RESEARCH COMMUNICATION

Risk Factors for Premenopausal Breast Cancer: A Case-control Study in Uruguay

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Abstract

In order to thoroughly analyze risk factors of breast cancer (BC) in premenopausal Uruguayan women, a case-control study was carried out at the Pereira Rossell Women's Hospital, Montevideo, where 253 incident BC cases and 497 frequency-matched healthy controls were interviewed on menstrual and reproductive story, were administered a short food frequency questionnaire and undertook a series of body measurements necessary to calculate body composition and somatotype. Odds ratio (OR) coefficients were taken as estimates of relative risk derived from unconditional logistic regression. Among the classical risk factors, only the family history of BC in first degree relatives was significantly associated with risk of premenopausal BC (OR=2.20, 95% CI 1.33-3.62). Interestingly, this risk factor was found to be stronger in women of ages >40 (OR=4.05, 95% CI 2.10-7.81), late menarche (OR= 2.39, 95% CI 1.18-4.85), early age for their first delivery (OR=3.02, 95% CI 1.26-7.22), short time between menarche and first delivery (OR=3.22, 95% CI 1.29-8.07), and with high parity (OR=4.10, 95% CI 1.79-9.36), although heterogeneity was detected only for age and parity. High consumption of red meat was positively associated with the disease risk (OR=2.20, 95% CI 1.35-3.60), in the same way as fried foods (OR=1.79, 95% CI 1.12-2.84). Conversely, a high intake of plant foods displayed a protective effect (OR=0.41, 95% CI 0.26-0.65). Except for hypertension (OR=1.55, 95% CI 1.03-2.35), none of the analyzed components of metabolic syndrome were associated to BC risk. Particular increases of risk for premenopausal BC were found for family history in first degree relatives in certain subsets derived from the menstrual-reproductive history. Preventive strategies could broaden their scope if new studies confirm the present results, in view of the limited prevention measures that premenopausal BC currently has.

Keywords: Breast cancer - premenopause - risk factors - nutrition - anthropometry - Uruguay

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Introduction

Established risk factors for breast cancer (BC) in women include certain reproductive factors, as earlier menarche, later age at first pregnancy, less breastfeeding, lower parity, and longer interval between births. The list can be completed with older age, a family history of BC (FHBC), greater height, adult weight gain, high birth weight, alcohol intake, high mammographic density and postmenopausal hormone use (Colditz, 2000). Less than 5% of the total BC incidence is explained by known BC susceptibility genes, mostly those conferring high risks, such as BRCA1 and BRCA2. It is presently not known how many such genes there still are, nor how many will fall into the class of rare high-risk (as BRCA) or of common low-risk susceptibility genes, nor if and how these factors interact with each other to cause susceptibility (a polygenic model). A positive FHBC remains among the most important ones established for the disease, despite the quoted uncertainty (Oldenburg et al., 2007).

Among the classical factors, lactation has been emphasized as protective. An old study reported that premenopausal women who had ever lactated had half of the risk of developing BC, as compared to premenopausal women who had never lactated (Odds Ratio OR=0.49, 95% confidence interval, CI 0.30–0.82) (McTiernan and Thomas, 1986). Recently, lactation has been studied in a prospective cohort study of parous premenopausal women, which found that having ever breastfed was inversely associated with incidence of BC among women with a FHBC (Stuebe et al., 2009), however, no association was observed among women without a FHBC.

Concerning anthropometry, it is accepted that higher values of body mass index (BMI) are associated with a reduced risk of BC in premenopausal women and with an increased risk in postmenopausal ones (Lahmann et al., 2004; WCRF, 2007). Absence of association in premenopausal women has been also described for certain anthropometric measures in some populations such as Chinese (Shu et al., 2001; Chow et al., 2005), Japanese (Hirose et al., 2001), or African American women (Hall et al., 2000), different from what has been consistently

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described in the Western and Caucasian societies. Recently, waist-to-hip ratio was also associated with an increase of risk in premenopausal Nigerian (Okobia et al., 2006) and Asian American women (Wu et al., 2007). Anyway, a recent study strongly suggested that lower overall adiposity and higher central adiposity are independent risk factors for premenopausal BC in the general population (Dettenborn, 2008). Their results support the possibility that differences in patterns of adiposity may contribute to familial risk of premenopausal BC, and suggest the importance of conducting other population-based studies of the link between body size characteristics and familial BC risk. Despite variations in the overall BC rates, the associations between classical factors (menstrual-reproductive and FHBC) and the risk of the disease appear to be similar across different racial groups, something supported by data from international epidemiologic studies (Pathak, 1992; Pike, 2002; Linos et al., 2008), but menopausal status deserves to be separately considered.

