Association Between Western and Mediterranean Dietary Patterns and Mammographic Density

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OBJECTIVE: To examine the association between two dietary patterns (Western and Mediterranean), previously linked to breast cancer risk, and mammographic density.

METHODS: This cross-sectional study included 3,584 women attending population-based breast cancer screening programs and recruited between October 7, 2007, and July 14, 2008 (participation rate 74.5%). Collected data included anthropometric measurements; demographic, obstetric, and gynecologic characteristics; family and personal health history; and diet in the preceding year. Mammographic density was blindly assessed by a single radiologist and classified into four categories: less than 10%, 10–25%, 25–50%, and greater than 50%. The association between adherence to either a Western or a Mediterranean dietary pattern and mammographic density was explored using multivariable ordinal logistic regression models with random center-specific intercepts. Models were adjusted for age, body mass index, parity, menopause, smoking, family history, hormonal treatment, and calorie and alcohol intake. Differences according to women’s characteristics were tested including interaction terms.

RESULTS: Women with a higher adherence to the Western dietary pattern were more likely to have high mammographic density (n=242 [27%]) than women with low adherence (n=169 [19%]) with a fully adjusted odds ratio (ORQ4vsQ1) of 1.25 (95% confidence interval [CI] 1.03–1.52). This association was confined to overweight–obese women (adjusted ORQ4vsQ1 [95% CI] 1.41 [1.13–1.76]). No association between Mediterranean dietary pattern and mammographic density was observed.

CONCLUSION: The Western dietary pattern was associated with increased mammographic density among overweight–obese women. Our results might inform specific dietary recommendations for women with high mammographic density.

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Breast cancer is the most common malignant tumor among women worldwide and one of the main causes of female mortality in medium- and high-income countries. Early detection and therapeutic advances have improved breast cancer prognosis, but the number of new cases keeps increasing.

*For a list of the membership of the DDM-Spain Research Group, see Appendix 1 online at http://links.lww.com/AOG/A841.
emphasizing the need to prioritize prevention as an indispensable tool to reduce the burden of disease.

High mammographic density is an important risk factor for breast cancer.\(^3\) Some results indicate a possible mediating effect of mammographic density in breast cancer risk,\(^4\) and this phenotype is currently being used to improve the discrimination of classic predictive models.\(^5\) Therefore, it is reasonable to presume that some of the factors associated with breast cancer onset might exert their effect by modifying mammographic density.

We have recently identified two dietary patterns associated with breast cancer risk: a Western dietary pattern associated with increased risk (odds ratio \(\text{OR}_{\text{high-vs-low adherence}} [95\% \text{ confidence interval [CI]} 1.46 [1.06–2.01]]) and a protective Mediterranean pattern (\(\text{OR}_{\text{high-vs-low adherence}} [95\% \text{ CI} 0.56 [0.40–0.79]]).\(^6\) The identification of dietary habits associated with mammographic density may inform the design of dietary recommendations for women attending screening who have high mammographic density and, therefore, are at higher risk for breast cancer.\(^7\) Unfortunately, because a few studies have explored the association between dietary patterns and mammographic density, current evidence remains inconclusive.\(^7,8\) The objective of this study is to explore the association between adherence to the Western and Mediterranean dietary patterns and mammographic density.

**MATERIALS AND METHODS**

In this cross-sectional study (“Determinants of Mammographic Density in Spain”), we recruited women aged 45–69 years attending breast cancer screening in one of the seven centers from the population-based public Spanish Breast Cancer Screening network. Women with a previous cancer diagnosis (except nonmelanoma skin cancers), attendees unable to respond to the questionnaire, or women with a physical limitation preventing the performance of the mammogram were excluded. Among those eligible, women were randomly selected on a daily basis from the list of attendees scheduled for that particular day, taking into account the number of interviews that could be scheduled for the day. These women were invited to participate and, if they accepted, their appointment was rescheduled to allow enough time for the interview before the mammogram. With an average participation rate of 74.5% (range 64.7–84.0% across centers) and a preset minimum sample size of 500 women for each of the seven sites, the recruitment period lasted from October 7, 2007, through July 14, 2008, during which a total of 3,384 women were recruited.

