RESEARCH COMMUNICATION

Nutrient Patterns and Risk of Breast Cancer in Uruguay

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Abstract

Objectives. To explore the role of nutrient patterns in the etiology of breast cancer (BC) among Uruguayan women. Methods. A principal component analysis was conducted. The study included 442 newly diagnosed cases of BC and 442 hospitalized controls. Results. Two dietary patterns derived from factor analysis and were labeled as high-meat and antioxidants patterns. Whereas the high-meat pattern was directly associated with BC risk (OR for the highest versus the lowest quartile = 3.50, 95 % CI 1.94-6.30, p-value for trend <0.0001), the antioxidants pattern displayed a protective effect (OR=0.44, 95 % CI 0.27-0.74). Its negative association was stronger for postmenopausal than for premenopausal women (OR=0.63, 95% CI 0.51-0.79 vs. OR=0.89, 95% CI 0.50-1.56, respectively). Both strata were heterogeneous (p=0.004). The high-meat pattern was more associated with BC risk among patients with family history of BC compared with participants without it, but results did not differ by histology. In contrast, the antioxidants pattern was more associated with non-ductal cancers (OR=0.50 [95 % CI 0.35-0.69]) than with ductal cancers (OR=0.72, 95 % CI 0.58-0.88, heterogeneity p-value=0.03). Conclusions. Results support an association between the high-meat and antioxidant dietary patterns and BC risk. Furthermore, findings suggest that gene-environmental interactions may be important in BC etiology.

Keywords: Breast cancer - diet - factor analysis - foods - nutrients

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Introduction

Breast cancer (BC) is the leading malignancy among Uruguayan women. Moreover, the incidence rates in Uruguay are among the highest in the World (Parkin et al., 2002). The causes are mostly unknown, but dietary factors and family history of BC (a possible marker of genetic structure) are strongly suspected of being related with the etiology of this malignancy (Ronco et al., 1996; 2003; 2006; De Stefani et al., 1997; Zheng et al., 1998; Hermann et al., 2002; Shannon et al., 2003). The Uruguayan diet is characterized by high consumption of red meat and a low intake of vegetables and fruits (Buiatti et al., 1993; Matos et al., 2002). In fact, beef consumption in Uruguay is the highest in the World (Matos and Brandani, 2002).

In a previous factor analysis study on food patterns and risk of BC conducted in Uruguay, the so-called Western pattern was characterized by high loadings on beef (Ronco et al., 2006). In fact, factor analysis has been widely used in recent yea rs in order to study the role of broad eating patterns and its relation with cancer sites. All the studies employed principal component analysis and they explored the role of eating different foods in the etiology of several cancer sites. To our knowledge, few studies of nutrient patterns in relation to cancer, more precisely to esophageal (De Stefani et al 2008), gastric (Palli et al 2001, Bertuccio et al 2009), lung (De Stefani et al 2008) and breast cancer (Edefonti et al 2008). Up to the moment, several studies on food patterns and risk of BC were conducted in developed countries (Terry et al., 2001; Sieri et al., 2004; Fung et al., 2005; Männistö et al, 2005; Velie et al, 2005; Murtaugh et al, 2008; Agurs-Collins et al, 2009; Brennan et al, 2010). Whereas the Swedish study identified a drinker pattern as a risk factor, the Italian one established that the salad vegetables pattern was protective against breast cancer. Finally, the US study found that the Western pattern was associated with increased breast cancer risk among smokers and the prudent pattern was protective among those with estrogen negative (ER-) tumors. The Uruguayan study (Ronco et al., 2006) reported an increased risk of BC associated with the Western pattern, whereas the healthy and traditional ones were protective.

Nutrients (and bioactive substances) could play an important role in breast carcinogenesis. Weisburger (2002) suggested that heterocyclic amines (HCA) could

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be major initiators in the process of breast carcinogenesis, whereas fats may act as promoters in a later step of this process. Weisburger's findings led us to think that both constituents (HCA and fats) should be clustered in the same factor or pattern. For these reasons, we decided to conduct an exploratory factor analysis on nutrients, bioactive substances and breast cancer.