According to a recent review (Michels et al., 2007), data on the role of diet in premenopausal BC are still sparse. Additional diet studies that consider BC outcomes more specifically according to estrogen- and progesterone-receptor status, are needed. There is evidence that diet may play a more important role in ER (-) BC than in ER(+) BC, however, some authors recognized that such associations may not be detected in analyses of overall BC (Kushi et al., 1995; Olsen et al., 2003; Fung et al., 2005).

In the last twenty years the disease risk in Uruguayan women has been thoroughly studied from the nutritional viewpoint (Ronco et al., 2010; Ronco and De Stéfani, 2012a), not only focusing on diet but also on the anthropometric associations . Concerning anthropometry, we have recently reported possible roles of somatotype and risk of BC, which were related to a positive association for high endomorphism among premenopausal women but not in postmenopausal ones (Ronco et al., 2008). On the other hand, the studies on body composition reported that fat weight, fat fraction, muscle weight, muscle fraction and the fat/muscle ratio had associations regarding the risk of BC (Ronco et al., 2009). Nevertheless, muscle fraction and endomorphism lost their association when the analyses in premenopausal women included terms for body composition and somatotype in the regression models (Ronco and De Stéfani, 2011).

In our opinion, classical as well as modern risk factors and their possible relationships in particular with premenopausal BC deserve detailed analyses. Taking into account the feasibility for such epidemiologic research in Uruguay and in the quoted population subset, we decided to perform the present study in order to explore the role of different variables in the etiology of premenopausal BC in the Uruguayan population.

Materials and Methods

A hospital-based case-control study was carried out during the period between June/2004 and December/2010 at the Unit of Radiology and Oncology, located at the Pereira Rossell Women's Hospital in Montevideo. The quoted Unit at our Hospital admits women coming from all the country, in order to perform diagnostic mammograms and ultrasonogramms in a predominantly asymptomatic population. Mammograms in the public health system are cost-free for women. Since the years 1993-2008 there has been an intensive educational activity through mass media for preventive purposes and also adult women can get a periodical control mammography by their own will or by prescription of specialists.

During the study period and after excluding the postmenopausal cases of BC for the study purposes, 253 incident cases of primary malignant BC were identified in the consulting population and enrolled into the study. Cytology was performed on biopsies of breast tissue obtained from patients who were classified as BIRADS categories 4 (suspicious of malignancy) and 5 (positive diagnosis of cancer) (Varas, 1992; American College of Radiology, 1998) on the basis of their mammogram. Since BC cases were interviewed and measured very soon, they have not experienced any post-diagnostic or treatment-induced weight change. Although women do not participate formally in a screening program, cancers are usually diagnosed at early stages (ca. 10% carcinoma in situ).

In the same time period and in the same institution, 505 healthy women with a negative diagnostic mammogram (BIRADS categories 1-2 [completely negative, only with findings not associated with pathology, e.g. benign calcifications and/or axillary lymphnodes]) (American College of Radiology, 1998) performed the same day of the interview, were randomly selected as controls. They were frequency-matched by age (± 5 years) to cases, being mandatory requirements for the controls not to be hospitalized at the moment of the interview and not being afflicted by a cancer. Most women of ages under 30 were examined only with ultrasonography, unless findings required also mammogram due to the high density of breasts at those ages. Normal older controls (ages >60) were relatively unfrequent in consulting at the Unit, and it was difficult to find completely normal mammograms in those women. After excluding 8 women who rejected the interview, a final number of 497 controls were recruited (response rate >98%). Therefore, 750 women consulting for a mammogram at our Center were included in the study. Interviews and measurements were performed by an only trained nurse, who was blinded regarding the objectives of the study, previously trained and periodically supervised during the study period. All interviews were conducted in the hospital and performed face to face, and a written consent was obtained from every interviewed subject. The research was approved by the ethical committee of the Hospital.

For the interview a questionnaire was used to assess the following sections: 1. socio-demographic variables; 2. menstrual and repro¬ductive events (age at menarche, age at first live birth, number of children, months of breastfeeding, menopausal status [pre/post]). Menopausal status was defined a priori: if according to the subject (aged ≥ 45 yrs) menstruations have ceased at least for six months having excluded pregnancy, she was classified as postmenopausal; 3. history of cancer in first and second

degree relatives; and 4. Frequency, duration and intensity of physical exercise. The latter was queried on activities out of the job time, even recreational or competitive, 5 years prior the interview. This assessment, whose method was not validated, was performed only as an exploratory tool in the studied group, whose restricted incomes limit their time and access to sport institutions; 5. Self reported weight at age 18; 6. A short food frequency questionnaire, including 12 items selected on a basis of relevance from previous studies (Ronco 1996; 1999; 2006a; 2006b); 7. Queries on personal medical history. Hormonal replacement therapy was not asked, because it is not usually prescribed to postmenopausal women who belong to the studied subpopulation. Hormonal Receptors' status was not among the variables initially examined in this study.

