealthful low-fat diet scores among 9971 women from the SUN cohort (1999–2019)

Premenopausal breast cancer (n = 87)	T1 (ref.)	T2	T3	P for trend
Overall low-fat diet score				
n	3791	3087	3093	
Median (range)	9 (0–12)	15 (13–18)	22 (19–30)	
Incidence cases	37	26	24	
Person-years of follow-up	38 407	30 686	28 651	
Incidence rate/10 000 person-years	9.6	8.4	8.3	
Age-adjusted model	1 (ref.)	0.82 (0.0–1.36)	0.80 (0.47–1.35)	0.397
Multivariable adjusted model	1 (ref.)	0.86 (0.52–1.42)	0.89 (0.53–1.49)	0.649
Repeated measurements	1 (ref.)	1.19 (0.66–2.13)	1.18 (0.65–2.12)	0.567
Unhealthful low-fat diet score				
n	3690	3047	3234	
Median (range)	11 (0–13)	16 (14–17)	20 (18–30)	
Incidence cases	35	25	27	
Person-years of follow-up	35 934	30 423	31 388	
Incidence rate/10 000 person-years	6.9	6.6	6.9	
Age-adjusted model	1 (ref.)	0.84 (0.50–1.41)	0.90 (0.54–1.49)	0.649
Multivariable adjusted model	1 (ref.)	0.88 (0.58–1.61)	0.97 (0.58–1.61)	0.850
Repeated measurements	1 (ref.)	0.92 (0.50–1.68)	1.07 (0.60–1.89)	0.870
Healthful low-fat diet score				
n	3339	3351	3281	
Median (range)	6 (0–10)	14 (11–18)	23 (19–30)	
Incidence cases	31	34	22	
Person-years of follow-up	39 817	32 349	25 579	
Incidence rate/10 000 person-years	7.7	10.5	8.6	
Age-adjusted model	1 (ref.)	1.48 (0.89–2.45)	0.93 (0.53–1.65)	0.808
Multivariable adjusted model	1 (ref.)	1.59 (0.98–2.58)	1.05 (0.61–1.81)	0.831
Repeated measurements	1 (ref.)	1.69 (0.95–3.00)	1.10 (0.58–2.08)	0.661

CI, confidence interval; SUN, Seguimiento Universidad de Navarra; MET, metabolic equivalent task; T, tertile; ref: reference category.
Results from Cox regression models. All Cox models were stratified for age (decades) and recruitment period. Multivariable adjusted model for height (continuous), years at university (continuous), family history of breast cancer (none, age <45 years and age ≥45 years), smoking status (never smoker, former smoker, or current smoker), lifetime tobacco exposure (pack-years), physical activity (MET, h/wk), TV watching (h/d), alcohol intake (g/d, continuous), BMI (<25, ≥25 and <30, or ≥30 kg/m^2), age of menarche (<10, 10–11, 12–13, or ≥14 years), history of pregnancy (age <25 years and nulliparous, age ≥25 years and nulliparous, first pregnancy age <25 years and <30 years old, or first pregnancy ≥30 years old), months of breastfeeding (continuous), coffee consumption (<1 or ≥1), energy intake (Kcal/d), and oral contraceptives (yes or no). Repeated measurements were adjusted for the same variables as multivariable adjusted model, using cumulative averages for all dietary variables.
The P value when we assigned the median value to each quartile and entered this as a continuous variable in the model.

presence of unsaturated fats. The non-significance in our other results may be partly due to limited statistical power in the present analysis. However, one possible explanation is that this Mediterranean population is mainly a middle-aged cohort, with eventual limited variability regarding macronutrient composition of diet and overall healthy lifestyles (e.g., mean BMI 22.2 kg/m^2 in the overall sample). Another possible explanation is that both the overall LFD score and the healthful LFD score are composed of macronutrients with effects that are not as harmful as the unhealthful score, whose total composition may lead to a complete detriment in health. This could be supported by observed differences regarding dietary instruments for evaluating dietary fat among other nutrients [34]. However, the semiquantitative FFQ used for dietary assessment in ourcohort was previously validated [23,24].

