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Traditional dietary pattern of South America is linked to breast cancer: an ongoing case-control study in Argentina.

Natalia Tumas[1], Camila Niclis[2], Laura R Aballay[3], Alberto R Osella[4], María del Pilar Díaz[5*]

[*]Correspondingauthor: María del Pilar Díaz

1. Statistics and Biostatistics Unit, School of Nutrition, Faculty of Medical Sciences, National University of Córdoba, Córdoba, Argentina.
Center of Research and Studies in Culture and Society, National Council of Scientific and Technical Research (CONICET), Córdoba, Argentina.
Mailingaddress: Enrique Barros esq.Enfermera Gordillo, Ciudad Universitaria,
CP 5000, Córdoba, Argentina.
Email address: nataliatumas@gmail.com

2. Statistics and Biostatistics Unit, School of Nutrition, Faculty of Medical Sciences, National University of Córdoba, Córdoba, Argentina.
National Council of Scientific and Technical Research (CONICET), Córdoba, Argentina.
Mailingaddress: Enrique Barros esq.Enfermera Gordillo, Ciudad Universitaria,
CP 5000, Córdoba, Argentina.
Email address: cniclis@gmail.com

3. Statistics and Biostatistics Unit, School of Nutrition, Faculty of Medical Sciences, National University of Córdoba, Córdoba, Argentina.
Mailingaddress: Enrique Barros esq.Enfermera Gordillo, Ciudad Universitaria,
CP 5000, Córdoba, Argentina.
Email address: laballay@fcm.unc.edu.ar

4.Laboratorio di Epidemiologia e Biostatistica, IRCCS Saverio de Bellis, Castellana Grotte, Italia.
Mailing address: Via Turi, 27. Zip: 70013 CastellanaGrotte, Bari, Italia.
Email address:arosella@irccsdebellis.it

5. Statistics and Biostatistics Unit, School of Nutrition, Faculty of Medical Sciences, National University of Córdoba, Córdoba, Argentina.
Mailing address: Enrique Barros esq.Enfermera Gordillo, Ciudad Universitaria,
CP 5000, Córdoba, Argentina.
Email address: pdiaz@fcm.unc.edu.ar
Telephone number: +54 351 4629530

Abstract

Introduction: Several studies have shown the effect of dietary patterns on breast cancer risk but none has been conducted in Argentina. The aim of this study was to extract dietary patterns from FFQ and to estimate their effect on breast cancer occurrence while taking into account aggregation factors (family history of breast cancer),and to explore the sensitivity of the estimates to changes in the assumptions. **Methods:** A Principal Component Exploratory Factor Analysis was applied to identify dietary patterns, which were then included as covariates in a multilevel logistic regression. Family history of BC was considered as a clustering variable. A multiple probabilistic sensitivity analysis was also performed.**Results:** The study included 100 cases and 294 controls. Four dietary patterns were identified. *Traditional* (fat meats, bakery products and vegetable oil and mayonnaise) (OR III tertilevs I 3.13, 95%CI 2.58–3.78), *Rural* (processed meat) (OR III tertilevs I 2.02, 95%CI 1.21–3.37) and *Starchy* (refined grains) (OR III tertilevs I 1.82, 95%CI 1.18–2.79) dietary patterns were positively associated with BC risk, whereas the *Prudent* pattern (fruit and non-starchy vegetables) (OR III tertilevs I 0.56, 95%CI 0.41–0.77) showed a protective effect. For *Traditional* pattern, the median bias-adjusted ORs (3.52) were higher than the conventional (2.76). **Conclusions***:* While the *Prudent* pattern was associated with a reduced risk of BC, *Traditional*, *Rural* and *Starchy* patterns showed a promoting effect. Despite the threats to validity, the nature of associations was not strongly affected.

Key words: dietary patterns, breast cancer, Argentina, multilevel, sensitivity analysis.

Introduction

Breast cancer is a worldwide leading cause of cancer mortality and the most common form of cancer affecting women [1]. Moreover, when both sexes are considered it also has the highest incidence[2]. In Argentina, the female breast cancer mortality rate was 20.7x100000 person-years (py) in 2000, higher than that reported in North America and in all other Latin American countries [3]. A breast cancer incidence of 75.45 x 100000py women was reported in 2004 in this country, and in Córdoba (a central Argentinean province)breast cancer represents 25% of total tumors among the female population [4].