Measurements

The following anthropometric measures were taken: height (measured to the nearest centimeter), weight (at intervals of 0.100 kg), circumferences (in cm): waist, hip, calf, tensed arm; skinfolds (in mm): tricipital, subscapular, abdominal, supraspinal, calf; and diameters (in mm): bistyloid (wrist), bicondyleal (elbow), bicondyleal (femur).

Anthropometric equipment included: 1) a height scale and headboard; 2) a weighing scale which was used along the whole study period with a weekly calibration; 3) a vernier caliper, for measurement of diameters; 4) a flexible plastic tape at intervals of 0.5 cm, for measurement of circumferences; and 5) a digital caliper FatTrack Pro ® (Accufitness, Greenwood Village, CO, USA), for skinfold measurements. If two consecutive measurements were similar, the obtained value was registered as valid. If both were different (± 1mm for skinfolds and diameters, ± 0.5 cm for circumferences) a third one was taken and the median value was then registered. Subjects were weighed wearing minimal clothing. Measurements were performed according to Carter's Instruction Manual (Carter, 2002).

Body composition and Somatotype

Anthropometric data were used to quantify body size and body proportions. The following body measures were determined: Body Mass Index, Fat weight (kg), muscle weight (kg), Fat fraction (%), Bone fraction (%), Muscle fraction (%), Residual fraction (%), and Fat/muscle ratio (FMR) calculated by the formula Fat fraction/ Muscle fraction, and somatotype (ST).

Calculations of body measures were based on the Faulkner protocol (Faulkner, 1968), according to the anatomic four compartments method of De Rose (De Rose, 1984). This widely known author worked mainly on Brazilian people, who are an important populational reference for South American neighbors like Uruguayans. Albeit a published validation was not available, it belongs to a recognized group of other methods which have been developed with the aim of calculating body composition (Jackson and Pollack, 1985; Heymsfield et al., 1997; Lee et al., 2000). The same methodology was followed in our first study on body composition (Ronco et al., 2009).

A ST is "a quantitative description of the present shape and composition of the human body" (Carter and Heath, 1990). A ST describes the human physique as a whole, which is broken down into three components: 1. Endomorphy (characterizing the relative fatness), 2. Mesomorphy (characterized by musculo-skeletal size), and 3. Ectomorphy (characterized by relative linearity or slenderness). Calculations of ST for each patient were done with the specialized software Somatotype® (Release 1.0, Sweat Technologies, Australia, 2001). Mean values

Table 1. Socio-demographic, Menstrual-reproductive Features and Family History of Cancer in the Studied Population

Variable	Controls		Cases		Global	Trend
Categories	Number	%	Number	%	p-value	
Age (yrs)						
<30	28	5.6	12	4.7		
30-34	49	9.9	23	9.1		
35-39	99	19.9	42	16.6		
40-44	148	29.8	62	24.5		
45-49	132	26.6	88	34.8		
≥50	41	8.2	26	10.3	0.18	0.05
Education (yrs)						
≤6	194	39.0	98	38.7		
7-12	250	50.3	135	53.4		
≥13	53	10.7	20	7.9	0.44	0.61
Urban/rural Status						
Urban	488	98.2	247	97.6		
Rural	9	1.8	6	2.4	0.60	
Menarche (age)						
≤11	121	24.3	53	20.9		
12	124	24.9	69	27.3		
13	124	24.9	70	27.7		
≥14	128	25.8	61	24.1	0.60	0.74
Nº of live Births						
Nulliparae	36	7.2	20	7.9		
1-2	242	48.7	121	47.8		
≥3	219	44.1	112	44.3	0.94	0.92
Age at first Delivery						
Nulliparae	36	7.2	20	7.9		
≤19	187	37.6	75	29.6		
20-23	150	30.2	66	26.1		
≥24	124	24.9	92	36.4	0.008	0.01
Time menarche -first delivery (yrs)						
≤6	171	37.1	67	28.8		
7-11	165	35.8	76	32.6		
≥12	125	27.1	90	38.6	0.006	0.002
Breastfeeding (months)						
No	57	11.5	34	13.4		
1-16	216	43.5	113	44.7		
≥17	224	45.1	106	41.9	0.61	0.33
Oral contracept.						
No	173	34.8	76	30.3		
Yes	324	65.2	175	69.7	0.21	
Breast Cancer in 1º degree						
No	461	92.8	216	85.4		
Yes	36	7.2	37	14.6	0.001	
Breast Cancer in 2º degree						
None	382	76.9	200	79.1		
1	91	18.3	35	13.8		
≥2	24	4.8	18	7.1	0.16	0.98
Other Cancers In 1º degree						
No	339	68.2	163	64.4		
Yes	158	31.8	90	35.6	0.30	
Total patients	497	100.0	253	100.0		

