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High adherence to Western dietary pattern increases breast cancer risk (an EPIC-Spain study)

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Abbreviations:

95%CI: 95% confidence interval.

BC: Breast Cancer.

BMI: Body Mass Index.

EPIC: European Prospective Investigation into Cancer and Nutrition.

ER: Estrogen receptor.

GEICAM: Spanish Group of Breast Cancer Research (Grupo Español de Investigación en Cáncer de Mama).

HCAs: Heterocyclic amines.

HER2: Human Epidermal Growth Factor Receptor 2.

HR: Hazard Ratio.

HRT: Hormonal Replacement Therapy.

IARC: International Agency for Research on Cancer.

ICD: International Classification of Diseases.

IQR: Interquartile Range.

MAPA: Ministry of Agriculture, Fisheries and Food (Ministerio de Agricultura, Pesca y Alimentación).

MCC-Spain: Multicase control study Spain.

NOCs: N-nitroso compounds.

PAHs: Polycyclic Aromatic Hydrocarbons.

PCA: Principal Component Analysis.

PR: Progesterone Receptor.

Q1: First quartile.

Q2: Second quartile.

Q3: Third quartile.

Q4: Fourth quartile.

TN: Triple Negative.

WCRF/AICR: World Cancer Research Fund/American Institute for Cancer Research.

Keywords: Dietary patterns; Diet, Western; Diet, Mediterranean; Breast Neoplasms.

ABSTRACT

Objective: To explore the association between three previously identified and validated dietary patterns (Western, Prudent and Mediterranean) and breast cancer risk by tumour subtype and menopausal status.

Methods: Data from the Spanish cohort of the European Prospective Investigation into Cancer and Nutrition study provided epidemiological information (including diet and cancer incidence) from 24892 women (639 breast cancer cases) recruited between 1992 and 1996. The associations between the adherence to the three dietary patterns and breast cancer risk (overall and by tumour subtype) was explored by fitting multivariate Cox proportional hazards regression models stratified by region among other variables. A possible interaction with menopausal status changing in time was explored.

Results: No clear association of the Prudent and Mediterranean dietary patterns with breast cancer risk was found. When compared to adherences in the first quartile, women with adherences in the third (Hazard Ratio (95% Confidence Interval) (HR(95%CI)):1.37 (1.07;1.77)) and fourth quartiles (1.37 (1.03;1.83)); p for curvature of splines=0.016) of the Western diet showed a non-linear increased risk, especially for postmenopausal (HR (95% CI) 1.30 (0.98;1.72) in the third and 1.42 (1.04;1.94) in the fourth quartiles; p for curvature of splines=0.081) and for estrogen or progesterone receptor positive with human epidermal growth factor receptor 2 negative tumours (HR (95% CI) 1.62 (1.10;2.38) and 1.71 (1.11;2.63) for the third and fourth quartiles respectively; p for curvature of splines=0.013).

Conclusions: Intake of foods such as high fat dairy products, red and processed meats, refined grains, sweets, caloric drinks, convenience food and sauces might be associated with higher breast cancer risk.

Introduction

According to the last global cancer statistics estimates, in 2020 breast cancer (BC) was the most commonly diagnosed and the fifth leading cause of cancer mortality globally (1). It's development has been associated to family history in first-degree relatives, height, benign breast disease, high mammographic breast density, early menarche (<12 years) or late menopause (>54 years), age at first birth over 30 years, high endogenous estrogen levels, oral contraceptive or postmenopausal hormone use, ionizing radiation exposure, high body mass index (BMI), alcohol intake, low physical activity level and not breastfeeding among other less relevant factors (2).

The most recent Word Cancer Research Fund and American Institute for Cancer Research (WCRF/AICR) report on diet, nutrition, physical activity and BC of 2018 (3), indicates that evidence is strong for a protective effect of physical activity, body fatness in young adulthood and lactation as well as for the detrimental effect of high adult attained height and adult weight gain (postmenopausal), greater birth weight (premenopausal), body fatness (postmenopausal) and alcohol intake. The evidence about the relationship between other dietary factors (including eating patterns) and BC risk is still considered insufficient to draw firm conclusions.

Some authors (4) suggest that this lack of conclusive evidence might be partly explained by the fact that the majority of the studies explore the association of individual foods and nutrients with BC risk, even though foods and nutrients are not consumed individually. Therefore, the use of dietary patterns might be a better strategy to explore the relationship between diet and disease, since they take into account the interactions between individual dietary factors (5). *A priori* and *a posteriori* dietary patterns are commonly used to explore the association between dietary patterns and risk of disease. The latter have the advantage of being extracted with statistical methods using the dietary information, which ensures their representativeness of the diet present in a particular population and their independence from disease.

Some research has explored the association between *a posteriori* dietary patterns and BC risk (6–31), but the WCRF/AICR considers that the existing evidence is not yet conclusive to draw firm conclusions (3). All these studies coincide in the identification of a healthy-type dietary pattern, usually labelled as Mediterranean/Healthy/Prudent, being in most cases protective against total BC risk (7,8,10–14,16,18,20–25,28,31). They also identify a Western type dietary pattern, frequently associated with an increased total BC risk (7–11,13,16,17,21,22,27,30,31). Despite the differences in risk-factor associations by hormone-receptor status highlighted in diverse studies (32), just a few of the previous references (6–31) explored differences by tumour subtype including human epidermal growth factor receptor 2 (HER2) status (33,34). In addition, during and after menopause, women experience diverse body, hormonal and psychological changes (35,36) that might modify their lifestyle habits and how they relate to their risk of BC. Many of the cited studies explore the effect of dietary patterns by menopausal status (8,9,11,12,14,21,23,25,26,28,29,31,37), but show mixed results.

Previous research also identified, in a group of healthy Spanish women, three dietary patterns (Western, Prudent and Mediterranean) differently associated to BC (33). After checking the reproducibility (38) and applicability (39) of these patterns, they were applied in the Spanish Multicase-Control Study on cancer (MCC-Spain) and the European Prospective Investigation into Cancer and Nutrition Spanish cohort (EPIC-Spain), showing similar associations for breast cancer (34) and other tumours (40–45).

The objective of this study is to apply these three dietary patterns over the EPIC-Spain data to explore their association with BC risk by menopausal status changing in time and tumour subtype in order to validate the previous results.

Materials and methods

Study population

The information used in the present work was obtained from the Spanish cohort of the EPIC study, that is a multicentric cohort designed to investigate the relationship between lifestyle, diet, environmental factors and cancer (46). EPIC-Spain recruited, between 1992 and 1996, 41437 healthy adults (25808 women) aged 29–69 in five Spanish regions from the north (Asturias, Gipuzkoa and Navarra) and south of Spain, including the Mediterranean shore (Murcia and Granada).

Epidemiological information, including sociodemographic characteristics, physical activity, reproductive and gynaecological data, alcohol consumption and smoking habit, educational level and medical history of previous illnesses was collected in a personal interview. Usual diet throughout the year prior to enrolment, accounting for seasonal variation, was collected using a computerized dietary history questionnaire, previously validated in Spain and administered in a personal interview by trained recruiters. In the same interview, anthropometric measurements (height, weight, and waist circumference) were measured using standardized procedures (46).

Women with implausible energy intakes under 750 or above 4500 kcal per day, with a BMI over 60 kg/m^2, and cases diagnosed during the first year of follow up were excluded from the analyses. Since the proportion of women with missing values in any of the variables included in the analyses was around 2.5%, a complete case analysis was carried out ignoring them as recommended in the bibliography for sets of data with less than 5% of missing values (47).

The ethical review boards from the International Agency for Research on Cancer (IARC) approved the study, and all the eligible participants gave their informed consent.

Cases ascertainment and follow-up period

Cases were defined as first occurrence of a primary malignant tumour of the breast (C50 of the ICD-10) and they were identified by linking the EPIC-Spain database with the population-based cancer registries of the five mentioned regions. Cases were sub-classified in the following intrinsic subtypes based on local pathology reports (48): (1) Estrogen receptor (ER) or progesterone receptor (PR) positive (+) tumours with HER2 negative (-), (2) HER2+ tumours irrespective of ER or PR status; and (3) triple-negative tumours (TN: ER-, PR- and HER2-). The ER, PR and HER2 positivity was defined according to ASCO/CAP guidelines (49,50).

Dates and causes of death were obtained by merging the cohort data with the population-based mortality registries of the National Institute of Statistics.

The first year of follow-up was excluded from the analyses to minimize the risk of reverse causation due to silent tumours not diagnosed at the time of recruitment that might have affected the diet of participants during the months prior to the interview. Follow-up period was defined from the age one year after recruitment to the age at diagnosis of any type of malignant tumour, death or last completed follow-up date, depending on which occurred first. Censoring dates for the last complete follow-up were 31st of December 2010 for Asturias, 30th of December 2013 for Gipuzkoa, 31st of December 2012 for Granada, 31st of December 2013 for Murcia and 31st of December 2011 for Navarra.