Scientific evidence suggests that life style factors such as diet, obesity and lack of physical activity, as well as certain reproductive choices, can modify the risk of breast cancer [5, 6]. Life style has significantly changed in the last 20 years worldwide (Swinburn BA, 2011). Argentina, like most Latin American developing countries, is undergoing a rapid epidemiological transition featuring a shift in dietary habits and physical activity patterns [7]. Dietary habits seem to play an important role in breast cancer etiology; however, apart from a consistent direct association between alcohol intake and breast cancer [8, 9], most of the relationships between foods or nutrients and this type of cancer remain controversial [10].

Results from studies of single nutrients and foods may be inconsistent because they cannot disaggregate individual effects of highly correlated foods or may be unable to account for synergistic interactions of food combinations and constituents [10, 11]. The use of dietary patterns encompasses the combined effects of multiple dietary components and offers an alternative dimension to probe diet-disease relationships and also has value in guiding dietary modification to reduce disease risk [12]. Exploratory factor analysis is a statistical tool that is increasingly being used for this purpose [13, 10, 14]. Exploratory factor analysis is a procedure that empirically determines whether a set of observed correlations (foods or nutrients) can, with reasonable accuracy, be thought of as reflecting, or as generated by, a small number of hypothetical underlying (latent) factors. This method creates "dietary patterns" by aggregating related foods/nutrients representing the eating patterns of the study population and distinguishes individuals by their predominant dietary choices [14].

A substantial amount of research has explored the influence of dietary patterns on breast cancer risk [16, 11, 17, 18, 15, 12, 19, 20]. However most of these were conducted in countries in which diets are very different to the typical Argentinean diet, characterized by a high consumption of animal protein and fats obtained mainly from red meat, a low fiber intake and high levels of alcohol consumption [21].

The issue of diet and breast cancer in Argentina has been considered in terms of foods and nutrients [22, 23] but never in terms of dietary patterns. Indeed, in this country only two studies about dietary patterns and cancer have been reported, namely colorectal [21] and urinary tract cancer [24].

Aim of this study was to extract dietary patterns from FFQ and to estimate their effect on breast cancer occurrence while taking into account aggregation factors (familiar history of breast cancer). Moreover, a sensitivity analysis of risk estimates by assuming different scenarios was performed.

Methods

Design and participants

This ongoing case-control study is conducted as part of a project named ''Environmental Epidemiology of Cancer in Córdoba'' (EECC) started in 2004 covering several aspects of cancer epidemiology [25,4, 26, 27], including case–control studies [21, 28] about the relationship of dietary and other environmental exposures with most the frequent cancers identified in Argentina: breast, prostate, colon, and bladder cancer.

The person-time experience that provided the data for this case-control study was generated from 2008 in the Córdoba population, the second most populated province (3,067,000 inhabitants, according to the last census) of the country.

Cases were 100 women under 85 years old with an incident of histologically confirmed breast cancer primary diagnosis (ICD-10th Edition, ICIE10:C50), identified by the Córdoba Tumor Registry. In the same time period, controls were randomly chosen from the electoral list. Controls were included after the verification of the absence of any neoplastic or related condition as well of conditions which changed alimentary habits for reasons of religion or custom. The verification was performed by asking questions aimed to exclude such conditions and contemplated in the questionnaire. 294 non-hospital controls matched by sex, age (± 5 y) and place of residence were considered. The area from which cases come includes rural and urban counties which are representative of the whole population of Córdoba province [25]. Less than 10% of subjects contacted refused to participate.No statistically significant differences in age and geographical area were found between them and included controls. However, a possible residual selection bias was taken into account and considered in the sensitivity analysis.

The study was approved by the Ethical Committee of the Faculty of Medical Sciences, University of Córdoba, and has therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki. All participants gave informed consent prior to their inclusion in the study.

Exposure Assessment

An at-home face-to-face interview based on a questionnaire was carried out by trained interviewers. The questionnaire included information on socio-demographic characteristics (age, residence, urban/rural status), smoking history (years of smoking, average number of cigarettes per day, type of tobacco and type of cigarette), alcohol consumption (type of beverage and grams per day), self-reported anthropometric characteristics, menstrual and reproductive history (age at menarche, age at menopause, parity, number of live births, breastfeeding), medical insurance, personal medical history and family history of cancer. Physical activity was measured by means of The International Physical Activity Questionnaire [29]. Answers to different items are then expressed as Metabolic Equivalent of Tasks (METs). Subsequently METS were categorized into low (<600 METs), moderate (600-1500 METs), and high (>1500 METs) categories of physical activity intensity.