Table 2. Mean Values of the Anthropometric Measurements and Derived Calculations (n = 750)

Variables	Controls Mean ± SD	Cases Mean ± SD	P-value
Height (cm)	159.77 ± 5.94	159.47 ± 5.98	0.52
Weight (kg)	67.89 ± 12.79	68.29 ± 15.58	0.70
Weight at age 18 (kg)	55.16 ± 9.09	54.81 ± 9.18	0.62
Circumferences (cm)			
Waist	89.76 ± 11.34	90.05 ± 13.77	0.76
Hip	100.55 ± 10.27	100.50 ± 14.17	0.96
Arm (tensed)	31.45 ± 3.42	31.53 ± 4.39	0.79
Calf	37.30 ± 5.29	37.16 ± 4.07	0.72
Diameters (mm)			
Bistiloid (wrist)	49.31 ± 3.05	50.02 ± 3.33	0.005
Bicondyleal (elbow)	60.57 ± 4.46	61.41 ± 5.35	0.03
Bicondyleal (knee)	88.37 ± 8.27	88.72 ± 8.63	0.60
Skinfolds (mm)			
Tricipital	24.92 ± 9.47	28.84 ± 11.31	<0.0001
Subscapular	26.07 ± 10.90	28.78 ± 13.79	0.005
Abdominal	46.08 ± 18.58	47.32 ± 19.53	0.42
Supraspinal	19.91 ± 9.23	22.56 ± 11.10	0.0009
Calf	31.73 ± 9.44	36.77 ± 11.99	<0.0001
Calculations			
B.M.I. (kg/m2)	26.60 ± 4.86	26.85 ± 5.98	0.55
B.M.I. at age 18 (kg/m2)	21.61 ± 3.40	21.57 ± 3.45	0.85
Fat weight (kg)	26.97 ± 7.90	29.37 ± 8.62	0.0003
Fat fraction (%)	39.66 ± 8.94	43.17 ± 8.25	<0.0001
Muscle weight (kg)	18.03 ± 7.20	15.59 ± 7.12	<0.0001
Muscle fraction (%)	26.37 ± 8.78	22.62 ± 7.97	<0.0001
Bone weight (kg)	8.71 ± 1.05	8.53 ± 1.38	0.005
Bone fraction (%)	13.10 ± 1.89	12.92 ± 2.41	0.27
Fat/muscle Ratio	1.94 ± 1.56	2.47 ± 1.83	0.0001
Endomorphy (score)	6.41 ± 1.86	6.92 ± 2.13	0.001
Mesomorphy (score)	5.03 ± 1.62	5.05 ± 1.95	0.93
Ectomorphy (score)	1.00 ± 1.03	1.10 ± 1.15	0.23

SD, standard deviation

of ST were calculated for all cases and all controls. Formulas applied to calculate body composition and ST as well as additional details of the techniques were described in our recent paper on diabetes and overweight in postmenopausal BC (Ronco et al., 2012b).

Statistical analysis

Mean values ± standard deviation of the studied variables were calculated, as well as correlations among body measures. Adjusted Odds Ratios (OR)s and 95% Confidence Intervals (CI)s for each variable were calculated by unconditional logistic regression (Breslow and Day, 1980). Potential confounders were included in the multivariate analysis. Equations included terms for age, urban/rural status, family history of BC in 1º degree, family history of BC in 2º degree, family history of other cancers in 1º degree, age at menarche, age at first live birth, years between menarche and first pregnancy, number of live births, months of breastfeeding, oral contraception and BMI as a basic anthropometric parameter. The likelihood ratio test was run to test heterogeneity among variables of interest. All the calculations were performed with the software STATA (version 10, College Station, Texas, USA 2007).

Results

Table 1 displays the general features of the study population. Taking into account some lack of controls with ages>60 when data entry was finished for this analysis, a very homogeneous population is described. Socio-demographic and lifestyle variables were very similar whereas menstrual and reproductive variables displayed some differences related to the age at first live birth, number of live births and number of months of breastfeeding. Besides, cases showed a higher percentage of participants with FHBC among first-degree relatives compared with controls (14.6% vs. 7.2%, p = 0.001), however, no significant differences were found for other type of family history of cancers in relatives.

