RESEARCH COMMUNICATION

Diabetes, Overweight and Risk of Postmenopausal Breast Cancer: A Case-Control Study in Uruguay

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Abstract

Obese postmenopausal women increase their risk of developing breast cancer (BC), in particular if they display an android-type pattern of adiposity, which is also associated to increased risks of diabetes mellitus, hypertension and cardiovascular disease. In order to explore the associations among anthropometry (body mass index, body composition, somatotype), some specific items of medical history (diabetes, hypertension, dislypidemias, hyperuricemia) and the risk of BC in Uruguayan women, a case-control study was carried out between 2004-2009 at our Oncology Unit. 912 women of ages between 23-69 years (367 new BC cases and 545 non hospitalized, age-matched controls with a normal mammography) were interviewed. Twenty body measurements were taken in order to calculate body composition and somatotype. Patients were queried on socio-demographics, reproductive history, family history of cancer, a brief food frequency questionnaire and on personal history of diabetes, dislypidemias, hyperuricemia, hypertension and gallbladder stones. Uni- and multivariate analyses were done, generating odds ratios (ORs) as an expression of relative risks. A personal history of diabetes was positively associated to BC risk (OR=1.64, 95% CI 1.00-2.69), being higher among postmenopausal women (OR=1.92, 95% CI 1.04-3.52). The risks of BC for diabetes in postmenopausal women with overweight combined with dislypidemia (OR=9.33, 95% CI 2.10-41.5) and high fat/muscle ratio (OR=7.81, 95% CI 2.01-30.3) were significantly high. As a conclusion, a personal history of diabetes and overweight was strongly associated to BC. The studied sample had a subset of high-risk of BC featured by postmenopausal overweight and diabetic women, who also had a personal history of hypertension and/or dyslipidemia. The present results could contribute to define new high risk groups and individuals for primary as well as for secondary prevention, since this pattern linked to the metabolic syndrome is usually not considered for BC prevention.

Keywords: Breast cancer - diabetes - epidemiology - metabolic syndrome - obesity - overweight - somatotype.

Asian Pacific J Cancer Prev, **13**, 139-146

Introduction

At the end of XIX century, hyperglycemia and diabetes were first associated to BC, being reported among patients with cancer (Freund, 1885). In 1930, tumour samples were reported to have higher rates of glucose utilization than did normal tissues (Warburg, 1930). Since the 1950s, incidence reports have described women with BC as having higher rates of diabetes than did healthy women (Glicksman 1956, Muck 1975).

Diabetes mellitus, metabolic syndrome and BC are all more prevalent in developed societies than in developing ones, where a sedentary lifestyle and a high intake of refined carbohydrates and saturated fats are more prevalent. However, developing countries are increasingly adopting many of the lifestyle characteristics of more affluent societies. While the urbanization process continues, educational levels increase and people change their habits, as a result of which the occurrence of BC increases. This is an outcome of several of these factors combined. Higher educational levels correspond to a decrease in the average number of pregnancies and births, an increase of age at the first birth, as well as shorter times of breastfeeding. Urbanization also implies an increase in job types that are less active than rural ones, this being favourable for the development of problems such as excess weight and obesity. Outdoor jobs performed by women, regardless of the conditions under which they are performed, are associated with high caloric- and fast-foods, as well as psychosocial stress. The diabetic condition induces change in several hormonal systems, including insulin, insulin-like growth factors, estrogen and other cytokines, and growth factors, that may affect BC risk (Xue and Michels, 2007, Larsson et al., 2007).

Metabolic syndrome or insulin resistance syndrome, first described by Reaven more than two decades ago (Reaven 1988) as syndrome X, is characterized by abdominal obesity, dislypidemia (e.g., high triglycerides and low HDL-cholesterol levels), high fasting blood glucose and high blood pressure levels. Both type-2