A validated Food Frequency Questioner (FFQ) [30] of 127 items was used. The FFQ was coupled with a validated photographic atlas based on standard portion sizes in Argentina [31]. FFQ focused on the five-year period before diagnosis for cases and before interview for controls. Daily intake quantification (calories, macro and micronutrients) was performed using the software Nutrio 2.0 [32]. Nutrio's database of food composition includes a nutritional food composition table of Argentina [33] and information from other biochemical determinations made at the local level [34]. Given the characteristics of the interview, missing values in a FFQ do not exist.

Statistical Analysis

Dietary patterns identification

Characterization of dietary patterns was performed on the 294 controls. A Principal Component Exploratory Factor Analysis (PCFA) and a Varimax rotation method were applied.

The 127 food items contained in the FFQ were grouped into 20 predefined food groups based on similarities in nutrient profile and culinary usage in Argentinean diet: hard cheeses, soft cheeses, milk and yogurt, lean meat (red meat with up to 14% of fat content and skinless chicken), fat meat (red meat with more than 14% of fat content and chicken with skin), processed meat (cold meats), eggs, starchy vegetables, non-starchy vegetables, fruits, whole grains, refined grains, pulses, bakery products, candies (ice cream, chocolates, peanut butter, *dulce de leche*- milk and sugar caramel -), added sugar and sweets (sugar, jam, honey, caramel), butter and milk cream, vegetable oils and mayonnaise, alcoholic beverages and non-alcoholic beverages.

The factorability of the correlation matrix was evaluated by applying the same criteria used previously [21]: factor eigenvalue greater than 1, statistical indicators such as Bartlett's test of sphericity and Kaiser–Meyer–Olkin (KMO) (in which values between 0.5 and 1.0 indicate factor analysis is appropriate). Also, Akaike Information (AIC) and Bayesian Information (BIC) were taken into account for parsimony and plausibility of the factors. The Varimax factor rotation technique was applied to the factor-loading matrix to facilitate interpretability of the factors. Each factor was labeled by its dominant food groups and those with absolute rotated factor loading ≥0.60 were considered. Then, cases and controls were scored by applying the regression method. These scoring coefficients indicate the degree to which each subject's diet conforms to each of the identified patterns [19]. All participants were then categorized into tertiles (low, medium and high) of each factor scores.

As a second step, each pattern was correlated with some life-style and socio-demographic characteristics, using direct and partial correlation coefficients. The proportion differences test was used for comparison of variables of interest between cases and controls.

Risk analysis

A multilevel logistic regression (MLR) model for the binary response (1 if a case, 0 otherwise) was fitted, considering that the individual probability of a positive outcome is dependent on both individual level as well as contextual or group variables (family history characteristics) of the subject. Covariates at first-level of MRL were tertiles of dietary patterns,total energy intake and selected recognized variables in breast cancer risk:Body Mass Index (BMI)[35], gynecological status[36], education[37]and physical activity[38], while family history of breast cancer was considered as a second-level or clustering variable. The model was fitted assuming Tertile I (TI) as the reference category (which represents subjects with the lowest intakes of the dominant foods). Only the variance was estimated in this second hierarchy. Unlike the classical logistic regression model, MLR was also used to avoid underestimating the standard error of the regression coefficient of aggregate risk factor, leading to overestimation of the significance of the risk factor [39]. This is an important aspect to consider, mainly because of the small sample size of this work. There is agreement that a small sample size at level two leads to biased estimates of the second-level standard errors, although only a variance (family history of breast cancer), and not regression coefficients, is estimated in our work.