Food groups and component loadings

The scores of adherence of EPIC-Spain participants to three previously identified dietary patterns (33) were calculated: a) Western dietary pattern, 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) Prudent dietary pattern, represented by high intakes of low-fat dairy products, vegetables, fruits, whole grains and juices; and c) Mediterranean dietary pattern, consisting of high intakes of fish, vegetables, legumes, boiled potatoes, fruits, olives and vegetable oil, and a low intake of juices.

These patterns were extracted from the control sample of the case-control EpiGEICAM study (33), and have subsequently been associated with different types of tumours (34,40–45). The dietary patterns were identified by applying principal components analysis (PCA) without rotation of the variance-covariance matrix over 26 inter-correlated food groups, obtaining a set of weights (pattern loadings) that represents the correlation between food consumption and the pattern scores for each dietary pattern. Pattern loadings can be used to apply such patterns in other samples, as explained in detail elsewhere (39). Briefly, adherence of the EPIC-Spain participants to these dietary patterns was calculated by grouping the food items derived from the dietary history questionnaire (excluding non-caloric and alcoholic beverages) into the same 26 food groups defined in the EpiGEICAM study. For items for which classification was not clear (i.e. sorting some dairy products into low and high-fat or separating the different types of fish), a weighted distribution among the corresponding groups was done based on the 1998 food consumption panel data elaborated for the Spanish Ministry of Agriculture, Fisheries and Food (MAPA)(51). In order to account for the distribution of these foods among cancer and non-cancer cases, we also used the information from the MCC-Spain study (52), to adjust the weights calculated with the MAPA information (**Table 1**).

The scores of adherence to the Western, Prudent and Mediterranean dietary patterns were then calculated as a linear combination of the weights for each food group and pattern published in the EpiGEICAM study (33) and the food group consumption reported by the participants of the EPIC-Spain study. The adherence to these three dietary patterns was modelled as a categorical variable (quartiles of the distribution among the whole EPIC-Spain sample) and as a continuous variable (one standard deviation (SD) increment in the score). We used the quartiles of the distribution for the whole EPIC sample (males and females) to ensure comparability of our results with the MCC-Spain study (34)(that also used non-sex specific cut points) and among different tumours within the EPIC study (44,45).

Statistical analyses

The distribution of the covariables among quartiles of adherence to the Western, Prudent and Mediterranean dietary patterns was described with median and interquartile range (IQR) for quantitative variables and number of participants and percentages for qualitative variables. P-values were calculated with Kruskal-Wallis tests for quantitative variables and chi-squared tests for qualitative variables, excluding missing values.

Multivariable Cox proportional hazards regression models were fitted to explore crude and adjusted associations between the adherence to the Western, Prudent and Mediterranean dietary patterns and BC risk (overall and by tumour subtype), using age as the time variable. The analyses by tumour subtype were restricted to each specific tumour category (no cases vs ER+/PR+ and HER2+; no cases vs HER2+; No cases vs TN). All models were stratified by region and included as potential confounders lifetime alcohol intake (grams per day), smoking habit (never, ex and current smoker), total energy intake (kcal per day), BMI in five categories (<18; 18-24.99; 25-29.99; 30-34.99; ≥35 kg/m^2), self-reported occupational and recreational physical activity (inactive; moderately inactive; moderately active; active), education (no formal education; primary school; secondary/technical school; university or more), menopausal status (pre and post menopausal), age at first delivery, family history of female BC (no mother or sister; mother; sister) and use of hormonal replacement therapy (HRT, yes or no). For the Western dietary pattern, models were also adjusted by the adherence to the Prudent and Mediterranean dietary patterns, and for the Prudent and Mediterranean dietary patterns models were also adjusted by the adherence to the Western dietary pattern. Since menopausal status was collected at recruitment, and taking into account that median age at menopause in Spain is 51.7 years old (53), we allowed this variable to change over time by splitting data of women that were premenopausal at recruitment to make them contribute both as pre and postmenopausal as follows: Premenopausal women 50 years old or younger at recruitment were considered premenopausal up to 52 years old and postmenopausal afterwards. Those premenopausal older than 50 at recruitment were assumed to be postmenopausal 2 years later. Afterwards an interaction term between menopausal status changing over time and the adherence to the three dietary patterns was included in the models.

The fulfilment of the proportional hazards assumption was checked visually with standardized survival curves by quartiles of adherence to the each pattern (**Figure 2**) and numerically by testing the nonzero slope in a generalized linear regression of the time-scaled Schoenfeld residuals on time. Smooth estimates of the standardized survival curves for breast cancer by quartile of each dietary pattern were obtained using spline-based survival models (54). These models parameterized the baseline log cumulative hazard as a natural cubic spline of log time with three internal knots at the 25th, 50th, and 75th percentiles of the uncensored log time distribution and assumed proportional hazards over time across dietary quartiles. The resulting survival curves for each quartile of dietary pattern were standardized to the distribution of baseline confounders in the overall study population. Analyses were performed using the stpm2 and standsurv commands in Stata. Violation of proportional hazards assumption was fixed stratifying by those variables that did not meet the assumption (see footnotes on **Tables 3-5**).

Nonlinear associations between BC incidence and scores of adherence to the three dietary patterns, overall, by menopausal status changing in time and by tumour subtype were modelled with restricted cubic splines with knots at the 5th, 35th, 65th and 95th percentiles as recommended by Harrell (55).

Finally, a sensitivity analysis was carried out considering death as a competing risk to evaluate its effect in the results.

All analyses were performed using Stata/MP version 17 (Statacorp, College Station, TX).

Results

After excluding 170 women (of which 5 BC cases) for implausible energy intakes under 750 or above 4500 kcal per day, 3 (all non-BC cases) with a BMI over 60 kg/m^2, and 105 cases diagnosed during the first year of follow up, the final sample size was of 25,530 women. Among them, 659 BC cases were identified during a median follow-up of 17.02 years (**Figure 1**). The sample size was reduced to 24,892 women and 639 BC cases due to missing values in some covariates: alcohol intake (n=134), smoking (n=14), education (n=197), family history of BC (n=98), age at first delivery (n=43) and use of hormonal replacement therapy (n=164). ER, PR or HER2 status was missing for 222 (34%) BC cases.

Women in the upper quartiles of adherence to the Western dietary pattern showed a higher alcohol and energy intake and lower age and BMI. They were also more likely to be current smokers, and less likely to have no formal education and to be premenopausal, physically active, nulliparous and users of HRT. Women in the highest quartile of adherence to the Prudent dietary pattern also showed higher alcohol and energy intake, slightly lower BMI, and were less likely to smoke and more likely to be highly educated, nulliparous and HRT users. No noticeable differences were observed for physical activity and age at recruitment among quartiles of adherence to this pattern. Finally, participants with higher adherence to the Mediterranean dietary pattern also showed higher alcohol and energy intake and lower BMI, were younger and more likely to be pre-menopausal, highly educated, slightly more active and to have children at slightly younger age. No meaningful differences across quartiles of adherence to this pattern were found for smoking habit or use of HRT. Additionally, no important differences were found for the distribution of family history of BC among quartiles of adherence to any of the three patterns explored (**Table 2**).

While no association of overall BC risk was found for high adherences to the Prudent and the Mediterranean dietary patterns, data showed an increased risk among women in the third (HR (95% CI):1.37 (1.07;1.77)) and fourth (HR (95% CI):1.37 (1.03;1.83)) quartiles of adherence to the Western dietary pattern (**Table 3**) when compared to women in the first quartile. Such increase in BC risk was not observed for adherences to the Western dietary pattern in the second quartile which is in agreement with the lack of linearity observed for this association (p for curvature of splines=0.016, **Figure 3**).

When exploring the association of dietary patterns with BC risk by menopausal status (**Table 4**), the increased risk found for medium to high adherences to the Western diet was only observed among postmenopausal also for adherences in the third (HR (95% CI):1.30 (0.98;1.72)) and fourth quartiles (HR (95% CI):1.42 (1.04;1.94)). This association showed again some degree of departure from linearity (p for curvature of splines=0.081) (**Figure 4**).

Similarly, the exploration of the association of the three dietary patterns with BC incidence by tumour subtype revealed an elevated risk of ER+ or PR+ with HER2- tumours non-linearly associated (p for curvature of splines=0.013, **Figure 5**) with adherences to the Western dietary pattern in the third (HR (95% CI):1.62 (1.10;2.38)) and fourth (HR (95% CI):1.71 (1.11;2.63)) quartiles (**Table 5**).

Finally, since sensitivity analyses revealed that considering death as a competing risk changes the estimation of the main effects in less than 2% (**Supplementary material, Table S1**) and do not modify the conclusions, results from non-competing risk analyses were presented for the sake of simplicity.

Discussion

Our results indicate a possible increased BC risk among women that present a medium to high adherence to the Western dietary pattern that is more noticeable during postmenopause and for ER+ or PR+ with HER2- tumours.

