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Adherence to the Western, Prudent and Mediterranean dietary patterns and breast cancer risk: MCC-Spain study. Adela Castelló, Elena Boldo, Beatriz Pérez-Gómez, Virginia Lope, Jone M. Altzibar, Vicente Martín, Gemma Castaño-Vinyals, Marcela Guevara, Trinidad Dierssen-Sotos, Adonina Tardón, Víctor Moreno, Montserrat Puig-Vives, Cristóbal Llorens-Ivorra, Juan Alguacil, Inés Gómez-Acebo, Jesús Castilla, Esther Gràcia-Lavedánb, Verónica Dávila-Batista, Manolis Kogevinas, Nuria Aragonés, Pilar Amianos, Marina Pollán.

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ABSTRACT

Objective: To externally validate the previously identified effect of the Western, Prudent and Mediterranean dietary patterns in breast cancer risk.

Study Design: MCC-Spain is a multicase-control study that collected epidemiological information on 1181 incident cases of female breast cancer and 1682 controls from 10 Spanish provinces. Western (high intakes of fatty and sugary products and red and processed meat), Prudent (high intakes of low-fat dairy products, vegetables, fruits, whole grains and juices) and Mediterranean (high intake of fish, vegetables, legumes, boiled potatoes, fruits, olives and vegetable oil, and a low intake of juices) dietary patterns derived in another Spanish case-control study were reconstructed in MCC-Spain. Their association with breast cancer was assessed using logistic regression models with random province-specific intercepts considering an interaction with menopausal status. Risk according to tumour subtypes -based on oestrogen (ER), progesterone (PR) and Human Epidermal Growth Factor 2 (HER2) receptors- (ER+/PR+&HER2-; HER2+; ER-/PR-&HER2-) was evaluated with multinomial regression models.

Main outcome measures: Breast cancer and histological subtype.

Results: Our results confirm most of the associations found in the previous case-control study. A high adherence to the Western dietary pattern might increase breast cancer risk in both pre ($OR_{4^{th}\,vs.1^{st}\,quartile}$(95%CI):1.68(1.02;2.79); $OR_{1SD\text{-}increase}$(95%CI): 1.19(1.02;1.40)) and postmenopausal ($OR_{4^{th}\,vs.1^{st}\,quartile}$(95%CI):1.48(1.07;2.05); $OR_{1SD\text{-}increase}$(95%CI): 1.14(1.01;1.29)) women. While a high adherence to the Prudent pattern did not show any effect on breast cancer, the Mediterranean dietary pattern could be protective, but only among postmenopausal women ($OR_{4^{th}\,vs.1^{st}\,quartile}$ (95%CI):0.72(95% CI 0.53;0.98); p-int=0.075). There were no significant differences by tumour subtype.

Conclusion: Dietary recommendations based on a departure from the Western dietary pattern in favour of the Mediterranean diet could reduce breast cancer risk in the general population.

Keywords: “Diet, Mediterranean”; “Diet, Western”; “Breast Neoplasms”; “prevention and control”; Population Attributable Fraction.

LIST OF ABBREVIATIONS

BC: Breast Cancer.

EpiGEICAM: Epidemiological study of the Spanish Group for Breast Cancer Research (Grupo Español de Investigación en Cáncer de Mama).

MCC-Spain: Multicase-Control study on Common tumours in Spain.

OR: Odds Ratio.

95%CI: 95%Confidence Interval.

FFQ: Food Frequency Questionnaire.

ER: Oestrogen Receptor.

PR: Progesterone Receptor.

HER2: Human Epidermal Growth Factor Receptor 2.

TN: Triple Negative.

SD: Standard Deviation.

IQI: Interquartile Interval.

BMI: Body Mass Index.

METs: Metabolic Equivalents.

Kcal: Kilocalories.

PAF: Population Attributable Fraction.

n: Number of Individuals.

p-int: p-value for the interaction.

p-het: p-value for the heterogeneity.

p-trend: p-value for trend.

INTRODUCTION

Breast cancer (BC) is the most common type of cancer among women worldwide and one of the main causes of female mortality in medium and high income countries [1, 2]. In the last decades, the absolute number of new cases due to BC has increased [2], emphasizing the need to prioritize prevention as an indispensable tool to reduce the burden of this disease.

According to the scientific evidence, diet, physical activity and weight contributes around 30-35% to the burden of cancer, providing major opportunities for prevention [3]. Recent reviews on research gaps and translational priorities on BC prevention highlight the need to implement sustainable changes in lifestyle based on these three factors as an essential tool to effectively reduce the number of BC cases [4]. However, apart from the deleterious effect of overweight and obesity, the only dietary element for which there is strong scientific evidence in relation to BC risk is alcohol, while data on other factors are more heterogeneous [5, 6]. Most studies exploring the effect of diet on BC risk are focused on evaluating the individual influence of food and nutrients, but some authors argue that overall dietary patterns may better capture dietary variability in the population’s diet while taking into account possible interactions between individual foods and nutrients [7, 8].