Materials and Methods

Selection of cases

In the time period 1996-2004 a case-control study on environmental factors and risk of cancer was conducted in Montevideo, Uruguay. All newly diagnosed and microscopically confirmed cases of BC occurring in the four major hospitals of Montevideo, Uruguay, were considered eligible for this study. In total 452 cases were identified. From this initial number, ten patients refused the interview, leaving a final number of 442 patients (response rate 97.8 %). Eighty four (84, 19.0 %) were premenopausal and 358 (81.0 %) were postmenopausal. Regarding the histologic pattern, 372 patients (84.2 %) showed infiltrating duct carcinoma followed by undifferentiated carcinoma (31, 7.0 %), inflammatory carcinoma (17, 3.8 %), lobular carcinoma (10, 2.3 %), infiltrating comedocarcinoma (5, 1.1 %), medullary carcinoma (3, 0.8 %), colloid carcinoma (2, 0.4 %) and squamous cell carcinoma (2, 0.4 %).

Selection of controls

In the same time period and in the same hospitals, 607 patients afflicted with non-neoplastic diseases, not related to tobacco smoking or alcohol drinking and without recent changes in their diet were considered eligible for the study. From this initial number, fifteen patients refused the interview leaving a final number of controls of 592 (response rate 97.5 %). From this pool of potential controls, four hundred and forty two controls (442) were frequency matched to the cases on age, residence and urban/rural status. The control patients presented the following diseases: abdominal hernia (99 patients, 22.4 %), eye disorders (76, 17.2 %), fractures (71, 16.1 %), varicose veins (46, 10.4 %), acute appendicitis (37, 8.4 %), hydatid cyst (33, 7.5 %), injuries (22, 5.0 %), osteoarticular disorders (18, 4.1 %), urinary stones (16, 3.6 %), skin diseases (14, 3.2 %) and blood disorders (10, 2.3 %).

Questionnaire

All patients were administered a structured questionnaire shortly after admittance to the hospitals. The questionnaire included sections on 1. Socio-demographic variables, 2. A complete history of tobacco smoking (age at start, age of quit, average number of cigarettes per day, type of tobacco and type of cigarette), 3. A complete history of alcohol drinking, 4. Occupational exposures based on job titles and their duration, 5. Menstrual and reproductive variables (age at menarche, age at menopause, number of live births, age at first live birth, age at last live birth, breastfeeding, spontaneous abortions, induced abortions, use of exogenous hormones, use of contraceptive drugs), 6. Self reported height and weight 5 years before the interview, 7. Family history of cancer in first degree relatives and 8. A food-frequency questionnaire (FFQ) on 64 foods. This FFQ is representative of the Uruguayan diet and was tested for reproducibility with good results (Ronco et al., 2006).

Nutrients and bioactive substances. Estimates of nutrient intakes were derived by use of a local table of the chemical composition of foods (Mazzei et al., 1995). Heterocyclic amines (HCA) values were derived from data published by Sinha and Rothman (1997). The following nutrients were included in the factor analysis: 1. total protein, 2. saturated fat, 3. monounsaturated fat, 4. linoleic acid, 5. alpha-linolenic acid, 6. cholesterol, 7. glucose, 8. fructose, 9. beta-carotene, 10. other carotenoids (alpha-carotene, lutein, lycopene, beta-cryptoxanthin), 11. vitamin C, 12. vitamin E, 13. flavonoids, 14. phytosterols, 15. 2-amino-3-methylimidazol[4,5-f]quinoline (IQ), 16. 2-amino-3,8-dimethylimidazol[4,5-f]quinoxaline (MeIQx) and 17. 2-amino-1-methyl-6-phenylimidazol [4,5-b]pyridine (PhIP). All constituents were included in the model as continuous after log-transformation.