Both the EpiGEICAM (33) and MCC-Spain (34) studies also found an increased risk of BC for women with a high adherence to the Western pattern. However, in both cases this effect seemed to be stronger among premenopausal women, while in the present work, postmenopausal women showed higher risk. A possible explanation for this discrepancy might be the differences in data collection. For both, EpiGEICAM and MCC-Spain, age was collected at recruitment together with dietary data and case and non-case status. However, in the EPIC study, the event might occur years after the dietary data were collected. As for the association by tumour subtype, the three studies find a stronger or more significant effect for ER+ or PR+ with HER2- than for triple negative tumours. However, MCC-Spain showed the strongest effect for HER2+ tumours, while EpiGEICAM did not find a substantial effect for this subtype. The different distribution of tumour subtypes among studies might be behind these differences (ER+ or PR+ with HER2-: 67% EpiGEICAM, 74% MCC-Spain and 63% EPIC; HER2+: 21% EpiGEICAM, 18% MCC-Spain and 31% EPIC; Triple Negative: 12% EpiGEICAM, 8% MCC-Spain and 6% EPIC) and suggests that in EPIC-Spain and, to some extent, also in MCC-Spain there may be an underrepresentation of TN tumours which proportion is around 10% of BC cases in Caucasian women (56). Also, the large amount of missing values in the information about tumour subtype might influence these results. However, we have analysed the unknown as a separate category and no associations were found for any of the patterns explored (data not shown), suggesting that this category might contain representation from all tumour subtypes.

On the other hand, while a high adherence to the Prudent dietary pattern was not consistently associated with BC in any of the three studies, a suggestive protective influence of the Mediterranean pattern was observed in EpiGEICAM, among all, pre and postmenopausal women and against ER+ or PR+ with HER2- and TN tumours and in MCC-Spain among postmenopausal. The lack of association with the Mediterranean dietary pattern found in our work might be explained by the fact that EPIC-Spain dietary data was collected between 1992-1996 and the adherence to this pattern has decreased over time (57). Therefore, many women included here as highly adherent to the Mediterranean pattern might have changed to a less healthy diet over the years diluting its protective potential.

As for the comparison of the EPIC results with other non-Spanish studies that extracted their own a posteriori dietary patterns (6–31), similar associations were found. From those identifying a Western type pattern (6–17,21–28,30,31), most of them report an increased risk of BC (7–11,13,16,17,21,22,27,30,31) for women presenting this type of diet. There is less agreement among the findings for the Prudent-type pattern (11,20,23,24,28–30), with some reporting an increased risk of BC (11), others claiming no association (29,30) and others finding potential benefit (20,23,24,28) of adhering to this diet. Finally, those identifying a Mediterranean-type diet (6–18,21,22,24–28,31) frequently report a decreased BC risk for compliers with this pattern (7,8,10–14,16,18,21,22,24,25,28). Again, the absence of an association with the Mediterranean dietary pattern found in EPIC might be explained by westernization of diet over the years diluting the beneficial influence of the Mediterranean diet sustained over time.

Among those studies showing an increased BC risk for women adherent to the Western dietary pattern, some explored a possible heterogeneity of the effects by menopausal status (8,9,11,16,21,31) with a few observing a stronger association among premenopausal (11,16) and the majority finding a stronger effect in postmenopausal women (8,9,21,31) in concordance with our results.

To our knowledge, only EpiGEICAM (33) and MCC-Spain (34) studies explored the association of a posteriori dietary patterns with BC by tumour subtype considering HER2 status. The rest of the studies that explore associations by tumour subtype, classify them on the basis of ER and PR status (7,9,13–16,20,28,31). Most of the studies finding a positive association between high adherence to the Western dietary pattern and BC risk by tumour subtype (9,13,16,20,31) report it to be stronger among ER+ tumours, with (13,31) or without (9,13) PR+, except for the case of Zhang et al. (16), that observed similar associations for ER+ or PR+; ER&PR+ and ER&PR- tumours, and Buck et al.(15) that found a protective effect of a mild Westernized diet (processed and red meat, garlic/onion and deep frying fat) against ER&PR- tumours.

Some biological mechanisms may underlie the observed associations. Our Western dietary pattern includes many foods that have been previously related to cancer risk. On one hand, cooking and processing meat (especially red meat) generates carcinogenic compounds such as heterocyclic amines (HCAs), polycyclic aromatic hydrocarbons (PAHs) and N-nitroso compounds (NOCs) which promote inflammation and oxidative stress (58). Furthermore, a high adherence to hyper caloric diets such as the Western increase BMI, one of the most important risk factors for postmenopausal BC (3). Our models are adjusted by BMI at baseline, but women with high adherence to this pattern might have experienced a bigger increase in their weight over the years, with the consequent increase in BC risk. A high consumption of sugary and fatty foods also leads to higher blood glucose, insulin and IGF1 levels, increasing cellular proliferation and promoting tumour growth (37). Also, several studies have shown that high consumption of n–6 polyunsaturated fatty acids (present mainly in refined vegetable oils used in cookies, crackers, sweets and fast food) is associated with a higher BC risk (59). Additionally, refined grains have high glycaemic index which increases the demand of insulin-IGF, directly related to cancer promotion (60).

The greater association detected among postmenopausal women could be explained by the diet-estrogen pathway. During menopause, ovarian estrogen production ceases and adipose tissue becomes the main source of these hormones, due to the aromatization of androstenedione to estrone, that is subsequently reduced to estradiol (61). Therefore, postmenopausal women presenting obesity have higher serum concentrations of estradiol and an increased BC risk (62). The Western dietary pattern could therefore increase the postmenopausal BC risk through increased BMI and increased estrogen levels. The increase in BMI associated with high adherence to the Western dietary pattern may also be responsible for the greater effect detected in ER/PR+ tumours, as reported in the meta-analysis by Suzuki et al (63).

Our study has some limitations, the most important being the impossibility to control for changes in diet over time. This may create a non-differential classification bias, since the diet registered may not adequately represent the whole story of exposure during the follow-up. In addition, the applied dietary patterns were obtained in a different sample. However, a previous study showed that the application of a posteriori dietary patterns to different populations might result in different adherence scores but this does not affect their validity (39). Furthermore, analysis by tumour subtype should be interpreted with caution given the substantial amount of missing data for this variable and the small sample size, which might result in a lack of power to find associations. Furthermore, grouping foods in exactly the same way as the original study (33) was not possible due to some differences in the nutritional information collected, but arbitrary decisions were avoided using the MAPA data on food consumption in Spain (51) and the nutritional information collected in MCC-Spain study (43) to distribute foods with ambiguous composition.

The longitudinal design of the present work is one of its main strengths, as it limits reverse causation and recall bias. Additionally, the sample size allowed the identification of a sufficient number of BC cases to detect heterogeneous effects by menopausal status and explore effect by tumour subtype. Furthermore, the use of dietary patterns allows considering interactions between foods and nutrients, and facilitates the translation of our results to the general population. Diet-quality indices (*a priori* dietary patterns) are widely used to study the association of diet as a whole with disease, but they present some limitations. On the one hand, their score system is mostly based on the existing evidence about the association between diet and cardiovascular disease (64), making them not fully applicable to other settings. Moreover, because they are predefined, they may not represent the diet of the population studied, which may prevent finding important associations. Also, these indices assign a positive score to healthy eating habits; thus, low scores reflect poor consumption of healthy foods, which is not always related to a high intake of unhealthy foods, leaving one part of the relationship between diet and disease unexplored. *A posteriori* dietary patterns (as the ones used here) overcome most of these limitations, since they are extracted with statistical methods from the dietary data of the sample under study, which guarantees their independence of the disease and their representativeness of the individuals' diet.

In conclusion, Intake of foods such as high fat dairy products, red and processed meats, refined grains, sweets, caloric drinks, convenience food and sauces might be associated with higher breast cancer risk.

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Author Contributions

The corresponding authors attest that all listed authors meet authorship criteria and that no others meeting the criteria were omitted. Conception and design of the study: MP, MJS, AC; data curation and formal analysis: AC, MRB; funding acquisition: PA, MG, JRQ, AD, MJS; writing original draft: AC; methodology; AC, VL, MRB. All authors contributed to the interpretation of the results and the critical revisions of the manuscript for important intellectual content and approved the final version for submission.

Conflict of interest statement

The authors declare that they have no competing interests.

Data Availability Statement

The data of this study is preserved by the EPIC-Spain research group. Data are subject to data sharing agreements and are not publicly available.

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FIGURE CAPTIONS

Figure 1: Sample selection.