Sensitivity Analysis

A multiple probabilistic sensitivity analysis was performed by assigning more conventional probability density distributions to the values of the bias parameters. The goal of such an analysis is to find a plausible range of estimates of the effect of interest and to assess how sensitive the conclusions are to changes in the assumptions [40].These density distributions were parameterized on the basis of internal and/or external validation or evidence. Differential misclassification was assumed by drawing the sensitivities and specificities from different trapezoidal distributions for cases and controls. Thus, a minimum of 0.70 and 0.75 and a maximum of 0.90 and 1 were assigned in case and control specificity respectively, while both sensitivities ranged from 0.75 to 1. Lower specificity was assigned in the cases group, taking into account the widely documented possibility of recall bias. In addition, a higher probability to select unexposed cases and controls was assumed, as respondents could have higher interest in health-related issues and have healthier habits than nonrespondents. However, only a small association between respondents-nonrespondents and breast cancer is expected. Thus, we assigned a prior lognormal distribution to the selection-bias factor with mean 0 and standard deviation 0.21, which yields 95% prior probability of the bias factor falling between exp(0-1.96*0.21)=0.7 and exp(0+1.96*0.21)=1.5. Finally, the potential confounding effect introduced by ignoring the effect of some reproductive characteristics was considered. Higher parity, higher time of breastfeeding and lower age at first birth are all well-known protective factors [41, 14] of breast cancer. These characteristics have a higher prevalence in exposed, since they are more common at a lower socioeconomic status like the traditional pattern. Thus, a prevalence of the confounder of 0.2 to 0.3 and 0.1 to 0.2 was assigned among exposed and unexposed respectively and a prior probability distribution was specified for the confounder-breast cancer OR that is lognormal with 95% confidence limits of ln(0.4) and ln(0.9). These limits imply that the mean of this prior distribution is {ln(0.4)+ln(0.9)}/2=-1.1268 with standard deviation {ln(0.4)+ln(0.9)}/(2*1.96)=-0.0575. The multiple probabilistic sensitivity analysis was applied only to the effect of *Traditional* pattern on the risk of breast cancer as it is the most characteristic pattern of the Argentinean diet.

Stata 11.2 software [42] was used for all analysis (factor analysis, its rotations and multilevel model fitting), including the user-written –episens- command [43] for sensitivity analysis.

Results

Selected study participant characteristics are shown in Table 1. Ages ranged from 24 to 88 years and, as expected from the matched design, were similar among cases and controls (58.67y±11.88y; 58.86y ± 13.94y, respectively). Cases had more frequentoverweight ($p<0.10$), presented low physical activity and higher levels of energy intake ($p<0.05$). The proportion of women who breastfed was similar in both groups, but the prevalence of lactation for six or more months was more frequent in woman with breast cancer (76 vs 84%). A minority of cases and controls had menarche before 12 years old. As regards the education variable, there was a similar distribution in cases and controls (most women presented medium educational level in both groups).

Dietary patterns

Four primary dietary patterns were identified (cumulative variance around 40%). The factor loadings matrix among controls is shown in Table 2. Overall estimated KMO values indicated that factor analysis was suitable for the dataset (KMO=0.65). Factor 1 displayed high loadings for fat meats, bakery products and vegetable oil and mayonnaise. This factor was called the *Traditional* pattern, explaining 13% of the variance. The second factor, defined as the *Rural*pattern, showed high loadings for processed meat and explains 10% of the variance. The third factor, defined the *Prudent* pattern, had the greatest absolute loadings on fruit and the non-starchy vegetables group, explaining 7% of the variance. The last pattern was characterized by high positive loadings of refined grains, and a negative loading for whole grain consumption, and was labeled the *Starchy* pattern.

Correlations between dietary patterns and other selected variables are shown in Table 3. The *Traditional*, *Rural* and *Starchy* patterns were associated positively with total energy intake (Pearson correlations).

Risk analysis

Adjusted odds ratios (OR) and the corresponding 95% confidence intervals (95%CI) for breast cancer by tertiles of dietary pattern scores are shown in Table 4. Four simultaneous dietary factors, together with BMI, educational level, total energy intake, gynecological status and physical activity were included in the multilevel model, considering family history of breast cancer as a clustering variable (Table 4). Women belonging to the second or third tertiles of the *Traditional* pattern had significantly higher risk for breast cancer than the reference (OR 1.63 95%CI 1.59–1.69, and OR 3.13, 95%CI 2.58–3.78, respectively). High scores for the *Rural* and *Starchy* patterns were also positively related to breast cancer risk (OR 2.02, 95%CI 1.21–3.37; OR 1.82, 95%CI 1.18–2.79, respectively), whereas the same category of the *Prudent* pattern showed a protective effect (OR 0.56, 95%CI 0.41–0.77). Moreover, women with BMI ≥25 kg/m^{2}had a higher risk of breast cancer compared with those without overweight (OR 1.52 95%CI 1.31–1.75). The highest category of total energy intake evidenced a promoting effect (OR 1.55 95%CI 1.29–1.88) and a lower education level was inversely associated with breast cancer (OR 0.56 95%CI 0.34–0.91).

Finally, results of the probabilistic sensitivity analysis show that the bias-adjusted median ORs (3.52) is higher than the conventional (2.76), but the ratio of 95% simulation limits including systematic and random error is 90% higher than the conventional (Table 4).