A recent publication that evaluated the association of dietary patterns with BC risk in a group of Spanish women –EpiGEICAM study- identified three dietary patterns [9] labelled as Western (associated with increased risk of BC), Prudent (not associated with BC) and Mediterranean (protective against BC). The great variability of diets across all the regions included in EpiGEICAM and the high prevalence of the Mediterranean diet in the Spanish population allowed the identification, over the same population, of two different patterns (Prudent and Mediterranean) commonly interchanged in the literature of data-driven patterns. However, the frequently ignored differences between these two patterns might be determinant in their association with disease risk. Therefore we believe that, the external validation of EpiGEICAM results is of great scientific interest.

The objective of the present study is to externally validate the effect of the Western, Prudent and Mediterranean dietary patterns in BC risk found in the EpiGEICAM study, [9] in an independent sample, globally, by menopausal status and tumour subtype.

METHODS

MCC-Spain (http://www.mccspain.org/) is a population-based multicase-control study conducted between 2008 and 2013 in 12 Spanish provinces to identify environmental, personal and genetic factors related to five common cancers, including BC [10]. The selection process of cases and controls has been previously described in detail [10, 11]. Briefly, a single set of population controls were frequency matched by age and sex with the overall distribution of all cancer cases. Controls were selected from the lists of residents assigned to different primary health-care centres that belonged to the same catchment area of the hospitals where the cases were recruited. Controls were contacted by phone, and those who agreed to participate attended a personal interview. BC cases were recruited in 20 hospitals from 10 of the participating provinces (Barcelona, Madrid, Navarra, Guipúzcoa, León, Asturias, Huelva, Cantabria, Valencia and Girona). Cases were identified as soon as possible after diagnosis, through active search that included periodical visits to the collaborating hospital departments. Histologically confirmed incident cases of BC (ICD10: C50, D05.1, D05.7) with no prior history of the disease, and diagnosed within the recruitment period were included. Participants able to answer the questionnaire, who lived in the study area for at least 6 months before the diagnosis and were 20-85 years old were invited to participate. MCC-Spain recruited 1738 incident BC cases and 1910 healthy women. Sample size was exclusively based on budgetary availability. However, with the current sample size we are able detect a significant OR of 1.27 for increases of one quartile in the adherence to the Western pattern and a significant OR of 0.77 for increases of one quartile in the adherence to the Mediterranean pattern with a statistical power over 80%. The response rate was 69% among BC cases and 54% among female controls.

A structured computerized epidemiological questionnaire was administered by trained personnel in a face-to-face interview to collect information on socio-demographic factors, lifestyle and personal/family medical history. Missing values on key variables were completed through subsequent telephone contact. Height and weight at different ages were self-reported and data for the year previous to the diagnostic (cases) /interview (controls) was used to compute body mass index (BMI) previous to BC diagnosis. At the end of the interview participants received the food frequency questionnaire (FFQ) in paper form, to be filled at home and returned by mail. This questionnaire, with 154-items, was a modified version from a previously validated instrument in Spain [12] to include regional products and refers to eating habits during the preceding year. Some questions about general dietary habits were included in the questionnaire and used to adjust the responses to the FFQ following the methodology described in Calvert et al. [13]. Implausible energy intakes (<750 or >= 4500 kcal) were excluded. Postmenopausal status was defined as absence of menstruation in the past 12 months.

Cases were subclassified by the following intrinsic subtypes based on local pathology reports [14]: (1) Oestrogen receptor (ER) positive (+) and/or progesterone receptor (PR) positive tumours with luminal human epidermal growth factor receptor 2 (HER2) negative (-) a; (2) HER2+ tumours irrespective of ER or PR results; (3) triple-negative (TN) tumours with ER-, PR- and HER2-. The ER, PR and HER2 positivity were defined according to ASCO/CAP guidelines [15].