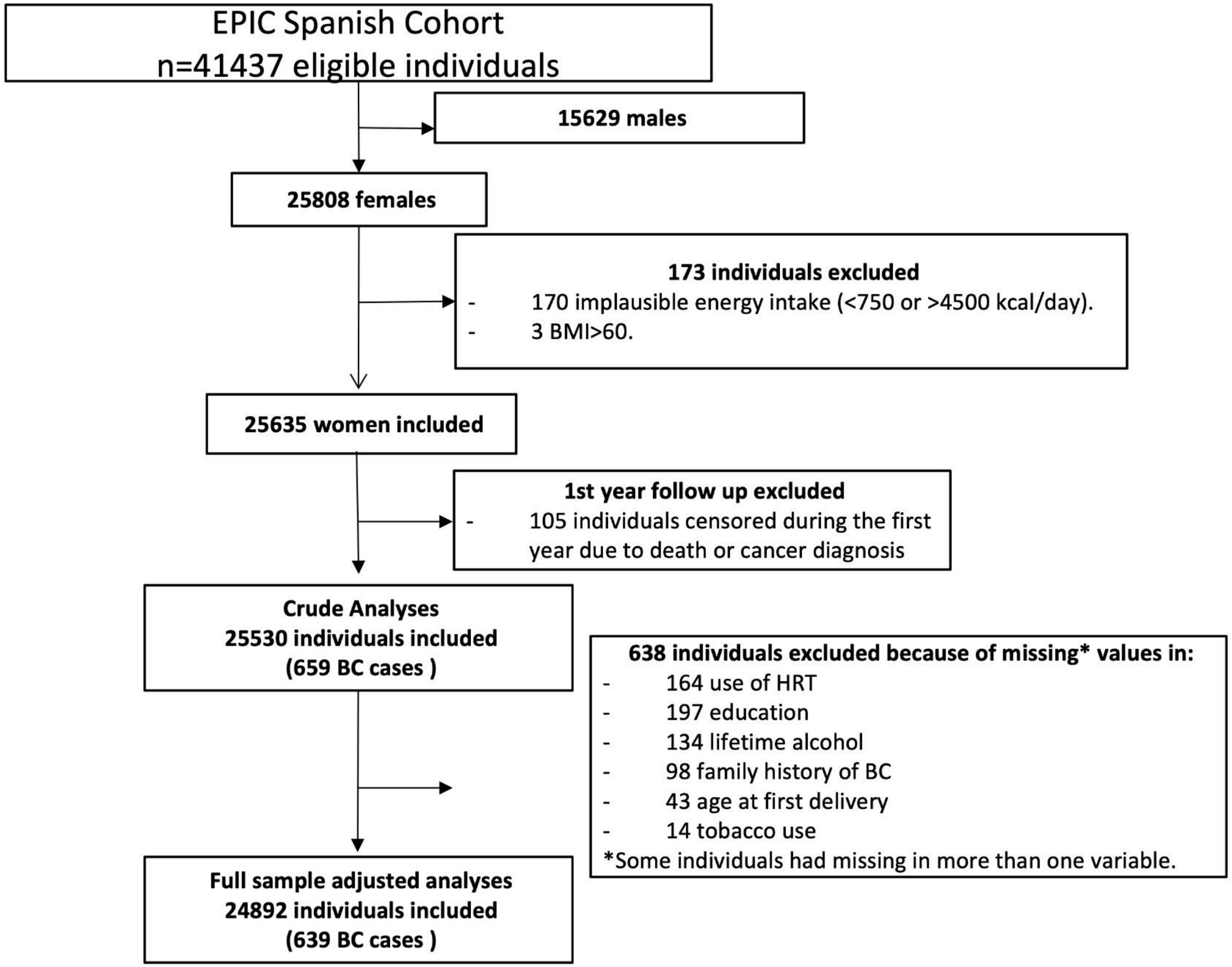
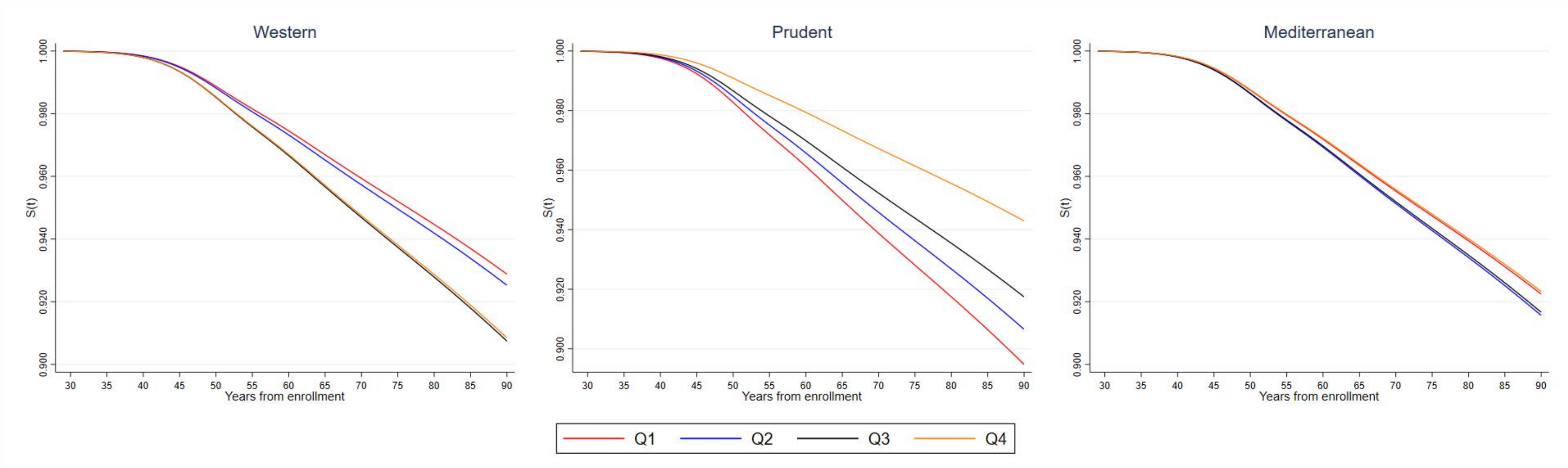


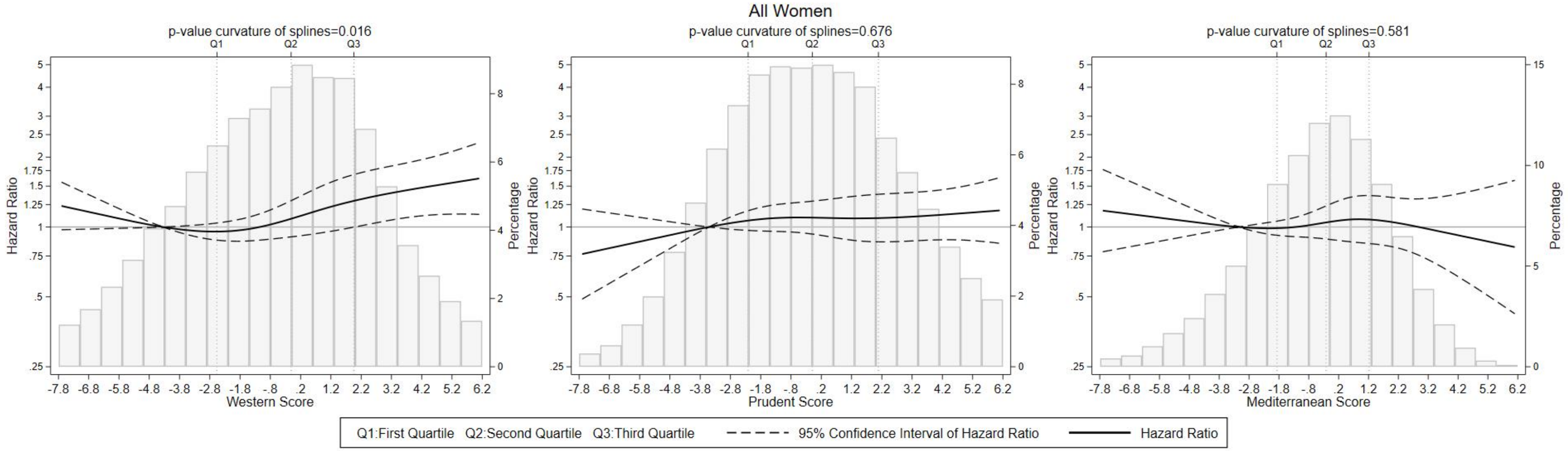
Figure 2: Standardized[a] survival curves for breast cancer by quartiles of adherence to the Western, Prudent and Mediterranean dietary patterns.



[a] Adjusted by lifetime alcohol intake, energy intake, BMI, physical activity, menopausal status, smoking, age at first delivery, use of hormonal replacement therapy, education at recruitment, family history of female breast cancer and centre. For Western dietary pattern, also adjusted by the adherence to the Prudent and Mediterranean dietary patterns. For Prudent and Mediterranean dietary patterns also adjusted by the adherence to the Western dietary pattern.