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diabetes and the metabolic syndrome have been associated with a state of chronic, low-grade, inflammation; inflammatory cytokines such as C-reactive protein may induce insulin resistance (Hanley et al., 2004), and C-reactive protein has been associated with risk of atherosclerotic cardiovascular disease and myocardial infarct (Wilson et al., 2006). Several studies have suggested a direct association between components of metabolic syndrome and BC risk (Xue and Michels, 2007; Vona-Davis et al., 2007; Rosato et al., 2011). Therefore, low HDL-cholesterol (Furberg et al., 2004), high blood glucose (Muti et al., 2002), high triglycerides (Potischman et al., 1991), postmenopausal overweight (World Cancer Research Fund, 2007), abdominal obesity (Connolly et al., 2002), hypertension (Soler et al., 1999), high levels of insulin (Hirose et al., 2003), C peptide (Verheus et al., 2006), and insulin-like growth factor I (IGF-I)(Campagnoli et al., 2008), have all been associated with increased BC risk. Metabolic and hormonal factors related to metabolic syndrome have also been implicated in BC prognosis (Goodwin et al., 2002; Rock et al., 2002; Pasanisi et al., 2006; Agnoli et al., 2010; Tsugane and Inoue, 2010).

Interestingly, the metabolic syndrome was also found associated with a decreased risk of incident BC in women below age 50 with high body mass index (BMI), and with an increased risk of BC mortality in women of ages above 60, according to a European study (Bjørge et al, 2010). New evidence emphasizes that metabolic syndrome increases the risk mainly in postmenopausal women (Capasso et al., 2011) and it has been found as significantly more prevalent in triple-negative BC patients as opposed to non-triple-negative patients (Maiti et al., 2010).

Furthermore, the increase in BC incidence has occurred in parallel with a steady increase in the frequency of type 2 Diabetes and metabolic syndrome (Xue and Michels, 2007). Although BC is still a major public health issue in developed societies, its incidence has been also rising in several developing countries over the past few years (Bray et al., 2004). International data (Ferlay et al., 2010) have located Uruguay among those with the highest rates in the world. Moreover, the capital city, Montevideo, has displayed the highest incidence rate for a city (Parkin et al., 2002). In fact, although this small South American country is a developing one, it shares some characteristics with developed regions, i.e. a very high level of red meat consumption, (FAO, 2010) a high human development index (50º in the world ranking according to United Nations, by factors as birth rate, infant mortality, life expectancy, literacy, among others) (United Nations, 2009) and an aged population (US Census Bureau, 2010). In other words, a developing country has shown a high occurrence of a disease which is typical of developed countries.

We and others have thoroughly studied possible links of nutrition and BC, from the dietary viewpoint (Ronco et al., 1996; 1999; 2002; 2003; 2006; 2010a,b,c,d; De Stéfani et al., 1997a,b; 1998) as well as from an anthropometric one (Ronco et al., 2008; 2009) and other epidemiologic ones (Ronco et al., 2007; 2009). In order to explore the associations among anthropometry (BMI, body composition, somatotype), some specific components of the metabolic syndrome in the medical history (diabetes, hypertension, dislypidemias, hyperuricemia) and the risk of BC in Uruguayan women, we decided to carry out the present epidemiologic case-control study, whose preliminary report was recently communicated (Ronco et al., 2010d).

Materials and Methods

The authors carried out a hospital-based case-control study on anthropometry and BC during the period between June/2004 and December/2009 at the Instituto de Radiología y Centro de Lucha Contra el Cáncer, which is a reference center of BC in Uruguay and is located at the Pereira Rossell Women's Hospital in Montevideo. It admits women coming from all the country and mainly belonging to the lowest socioeconomic strata, who pertain to the public hospital health system. Currently, around 50 diagnostic mammograms in a predominantly asymptomatic population are daily performed.

During the study period, 367 incident cases of BC up to age 69 were identified in the screening population and enrolled into the study. Cases were women with new incident and histologically diagnosed carcinomas – interviewed between 0 and 10 days after their diagnosis-. Potential cases with ages 70 or higher were not taken into account, regarding the lack of healthy controls to match them and also to reduce a possible recall bias. Their recruitment was performed in patients with mamographically BI-RADS 4 (suspicious of malignancy) and 5 (highly suspicious of cancer) lesions (Varas et al., 1992; Feig, 1999), and a positive cytologic (on site) study, which was furtherly histologically confirmed, according to its high correlation with histopathology (Jaumandreu et al., 2001). Initially, no information on cancer stage was collected through the study period.