Several biological mechanisms might support the dietary fat–-breast cancer hypothesis [9,10,34,40,41–44]. First, fat intake may raise endogenous estrogen concentrations [34]. Intervention studies indicated that reducing fat intake could lead to lower serum sex hormone concentrations and it is hypothesized, therefore, that lower fat intake may reduce breast cancer risk [40,41]. Second, the consumption of fat, especially saturated fat, may also increase breast cancer risk through a negative effect on insulin resistance [42] and insulin growth factor 1 [43] and its influence on inflammatory markers [9,10]. Also, dietary fats may influence the process of carcinogenesis by modulating intracellular cascades [44]. A suggestion that a high-fat diet promoted mammary tumor growth was reported >50 y ago, but it was based on a mouse model [45]. From that time, some studies have looked at specific types of fat. For example, polyunsaturated fatty acids, such as linoleic acid (which is found in vegetable oils and is a precursor of prostaglandins), may promote tumor growth [46,47]. However, the evidence from these preclinical models does not appear to be consistent with well-conducted and analyzed prospective epidemiologic studies, with appropriate control for confounding and including many thousands of cases of breast cancer. They have failed to report a strong relationship between dietary fat and new-onset breast cancer. In addition, there is a real lack at this time of published randomized controlled data in this area [48].

Nevertheless, it is important to select healthy fats in the LFDs and include healthy food choices—healthy carbohydrates—as replacements for foods rich in fat in an LFD. What seems to be clear is that a dietary pattern is not healthier due to a reduction in the percentage of fat per se but rather due to the sum of quality of the macronutrients and the food sources of those macronutrients.

Potential limitations also need to be considered. First, our statistical power could be limiteddue to the observed number of incident cases of breast cancer, especially when considering postmenopausal breast cancer. Furthermore, our cohort mostly represents young Mediterranean women, among whom the incidence of breast cancer is lower, although this could help us to contribute to preventive strategies at an earlier adulthood. Second, a priori information on breast cancer incidence was self-reported from questionnaries Nevertheless, the identified age-adjusted incidence was consistent with the reported incidence of breast cancer

Table 4
Hazard ratio and 95 CIs of confirmed postmenopausal breast cancer according to tertiles of the overall low-fat diet score and healthful and unhealthful low-fat diet scores in 3299 women from the SUN cohort (1999–2019).

Postmenopausal breast cancer (n = 57)	T1 (ref.)	T2	T3	P for trend
Overall low-fat diet score				
n	1228	1009	1062	
Median (range)	10 (0–13)	17 (14–19)	23 (20–30)	
Incidence cases	16	19	22	
Person-years of follow-up	7066	6279	9144	
Incidence rate/10 000 person-years	2.2	3	2.4	
Age-adjusted model	1 (ref.)	1.11 (0.58–2.10)	1.01 (0.53–1.91)	0.943
Multivariable adjusted model	1 (ref.)	1.18 (0.61–2.30)	1.10 (0.58–2.07)	0.746
Repeated measurements	1 (ref.)	1.69 (0.75–3.79)	1.41 (0.66–3.02)	0.336
Unhealthful low-fat diet score				
n	1325	947	1027	
Median (range)	10 (0–13)	16 (14–17)	20 (18–30)	
Incidence cases	16	24	17	
Person-years of follow-up	9315	6200	6975	
Incidence rate/10 000 person-years	1.7	3.8	2.4	
Age-adjusted model	1 (ref.)	2.19 (1.16–4.13)	1.42 (0.722.82)	0.186
Multivariable adjusted model	1 (ref.)	2.18 (1.15–4.13)	1.46 (0.74–2.88)	0.125
Repeated measurements	1 (ref.)	1.88 (0.85–4.16)	1.63 (0.77–3.48)	0.145
Healthful low-fat diet score				
n	1125	1133	1041	
Median (range)	9 (0–13)	18 (14–21)	26 (22–30)	
Incidence cases	16	17	24	
Person-years of follow-up	5489	7157	9844	
Incidence rate/10 000 person-years	2.9	2.3	2.4	
Age-adjusted model	1 (ref.)	0.83 (0.43–1.60)	1.05 (0.55–1.99)	0.882
Multivariable adjusted model	1 (ref.)	0.90 (0.46–1.77)	1.18 (0.63–2.22)	0.629
Repeated measurements	1 (ref.)	0.94 (0.41–2.19)	1.45 (0.65–3.27)	0.310