Discussion

This work identified 4 dietary patterns that explained about 37 % of the total variance in dietary intakes. These preliminary results show that the *Traditional* (fat meats, bakery products and vegetable oil and mayonnaise), *Rural* (processed meat) and *Starchy* patterns (refined grains) were positively associated, whereas the*Prudent* pattern (fruit and non-starchy vegetables group) was negatively associated with an increased risk of breast cancer. BMI and total energy intake also have a promoting effect on breast cancer occurrence, while low educational level has a preventive effect. Because it is well-established in genetic epidemiology that family history is an important indicator of family aggregation of disease, we proposed a modeling approach including breast cancer family history as a possible clustering variable of subjects. Although the portion of explained variability was not significant, we decided to maintain it for possible interpretations and comparisons with similar approaches in risk factors in cancer studies. A woman's risk of breast cancer approximately doubles if she has a first-degree relative (mother, sister, daughter) who has been diagnosed with breast cancer. About 15% of women who got breast cancer had a family member diagnosed with it.

To our knowledge, no study on breast cancer and diet had been published applying factor analysis in Argentina. In the present study an elevated risk of breast cancer was evident for second and third tertiles of the *Traditional* pattern. Similar patterns were found by several researchers, frequently named the Western pattern [44, 20, 45, 46] and, as in our study, most of these had a promoting effect on breast cancer occurrence. Conversely, a recent systematic review and meta-analysis on dietary patterns and breast cancer risk concluded there was no evidence of a difference in the risk of breast cancer between the highest and the lowest categories of *Western/unhealthy* dietary patterns [47].

In a case–control study carried out in Córdoba city (Argentina) to describe the role of dietary patterns on the risk of developing urinary tract tumors, two dietary patterns similar to our *Traditional* and *Prudent* patterns were identified [24]. However, a multiple correspondence analysis was used to explore dietary patterns and both sexes were considered.

Barbecued red meat is most prevalent in the Argentinean population, where there is traditionally a high consumption of animal protein and fats obtained mainly from red meat [48, 21]. Particularly in Córdoba province, Navarro et al. [48] reported a high intake of meat and meat products, with a mean of about 280 g/d. There has been no clear scientific consensus as to whether red and processed meat intake increases the risk of breast cancer. Results from a recent review and meta-analysis of red and processed meat consumption and breast cancer concluded that it did not appear to be independently associated with increasing the risk of breast cancer [49].

The *Rural* pattern, basically composed of processed meat, was also reported in other studies, named as the *Western* pattern [50]. This pattern displayed a 2-fold increase in risk for the higher category in the Montevideo (Uruguay) population, and the same result was observed in our study in Córdoba (Argentina). Uruguay's major ethnic streams and diet are similar to the Argentinean, though recently the existence of country-specific patterns has been emphasized [51].Although our *Traditional* and *Rural* patterns had differences with the Southern Cone pattern identified by Pou et al. in Córdoba province, it is clear that red meat is present in all of them. The main distinction between those patterns might be explained by the differences in drinking habits between female and male genders. Traditionally, Argentinean women drink less alcohol than men, which could explain the absence of high loadings on alcoholic beverages.According to the National Risk Factors Survey in Argentina in 2009, regular alcohol risk consumption and episodic excessive alcohol consumption in Córdoba province were higher in men than in women (16.8 vs. 7.8% and 18 vs. 4.4%, respectively) [52].

We detected that the *Prudent* pattern, basically composed of fruits and non-starchy vegetables, results in a reduction of breast cancer risk. That had also been reported in other epidemiological research [17, 49, 51]. However, in a previous study this pattern showed a null [12, 53, 46] or positive association with breast cancer risk [20]. On the other hand, a pooled analysis of 8 cohort studies found no overall association between fruit and vegetable intake and breast cancer risk [54], while other research evidenced an inverse association [55, 56].

The *Starchy* pattern showed high positive loadings for refined grains and a high negative load for whole grains. This pattern could be integrated into the starch-rich pattern identified by Edelfonti et al. (2008) as well as with the Canteen pattern identified by Sieri et al. (2004). Our *Starchy* pattern was positively associated with breast cancer risk, which is consistent with the results of Edelfonti et al. (2008). In contrast, the Canteen pattern (pasta and tomato sauce, by Sieri et al.) did not show any association with breast cancer occurrence. Other research studies linked frequent consumption of whole grains with a significantly decreased risk of most cancers, including breast cancer [57]. On the other hand, Nicodemus et al. reported a null association between whole and refined grain intake and postmenopausal breast cancer risk [58].