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, 559 healthy women with a negative diagnostic mammogram (BI-RADS categories 1 [completely negative]-2 [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 mammography due to the high density of breasts at those ages. Normal aged controls were relatively unfrequent in consulting at the Institute, and it was difficult to find completely normal mammographies in the older women. After excluding 12 women who had had a previous cancer in the past and 2 who rejected the interview, a final number of 545 controls were recruited

(response rate 97.5%). Therefore, 912 women consulting for a mammography 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. People affiliated to the public health system are prone to cooperate with surveys and studies, therefore a high participation is always expected. The research was approved by the ethical committee of the Hospital.

The questionnaire included the following sections: 1) Socio-demographic variables; 2) Menstrual-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) menstruations have ceased at least for 6 months, excluding pregnancy, she was classified as postmenopausal; 3) History of cancers in first and second degree relatives; 4) Physical exercise (yes/no), frequency, duration and intensity; 5) Self reported weight at age 18; 6) A short food frequency questionnaire; 7) Queries on personal history of components of metabolic syndrome and others: diabetes, hypertension, dislypidemia, hyperuricemia, bile lithiasis. Hormonal replacement therapy was not asked, because it is not usually prescribed to postmenopausal women who belong to the studied subpopulation. Physical exercise 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. The analyses were focused mainly on the components of metabolic syndrome. The ER status was not among the variables examined in this study.

Concerning anthropometry, the following measurements were performed: a) height (measured to the nearest centimeter); b) weight (at intervals of 0.100 kg); c) circumferences (in cm): (waist, hip, flexed and tensed arm, calf); d)skinfolds (in mm): tricipital, subscapular, supraspinal, calf); e) diameters (in mm): bicondyleal (femur) and bicondyleal (humerus).

Anthropometric equipment included a height scale and headboard, a weighing scale, a vernier caliper, a flexible plastic tape, and a skinfold caliper. The same mechanical scale was used along the whole study period, with a weekly calibration. Subjects were weighed wearing minimal clothing. For body measurements a plastic centimeter at intervals of 0.5 cm (for circumferences), a vernier caliper (for diameters) and a digital caliper (for skinfolds) were used. Regarding these latter, if two consecutive measurements were similar, the obtained value was registered as valid. If both were different, a third one was taken and the median value was then registered. Measurements were performed according to Carter's Instruction Manual (Carter, 2002).

Body composition

Anthropometric data were used to quantify body size and body proportions. The following body measures were determined:

Body Mass Index = Weight /Height2 (Quetelet's Index)
Fat fraction (%) = (subescapular + tricipital+supraspinal +abdominal skinfolds in mm) x 0.153 + 5.783
Bone fraction (%)=3.02 x (height 2 x bistiloid diameter in m x bicondyleal femoral diameter in m) ^{0,712}
Muscle fraction (%)=100.0 - (fat % + bone% + residual %)
Residual fraction (%) = 20.9% (pre-established)
Fat weight = Total weight x (Fat fraction/100)
Muscle weight = Total weight x (Muscle fraction /100)
Fat-to-muscle ratio (FMR) = Fat fraction/ Muscle fraction

Calculations of body measures were based on the Faulkner protocol (Faulkner 1968), according to the anatomic four compartments method of De Rose (1984).

Somatotype

Calculations of somatotype for each patient were done with the specialized software Somatotype® (Release 1.0, Sweat Technologies, Australia, 2001). For them, the following measurements were taken into account: height, weight, four skinfolds (triceps, subscapular, supraspinal, mid calf), two circumferences (tensed arm, calf) and two bone breadths (humerus, femur). Mean values of somatotype were calculated for all cases and all controls. Formulas applied to calculate somatotype are the following:

Endomorphy = - 0.7182 + 0.1451 (Σ) - 0.00068 (Σ^2) + 0.0000014 (Σ^3); Mesomorphy = (0.858 HB + 0.601 FB +0.188 CAG + 0.161 CCG) - (0.131 H) + 4.5; Ectomorphy: If HWR ≥ 40.75, then Ectomorphy = 0.732 HWR - 28.58 If HWR < 40.75 and > 38.25, then Ectomorphy = 0.463 HWR - 17.63; If HWR ≤ 38.25, then Ectomorphy = 0.1
Where: Σ = (sum of triceps, subscapular and supraspinale skinfolds) multiplied by (170.18/height in cm); HB = humerus breadth; FB = femur breadth; CAG = corrected arm girth; CCG = corrected calf girth; H = height; HWR = height / cube root of weight.