Here, three dietary patterns identified in a previous case-control study are examined [9]: a) a Western pattern positively associated with BC risk and characterized by high intakes of high-fat dairy products, processed meat, refined grains, sweets, caloric drinks, convenience food and sauces and low intakes of low-fat dairy products and whole grains; b) a Prudent pattern that showed no relationship with BC risk and consisted of high intakes of low-fat dairy products, vegetables, fruits, whole grains and juices; and c) a Mediterranean pattern that proved to be protective and was characterized for a high intake of fish, vegetables, legumes, boiled potatoes, fruits, olives and vegetable oil, and a low intake of juices. These patterns were identified in the EpiGEICAM study applying principal components analysis (PCA) without rotation of the variance-covariance matrix over 26 inter-correlated food groups. PCA reports a set of weights (pattern loadings) associated with each food group that represents the correlation between food consumption and the pattern scores and can be used to reproduce such patterns in other samples as explained in detail elsewhere [16, 17]. Briefly, 146 of the 154 items of the MCC-Spain FFQ (excluding non-caloric and alcoholic beverages) were grouped into the same 26 food groups published in the original article [9] (**Table 1**). The scores of adherence of the MCC-Spain women to the Western, Prudent and Mediterranean dietary patterns were calculated afterwards as a linear combination of the loadings for each food group and pattern published in the EpiGEICAM study (L_W, L_P and L_M from **Table 1**) [9] and the food group consumption reported by the participants in the current study as follows:

$$P_{ki} = \sum_{j=1,...26} L_{kj} \cdot C_{ji}$$

Where,

P= Pattern Scores of participants from MCC-Spain study.

L=Pattern loadings from the EpiGEICAM study.

C= Centred food group consumption.

k=Western, Prudent and Mediterranean dietary patterns.

i=1, 2713 women from MCC-Spain study (1124 cases and 1589 controls)

j=1, 26 food groups

Adjusted associations between adherence to each dietary pattern and BC risk (outcome: 0=control, 1=BC case) were evaluated using binary logistic regression models with random province-specific intercepts. As fixed-effects terms, menopausal status; age (years); education; body mass index (BMI, kg/m^2); age at first delivery (years); family history of breast cancer; physical activity (metabolic equivalents (METs)) during the 10 years before diagnosis/interview; smoking status; caloric intake (kcal/day) and alcohol intake (ethanol grs/day) were considered as confounders. Both, categorical (grouping the scores of adherence into quartiles according to the distribution among controls) and continuous (1-SD increase) associations of these dietary scores with BC were examined in separate models. The association between the adherence to the Western, Prudent and Mediterranean dietary patterns and BC risk among pre and postmenopausal women was estimated including in the models the corresponding interaction terms, the p-values of the interaction served to test heterogeneity of effects according to menopausal status.

Multinomial logistic regression was used to evaluate the association of the adherence to the Western, Prudent and Mediterranean dietary patterns with each of the aforementioned intrinsic BC subtypes (outcome: 0=control, 1=BC cases with ER/PR+ tumours; 2=BC cases with HER2+ tumours; 3=BC cases with TN tumours). These models were adjusted by menopausal status, age, education, BMI, age at first delivery, family history of breast cancer, physical activity (METs), smoking status, caloric intake, alcohol intake and province. Physical activity included recreational and household activities performed during the last 10 years, translated into metabolic equivalent values (METs), according to the Ainsworth's Compendium of Physical Activities [18]

Finally, assuming a causal relationship between the adherence to each of the patterns and BC risk for all analyses, the population attributable fraction (PAF%) was calculated using Levi's formula [19] to estimate the proportion of breast cancer cases in this population that hypothetically would not have occurred if all participants were in the most beneficial quartile of adherence to dietary patterns (first quartile for Western and fourth quartile for Prudent and Mediterranean patterns). Confidence intervals for PAFs were computed using bootstrap with 1000 iterations.

Analyses were performed using STATA/MP (version 14.1, 2015, StataCorp LP) and statistical significance was set at 2-sided $p < 0.05$.

The protocol of MCC-Spain was approved by each of the Ethics Committee of the participating institutions. The specific study reported here was approved by the Instituto de Salud Carlos III Ethics Committee, with reference CEI PI 44_2012. All participants were informed about the study objectives and signed an informed consent.

RESULTS

Initially, data on 1910 controls and 1738 cases of BC were recruited from which 1589 controls and 1437 cases returned the diet questionnaire. Cases that provided dietary information later than 6 months after diagnosis were excluded (n=313). Therefore, 1124 cases and 1589 controls aged 24 to 85 years were included in this study. The multivariable analyses were carried out over 1063 cases and 1469 controls because data on either BMI, physical activity, age at first delivery or smoking status was missing for 61 cases and 120 controls.

BC cases were more adherent to the Western pattern and reported higher energy intake than controls, while no differences in the scores of adherence to the Prudent and Mediterranean patterns were observed in univariate analyses. BC cases were also slightly younger, had a higher proportion of pre-menopausal women and showed a higher prevalence of ever smokers, a lower proportion of women with no formal education and a higher proportion of women with family history of BC (**Table 2)**.