The company Demometrica (http://www.demometrica.com/) provided trained interviewers (one per center) to collect anthropometric, demographic, occupational, physical activity, obstetric and gynecologic data as well as family and personal history (including weight and height at age 18 years). Data were entered in a data file at Demometrica headquarters. An internal validation was performed using a random sample of 10% of the questionnaires. In addition, all questionnaires were digitalized to make them easily accessible to researchers for checking for possible inconsistencies and unusual values. One hundred fifty women were reinterviewed to verify their answers. This second interview took place between 2 and 9 months after the first one and results from both interviews were highly concordant.

Smoking status was defined as “current smoker” for those women who smoke at the time of mammography or quit less than 6 months before and as “non-smoker” otherwise. Dietary intake during the preceding year was collected using a 117-item food frequency questionnaire (Appendix 2, available online at http://links.lww.com/AOG/A842) similar to the Willett questionnaire\(^9\) and suitably adapted to and validated in Spanish adult populations.\(^10,11\) Postmenopausal status was defined as self-reported absence of menstruation in the last 12 months. Weight, height, and waist and hip circumferences were measured twice using the same protocol and identical balance scales, stadiometers, and measuring tapes. A third measure was taken when the first two were not similar.

Mammographic density was blindly assessed by a single radiologist unaware of the survey data. He read the craniocaudal mammogram of the left breast using a visual semiquantitative score with six categories proposed by Boyd\(^12\) based on percentage of dense tissue in the breast: categories A (0%), B (0–10%), C (10–25%), D (25–50%), E (50–75%), and F (greater than 75%). This scale has been associated with subsequent development of sporadic and familial breast cancer.\(^3,13\) Given the small percentage of women in categories A (4%) and F (5%), the two lowest and two highest categories were grouped together, creating the definitive outcome variable categorized as: less than 10%, 10–25%, 25–50%, and greater than 50%.

We examined two dietary patterns identified in a previous case–control study\(^6\) as being associated with breast cancer risk: 1) the Western dietary pattern, characterized by a high intake of high-fat dairy products, processed meat, refined grains, sweets, caloric drinks, convenience food, and sauces and by low intakes of low-fat dairy products and whole grain was...
associated with an increased risk of breast cancer; and 2) the Mediterranean dietary pattern characterized by a high intake of fish, vegetables, legumes, boiled potatoes, fruits, olives, and vegetable oil and a low intake of juices was associated with a reduced risk of breast cancer. These two dietary patterns were identified applying principal components analysis without rotation of the variance–covariance matrix over 26 intercorrelated food groups. This method reports a set of weights (pattern loadings) associated with each food group that represents the correlation between food consumption and the component and pattern scores that can be used to reproduce such patterns in other samples as explained in detail in Castelló et al. Briefly, we grouped 95 of the 117 items of the food frequency questionnaire (excluding noncaloric and alcoholic beverages) into 26 food groups (Table 1) and calculated the level of adherence scores for the Western and Mediterranean dietary patterns as a linear combination of the weights for each food group and pattern published in Castelló et al and the food group consumption reported by the participants in the current study.

Regarding the statistical analysis, first, we calculated basic descriptive statistics of the anthropometric, sociodemographic, and lifestyle characteristics for all women and by categories of mammographic density. Normally distributed continuous variables were described using the mean ± standard deviation. Differences across categories of mammographic density were tested with analysis of variance tests. Nonnormally distributed continuous variables were described using the median (interquartile interval) and differences by mammographic density were tested with nonparametric Kruskal-Wallis tests. Categorical variables were described using the number of cases and corresponding percentages, and differences by mammographic density were tested with χ² tests.