CI, confidence interval; SUN, Seguimiento Universidad de Navarra; MET, metabolic equivalent task; T, tertile; ref: reference category .
Results from Cox regression models. All Cox models were stratified for age (decades) and recruitment period. Multivariable adjusted model for height (continuous), years at university (continuous), family history of breast cancer (none, age <45 years and age ≥45 years)), smoking status(never smoker, former smoker, or current smoker), lifetime tobacco exposure (pack-years), physical activity (MET, h/wk), TV watching (h/d), alcohol intake (g/d, continuous), BMI (<25, ≥25 and <30, or ≥30 kg/m^2), age of menarche (<10, 10–11, 12–13, or ≥14 years), age at menopause (age <50 or ≥50 years), history of pregnancy (age <25 years and nulliparous, age ≥25 years and nulliparous, first pregnancy age <25 years and <30 yearsold, or first pregnancy age ≥30 years old), months of breastfeeding (continuous), use of hormone replacement therapy (yes or no), coffee consumption (<1 or ≥1), and energy intake (Kcal/d). Repeated measurements were adjusted for the same variables as multivariable adjusted model, using cumulative averages for all dietary variables.
The P value when we assigned the median value to each quartile and entered this as a continuous variable in the model.

in the Spanish population [49]. In addition, to avoid false-positive results, breast cancer cases were confirmed by a blinded trained oncologist. Third, self-reported information of exposure could denote some degree of misclassification which, in turn, may have biased our results toward the null. However, it is noteworthy that we used a previously validated semiquantitative FFQ for dietary assessment [23,24]. Also, our results may be taken into consideration in future meta-analyses and contribute to the evidence regarding this topic, despite not being statistically significant. Fourth, we did not have a representative sample of the general population, but lack of representativeness does not preclude addressing measures of association. Fifth, associations derived from an observational study may partly result from residual confounding. Nevertheless, we carefully adjusted all results for a wide range of known breast cancer risk factors. Finally, we acknowledge the inability to assess breast cancer subtypes. Therefore, we acknowledge that these a priori index approaches are limited by the current level of evidence on diet–breast cancer relationship as well as the uncertainties accompanying the creation of the various scores themselves.

The major strengths of this study include its longitudinal and prospective design (avoiding reverse causation), exhaustive data collection, and data analysis. We evaluated these scores at baseline and after 10 y of follow-up by cumulative average method, trying to capture the relationship of a time-varying exposure, such as diet, on the development of breast cancer, and the results barely changed. Furthermore, the distinctions between healthful and unhealthful LFDs used in previous findings with mortality by Shan et al. [18] are based on existing knowledge on the association of health outcomes beyond specifically breast cancer. Other strengths are its large sample size, high retention (91%), long follow-up period, and wide array of potential confounders included in the multivariable analysis, reducing residual confounding.

Conclusion

In this Mediterranean prospective cohort study, non-significant associations were observed. However, our results suggested a potential association between adherence to an unhealthful LFD and postmenopausal breast cancer. From a public health point of view, dietary recommendations should focus not only on the quantity of macronutrients but also on the quality of the food sources to best achieve a macronutritional balance. Future studies should address the relationship between these scores and breast cancer subtypes with more breast cancer cases and long follow-up.

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Supplementary materials

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