The results from the multivariable analyses summarized in **Table 3,** showed that a higher adherence to the Western pattern might be associated with higher odds of BC, with the OR for the top versus the bottom quartile being 1.53 (95% CI 1.15;2.02) with a clear dose-response trend. This association was slightly stronger in premenopausal ($OR_{\text{fourth vs. first quartile}}$ (95%CI): 1.68(1.02;2.79; p-trend=0.048)) than in postmenopausal ($OR_{\text{fourth vs. first quartile}}$ (95%CI): 1.48 (1.07;2.05); p-trend=0.012) women, but these differences were not statistically significant (p-int=0.650). The percentage of preventable BC if all women were in the lowest category of adherence to the Western pattern was estimated at 24% (95%CI:8%;40%) for all women, 34% (95%CI:-1%;68%) for premenopausal and 20% (95%CI:4%;37%) for postmenopausal women. The level of adherence to the Prudent pattern did not seem to be related to BC risk. A high adherence to the Mediterranean pattern seemed to be protective only among post-menopausal, with an OR for the top vs the bottom quartile of adherence of 0.72 (95% CI: 0.53;0.98) and a p-value for the heterogeneity of effects in pre and postmenopausal women close to the statistical significance (p-int=0.075). The PAF% was estimated to be 18%(95%CI: 2%;35%) if all postmenopausal women were in the highest category of adherence to the Mediterranean dietary pattern.

Finally, the positive association found between a high adherence to the Western dietary pattern and BC risk was only observed for ER/PR+ ($OR_{\text{fourth vs. first quartile}}$ (95%CI): 1.45 (1.06;1.99)) and HER2+ ($OR_{\text{fourth vs. first quartile}}$ (95%CI): 1.94 (1.09;3.45)) tumours, but heterogeneity of effects among tumour subtypes was not significant. The estimation of the PAF% indicates that, assuming causal relationship between the adherence to the Western dietary pattern and BC risk 20% (95%CI: 2%;39%) of ER/PR+ tumours and 40% (95%CI: 13%;67%) HER2+ tumours could have been prevented if all participant women would have been in the lowest category of adherence to this dietary pattern **(Table 4)**.

DISCUSSION

Our results suggest that a high adherence to the Western diet might be positively associated with BC risk, both in pre and postmenopausal women. On the other hand, a high adherence to the Mediterranean dietary pattern seems to be protective against postmenopausal BC, while a Prudent diet did not seem to have any effect on BC risk.

The EpiGEICAM study [9] also found an increased risk of BC for women with a high Western pattern score that was stronger in premenopausal women. Recent reviews also claim that this type of diet is associated with increased risk of BC [20, 21] especially among pre-menopausal women [22]. The differences found by menopausal status might be related to the greater adherence to the Western pattern observed in younger women (data not shown: $Mean(SD)_{\text{pre-menopausal}}$: 0.65

(3.23) and Mean(SD)$_{postmenopausal}$: -1.17(3.34)). A recent study [23] also reports a positive association between mammographic density, one of the most important risk factors for breast cancer [24], and the Western dietary pattern in a different sample of Spanish women. Regarding Mediterranean dietary pattern, we only found a potential protective effect among postmenopausal women, while the EpiGEICAM study [9] reported an association for both subgroups, in agreement with most recent reviews [20, 21, 25]. This might be explained by the fact that two out of three women in the present study were postmenopausal, while the premenopausal group represented 55% of the population included in the original study [9]. Finally, the prudent pattern was not associated with BC risk, as occurred in the previous study [9]. The stronger protective effect of the Mediterranean pattern in TN tumours found in the EpiGEICAM study [9] and suggested by other authors [26, 27] was not confirmed here. The estimated ORs were lower for this type of tumour, but far from statistical significance. It should be borne in mind that the number of TN tumours was too small (76 cases) to reach any conclusion. In fact, the distribution of cases by tumour subtype was significantly more homogeneous in MCC-Spain study (75% ER/PR+, 17% HER+ and 8% TN) than in EpiGEICAM [9] (67% of ER/PR+, 21% HER+, 12% TN), making it more difficult to find heterogeneity of effects.

The reproducibility of the three data-driven patterns found in the EpiGEICAM study [9] was verified using a sample of more than 3500 women who attended breast cancer screening [16]. Interestingly, the identified Western pattern [16] was virtually identical to the original reported [9], while the Mediterranean was not as highly reproducible as the Western pattern. This lower reproducibility of the Mediterranean pattern [16] may explain why its original protective effect is less accentuated in the present study. In fact, a study exploring the applicability of patterns associated with BC in the literature to our context, showed more consistent results for patterns labelled as “Western” than for the different versions of Mediterranean/Healthy patterns [17]. Interestingly, it is common to assume that Western/Unhealthy and Mediterranean/Prudent patterns are inversely correlated. However, the fact that both types of patterns are identified in numerous studies using statistical procedures that extract uncorrelated patterns over the same population [20, 25], demonstrates that this assumption is not always true. Taking this into account and given the significance and strength of the associations found with the Western pattern, we believe that it is important to focus, not only on the exploration of the potential protective effect of the Mediterranean dietary pattern (as most of the literature do), but also on the harmful effects of diets like the Western to determine which dietary habits should be recommended and which avoided in order to reduce BC risk.