Associations between adherence to either dietary pattern and mammographic density were evaluated using ordinal logistic regression models with random center-specific intercepts including center as a random effect. As fixed-effects terms, age, body mass index (BMI, calculated as weight [kg]/height [m]²), parity, menopausal and smoking status, family history of breast cancer, use of hormonal therapy, and calorie and alcohol intake were considered as potential confounders. Three mixed models were adjusted to explore the confounding effect of different sets of variables. Model 1 was adjusted for only age and BMI (in addition to the random-effects term); model 2 also included parity, menopausal and smoking status, family history of breast cancer, and use of hormonal therapy. Finally, calorie and alcohol intake were added to model 3. Both categorical (grouping the scores of adherence into quartiles) and continuous (one-standard deviation increase) associations with the scores were examined with all three models. For model 3, nonlinear associations between the adherence to each pattern and mammographic density were assessed by fitting fractional polynomials.

With regard to the sample size, 22.8% of women had a mammographic density of greater than 50%. Therefore, our data allowed us to detect differences of 8% or more in the percentage of women classified in this category between extreme quartiles of adherence to each dietary pattern with a power of 80%.

Finally, when significant associations were found, separate analyses were performed by categories of all potential confounders mentioned and represented in forest plots. Heterogeneity of effects was tested in model 3 by including an interaction term between the score of adherence and the corresponding variable.

Analyses were performed using STATA/MP 14.0, and statistical significance was set at two-sided P < .05.

The protocol study “Determinants of Mammographic Density in Spain” was formally approved by the bioethics and animal welfare committee at the Carlos III Institute of Health and all participants signed informed consent, including permission to publish the results from the research.

RESULTS

Thirty-six participants were excluded from analyses: 10 women who developed breast cancer within 6 months of study entry and mammography, 16 who did not have mammographic density assessment, two who did not have BMI information, and eight who reported a daily kilocalorie intake under 750 or above 4,500. Therefore, analyses included data from 3,548 women for whom we had complete information regarding all the variables of interest. As expected, premenopausal and perimenopausal women showed a higher percentage of dense tissue (higher mammographic density). An elevated mammographic density was also associated with a family history of breast cancer, tobacco use, high calorie and alcohol intake, younger age, and lower BMI and parity (Table 2).

Crude associations summarized in Table 2 showed that, compared with women in the lowest quartile of adherence to the Western dietary pattern, a higher proportion of those in the highest quartile had a mammographic density of greater than 50% (19% [n=169] compared with 27% [n=242],
Table 1. Composition of Food Groups Based on the Food Frequency Questionnaire of the “Determinants of Mammographic Density in Spain” Study

| Food Group          | Food*                                                                 |
|---------------------|----------------------------------------------------------------------|
| High-fat dairy      | Whole-fat milk, w, A+D-enriched milk, double cream, condensed milk, whole-fat yogurt, semicured, cured or creamy cheese, custard, flan, pudding, ice cream |
| Low-fat dairy       | Semiskimmed and skimmed milk, omega3-enriched milk, +D-enriched milk, soy milk, soy yogurt, skimmed yogurt, cottage or fresh white cheese |
| Eggs                | Eggs                                                                 |
| White meat          | Chicken with skin, skinless chicken, game (eg, turkey, rabbit)       |
| Red meat            | Pork, beef, lamb, liver (beef, pork, or chicken), entrails, hamburger |
| Processed meat      | Serrano ham and other cold meat, sausages, bacon, pate, foie-gras     |
| White fish          | 1/3× all kinds of fried fish, fresh white fish (hake, sea bass, sea bream) |
| Oily fish           | 1/3× all kinds of fried fish, fresh blue fish (tuna, swordfish, sardines, anchovies, salmon), canned tuna, canned sardines or mackerel, salted and smoked fish |
| Seafood and shellfish| 1/3× all kinds of fried fish, clams, mussels, oysters, squid, cuttlefish, octopus, prawn, crab, shrimp, lobster |
| Leafy vegetables    | Spinach, chard, lettuce, endive, escarole                           |
| Fruiting vegetables | Tomato, eggplant, zucchini, cucumber, pepper, artichoke               |
| Root vegetables     | Carrot, pumpkin                                                      |
| Other vegetables    | Cooked cabbage, cauliflower or broccoli, onion, green beans, asparagus, mushrooms, corn, garlic, vegetable soup |
| Legumes             | Legumes, soy sprouts                                                 |
| Potatoes            | Roasted or boiled potatoes                                           |
| Fruits              | Orange, mandarin, banana, apple, pear, peach, nectarine, apricot, watermelon, melon, grapes, plums or prunes (dried or fresh), strawberries, kiwi |
| Nuts                | Almonds, peanuts, pine nuts, hazelnut                                 |
| Refined grains      | White flour bread, rice, pasta                                       |
| Whole grains        | Whole-grain bread and partial whole-grain bread, breakfast cereals, wheat germs |
| Olives and          | Olives, added olive oil to salads, bread and dishes, other vegetable oils (sunflower, corn, soybean) |
| vegetable oil       |                                                                      |
| Other edible fats   | Margarine, butter                                                    |
| Sweets              | Chocolate and other sweets, cocoa powder, plain cookies, chocolate cookies, pastries (croissant, donut, cake, pie or similar) |