Mean values of the anthropometric parameters are presented in Table 2. Significant differences between cases and controls were found for most skinfold thickness parameters. Fat weight and fraction (%), muscle weight and fraction (%) and fat/muscle ratio displayed also significant differences.

Table 3 shows the adjusted ORs of BC for the classical menstrual-reproductive variables as well as the family history of cancers. Only FHBC in first degree relatives and late age at menarche displayed significant trends

Table 3. Crude and Adjusted Odds Ratios of Breast Cancer for the Classical Menstrual-reproductive and Family Variables

Variable Categories	Crude OR (95% CI)	Adjust. OR (95% CI)	Trend (p-value)
Age at menarche			
<=11	1.00 (reference)	1.00 (reference)	
12	1.28 (0.83-1.99)	1.45 (0.92-2.28)	
13	1.28 (0.83-1.98)	1.37 (0.87-2.16)	
>=14	1.12 (0.72-1.16)	1.46 (0.91-2.34)	0.003
Age at 1st birth			
Nulliparae	1.00 (reference)	1.00 (reference)	
<20	0.72 (0.39-1.33)	0.82 (0.17-3.56)	
20-23	0.79 (0.43-1.47)	0.82 (0.23-2.89)	
>23	1.33 (0.72-2.46)	1.28 (0.49-3.35)	0.86
Time menarche-1st delivery (yrs)			
1-6	1.00 (reference)	1.00 (reference)	
7-11	1.19 (0.80-1.76)	1.21 (0.68-2.15)	
>=12	1.85 (1.25-2.75)	1.94 (0.72-5.24)	0.26
Nº of live births			
Nulliparae	1.00 (reference)	1.00 (reference)	
1-2	0.84 (0.46-1.52)	0.96 (0.72-1.26)	
>=3	0.82 (0.45-1.50)	0.77 (0.12-4.93)	0.62
Oral contracept.			
No	1.00 (reference)	1.00 (reference)	
Yes	1.20 (0.87-1.67)	1.20 (0.86-1.68)	0.26
Breastfeeding (months)			
No	1.00 (reference)	1.00 (reference)	
1-16	0.83 (0.51-1.35)	0.80 (0.40-1.61)	
>=17	0.76 (0.47-1.24)	0.74 (0.36-1.52)	0.30
Family history of BC in 1st degree			
No	1.00 (reference)	1.00 (reference)	
Yes	2.18 (1.34-3.54)	2.20 (1.33-3.62)	0.002
Family history of BC in 2nd degree			
No	1.00 (reference)	1.00 (reference)	
Yes	0.99 (0.76-1.30)	0.96 (0.73-1.27)	0.97
Family history of OC in 1st degree			
No	1.00 (reference)	1.00 (reference)	
Yes	1.11 (0.80-1.54)	1.18 (0.84-1.66)	0. 53

Regression models including: age (categorical), age at menarche (categorical), number of live births (categorical), age at first delivery (categorical), years between menarche and first delivery (categorical), breastfeeding (categorical), oral contraception (yes/no), family history of breast cancer in 1st degree (yes/no), family history of breast cancer in 2nd degree (yes/no) and family history of other cancers in 1st degree (yes/no); BC, breast cancer; OC, other cancers

Table 4. Adjusted Odds Ratios of Breast Cancer for the Family History of the Disease in first Degree Relatives, Stratified by Selected Variables

Variable	Categories	OR (95% CI)	Heterogeneity (p)
Age (yrs)	≤39	0.82 (0.32-2.08)	
	≥40	4.05 (2.10-7.81)	0.003
Age at menarche	≤12	1.76 (0.86-3.57)	
(yrs)	≥13	2.39 (1.18-4.85)	0.90
Age at 1st birth	Nulliparae	0.77 (0.08-7.54)	
(yrs)	<20	3.02 (1.26-7.22)	
	20-23	3.06 (1.09-8.58)	
	>23	1.25 (0.51-3.03)	0.25
Time menarche-	1-6	3.22 (1.29-8.07)	
1st delivery (yrs)	7-11	2.65 (1.03-6.84)	
	≥12	1.43 (0.57-3.55)	0.40
Nº of live births	1-2	1.50 (0.75-2.99)	
	≥3	4.10 (1.79-9.36)	0.03
Oral contracept.	No	2.67 (1.04-6.83)	
	Yes	2.03 (1.11-3.68)	0.60
Breastfeeding	No	1.01 (0.23-4.47)	
(months)	1-16	3.37 (1.53-7.46)	
	≥17	1.84 (0.85-3.97)	0.25
Fat fraction (%)	≤37.2	3.73 (1.03-13.4)	
	37.3-45.4	1.95 (0.84-4.49)	
	≥45.5	1.83 (0.80-4.15)	0.79
Endomorphism	I-II	2.26 (1.08-4.68)	
(tertiles)	III	2.07 (0.97-4.41)	0.74
Ectomorphism	I-II	1.43 (0.72-2.85)	
(tertiles)	III	3.22 (1.26-8.24)	0.29