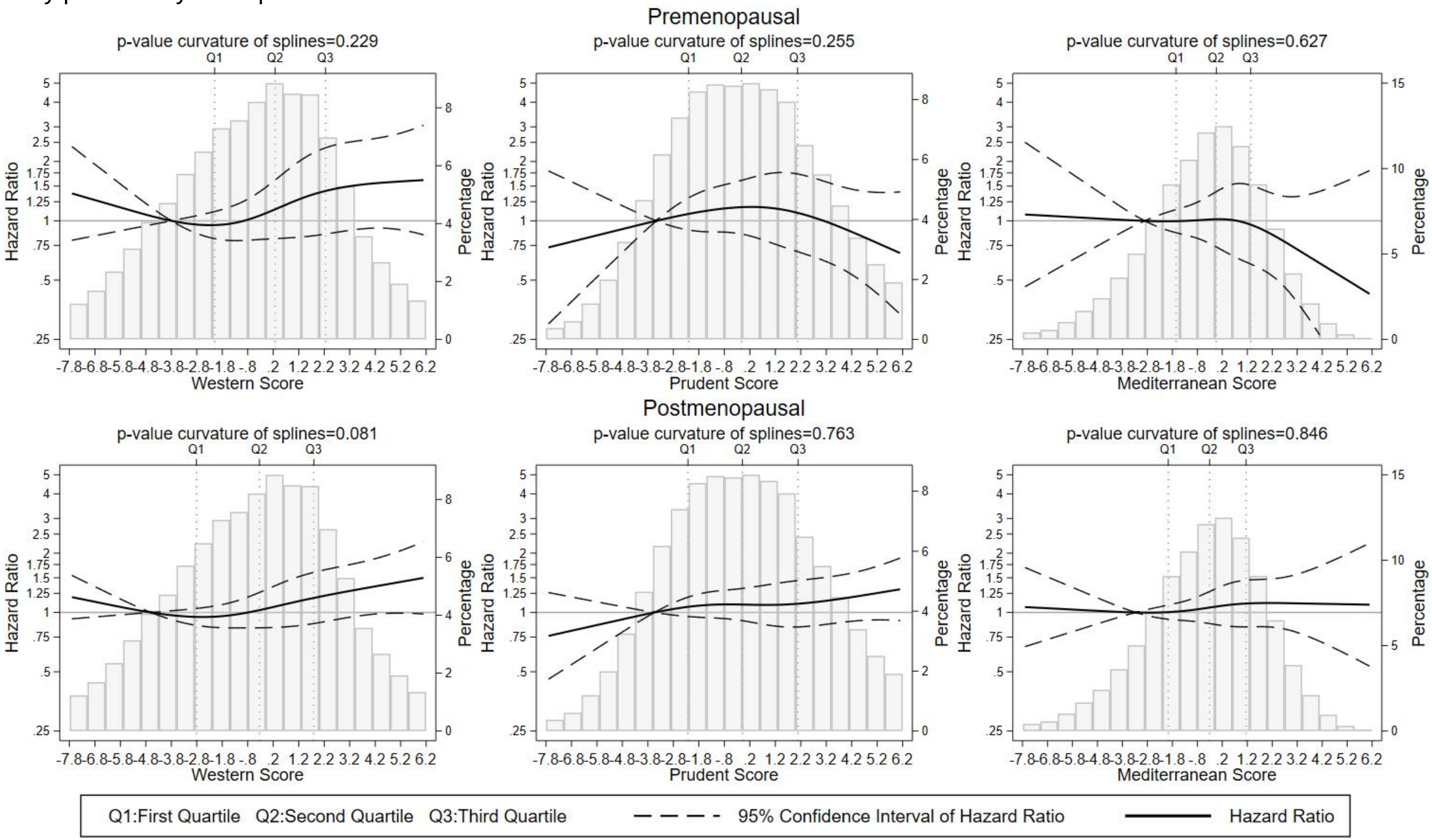
Age	30	33	36	39	42	45	48	51	54	57	60	63	66	69	72	75	78	81	84	87	90
Women At risk	0	5	290	3166	5953	8752	11620	14355	15009	14459	13759	12732	11232	8660	6318	4367	2482	958	125	3	1

Figure 3: Non-linear association between breast cancer incidence and scores of adherence to Western, Prudent and Mediterranean dietary patterns.



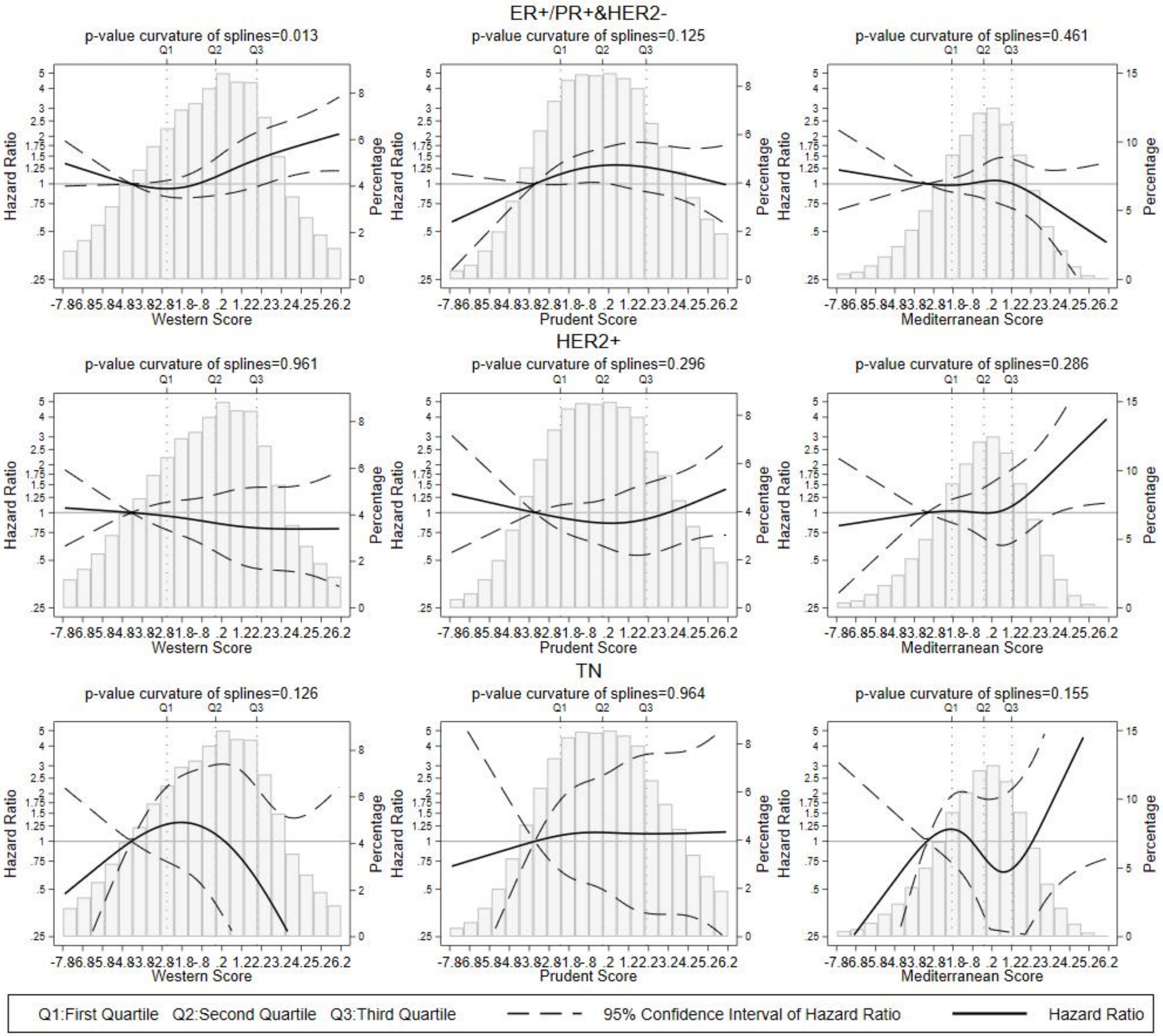
Adjusted by lifetime alcohol intake, energy intake, BMI, physical activity, menopausal status, smoking, age at first delivery, use of hormonal replacement therapy, family history of female breast cancer, education and centre. For the Western dietary pattern, also adjusted by the adherence to the Prudent and Mediterranean dietary patterns. For the Prudent and Mediterranean dietary patterns also adjusted by the adherence to the Western dietary pattern.

Figure 4: Non-linear association between breast cancer incidence and scores of adherence to Western, Prudent and Mediterranean dietary patterns by menopausal status.



Adjusted by lifetime alcohol intake, energy intake, BMI, physical activity, age at first delivery, smoking, use of hormonal replacement therapy, family history of female breast cancer, education and centre. For the Western dietary pattern, also adjusted by the adherence to the Prudent and Mediterranean dietary patterns. For the Prudent and Mediterranean dietary patterns also adjusted by the adherence to the Western dietary pattern.

Figure 5: Non-linear association between breast cancer incidence and scores of adherence to Western, Prudent and Mediterranean dietary patterns by tumour subtype.



Adjusted by lifetime alcohol intake, energy intake, BMI, physical activity, menopausal status, age at first delivery, smoking, use of hormonal replacement therapy, family history of female breast cancer, education and centre. For the Western dietary pattern, also adjusted by the adherence to the Prudent and Mediterranean dietary patterns. For the Prudent and Mediterranean dietary patterns also adjusted by the adherence to the Western dietary pattern.