In spite of the high consistency of the increased risk of BC associated with the Western pattern in our context, results provided by other authors are less consistent [28, 29] and some of the most recent reviews conclude that the existing evidence linking the Western diet with BC is still insufficient [20, 25, 30]. Regarding the Mediterranean pattern, results, as expected, are more heterogeneous: while some studies report a null [28, 31] others defend a protective effect [20, 21, 25]. These differences could be due to several reasons. As has been previously shown [17], disparities in the composition and labelling of the patterns explored might represent different dietary habits studied under a common label. Additionally, the fact that most studies on dietary patterns and BC risk are carried out in western countries with lower variability on their diet, may also explain some null results [5].

Our results should be interpreted in the context of the study´s limitations. Recall bias is always a concern in case-control studies, especially when evaluating the effect of self-reported dietary information. Anticipating the existence of this bias, some questions about general dietary habits were included in the questionnaire and used to adjust the responses to the FFQ following the methodology described in Calvert et al. [13]. In order to minimize even more the effect of this possible bias, only cases that responded to the questionnaire within the 6 months following the diagnosis were included. Additionally, the consistency and strength of the associations found deem it unlikely that our findings are a result of recall bias. On the other hand, statistical power was limited for the subgroups analyses, especially when evaluating the association with BC risk by tumour subtype.

One of the main strengths of the current research is the recruitment of histologically incident confirmed cases of BC and population controls. The great geographical variability of the recruited participants, coming from 10 provinces around the country, ensured the representation of the different diets coexisting within Spain. Furthermore, the actual sample size allowed the evaluation of potential interactions by menopausal status and explore possible differences by tumour subtypes.

Given the lack of agreement between studies regarding the association of the Western and Mediterranean dietary patterns with BC risk in the literature and the consistency of the results found in the current study of BC and the past studies on BC [9] and mammographic density [23] carried out in different samples of adult Spanish women, our study adds valuable evidence regarding the association between these two dietary patterns and BC risk. If a country like Spain, with a high compliance with the Mediterranean diet and a moderate adherence to the Western diet, can benefit from abandoning the latter in favour of the former, the benefit in non-Mediterranean countries with higher BC incidence might be even greater.

CONCLUSION

Breast cancer risk could be reduced in the general population by providing dietary recommendations based on decreasing the consumption of high-fat dairy products, red and processed meat, refined grains, sweets, caloric drinks, juices, convenience food and sauces –characteristic of the Western pattern- in favour of an increase in the intake of whole fruits, vegetables, legumes, vegetable oil, nuts and fish, the main components of the Mediterranean diet.

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Table 1: Composition of food groups based on the food frequency questionnaire of the MCC-Spain study and component loadings for each pattern identified in the previous study[9].