In this study, age at menarche and age at first birth did not show any association with breast cancer occurrence. Nevertheless, it is known that these are two well-established breast cancer risk factors [59, 60], marking the beginning and end of a period over which the nulligravid breast is undifferentiated and particularly susceptible to the potentially carcinogenic effects of endogenous hormones that circulate with menstrual cycling [61-63]. In most populations, women's average age at menarche has been declining in successive birth cohorts [64] contributing to increasing incidence of breast cancer worldwide[65-67]. Results from research in Eastern China in 2008 showed a gradual shift towards an earlier age at menarche, and shorter breastfeeding lengths [68]. The protective effect of breastfeeding seems greater for women who had extended periods of breastfeeding during their lifetime [69-75]. However other research, including ours, found no association between time of breastfeeding and breast cancer risk [76- 78].

In this work, physical activity and BMI did not show association with breast cancer risk, which is consistent with results from other studies [79-81].On the other hand, a meta-analysis showed a 6% decrease in risk for each additional hour of physical activity per week [82], and several studies found a positive association between BMI and breast cancer risk [83-85].

Because of the nature of this study, the possibility of systematic errors must be considered. Case-control studies were commonly affected by recall bias caused by “rumination” in cases regarding the possible causes of their disease. On the other hand, it is known that in general, the low specificity is associated with a higher degree of bias when the exposure prevalence is low [86], but the Argentinean population showed a high exposure prevalence given the dietary patterns found in the present and in other recent studies [21, 24]. Further, our FFQ had a satisfactory level of validity and reproducibility [30].

Interviewer bias is also a potential threat to any case-control study. However, we implemented several procedures to minimize the likelihood of its occurrence, including the development of a detailed manual of operations, the training of staff, the standardization of data collection procedures, and the monitoring of data collection activities. Moreover, most of interviewers were masked with regard to the main study hypothesis which may remove an important source of bias, particularly when they are familiar with the case-control status of study participants.

In order to avoid potentially important confounding factors we tried to make cases and controls as similar as possible by matching by sex, age and place of residence, and they were interviewed in the same period of time, all of which also reduces the possibility of selection bias. Nevertheless, residual confounding may be present as we are not sure whether the study base was selected in such a way as to include covariant factors that do not occur in the general population and whether the sample size is sufficient to detect a reliable effect of dietary pattern exposure on breast cancer occurrence [21]. For instance, some reproductive characteristics (parity, time of breastfeeding and age at first birth), which have a recognized/known protective effect for breast cancer and a possible association with the exposure, must be considered.

For this purpose, a multiple probabilistic sensitivity analysis was carried out. As expected, the OR for the traditional pattern increased 30%. Most of this increase may be attributed to heterogeneity caused by unobserved confounding, which was named here as reproductive characteristics. In fact, among women with fewer years of schooling, there was an important protective effect of the exposure of interest. No evidence of important influence of selection and classification (although non-differential classification was assumed) bias was observed. In this sense, it is worth noting that the Argentinean population's exposure to the *Traditional* pattern is intensive, as almost all the population may be located at the highest level of exposure [48, 21].

Conclusions

Summing up, the present study identified four dietary patterns named as *Traditional*, *Rural*, *Prudent* and *Starchy*. Whereas the *Prudent*pattern was associated with a reduced risk of breast cancer, the *Traditional*, *Rural* and *Starchy* patterns showed a promoting effect. Our results support the hypothesis of an association between dietary patterns and breast cancer. Further studies could reassure the validity of our findings. In particular, confirmatory factor analysis could clarify the dietary patterns found in this study. The particular alimentary habits of this region turn necessary to deepen the study of dietary patterns and its effect on breast cancer occurrence.

List of abbreviations

BC: Breast Cancer; OR: odds ratio; py: person-years; EECC:Environmental Epidemiology of Cancer in Córdoba; METs: Metabolic Equivalent of Tasks; FFQ: Food Frequency Questioner; PCFA: Principal Component Factor Analysis; KMO: Kaiser–Meyer–Olkin; AIC: Akaike Information; BIC: Bayesian Information; MLR: Multilevel Logistic Regression; BMI:Body Mass Index;TI: Tertile I.

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Conflict of interest

On behalf of all authors, the corresponding author states that there is no conflict of interest.

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