(continued)

Multivariable analyses supported these findings confirming that, although breast density did not differ by level of adherence to the Mediterranean dietary pattern (adjusted odds ratio [OR]Q4 vs Q1) 0.99 [0.81–1.21] and adjusted OR-standard deviation increase [95% CI] 1.02 [0.95–1.09]), those with a high adherence to the Western dietary pattern had higher mammographic density (adjusted ORQ4 vs Q1) 1.25 [1.03–1.52] and adjusted OR-standard deviation increase [95% CI] 1.09 [1.02–1.18] (Table 3). No statistically significant departure from linearity was observed in this association when the analysis with fractional polynomials was performed (data not shown).

Stratified analysis by subgroups revealed that the effect of the Western dietary pattern on mammographic density was confined to women with BMIs higher than 25 (adjusted ORQ4 vs Q1) 1.41 [1.13–1.76], heterogeneity P value=.068. Our results also suggested some differences according to parity, calorie intake, and tobacco consumption, but none of the interaction terms reached statistical significance (Fig. 1).

DISCUSSION
Our results suggest that, whereas the Mediterranean diet was not related to mammographic density,
a higher adherence to the Western dietary pattern was associated with higher mammographic density. Subgroup analyses suggest that this effect may be confined to overweight and obese women and to be stronger among parous, nonsmokers, and women with elevated calorie intake. However, our tests for heterogeneity approached significance at best, probably for lack of power. Thus, larger studies are needed to confirm these potential differential effects of diet on mammographic density.

Taking into account that high mammographic density is considered one of the key risk factors for breast cancer, further research is needed to understand the role of dietary patterns in the development of breast cancer and to develop interventions to reduce mammographic density.
breast cancer, we expected to identify associations between dietary patterns and mammographic density similar in direction to those found for dietary patterns and breast cancer by Castelló et al. However, although we found a positive association for the Western dietary pattern, mammographic density was not influenced by adherence to the Mediterranean dietary pattern.

Our findings support previous studies exploring the association between mammographic density and specific nutrients or foods included in the Western dietary pattern that reported positive associations with total energy; high-density foods; total, saturated, and cholesterol fats; proteins; and meat. Not surprisingly, a Western-type diet contrasts with the recommendations issued by the World Cancer Research Fund and the American Association for Cancer Research to reduce cancer burden. Adherence to these recommendations has been positively associated with a reduction of breast cancer risk and mammographic density in our context.

On the other hand, a weak inverse association with the Mediterranean dietary pattern or with some of its main components such as olive oil, vegetables, and fiber has been previously reported. Others have found an absence or even a positive association of some of these items with mammographic density. These inconclusive findings suggest that a reduction in mammographic density may not be one of the key mechanisms through which the Mediterranean diet lowers breast cancer risk. A possible explanation for the contradictory effect of a Mediterranean diet on mammographic density and breast cancer is that this diet could be influencing the fat deposit of the breast without altering the percentage of dense tissue. Obesity, a condition inversely associated with mammographic density, increases breast cancer risk through several mechanisms, including the inflammatory effect of adipokines, whereas the Mediterranean diet seems to counteract an inflammatory state.