FOOD GROUP	FOOD[a]	L_W[b]	L_P[b]	L_M[b]
HIGH-FAT DAIRY	Whole-fat milk, condensed milk, whole-fat yogurt, semi-cured, cured, or creamy cheese, blue cheese, custard, milk shake, ice-cream, double cream.	0.60	-0.11	0.20
LOW-FAT DAIRY	Semi-skimmed and skimmed milk, soy milk, skimmed yogurt, curd, cottage or fresh white cheese.	-0.49	0.60	-0.01
EGGS	Eggs.	0.19	0.08	0.16
WHITE MEAT	Chicken, rabbit and duck.	0.08	0.17	0.18
RED MEAT	Pork, beef, lamb, liver (beef, pork or chicken), entrails, hamburgers (pork or beef) and meatballs (pork or beef).	0.27	0.09	0.22
PROCESSED MEAT	Sausages, serrano ham and other cold meat, bacon, pâté, foie-gras.	0.36	0.10	0.26
WHITE FISH	Fresh or frozen white fish (hake, sea bass, sea bream), ½·salted fish and ½·smoked fish.	0.01	0.24	0.34
OILY FISH	Fresh or frozen blue fish (tuna, swordfish, sardines, anchovies, salmon), canned fish, ½·salted fish and ½·smoked fish.	0.05	0.24	0.44
SEAFOOD/SHELLFISH	Clams, mussels, oysters, squid, cuttlefish, octopus, prawn, crab, shrimp and similar products.	0.17	0.27	0.35
LEAFY VEGETABLES	Spinach, chard, lettuce and other leafy vegetables.	-0.11	0.34	0.40
FRUITING VEGETABLES	Tomato, eggplant, zucchini, cucumber, pepper, artichoke and avocado.	0.00	0.36	0.45
ROOT VEGETABLES	Carrot, pumpkin and radish.	0.05	0.35	0.44
OTHER VEGETABLES	Cooked cabbage, cauliflower or broccoli, onion, green beans, asparagus, mushrooms, corn, garlic, gazpacho, vegetable soup and other vegetables.	-0.04	0.40	0.42
LEGUMES	Peas, lentils, chickpeas, beans and broad beans.	0.21	0.15	0.34
POTATOES	Roasted or boiled potatoes and sweet potatoes.	0.17	0.25	0.40
FRUITS	Orange, grapefruit, mandarin, banana, apple, pear, grapes, kiwi, strawberries, cherries, peach, figs, melon or watermelon, prunes, mango and papaya and other fresh or dried fruits.	-0.07	0.31	0.31
NUTS	Almonds, peanuts, pine nuts, hazelnut	0.18	0.22	0.29
REFINED GRAINS	White-flour bread, rice, pasta	0.37	0.15	0.23
WHOLE GRAINS	Whole-grain bread and breakfast cereals	-0.43	0.47	-0.06
OLIVES AND VEGETABLE OIL	Olives, added olive oil to salads, bread and dishes, other vegetable oils (sunflower, corn, and soybean).	0.12	0.19	0.34
OTHER EDIBLE FATS	Margarine, butter and lard.	0.22	0.02	0.11
SWEETS	Chocolate and other sweets, cocoa powder, plain cookies, chocolate cookies, pastries (croissant, donut, cake, pie or similar)	0.35	0.18	0.05
SUGARY	Jam, honey, sugar and fruit in sugar syrup.	0.24	0.05	0.00
JUICES	Tomato juice, freshly squeezed orange juice, juice (other than freshly squeezed)	0.25	0.67	-0.39
CALORIC DRINKS	Sugar-sweetened soft drinks and nut milk.	0.74	0.21	-0.25
CONVENIENCE FOOD AND SAUCES	Croquette, fish sticks, dumplings, kebab, fried potatoes, crisps, pizza, instant soup, mayonnaise, tomato sauce, hot sauce, ketchup and other sauces.	0.47	0.12	0.24

[a] Log-transformed centred intake in grams.

[b] Component loadings for the W: Western; P: Prudent; M: Mediterranean dietary patterns.

Table 2. Distribution of scores of adherence to the Western, Prudent and Mediterranean dietary

patterns and other baseline characteristics for breast cancer cases and controls.

	Co n=1589	Ca n=1124	p
Western mean±SD[a]	-0.83±3.29	-0.22±3.23	<0.001[a]
Prudent mean±SD[a]	0.39±2.91	0.47±2.92	0.440[a]
Mediterranean mean±SD[a]	-0.22±2.59	-0.25±2.48	0.783[a]
Energy (kcal/day) mean±SD[a]	1763.11±508.25	1815.47±526.31	0.009[a]
Alcohol (g/day) median(IQ)[b]	1.62 (0.00;7.62)	1.69 (0.00;7.92)	0.060[b]
BMI (kg/m2) mean±SD[a]	25.63±4.85	25.64±4.69	0.928[a]
Physical activity (METs) median(IQ)[b]	45.45 (0.00;189.00)	30.00 (0.00;189.00)	0.155[b]
Age (years) mean±SD[a]	58.82±13.00	56.19±12.35	<0.001[a]
Menopausal Status n(%[c])			<0.001[c]
Pre-menopausal	468 (29%)	419 (37%)	
Post-menopausal	1120 (70%)	704 (63%)	
Unknown	1 (0%)	1 (0%)	
Smoking n(%[c])			0.007[c]
Never Smoker	956 (60%)	616 (55%)	
Former Smoker	314 (20%)	225 (20%)	
Current Smoker	317 (20%)	279 (25%)	
Unknown	2 (0%)	4 (0%)	
Education n(%[c])			0.024[c]
No formal Education	265 (17%)	152 (14%)	
Primary School	472 (30%)	376 (33%)	
Secondary School	505 (32%)	376 (33%)	
University or more	347 (22%)	220 (20%)	
Family history of BC n(%[c])			<0.001[c]
No	1361 (86%)	841 (75%)	
2nd Degree	88 (6%)	119 (11%)	
One of 1st degrees	131 (8%)	143 (13%)	
More than one of 1st degree	9 (1%)	21 (2%)	
Age at first delivery n(%[c])			0.296[c]
25-29 years old	513 (32%)	342 (30%)	
<20	56 (4%)	45 (4%)	
20-24	392 (25%)	260 (23%)	
>29	324 (20%)	228 (20%)	
Nulliparous	297 (19%)	239 (21%)	
Unknown	7 (0%)	10 (1%)	

[a] Mean and standard deviation (mean±sd) were used to describe normally distributed continuous variables and differences between cases and controls were tested two sided Student T-tests for independent samples.