Table 1: Composition of food groups based on the dietary history questionnaire of the EPIC-Spain study and component loadings obtained with the data of EPIGEICAM study (33).

FOOD GROUP	FOOD[a]	West[b]	Prud[b]	Med[b]
HIGH-FAT DAIRY	Whole-fat milk, milk, milk beverages, curd and yogurt; cream desserts; dairy creams; portion of unknown fat content diary[c].	0.60	-0.11	0.20
LOW FAT DAIRY	Semi-skimmed and skimmed milk, milk beverages, curd and yogurt; Cottage or fresh white cheese. portion of unknown fat content diary[c].	-0.49	0.60	-0.01
EGGS	Eggs.	0.19	0.08	0.16
WHITE MEAT	Poultry and game.	0.08	0.17	0.18
RED MEAT	Red meat (Pork, beef, veal, lamb, etc.); liver; entrails; hamburgers: meatballs; grounded meat; non-specified or mixed meat and derivates.	0.27	0.09	0.22
PROCESSED MEAT	Serrano ham and other cold meat; bacon; other processed meats; non-specified or mixed processed meat.	0.36	0.10	0.26
WHITE FISH	Fresh or frozen white fish (hake, sea bass, sea bream); 2/3·processed white fish; ½·fish eggs; ½·fish liver; 1/3·non classified fish and seafood.	0.01	0.22	0.34
OILY FISH	Fresh frozen or processed blue fish (tuna, swordfish, sardines, anchovies, salmon); 2/3·processed blue fish; ½·fish eggs; ½·fish liver; 1/3·non classified fish and seafood.	0.05	0.24	0.44
SEAFOOD/SHELLFISH	Crustaceans and mollusks; 1/3·non classified fish and seafood.	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. Cabbage; mushrooms; grain or pod vegetables; onion and garlic; tail or sprout vegetables; mixed salads or vegetables; non-classified vegetables.	-0.04	0.40	0.42
LEGUMES	Peas, lentils, chickpeas, beans and broad beans	0.21	0.15	0.34
POTATOES	Potatoes and other tubers.	0.17	0.25	0.40
FRUITS	All kind of fruits.	-0.07	0.31	0.31
NUTS	Nuts and seeds.	0.18	0.22	0.29
REFINED GRAINS	Flour, flakes, starch, semolina flour; pasta, rice, other unspecified or combined grains; pasta; other grains; cereal-based products such as pasta; 1/3·unspecified or mixed bread, biscuits, cookies; ½·unspecified bread; White bread; 1/3·rusks, unspecified cookies; ½·biscuits, white cookies; ½·unspecified or combined dough or pastry; bread and pizza dough; 2/3·unspecified white bread, biscuits, or mixes.	0.37	0.15	0.23
WHOLE GRAINS	Unspecified or combined cereal products: ½ · unspecified bread; non-white bread; breakfast cereals; 1/3 · unspecified or mixed bread, biscuits, biscuits; 2/3 · non-white bread, biscuit, unspecified or mixed biscuits; 1/3 · rusks, unspecified biscuits; ½ · biscuits, not white cookies.	-0.43	0.47	0.06
OLIVES AND VEGETABLE OIL	Olives; vegetable oils.	0.12	0.19	0.34
OTHER EDIBLE FATS	Margarine; butter; oil of marine origin; other animal edible fats.	0.22	0.02	0.11
SWEETS	1/3 * biscuits, unspecified cookies; ½ * biscuits, white cookies; 1/2 · biscuits, non-white biscuits; ½ · unspecified or combined dough or pastry; cupcakes; 1/3 · unspecified or mixed bread, biscuits, biscuits; 1/3 · white bread, biscotti, cookies not specified or mixed; 1/3 · non-white bread, biscuit, cookies not specified or mixed; chocolate, candy, bar, pasta, confectionery; non-chocolate confectionery, candied fruit; sorbet, water ice; cakes and cookies	0.35	0.18	0.05
SUGARY	Jam, Honey, Sugar and fruit in sugar syrup.	0.24	0.05	0.00
JUICES	Vegetable and fruit juices.	0.25	0.67	-0.39
CALORIC DRINKS	Sugar-sweetened soft drinks; unclassified non-alcoholic drinks.	0.74	0.21	-0.25
CONVENIENCE FOOD AND SAUCES	Crackers and snack cookies; Egg derivates; 1/3·processed white fish; 1/3·processed blue fish; tomato sauces; other/unsorted or mixed sauces; aioli sauces; mayonnaise and other creamy sauces; snacks; non-dairy creams; fried products; ½·condiments and sauces not classified; vegetarian products and dishes; other dietary products.	0.47	0.12	0.24

[a] Log-transformed centred intake in grams.
[b] West=Western; Prud=Prudent; Med=Mediterranean.
[c] For non-cancer cases: Portion in high-fat dairy=0.65·Unknown and Portion in low-fat dairy=0.35·Unknown
For BC cancer cases: Portion in high-fat dairy=0.62·Unknown and Portion in low-fat dairy=0.38·Unknown
For cases of other tumours: Portion in high-fat dairy=0.68·Unknown and Portion in low-fat dairy=0.32·Unknown

Table 2: Baseline characteristics of the 25,530 women from the EPIC-Spain study for the full sample and by level of adherence to the Western, Prudent and Mediterranean dietary patterns.