It is worth mentioning that the effect of the Western dietary pattern on mammographic density was observed only among overweight and obese women. Adipocytes are potent endocrine cells that produce hormones and growth factors; obesity strongly influences this endocrine milieu. Our results may reflect a synergic effect of this dietary pattern and the local adipose tissue on the fibroglandular component of the breast.

For its kind, this is a fairly large and carefully conducted study on risk factors and mammographic density; however, it presents some limitations. First, the sample size was insufficient to detect significant

| Dietary Pattern | Model 1* [OR (95% CI)]† | Model 2* [aOR (95% CI)]‡ | Model 3* [aOR (95% CI)]§ |
|----------------|-------------------------|-------------------------|-------------------------|
| Western Quartiles ||||
| 1 | 1 | 1 | 1 |
| 2 | 1.11 (0.93–1.32) | 1.09 (0.92–1.3) | 1.06 (0.89–1.27) |
| 3 | 1.13 (0.95–1.35) | 1.11 (0.93–1.32) | 1.05 (0.87–1.26) |
| 4 | 1.34 (1.12–1.59) | 1.35 (1.13–1.61) | 1.25 (1.03–1.52) |
| P ‡ | .002 | .001 | .039 |
| Per 1-SD increase | 1.11 (1.05–1.19) | 1.12 (1.05–1.20) | 1.09 (1.02–1.18) |
| Mediterranean Quartiles ||||
| 1 | 1 | 1 | 1 |
| 2 | 1.07 (0.90–1.27) | 1.06 (0.89–1.26) | 1.01 (0.85–1.20) |
| 3 | 1.06 (0.89–1.27) | 1.05 (0.88–1.25) | 0.97 (0.80–1.16) |
| 4 | 1.12 (0.94–1.34) | 1.12 (0.94–1.34) | 0.99 (0.81–1.21) |
| P ‡ | .234 | .228 | .811 |
| Per 1-SD increase | 1.06 (0.99–1.13) | 1.06 (1.00–1.13) | 1.02 (0.95–1.09) |

OR, odds ratio; CI, confidence interval; aOR, adjusted odds ratio; SD, standard deviation.
* All models included center as a random effect.
† OR and 95% CI adjusted for age and body mass index (BMI).
‡ OR and 95% CI adjusted for age, BMI, parity, menopausal and smoking status, family history of breast cancer, and use of hormone replacement therapy.
§ OR and 95% CI adjusted for age, BMI, parity, menopausal and smoking status, family history of breast cancer, use of hormone replacement therapy, and calorie and alcohol intake.
¶ P for trend resulting from the Wald test associated to the categorical variable include as continuous in the regression models.
# OR and 95% CI per one-standard deviation increase in the score of adherence to the specified dietary pattern.
interactions even when some differences by subgroups are observed. Second, the representativeness of the selected sample might be slightly biased because healthy screening participants might be more concerned about their health than nonparticipants. However, participation rates in Spanish breast cancer screening programs are high and women in our study are very similar to the women in the Spanish National Health Survey in terms of age range, socioeconomic level, prevalence of smoking, and physical activity.

Third, the visual assessment of breast density by a single radiologist may imply a degree of subjectivity. However, the radiologist had very high intraobserver concordance, and we have confirmed that the visual scale used here is a predictor of subsequent breast cancer development risk. Additionally, the collection of data with different mammographic devices and interviewers in different centers might introduce some heterogeneity. These unmeasured sources of variability were taken into account by including random center-specific intercepts in our regression models. Finally, it should be noted that the cross-sectional design of the current study precludes the establishment of causal relationships between adherence to dietary patterns and mammographic density. However, it is hard to think that this association is acting in the other direction because information on diet was collected before the mammographic exploration.

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Fig. 1. Adjusted odds ratios (aORs) and 95% confidence intervals (CIs) for the risk of high mammographic density in women in the fourth quartile of adherence to the Western dietary pattern according to the women’s characteristics. All interaction models were adjusted for all of the variables in the figure and included center as a random effect.

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