[b] Median and interquartile interval (median(IQ)) were used to describe non-normally distributed continuous variables and differences between cases and controls were tested with non-parametric rank-sum tests.

[c] Categorical variables were described using the number of cases and corresponding percentages (n(%); percentages might not add up 100 because of rounding), and differences between cases and controls were tested with chi-square tests.

Table 3. Adjusted odds ratios for the association between breast cancer incidence and scores of adherence to Western, Prudent and Mediterranean diet patterns both, overall and by menopausal status.

		All women				Premenopausal[a]		Postmenopausal[a]		
		n=2713		n=2532		n=857		n=1675		
		Co/Ca	OR[b](95%CI)	Co/Ca	aOR[c](95%CI)	Co/Ca	aOR[c](95%CI)	Co/Ca	aOR[c](95%CI)	p-int
WESTERN										
Quartiles	Q1	397/205	1	356/186	1	58/33	1	298/153	1	
	Q2	398/258	1.28 (1.02;1.62)	363/247	1.25 (0.97;1.61)	95/79	1.38 (0.81;2.35)	268/168	1.22 (0.92;1.62)	
	Q3	396/312	1.59 (1.27;2.00)	378/299	1.40 (1.09;1.81)	127/119	1.53 (0.92;2.55)	251/180	1.37 (1.02;1.84)	
	Q4	398/349	1.80 (1.44;2.26)	372/331	1.53 (1.15;2.02)	171/175	1.68 (1.02;2.79)	201/156	1.48 (1.07;2.05)	
p-trend			<0.001		0.003		0.048		0.012	
1SD-increase			1.24 (1.14;1.34)		1.16 (1.05;1.28)		1.19 (1.02;1.40)		1.14 (1.01;1.29)	0.65
PAF%[d]					24%(8%;40%)		34%(-1%;68%)		20%(4%;37%)	
PRUDENT										
Quartiles	Q1	398/281	1	354/257	1	102/87	1	252/170	1	
	Q2	397/253	0.90 (0.72;1.13)	366/236	0.87 (0.69;1.11)	117/90	0.95 (0.63;1.43)	249/146	0.84 (0.62;1.12)	
	Q3	397/315	1.13 (0.91;1.40)	370/302	1.09 (0.86;1.38)	122/130	1.21 (0.82;1.79)	248/172	1.02 (0.77;1.37)	
	Q4	397/275	1.02 (0.81;1.27)	379/268	0.92 (0.70;1.20)	110/99	1.00 (0.65;1.53)	269/169	0.89 (0.65;1.21)	
p-trend			0.441		0.952		0.633		0.806	
1SD-increase			1.04 (0.97;1.13)		1.02 (0.93;1.12)		1.07 (0.92;1.25)		1.00 (0.89;1.12)	0.45
PAF%[d]					5%(-10%;20%)		5%(-19%;29%)		6%(-13%;24%)	
MEDITERRANEAN										
Quartiles	Q1	397/280	1	368/260	1	125/90	1	243/170	1	
	Q2	398/300	1.06 (0.86;1.32)	364/283	1.05 (0.83;1.32)	116/115	1.36 (0.93;2.00)	248/168	0.91 (0.68;1.21)	
	Q3	396/275	0.98 (0.79;1.22)	367/262	0.97 (0.76;1.23)	110/94	1.12 (0.75;1.67)	257/168	0.89 (0.67;1.20)	
	Q4	398/269	0.95 (0.76;1.19)	370/258	0.90 (0.69;1.17)	100/107	1.39 (0.92;2.11)	270/151	0.72 (0.53;0.98)	
p-trend			0.527		0.347		0.242		0.044	
1SD-increase			0.98 (0.91;1.07)		0.97 (0.88;1.07)		1.08 (0.93;1.26)		0.92 (0.83;1.03)	0.075
PAF%[d]					8%(-7%;23%)		-14%(-42%;14%)		18%(2%;35%)	

[a] OR for pre and postmenopausal women calculated including in the models (6 models in total) an interaction term between menopausal status and the level of adherence to each of the 3 dietary patterns measured as a categorical (quartiles of adherence) and as a continuous (1-SD increase) variable.

[b] Unadjusted odds ratio of breast cancer associated to the adherence to the Western, Prudent and Mediterranean diet patterns including province of residence as a random effect term.