	Full sample		Western					Prudent					Mediterranean			
	TOTAL	**Q1**	**Q2**	**Q3**	**Q4**	**p[a]**	**Q1**	**Q2**	**Q3**	**Q4**	**p[a]**	**Q1**	**Q2**	**Q3**	**Q4**	**p[a]**
	n= 24892	**n= 7637**	**n= 6527**	**n= 5818**	**n= 4910**		**n= 6425**	**n= 5869**	**n= 6266**	**n= 6332**		**n= 7732**	**n= 6972**	**n= 5996**	**n= 4192**	
Alcohol (grs of ethanol/day) median(IQR)[b]	1.10 (0.00; 6.09)	0.34 (0.00; 4.35)	1.06 (0.00; 5.92)	1.41 (0.00; 7.06)	2.06 (0.00; 7.96)	0.000	0.24 (0.00; 5.09)	0.95 (0.00; 6.05)	1.28 (0.00; 6.31)	1.81 (0.00; 6.65)	0.000	0.16 (0.00; 4.22)	0.94 (0.00; 5.76)	1.64 (0.00; 6.90)	2.57 (0.01; 8.73)	0.000
Energy (kcal/day) median(IQR)[c]	1805 (1487; 2183)	1534 (1271; 1814)	1748 (1472; 2069)	1908 (1651; 2229)	2263 (1924; 2651)	0.000	1634 (1354; 1953)	1818 (1492; 2191)	1822 (1511; 2219)	1960 (1639; 2353)	0.000	1492 (1240; 1795)	1741 (1493; 2041)	1944 (1680; 2259)	2324 (2007; 2696)	0.000
BMI (kg/m^2) median(IQR)[c]	27.48 (24.72; 30.90)	28.15 (25.35; 31.53)	27.63 (24.91; 31.09)	27.14 (24.40; 30.39)	26.52 (23.93; 30.09)	0.000	27.82 (24.97; 31.17)	27.58 (24.72; 31.04)	27.45 (24.71; 30.90)	27.11 (24.49; 30.54)	0.000	27.95 (25.09; 31.48)	27.47 (24.67; 30.89)	27.09 (24.54; 30.52)	27.04 (24.34; 30.41)	0.000
Age at recruitment (years) median(IQR)c	47.56 (41.25; 54.77)	50.12 (43.47; 57.33)	48.00 (41.87; 55.09)	46.41 (40.67; 53.28)	44.56 (39.20; 50.63)	0.000	47.69 (41.38; 55.53)	47.40 (41.29; 54.46)	47.72 (41.07; 54.70)	47.42 (41.28; 54.39)	0.030	49.25 (42.25; 57.19)	47.76 (41.18; 55.01)	46.61 (40.86; 53.01)	46.18 (40.55; 51.98)	0.000
Event						0.000					0.104					1E-08
Alive with no BC	23533 (95%)	7164 (94%)	6179 (95%)	5507 (95%)	4683 (95%)		6058 (94%)	5568 (95%)	5913 (94%)	5994 (95%)		7247 (94%)	6583 (94%)	5699 (95%)	4004 (96%)	
Breast Cancer	639 (3%)	183 (2%)	156 (2%)	164 (3%)	136 (3%)		153 (2%)	154 (3%)	177 (3%)	155 (2%)		187 (2%)	185 (3%)	160 (3%)	107 (3%)	
Death	720 (3%)	290 (4%)	192 (3%)	147 (3%)	91 (2%)		214 (3%)	147 (3%)	176 (3%)	183 (3%)		298 (4%)	204 (3%)	137 (2%)	81 (2%)	
Subtype						0.590					0.230					0.371
ER+/PR+&HER2-	268 (42%)	80 (44%)	64 (41%)	70 (43%)	54 (40%)		66 (43%)	67 (44%)	80 (45%)	55 (35%)		89 (48%)	77 (42%)	66 (41%)	36 (34%)	
HER2+	127 (20%)	33 (18%)	42 (27%)	28 (17%)	24 (18%)		39 (25%)	24 (16%)	30 (17%)	34 (22%)		34 (18%)	37 (20%)	27 (17%)	29 (27%)	
TN	28 (4%)	10 (5%)	8 (5%)	5 (3%)	5 (4%)		6 (4%)	6 (4%)	9 (5%)	7 (5%)		10 (5%)	8 (4%)	4 (3%)	6 (6%)	
Unknown	216 (34%)	60 (33%)	42 (27%)	61 (37%)	53 (39%)		42 (27%)	57 (37%)	58 (33%)	59 (38%)		54 (29%)	63 (34%)	63 (39%)	36 (34%)	
Physical Activity n(%)						0.001					0.000					0.007
Inactive	1256 (5%)	348 (5%)	353 (5%)	280 (5%)	275 (6%)		263 (4%)	276 (5%)	353 (6%)	364 (6%)		424 (5%)	364 (5%)	276 (5%)	192 (5%)	
Moderately inactive	3360 (13%)	986 (13%)	935 (14%)	767 (13%)	672 (14%)		857 (13%)	786 (13%)	826 (13%)	891 (14%)		1121 (14%)	925 (13%)	761 (13%)	553 (13%)	
Moderately active	17985 (72%)	5531 (72%)	4647 (71%)	4250 (73%)	3557 (72%)		4760 (74%)	4328 (74%)	4501 (72%)	4396 (69%)		5514 (71%)	5048 (72%)	4381 (73%)	3042 (73%)	
Active	2291 (9%)	772 (10%)	592 (9%)	521 (9%)	406 (8%)		545 (8%)	479 (8%)	586 (9%)	681 (11%)		673 (9%)	635 (9%)	578 (10%)	405 (10%)	
Smoking n(%)						0.000					0.000					0.006
Never Smoker	17720 (71%)	5757 (75%)	4662 (71%)	4055 (70%)	3246 (66%)		4583 (71%)	4210 (72%)	4463 (71%)	4464 (70%)		5572 (72%)	4945 (71%)	4246 (71%)	2957 (71%)	
Former Smoker	2483 (10%)	803 (11%)	695 (11%)	530 (9%)	455 (9%)		437 (7%)	534 (9%)	685 (11%)	827 (13%)		693 (9%)	689 (10%)	656 (11%)	445 (11%)	
Current Smoker	4689 (19%)	1077 (14%)	1170 (18%)	1233 (21%)	1209 (25%)		1405 (22%)	1125 (19%)	1118 (18%)	1041 (16%)		1467 (19%)	1338 (19%)	1094 (18%)	790 (19%)	
Unknown						0.000					0.000					0.000
Education n(%)	9816 (39%)	3289 (43%)	2597 (40%)	2186 (38%)	1744 (36%)		2751 (43%)	2305 (39%)	2449 (39%)	2311 (36%)		3348 (43%)	2781 (40%)	2217 (37%)	1470 (35%)	
No formal Education	9905 (40%)	2862 (37%)	2567 (39%)	2382 (41%)	2094 (43%)		2641 (41%)	2448 (42%)	2473 (39%)	2343 (37%)		2975 (38%)	2676 (38%)	2480 (41%)	1774 (42%)	
Primary School	2765 (11%)	794 (10%)	727 (11%)	672 (12%)	572 (12%)		637 (10%)	622 (11%)	688 (11%)	818 (13%)		776 (10%)	830 (12%)	687 (11%)	472 (11%)	

Secondary/Technical School	2406 (10%)	692 (9%)	636 (10%)	578 (10%)	500 (10%)		396 (6%)	494 (8%)	656 (10%)	860 (14%)		633 (8%)	685 (10%)	612 (10%)	476 (11%)	
University or more						0.361					0.855					0.699
Unknown	23801 (96%)	7298 (96%)	6216 (95%)	5574 (96%)	4713 (96%)		6144 (96%)	5619 (96%)	5987 (96%)	6051 (96%)		7402 (96%)	6682 (96%)	5718 (95%)	3999 (95%)	
Family history of BC n(%)	662 (3%)	195 (3%)	191 (3%)	152 (3%)	124 (3%)		172 (3%)	155 (3%)	159 (3%)	176 (3%)		204 (3%)	171 (2%)	174 (3%)	113 (3%)	
No mother/sister	429 (2%)	144 (2%)	120 (2%)	92 (2%)	73 (1%)		109 (2%)	95 (2%)	120 (2%)	105 (2%)		126 (2%)	119 (2%)	104 (2%)	80 (2%)	
Mother						0.000					0.000					0.000
Sister	1472 (6%)	427 (6%)	390 (6%)	336 (6%)	319 (6%)		494 (8%)	332 (6%)	331 (5%)	315 (5%)		532 (7%)	383 (5%)	315 (5%)	242 (6%)	
Unknown	10056 (40%)	3020 (40%)	2623 (40%)	2366 (41%)	2047 (42%)		2535 (39%)	2396 (41%)	2570 (41%)	2555 (40%)		2980 (39%)	2808 (40%)	2536 (42%)	1732 (41%)	
Age at first delivery n(%)	8327 (33%)	2521 (33%)	2168 (33%)	1970 (34%)	1668 (34%)		2150 (33%)	1987 (34%)	2079 (33%)	2111 (33%)		2517 (33%)	2337 (34%)	2007 (33%)	1466 (35%)	
<20	1760 (7%)	552 (7%)	474 (7%)	430 (7%)	304 (6%)		489 (8%)	417 (7%)	445 (7%)	409 (6%)		550 (7%)	517 (7%)	436 (7%)	257 (6%)	
20-24	439 (2%)	147 (2%)	109 (2%)	102 (2%)	81 (2%)		131 (2%)	85 (1%)	109 (2%)	114 (2%)		131 (2%)	129 (2%)	114 (2%)	65 (2%)	
25-29 yo	2838 (11%)	970 (13%)	763 (12%)	614 (11%)	491 (10%)		626 (10%)	652 (11%)	732 (12%)	828 (13%)		1022 (13%)	798 (11%)	588 (10%)	430 (10%)	
29-35						0.000					0.161					0.000
>35	13413 (54%)	3275 (43%)	3429 (53%)	3421 (59%)	3288 (67%)		3425 (53%)	3237 (55%)	3352 (53%)	3399 (54%)		3623 (47%)	3703 (53%)	3537 (59%)	2550 (61%)	
Nuliparous	11479 (46%)	4362 (57%)	3098 (47%)	2397 (41%)	1622 (33%)		3000 (47%)	2632 (45%)	2914 (47%)	2933 (46%)		4109 (53%)	3269 (47%)	2459 (41%)	1642 (39%)	
Unknown						0.000					0.000					0.011
Menopausal Status n(%)	22538 (91%)	6657 (87%)	5911 (91%)	5380 (92%)	4590 (93%)		5935 (92%)	5386 (92%)	5603 (89%)	5614 (89%)		6936 (90%)	6313 (91%)	5470 (91%)	3819 (91%)	
Pre-menopausal	2354 (9%)	980 (13%)	616 (9%)	438 (8%)	320 (7%)		490 (8%)	483 (8%)	663 (11%)	718 (11%)		796 (10%)	659 (9%)	526 (9%)	373 (9%)	
Post-menopausal	1.10 (0.00; 6.09)	0.34 (0.00; 4.35)	1.06 (0.00; 5.92)	1.41 (0.00; 7.06)	2.06 (0.00; 7.96)	0.000	0.24 (0.00; 5.09)	0.95 (0.00; 6.05)	1.28 (0.00; 6.31)	1.81 (0.00; 6.65)	0.000	0.16 (0.00; 4.22)	0.94 (0.00; 5.76)	1.64 (0.00; 6.90)	2.57 (0.01; 8.73)	0.000
Ever use Hormonal Replacement Therapy n(%)	1805 (1487; 2183)	1534 (1271; 1814)	1748 (1472; 2069)	1908 (1651; 2229)	2263 (1924; 2651)	0.000	1634 (1354; 1953)	1818 (1492; 2191)	1822 (1511; 2219)	1960 (1639; 2353)	0.000	1492 (1240; 1795)	1741 (1493; 2041)	1944 (1680; 2259)	2324 (2007; 2696)	0.000
No	27.48 (24.72; 30.90)	28.15 (25.35; 31.53)	27.63 (24.91; 31.09)	27.14 (24.40; 30.39)	26.52 (23.93; 30.09)	0.000	27.82 (24.97; 31.17)	27.58 (24.72; 31.04)	27.45 (24.71; 30.90)	27.11 (24.49; 30.54)	0.000	27.95 (25.09; 31.48)	27.47 (24.67; 30.89)	27.09 (24.54; 30.52)	27.04 (24.34; 30.41)	0.000
Yes	47.56 (41.25; 54.77)	50.12 (43.47; 57.33)	48.00 (41.87; 55.09)	46.41 (40.67; 53.28)	44.56 (39.20; 50.63)	0.000	47.69 (41.38; 55.53)	47.40 (41.29; 54.46)	47.72 (41.07; 54.70)	47.42 (41.28; 54.39)	0.030	49.25 (42.25; 57.19)	47.76 (41.18; 55.01)	46.61 (40.86; 53.01)	46.18 (40.55; 51.98)	0.000
Unknown						0.000					0.104					1E-08

[a] p-value calculated ignoring missing values.