Statistical analysis

Exploratory factor analysis (principal components) was used to derive broad nutrient patterns based on the 17 variables in our data. Two factors were retained being the criteria for extraction an eigenvalue equal or greater than one and the Scree test. Since the factors were rather highly correlated (rho=0.41), they were rotated by the promax (oblique) method after normalization by the Horst criteria in order to obtain a simpler structure with greater interpretability (Harman, 1976; Kim and Mueller, 1978; Kline, 2002). In order to obtain the best solution for the rotated model we followed the Thurstone criteria (Thurstone, 1947), that is the same number of zero loadings as retained factors and a small number of high loadings for each pattern. Positive factor loadings indicate that the nutrient group is directly associated with the pattern, whereas that negative loadings indicate an inverse association with the factor. Labeling of factors was arbitrary and was based on our interpretation of the data. Nutrients (or foods) with loadings higher than 0.30 were considered as statistically significant. Then we scored each rotated factor using the predict command in STATA (2005). Scores were used to assess the associations of the nutrient patterns with risk factors for BC and to assess the risk of BC associated with each pattern.

Relative risks, approximated by the odds ratios for the scores of the dietary patterns, were estimated by unconditional multiple logistic regression (Breslow and Day, 1980). The following covariates were included in the multivariable model: age (continuous), residence, urban/rural status, education (categorical), family history of BC in first degree-relatives, body mass index (categorical), menopausal status, age at menarche (categorical), parity (categorical) and total energy intake (continuous). Estimates for each nutritional pattern, in models including the same terms as previously, were sequentially stratified by: menopausal status (pre-, post-), alcohol drinking (never, ever), tobacco smoking (never, ever), family

history of BC (no, yes), as well as by histologic type (ductal carcinoma, others). Finally we performed a cluster analysis of partition type (Kmeans cluster analysis) to estimate ORs of HCA and fats separately. All calculations were performed with the STATA program (2005).

Results

Table 1 shows the general features of the population studied. As a result of the frequency matched design, age, residence and urban/rural status were very similar. Also education and monthly income in US dollars were similar. On the other hand, cases showed a much higher proportion of relatives with BC compared with controls (OR 2.8, 95 % CI 1.8-4.2). Cases were slightly leaner compared with controls, but the differences were not significant. Total energy intake was significantly higher among cases compared with controls, whereas there was no difference by menopausal status. Early age at menarche and low parity were associated with increased risk of breast cancer. Finally, a longer duration of breastfeeding was associated with a reduction in risk of 40 %.

Table 1. Distribution of Sociodemographic Variables and Selected Risk Factors

Variable	Category	Cases	Controls	p-value
Age (years)	30-39	38 (8.6)	38 (8.6)	
	40-49	67 (15.2)	67 (15.2)	
	50-59	108 (24.4)	108 (24.4)	
	60-69	109 (24.7)	109 (24.7)	
	70-79	103 (23.3)	103 (23.3)	
	80-89	17 (3.8)	17 (3.8)	1.00
Residence	Montevideo	228 (51.6)	228 (51.6)	
	Others	214 (48.4)	214 (48.4)	1.00
Urban /Rural Status	Urban	372 (84.2)	379 (85.7)	
	Rural	70 (15.8)	63 (14.3)	0.51
Education (years)	0-2	153 (34.6)	136 (30.8)	
	3-5	176 (39.8)	219 (49.5)	
	≥6	113 (25.6)	87 (19.7)	0.01
Income (US dollars)	≤149	160 (36.2)	148 (33.5)	
	≥150	152 (34.4)	161 (36.4)	
	Unknown	130 (29.4)	133 (30.1)	0.68
Family History	No	350 (79.2)	404 (91.4)	
	Yes	92 (20.8)	38 (8.6)	<0.0001
BMI	≤23.5	123 (27.8)	112 (25.3)	
	23.6-26.8	103 (23.3)	110 (24.9)	
	26.9-30.4	115 (26.0)	110 (24.9)	
	≥30.5	101 (22.9)	110 (24.9)	0.74
Menopausal Status	Pre-	84 (19.0)	90 (20.4)	
	Post-	358 (81.0)	352 (79.6)	0.61
Age of Menarche	15+	42 (9.5)	71 (16.1)	
	12-14	294 (66.5)	302 (68.3)	
	≤11	106 (24.0)	69 (15.6)	<0.0001
Parity	Nuliparae	88 (19.9)	56 (12.7)	
	1-2	176 (39.8)	155 (35.1)	
	3-4	107 (24.2)	119 (26.9)	
	5+	71 (16.1)	112 (25.3)	0.001
N° of patients		442 (100.0)	442 (100.0)	