Regression models including: age (categorical), age at menarche (categorical), number of live births (categorical), age at first delivery (categorical), years between menarche and first delivery (categorical), breastfeeding (categorical), oral contraception (yes/no), Body Mass Index (continuous), family history of breast cancer in 2nd degree (yes/no) and family history of other cancers in 1st degree (yes/no)

(p-value 0.002 and 0.003, respectively), albeit the latter did not reach significant ORs.

Adjusted ORs of BC for the FHBC in first degree relatives, stratified by selected menstrual-reproductive variables are presented in Table 4. Interestingly, the quoted risk factor was found to be stronger in women of ages >40 (OR=4.05, 95% CI 2.10-7.81), late menarche (OR= 2.39, 95% CI 1.18-4.85), early ages for their first delivery (OR=3.02, 95% CI 1.26-7.22), short time between menarche and first delivery (OR=3.22, 95% CI 1.29-8.07), and with high parity (OR=4.10, 95% CI 1.79-9.36), although heterogeneity was detected only for age and parity.

The analysis of anthropometric measurements comparing by FHBC is shown in Table 5. Mean values of some variables were significantly different (total weight, waist, hip, bone weight, tensed arm, tricipital and calf skinfold, BMI) and several differences were borderline (abdominal skinfold, fat weight, endomorphy). In other words, women with FHBC were heavier, with larger circumferences and with some thicker skinfolds than those without FHBC.

Table 6 shows the risk estimates for the personal history of diseases related to the metabolic syndrome. Except for hypertension (OR=1.55, 95% CI 1.03-2.35), none of the analyzed components of metabolic syndrome

Table 5. Comparison of Anthropometric Measures and Calculations in Control Population with Absence or Presence of FHBC in First Degree

Variables Categories	Without FHBC (n=461) Mean ± SD	With FHBC (n=36) Mean ± SD	P-value
Height (cm)	159.68 ± 5.94	160.92 ± 5.93	0.23
Weight (kg)	67.45 ± 12.43	73.49 ± 15.86	0.006
Weight at age 18 (kg)	55.07 ± 9.19	56.28 ± 7.70	0.44
Circumferences			
Waist	89.45 ± 11.11	93.72 ± 13.49	0.03
Hip	100.23 ± 9.97	104.72 ± 13.04	0.01
Arm (tensed)	31.36 ± 3.36	32.62 ± 3.97	0.03
Calf	37.21 ± 5.36	38.50 ± 4.11	0.16
Diameters (mm)			
Bistiloid (wrist)	49.27 ± 3.06	49.81 ± 2.89	0.31
Bicondyleal (elbow)	60.52 ± 4.42	61.31 ± 5.00	0.31
Bicondyleal (knee)	88.18 ± 8.06	90.81 ± 10.39	0.07
Skinfolds (mm)			
Tricipital	24.68 ± 9.39	28.00 ± 10.06	0.04
Subscapular	25.92 ± 10.91	28.03 ± 10.71	0.26
Abdominal	45.66 ± 18.31	51.56 ± 21.29	0.07
Supraspinal	19.72 ± 9.13	22.47 ± 10.22	0.08
Calf	31.46 ± 9.26	35.19 ± 11.14	0.02
Calculations			
B.M.I. (kg/m^2)	26.47 ± 4.76	28.35 ± 5.89	0.02
B.M.I. at age 18 (kg/m^2)	21.61 ± 3.47	21.70 ± 2.48	0.88
Fat weight (kg)	26.79 ± 7.84	29.23 ± 8.36	0.07
Fat fraction (%)	39.66 ± 9.06	39.59 ± 7.47	0.96
Muscle weight (kg)	17.89 ± 7.19	19.85 ± 7.20	0.11
Muscle fraction (%)	26.33 ± 8.91	26.89 ± 6.95	0.72
Bone weight (kg)	8.68 ± 1.04	9.05 ± 1.17	0.05
Bone fraction (%)	13.14 ± 1.89	12.62 ± 1.87	0.12
Fat/muscle Ratio	1.99 ± 0.82	2.08 ± 0.77	0.54
Endomorphy (score)	6.37 ± 1.85	6.91 ± 1.84	0.09
Mesomorphy (score)	5.00 ± 1.62	5.40 ± 1.71	0.16
Ectomorphy (score)	1.01 ± 1.04	0.82 ± 0.88	0.27