[b] Alcohol was missing for 125 (0.5%) healthy individuals and for 9 (1,3%) breast cancer cases.

[c] Alcohol and energy intake, BMI and age were normally distributed but with unequal variances among quartile groups for all three dietary patterns.

Table 3: Crude and adjusted hazard ratio for the association between breast cancer incidence and scores of adherence to Western, Prudent and Mediterranean dietary patterns.

			Crude n=24892			Adjusted n=24892		
				95% CI			95% CI	
	Woman-years	Number of events	HR[a,b]	LL[c]	UL[c]	HR[a,d]	LL[c]	UL[c]
	408208	639						
WESTERN								
Quartiles								
Q1	123075	179	1.00			1.00		
Q2	106101	154	1.00	0.80	1.25	1.07	0.84	1.34
Q3	94076	163	1.22	0.98	1.52	1.37	1.07	1.77
Q4	79782	133	1.20	0.95	1.52	1.37	1.03	1.83
p-trend			0.044			0.009		
1SD-increase			1.06	0.97	1.15	1.10	0.99	1.22
PRUDENT								
Quartiles								
Q1	101745	151	1.00			1.00		
Q2	94859	153	1.05	0.84	1.33	1.08	0.85	1.36
Q3	102098	171	1.05	0.84	1.32	1.11	0.87	1.40
Q4	104333	154	0.97	0.76	1.23	1.04	0.80	1.36
p-trend			0.798			0.714		
1SD-increase			1.02	0.94	1.11	1.06	0.96	1.16
MEDITERRANEAN								
Quartiles								
Q1	123453	185	1.00			1.00		
Q2	112878	183	1.10	0.89	1.35	1.09	0.88	1.35
Q3	97528	157	1.10	0.89	1.37	1.09	0.86	1.38
Q4	69175	104	0.98	0.76	1.26	0.95	0.72	1.27
p-trend			0.922			0.951		
1SD-increase			1.00	0.92	1.09	0.99	0.90	1.10

[a] Proportional hazards assumption was fulfilled in all cases.

[b] HR of breast cancer stratified by centre.

[c] LL: Lower limit, UL: Upper limit

[d] HR of breast cancer stratified by centre, BMI, family history of female breast cancer and educational level and adjusted by lifetime alcohol intake, energy intake, BMI, physical activity, smoking, menopausal status changing in time, age at first delivery and use of hormonal replacement therapy. For the Western dietary pattern, also adjusted by the adherence to the Prudent and Mediterranean dietary patterns. For the Prudent and Mediterranean dietary patterns also adjusted by the adherence to the Western dietary pattern.

Table 4: Hazard ratio for the association between breast cancer incidence and scores of adherence to Western, Prudent and Mediterranean dietary patterns by menopausal status changing in time.

	Premenopausal n=13413[a]					**Postmenopausal n=23459[a]**					**p-int**
				(95%CI)					**(95%CI)**		
	Woman-years	**Number of events**	**HR[b,c]**	**LL**	**UL**	**Woman-years**	**Number of events**	**HR[b,c]**	**LL**	**UL**	
	116704	**162**				**286330**	**467**				
WESTERN											
Quartiles											0.286
Q1	27091	37	1.00			95984	142	1.00			
Q2	28876	31	0.83	0.50	1.36	77226	123	1.14	0.89	1.48	
Q3	30066	53	1.48	0.94	2.32	64010	110	1.30	0.98	1.72	
Q4	30672	41	1.13	0.69	1.84	49110	92	1.42	1.04	1.94	
p-trend			0.231					0.021			
1SD-increase			1.07	0.90	1.28			1.09	0.97	1.22	0.827
PRUDENT											
Quartiles											0.431
Q1	29641	40	1.00			72104	111	1.00			
Q2	27784	40	1.02	0.65	1.61	67075	113	1.12	0.85	1.46	
Q3	29410	49	1.16	0.75	1.81	72687	122	1.14	0.87	1.50	
Q4	29870	33	0.76	0.47	1.25	74464	121	1.12	0.83	1.49	
p-trend			0.422					0.451			
1SD-increase			0.96	0.82	1.14			1.08	0.98	1.20	0.216
MEDITERRANEAN											
Quartiles											0.345
Q1	31497	45	1.00			91956	140	1.00			
Q2	32661	53	1.20	0.80	1.81	80217	130	1.06	0.83	1.36	
Q3	30336	38	0.88	0.57	1.38	67192	119	1.14	0.88	1.48	
Q4	22210	26	0.77	0.46	1.30	46965	78	1.03	0.75	1.41	
p-trend			0.219					0.623			
1SD-increase			0.90	0.76	1.07			1.03	0.93	1.16	0.157

[a] Menopausal status changes during the follow up. Therefore, premenopausal women at recruitment contributed as premenopausal and postmenopausal. So the sum of the number of pre and postmenopausal women do not necessarily add to the total number of women.

[b] Proportional hazards assumption was fulfilled in all cases

[c] HR of breast cancer stratified by centre, BMI and family history of female breast cancer and adjusted by lifetime alcohol intake, energy intake, BMI, physical activity, smoking, educational level, age at first delivery and use of hormonal replacement therapy and including an interaction menopausal status changing in time. For the Western dietary pattern, also adjusted by the adherence to the Prudent and Mediterranean dietary patterns. For the Prudent and Mediterranean dietary patterns also adjusted by the adherence to the Western dietary pattern.

Table 5: Adjusted hazard ratios for the association between breast cancer incidence and scores of adherence to Western, Prudent and Mediterranean dietary patterns by tumour subtype.

	ER+/PR+&HER2- n=24521					HER2+ n=24380					TN n=24281				
	Woman-years	Number of events	HR[a,b]	(95%CI) LL	UL	Woman-years	Number of events	HR[a,b]	(95%CI) LL	UL	Woman-years	Number of events	HR[a,b]	(95%CI) LL	UL
	405138	268				403906	127				402910	28			
WESTERN															
Quartiles															
Q1	122281	78	1			121886	32	1			121674	10	1		
Q2	105308	63	1.13	0.79	1.62	105164	41	1.49	0.91	2.46	104813	8	0.90	0.32	2.58
Q3	93288	70	1.62	1.10	2.38	92900	27	1.08	0.59	1.98	92677	5	0.69	0.19	2.55
Q4	79113	54	1.71	1.11	2.63	78812	23	1.17	0.60	2.28	78627	4	0.54	0.12	2.51
p-trend			0.005					0.913					0.406		
1SD-increase			1.16	0.99	1.37			0.96	0.75	1.23			0.79	0.46	1.36
PRUDENT															
Quartiles															
Q1	101025	65	1.00			100757	39	1.00			100420	5	1.00		
Q2	94195	67	1.24	0.87	1.76	93795	23	0.62	0.36	1.05	93628	6	1.53	0.44	5.23
Q3	101314	78	1.44	1.01	2.06	100881	28	0.76	0.45	1.28	100693	9	1.78	0.52	6.05
Q4	103457	55	1.16	0.77	1.75	103330	33	0.94	0.55	1.61	103050	7	1.38	0.36	5.28
p-trend			0.291					0.928					0.634		
1SD-increase			1.09	0.95	1.26			1.05	0.85	1.29			1.10	0.71	1.72
MEDITERRANEAN															
Quartiles															
Q1	122655	88	1.00			122229	34	1.00			121976	9	1.00		
Q2	111997	76	1.01	0.74	1.39	111624	36	1.21	0.75	1.97	111340	8	1.28	0.47	3.45
Q3	96794	66	1.07	0.75	1.51	96441	26	1.05	0.60	1.81	96207	4	0.73	0.20	2.61
Q4	68544	35	0.82	0.52	1.30	68470	27	1.48	0.81	2.68	68268	6	1.30	0.35	4.89
p-trend			0.636					0.324					0.927		
1SD-increase			0.94	0.81	1.10			1.19	0.94	1.50			1.22	0.75	1.99

[a] Proportional hazards assumption was fulfilled in all cases

[b] HR of breast cancer by tumour subtype, stratified by centre, BMI and family history of female breast cancer and adjusted by lifetime alcohol intake, energy intake, physical activity, smoking, educational level, menopausal status changing in time, age at first delivery and use of hormonal replacement therapy. For the Western dietary pattern, also adjusted by the adherence to the Prudent and Mediterranean dietary patterns. For the Prudent and Mediterranean dietary patterns also adjusted by the adherence to the Western dietary pattern.