N°(%); Family History of Breast Cancer; BMI: Body Mass Index

Table 2. Factor-loading Matrix among Controls[1,2]

Nutrient	Factor 1	Factor 2	Communality
Protein	**0.68**	0.33	0.77
Saturated fat	**0.92**	0.05	0.88
Monounsaturated fat	**0.95**	0.02	0.91
Linoleic acid	**0.91**	0.03	0.85
Linolenic acid	**0.88**	0.11	0.87
Cholesterol	**0.77**	0.21	0.67
Glucose	-0.13	**0.85**	0.66
Fructose	-0.16	**0.82**	0.58
Vitamin C	0.03	**0.84**	0.73
Vitamin E	0.33	**0.71**	0.82
Beta-caroteno	-0.03	**0.65**	0.41
Other carotenoids	-0.11	**0.78**	0.55
Flavonoids	0.16	**0.66**	0.55
Phytosterols	0.03	**0.73**	0.56
IQ[3]	**0.92**	-0.24	0.72
MeIQx[4]	**0.75**	-0.17	0.50
PhIP[5]	**0.79**	-0.13	0.56
Variance (%)	0.45	0.36	0.81[6]

[1]Loadings higher than 0.39 are typed in bold; [2]Sampling adequacy = 0.84; [3](2-amino-3-methylimidazol[4,5-f] quinoline); [4](2-amino-3,8-dimethylimidazol[4,5-f] quinoxaline); [5](2-amino-1-methyl-6-phenylimidazol[4,5-b] pyridine); [6]Total variance (including error variance): 81 %

Table 3. Correlations between Nutrient Patterns and Selected Variables[1]

Variables	Factor 1 High meat	Factor 2 Antioxidants
Age[2]	**-0.17**	-0.00
Residence[3]	0.00	-0.08
Education[3]	**0.10**	0.08
Family history[3]	0.04	**0.11**
Body mass index[3]	0.09	0.04
Smoking intensity[3]	**0.16**	0.02
Smoking duration[3]	**0.14**	0.03
Alcohol drinking[3]	**0.13**	0.06
Menopausal status[3]	**-0.13**	0.07
Menarche[3]	-0.05	0.06
Parity[3]	0.09	-0.02
Fried red meat[2]	**0.81**	-0.01
White meat[2]	0.01	**0.11**
Processed meat[2]	**0.16**	0.06
High-fat foods[2]	**0.13**	**-0.14**
Total vegetables[2]	0.04	**0.55**
Total fruits	-0.03	**0.60**
Total vegetables & fruits[2]	-0.00	**0.71**

[1]Significant correlations (>0.09) are typed in bold; [2]Pearson correlations; [3]Spearman correlations

Factor-loading matrix among controls is shown in Table 2. The procedure retained 2 factors. Factor 1 was characterized by high positive loadings on protein, saturated fat, monounsaturated fat (MUFA), linoleic acid, alpha-linolenic acid, cholesterol and HCA (Iq, MeIQx, PhIP). Since these constituents are found mainly in cooked red meat, we labeled this factor as the high-meat pattern, explaining 45 % of the variance. Factor 2 presented high positive loadings on glucose, fructose, vitamin C, vitamin E, carotenoids, flavonoids and phytosterols. We

Table 4. Odds Ratios of Breast Cancer for Scored Nutrient Patterns

Scored Pattern	Cases/Controls	OR[1](95%CI)	OR[2](95%CI)
High-meat			
Low	54/110	1.0 (reference)	1.0 (reference)
2	83/111	1.57 (1.01-2.43)	1.66 (1.01-2.73)
3	121/111	2.41 (1.58-3.70)	2.25 (1.34-3.77)
High	184/110	3.81 (2.50-5.79)	3.50 (1.94-6.30)
p-value for trend		<0.0001	<0.0001
Antioxidants			
Low	107/110	1.0 (reference)	1.0 (reference)
2	119/111	0.96 (0.65-1.42)	0.88 (0.58-1.34)
3	118/111	0.87 (0.59-1.29)	0.68 (0.44-1.06)
High	98/110	0.64 (0.42-0.96)	0.44 (0.27-0.74)
p-value for trend		0.03	0.001

[1]Unadjusted; [2] Adjusted for age, residence, urban/rural status, education, family history of breast cancer in first-degree relatives, body mass index, menopausal status, age at menarche, parity, total energy intake and both patterns.