[c] Odds ratio of breast cancer associated to the adherence to the Western, Prudent and Mediterranean diet patterns adjusted by menopausal status, age, education, BMI, age at first delivery, family history of breast cancer, physical activity, smoking status, caloric intake and alcohol intake as fixed effects and province of residence as a random effect term.

$$PAF = \frac{PF_{Q1}\cdot(OR_{Q1}-1)+PF_{Q2}\cdot(OR_{Q2}-1)+PF_{Q3}\cdot(OR_{Q3}-1)+F_{Q4}\cdot(OR_{Q4}-1)}{1+[PF_{Q1}\cdot(OR_{Q1}-1)+PF_{Q2}\cdot(OR_{Q2}-1)+PF_{Q3}\cdot(OR_{Q3}-1)+F_{Q4}\cdot(OR_{Q4}-1)]}\bullet 100$$

[d] PAF= Population Atributable Fraction

PF=Proportion of population in the specific exposure category

OR= Odds ratio for the especific exposure category

Table 4. Adjusted odds ratios for the association between breast cancer incidence and scores of adherence to Western, Prudent and Mediterranean diet patterns by tumour subtype.

			ER/PR+ n=721		HER2+ n=171		TN n=76		
		Co	**Ca**	**aOR[a](95%CI)**	**Ca**	**aOR[a](95%CI)**	**Ca**	**aOR[a](95%CI)**	**p-het**
WESTERN									
Quartiles	Q1	356	133	1.00	27	1.00	13	1.00	
	Q2	363	162	1.16 (0.87;1.54)	47	1.78 (1.07;2.97)	18	1.26 (0.59;2.67)	
	Q3	378	199	1.29 (0.97;1.72)	45	1.63 (0.95;2.77)	25	1.67 (0.80;3.50)	
	Q4	372	227	1.45 (1.06;1.99)	52	1.94 (1.09;3.45)	20	1.23 (0.53;2.86)	
p-trend				0.016		0.057		0.519	
1SD-increase				1.17 (1.04;1.31)		1.16 (0.95;1.42)		1.15 (0.85;1.54)	0.993
PAF%[b]				20%(2%;39%)		40%(13%;67%)		25%(-23%;74%)	
PRUDENT									
Quartiles	Q1	354	177	1.00	37	1.00	19	1.00	
	Q2	366	155	0.82 (0.62;1.07)	47	1.30 (0.81;2.09)	18	0.83 (0.42;1.65)	
	Q3	370	200	1.04 (0.79;1.36)	47	1.31 (0.81;2.11)	20	0.85 (0.43;1.69)	
	Q4	379	189	0.95 (0.70;1.29)	40	1.12 (0.65;1.93)	19	0.85 (0.39;1.84)	
p-trend				0.785		0.664		0.709	
1SD-increase				1.02 (0.91;1.14)		1.09 (0.90;1.33)		0.99 (0.75;1.32)	0.771
PAF%[b]				1%(-16%;17%)		6%(-26%;39%)		4%(-42%;49%)	
MEDITERRANEAN									
Quartiles	Q1	368	174	1.00	42	1.00	19	1.00	
	Q2	364	186	1.00 (0.76;1.30)	50	1.18 (0.75;1.85)	21	0.94 (0.48;1.81)	
	Q3	367	182	0.98 (0.74;1.29)	42	0.98 (0.60;1.58)	18	0.73 (0.36;1.48)	
	Q4	370	179	0.91 (0.67;1.23)	37	0.86 (0.51;1.47)	18	0.73 (0.34;1.55)	
p-trend				0.536		0.453		0.322	
1SD-increase				0.96 (0.86;1.07)		0.97 (0.80;1.16)		0.91 (0.69;1.19)	0.917
PAF%[b]				6%(-10%;23%)		15%(-16%;47%)		15%(-25%;55%)	

[a] Odds ratio of breast cancer associated to the adherence to the Western, Prudent and Mediterranean diet patterns adjusted by menopausal status, age, education, BMI, age at first delivery, family history of breast cancer, physical activity, smoking status, caloric intake, alcohol intake and province of residence as fixed effects terms.

$$PAF = \frac{PF_{Q1}\cdot\left(OR_{Q1}-1\right)+PF_{Q2}\cdot\left(OR_{Q2}-1\right)+PF_{Q3}\cdot\left(OR_{Q3}-1\right)+F_{Q4}\cdot\left(OR_{Q4}-1\right)}{1+[PF_{Q1}\cdot\left(OR_{Q1}-1\right)+PF_{Q2}\cdot\left(OR_{Q2}-1\right)+PF_{Q3}\cdot\left(OR_{Q3}-1\right)+F_{Q4}\cdot\left(OR_{Q4}-1\right)]}\bullet 100$$

[b] PAF= Population Atributable Fraction

PF=Proportion of population in the specific exposure category

OR= Odds ratio for the especific exposure category