SD, standard deviation; FHBC, Family history of BC

Table 6. Adjusted Odds Ratios of Breast Cancer for the Personal History of Diseases Related to the Metabolic Syndrome

Variable	Categories	Crude OR (95% CI)	Adjusted OR (95% CI)
Hypertension	No	1.00 (reference)	1.00 (reference)
	Yes	1.78 (1.20-2.63)	1.55 (1.03-2.35)
Diabetes	No	1.00 (reference)	1.00 (reference)
	Yes	1.39 (0.65-2.99)	1.31 (0.59-2.89)
Dyslipidemia	No	1.00 (reference)	1.00 (reference)
	Yes	0.81 (0.49-1.35)	0.70 (0.40-1.20)
B.M.I.	NW	1.00 (reference)	1.00 (reference)
	OW-OB	0.89 (0.66-1.21)	0.90 (0.65-1.24)
Hyperuricemia	No	1.00 (reference)	1.00 (reference)
	Yes	2.75 (1.08-7.01)	1.93 (0.73-5.12)
Bile lithiasis	No	1.00 (reference)	1.00 (reference)
	Yes	0.99 (0.61-1.61)	0.82 (0.49-1.38)
Grouped items	None	1.00 (reference)	1.00 (reference)
	1	0.70 (0.47-1.06)	0.66 (0.39-1.13)
	2	0.90 (0.55-1.46)	0.83 (0.43-1.62)
	≥3	1.52 (0.86-2.70)	1.16 (0.52-2.60)

Abbreviations: BMI, body mass index; NW, normal weight (<25 kg/m^2); OW-OB, overweight-obese (≥25 kg/m^2); Regression model including: age (categorical), education (categorical), urban/rural status (binary), age at menarche (categorical), number of live births (categorical), age at first delivery (categorical), years between menarche and first delivery (categorical), breastfeeding (categorical), oral contraception (yes/no), family history of breast cancer in 1st degree (yes/no), family history of breast cancer in 2nd degree (yes/no) and family history of other cancers in 1st degree (yes/no)

Table 7. Adjusted Odds Ratios of Breast Cancer for the Dietary Items

Variable	II	III	IV	Trend
Beef+Barbecue	1.30 (0.88-1.92)	1.87 (1.22-2.88)	-----	0.004
Milanesa*	1.29 (0.87-1.92)	1.57 (1.02-2.43)	-----	0.04
Eggs	1.95 (1.31-2.92)	1.31 (0.86-1.98)	-----	0.20
Milk	0.88 (0.59-1.31)	1.33 (0.90-1.97)	-----	0.16
Cheese	1.28 (0.85-1.91)	1.37 (0.92-2.05)	-----	0.12
Biscuits	1.39 (0.94-2.07)	1.08 (0.71-1.64)	-----	0.69
Tortas fritas **	0.88 (0.58-1.32)	1.35 (0.91-1.99)	-----	0.18
Skinless chicken	1.18 (0.83-1.69)	0.94 (0.59-1.51)	-----	0.93
Fried fish	0.90 (0.61-1.33)	1.03 (0.69-1.52)	-----	0.95
Not fried fish	1.10 (0.78-1.53)	-----	-----	0.60
Tomatoes	0.84 (0.57-1.24)	0.77 (0.51-1.16)	-----	0.20
Oranges	1.07 (0.73-1.55)	0.86 (0.55-1.32)	-----	0.54
Red meat	1.83 (1.09-3.09)	1.14 (0.70-1.86)	2.20 (1.35-3.60)	0.02
Fried foods	0.82 (0.51-1.32)	1.16 (0.72-1.87)	1.79 (1.12-2.84)	0.005
Plant foods	0.83 (0.54-1.28)	0.57 (0.37-0.89)	0.41 (0.26-0.65)	<0.0001

*A typical form of fried meat; **Large and flat fried doughnuts, typical of the country; Eggs, biscuits, tortas fritas and oranges were measured in Units/year. The other items were measured in Servings/year. Red meat, beef+barbecue+milanesas; Fried foods, milanesas+tortas fritas+fried fish; Plant foods, tomatoes+oranges; Regression model including: age (categorical), age at menarche (categorical), number of live births (categorical), age at first delivery (categorical), years between menarche and first delivery (categorical), breastfeeding (categorical), oral contraception (yes/no), family history of breast cancer in 1st degree (yes/no), family history of breast cancer in 2nd degree (yes/no) and family history of other cancers in 1st degree (yes/no)

were associated to BC risk. Nevertheless, when continuous terms for endomorphy or fat weight were entered into the regression model, the estimates for hypertension lost their statistical significance (results not shown).