Table 5. Odds Ratios of Breast Cancer for Nutrient Patterns by Menopausal Status, Family History among First-degree Relatives and Histologic Type[1]

Pattern	OR (95%CI)	OR (95%CI)	Heterogeneity
	Menopausal Status		
	Premenopausal	Postmenopausal	
High-meat	1.45 (0.83-2.62)	1.72 (1.32-2.26)	0.41
Antioxidants	0.89 (0.50-1.56)	0.63 (0.51-0.79)	0.005
	Family history of breast cancer		
	No	Yes	
High-meat	1.54 (1.20-1.98)	4.49 (1.67-12.0)	0.02
Antioxidants	0.74 (0.60-0.90)	0.17 (0.06-0.48)	0.33
	Histology		
	Ductal	Other types	
High-meat	1.60 (1.25-2.05)	1.65 (1.06-2.55)	0.90
Antioxidants	0.72 (0.58-0.88)	0.50 (0.35-0.69)	0.03

[1]Adjusted for age, residence, urban/rural status, education, body mass index, menarche, parity, total energy intake and both nutrient patterns entered into the model as continuous variables

labeled this factor as the antioxidants pattern. This pattern explained 36 % of the variance. Both factors showed high communalities (more than 0.70) in 14 of 17 nutrients and bioactive substances (82 %). Furthermore, they were characterized by more than 2 zero loadings per eigenvalue. The sampling adequacy, tested by the Kaiser procedure, was very high (0.84). We considered that we reached a simple structure, which was reliable and reproducible.

Correlations between both patterns and several variables (socio-demographic, environmental and dietary) are shown in Table III. Factor 1 was associated with higher education, lower age, higher smoking intensity and duration, higher alcohol intake and with premenopausal status. Concerning food groups, the factor 1 was directly correlated with fried red meat, processed meat and high-fat foods. On the other hand, Factor 2 was directly associated with family history of BC among first-degree relatives, white meat, total vegetables, total fruits and total vegetables and fruits intakes (rho=0.71), but inversely associated with intake of high-fat foods.

Table 6. Interaction between Fats and Heterocyclic Amines[1]

Heterocyclic Amines	Fats	Cases/Controls	OR (95%CI)
Low	Low	71/133	1.0 (reference)
Low	High	132/155	1.80 (1.18-2.76)
High	Low	169/113	3.04 (1.86-4.97)
High	High	70/ 41	4.00 (1.99-8.01)

[1]Adjusted for age, residence, urban/rural status, education, family history of breast cancer, body mass index, menopausal status, age at menarche

Odds ratios of BC for scored patterns are shown in Table IV. The high-meat pattern was directly associated with BC risk (OR for the highest versus the lowest quartile was 3.50, 95 % CI 1.94-6.30, p-value <0.0001). The antioxidants pattern displayed a significant protective effect (OR 0.44, 95 % CI 0.27-0.74, p-value for trend=0.001).

In Table V nutrient patterns were stratified by menopausal status, family history of BC and histologic types of BC. Both nutrient patterns were entered into the model as continuous terms. The antioxidants pattern was more strongly protective among postmenopausal than among premenopausal BC cases (p for heterogeneity = 0.005). The high-meat pattern was more strongly associated with BC among patients with family history of BC than among the participants without family history (p for heterogeneity = 0.02). Also the antioxidants pattern was strongly protective among patients with family history of BC (OR 0.17, 95 % CI 0.06-0.48). Patients with non-ductal BC showed an OR of 0.50 (95 % CI 0.35-0.69) compared with women afflicted by ductal carcinoma (OR 0.72, 95 % CI 0.58-0.88, p-value for heterogeneity=0.03) for the antioxidants pattern. Smokers and drinkers displayed similar ORs when compared with abstainers (results not shown).

The joint effect of heterocyclic amines and total fats is shown in Table VI. Whereas fats displayed a lower risk than HCAs, the joint effect of high consumption of both variables displayed a four-fold increase of risk of BC.

Discussion

By use of factor analysis we identified of two nutrient patterns (high-meat and antioxidants) which were strongly associated with the risk of BC. Whereas the high-meat pattern was associated with a strong increase in risk, the antioxidants pattern was associated with a reduction in the risk of BC.

The high-meat pattern was highly correlated with red and processed meat intake and both food groups are important sources of both fat and of heterocyclic amines (Sinha, 2002). Heterocyclic amines are established mammary carcinogens (Sinha, 2002) and some previous studies have suggested that well done red meat was a strong risk factor for BC (Zheng et al., 1998; Sinha et al., 1998; 2002; Snyderwine et al., 1998). The Uruguayan

population is characterized by a high intake of barbecued meat (Matos and Brandani, 2002) and it is possible, but not proven, that this dietary practice may partly explain the high BC rates in this population. Furthermore, the high-meat pattern displayed a four-fold increase in risk in patients with family history of BC. This finding suggests a possible gene-environmental interaction in BC. Thus, heterocyclic amines and fats should be considered as strong candidates in the causation of BC.

On the other hand, the antioxidants pattern was positively loaded with vegetables and fruits and showed a strong reduction in the risk of BC. Previous studies on dietary patterns and BC, conducted by factor analysis, showed a similar reduction in risk for a salads pattern (Sieri et al., 2004). Our findings with regard to the antioxidant pattern are similar to those related with vegetable and fruit intakes (as a source of antioxidants) in our previous study on food patterns (Ronco et al., 2006) and in a prospective study (Smith-Warner et al., 2001). Moreover, we previously found a protective effect mainly for fruits, but in particular for citrus fruits (Ronco et al., 2006).

Besides, the antioxidants pattern showed a positive correlation with white meat consumption. In a previous study (Ronco et al., 2003) this food group was found to be moderately protective for Uruguayan women. Results were mainly based on two cooking methods which were significantly and negatively associated with a reduction of risk: skinless chicken and not fried fish. Therefore, the antioxidants pattern is likely to be the nutrient correlate of the healthy or prudent eating style.

It has been suggested that nutrients (and bioactive substances) are not ideal for its use in factor analysis (Martínez et al., 1998). On the other hand, taking into account that nutrients may mediate the biological effects of various foods and food groups upon cancer risk, we think that this approach is valuable. Factor analysis has limitations related with several steps in this procedure. More precisely, it is necessary to study carefully the source of nutrients. This applies to the conversion of foods into nutrients. In other words, it is essential to have a reliable Table of chemical composition of foods.

As other case–control studies, our study has limitations and strengths. All case-control studies may be prone to selection bias, but we tried to minimize this bias by frequency matching cases and controls on age, residence and urban/rural status. Paradoxically, hospitalized controls could alleviate the magnitude of recall bias, since they may be subjected to the same forces of recall as the cases. Interviewer bias is unlikely taking into account that cases and controls were drawn from a large on-going study on environmental factors and human cancer and both interviewers were mostly unaware about the role of diet in cancer. The same applies to patients since they were drawn from public hospitals and were characterized by a low educational level and low income, that is, they are drawn from a well-defined low socioeconomic class in Uruguay. Another limitation is related to the application of HCA values collected in US in a Uruguayan database. The lack of Uruguayan values of HCAs forced us to use a foreign Table of HCA content of meats. The high correlation (rho=0.81) between fried red meat (a marker of HCAs) and high-meat pattern gives support for the use of the US Table in our study. Another limitation of this study is the lack of validation of our FFQ. Nevertheless, the instrument was tested for reproducibility and the results were reasonably reliable (Ronco et al., 2006) The study also has strengths. Perhaps, the high response rate for cases and controls and the adjustment for many important confounding factors are the major strengths. Also the high sampling adequacy and the high value of the total variance explained by the model are remarkable strengths.

Our principal components study explored nutrients and their possible association with the risk of breast cancer, having found two opposite patterns, labeled as high-meat and antioxidants. Each one represents very different nutritional styles, which bring plausible basis for the role of HCA and fats in the etiology of breast cancer. This finding is perhaps more marked for those with a family history of the disease, taking into account the role of gene-environmental interaction involving dietary constituents (nutrients and bioactive substances) in patients with a family history of BC, a probable marker of genetic structure of this malignancy.

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