Finally, the adjusted ORs of BC for the asked dietary items are shown in Table 7. Both types of red meat preparation were positively and significantly associated to the disease (OR=1.87, 95% CI 1.22-2.88 and OR=1.57, 95% CI 1.02-2.43 for grilled and fried red meat respectively). Their combination showed a stronger association (OR=2.20, 95% 1.35-3.60). Fried foods were also positively and significantly associated (OR=1.79, 95% CI 1.12-2.84). Conversely, plant intake (tomatoes and oranges combined) displayed a negative and also significant association (OR= 0.41, 95% CI 0.26-0.65), albeit the individual foods did not.

Discussion

Our results confirm the risk association between FHBC in first degree relatives and premenopausal women, almost doubling the estimates compared to the absence of family history. Nevertheless, the FHBC in the analyzed sample was stronger in women of ages >40, late menarche, early age for the first delivery, short time between menarche and first delivery, and also with high parity. Although heterogeneity was detected only for age and parity, results were somehow unexpected. Anyway, Colditz et al. (1996) reported that among women with a FHBC, reproductive risk factors had associations that were different from those observed among those without a family history of the disease. These authors described little protection from later age at menarche, no protection from multiple births when compared with nulliparity, nor from early, as compared with later, age at first birth, and also an adverse effect of first pregnancy on risk of BC among women with a FHBC that was around 50% greater in magnitude than among those without a family history. Hence, our observations are in general aligned with those of the quoted paper.

The control population showed differences in the anthropometric measurements and calculations of women having or not a family history of the disease. Although the subset with FHBC was small (n=36), mean values of some variables were significantly different (total weight, waist, hip, bone weight, tensed arm, tricipital and calf skinfold, BMI) and several differences were borderline (abdominal skinfold, fat weight, endomorphy) or even not significant. In other words, women with FHBC were heavier, with larger circumferences and with some thicker skinfolds than those without FHBC. The displayed trend supports the hypothesis issued by Dettenborn et al. (2008), who suggested that differences in patterns of adiposity may contribute to familial risk of premenopausal BC.

Our results are aligned with part of the literature produced in the last years, regarding the risk increase associated to higher meat and fat intakes among premenopausal women (Kruk, 2007; Taylor et al., 2009). The meta-analysis performed by the latter reported significant risk increases derived only from case-control studies but not from cohort ones, something notably repeated in epidemiologic research. Our findings of reduced risks associated to plant foods emphasize what Ambrosone et al stated more than a decade ago (1999), when they suggested that super oxide dismutase and oxidative stress play a significant role in BC risk, particularly in premenopausal women, after having found more pronounced risks among women below the median consumption of fruits and vegetables and of dietary ascorbic acid and α-tocopherol.

As other case-control studies, limitations and strengths should be recognized. A major limitation is related to the current sample size; it would be desirable to analyze a larger one, in order to have enough statistical power for certain results, in particular in some subsets. Unavailability of validation of the applied anthropometric method for calculating body composition, despite its wide use at a regional level, is a limitation that we recognize. Since occupational activity was not registered in our study, we were able to analyze only exercise as a leisure activity. Albeit physical exercise has not shown differences between cases and controls, we cannot preclude the possibility that occupational or daily living activities are different between them. Since this information was not measured, we are not able to go further. Future studies should clarify the point. To be recognized among the limitations, we should include the information derived from the brief food frequency questionnaire, which was only exploratory and did not allow the possibility to control for energy intake in the logistic models we ran.

On the other hand, both, cases and controls, belong to a very homogeneous base population. They came from the same healthcare system, they were matched by age, and socio-demographic variables were mostly similar. Furthermore, FHBC in first degree relatives and some other classical reproductive risk factors for BC showed significant differences. Women with normal mammograms that is, not only cancer-free women- were selected as controls, in order to reduce the possibility of biasing

results due to an association of benign breast diseases with the analyzed anthropometric items. Finally, a high participation was achieved making selection bias less likely. People affiliated to the public health system are prone to cooperate with surveys and with studies, therefore a high participation is always expected. Anyway, we need caution in the interpretation of results, since generalization is limited due to the population features: they have mid-to-low educational level and belong to low socioeconomic classes of a developing country.

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