CAG and CCG are the girths corrected for the triceps or calf skinfolds respectively as follows: CAG =flexed arm girth - triceps skinfold/10; CCG = maximal calf girth - calf skinfold/10.

Statistic analysis

Calculations of mean ± standard deviation for each variable were made. Based on the measurements done, the following calculations were made: Body Mass Index (BMI, kg/m^2), BMI at age 18 (kg/m^2), BMI difference (current-18 yrs), weight difference (id.) and waist-to-hip ratio. Somatotype variables were categorized in tertiles, according to the controls distribution. Crude and adjusted Odds Ratios (OR)s and 95% Confidence Intervals (CI) s were calculated by unconditional logistic regression (Breslow and Day, 1980) . Potential confounders were included in the multivariate analysis. ORs were calculated including age, residence, age at menarche, parity, age at first live birth, months of breastfeeding, use of oral contraceptives, BMI, menopausal status, family history of BC, and intake of beef, tomatoes and oranges. For analysis purposes, stratifications by menopausal status (pre- /post-), by levels of body mass index (normoweight,

Table 1. General Features of the Study Population: Sociodemographic, Menstrual, Reproductive and Other Selected Variables of Interest

Variable		Cases	%	Controls	%	p-value
Age	<30	11	3.0	18	3.3	
(yrs)	30-39	53	14.4	100	18.3	
	40-49	131	35.7	200	36.7	
	50-59	99	27.0	148	27.2	
	60-69	73	19.9	79	14.5	0.21
Urban/rural Status						
	Urban	356	97.0	529	97.1	
	Rural	11	3.0	16	2.9	0.96
Education (yrs)						
	≤6	173	47.1	246	45.1	
	7-10	125	34.1	197	36.1	
	≥11	69	18.8	102	18.7	0.79
Age at menarche						
	≤11	99	27.0	139	25.5	
	12	90	24.5	133	24.4	
	13	91	24.8	131	24.0	
	≥14	87	23.7	142	26.1	0.87
Menopausal status						
	Pre-	202	55.0	284	52.1	
	Post-	165	45.0	261	47.9	0.38
Age at first live birth						
	Nulli	37	10.1	37	6.8	
	14-22	169	46.0	319	58.5	
	≥23	161	43.9	189	34.7	<0.001
Full-term Pregnancies						
	1	66	18.0	73	13.4	
	2	111	30.2	170	31.2	
	≥3	153	41.7	265	48.6	0.04
Breastfeeding (months)						
	No	65	17.7	76	13.9	
	1-12	158	43.1	205	37.6	
	13-24	51	13.9	96	17.6	
	≥25	93	25.3	168	30.8	0.05
Family history of BC (1º degree)						
	No	305	83.1	493	90.5	
	Yes	62	16.9	52	9.5	0.001
Oral contraception						
	No	131	35.7	203	37.2	
	Yes	236	64.3	342	62.8	0.63
Physical exercise						
	No	214	58.3	298	54.7	
	Yes	153	41.7	247	45.3	0.28
Total patients		367	100.0	545	100.0	

Relative frequencies and p-value of differences between cases (n=367) and controls (n=545).

overweight-obese) and by endomorphism [low-mid (≤7.6), high (≥7.7)] were also done. All the calculations were performed with the software STATA® (Release 10, College Station, Texas, USA 1999).

Results

Regarding the general features of the study population and taking into account some lack of older controls (≥60 yr) when data entry was finished for this analysis (December 2009), a very homogeneous population is described (Table 1). Age -as a consequence of the matching design-, socio-demographic and lifestyle variables were very similar in both series. Besides, 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. Cases showed a higher percentage of participants with family history of BC among first-degree relatives compared with controls (16.9% vs. 9.5%, p = 0.02). In the studied population, the physical activity in leisure time was not different for both cases and controls.

Table 2. Anthropometric Measurements of the Sample

Variable	Controls	Cases	Dif.(p)
Height (m)	1.58 ± 0.06	1.58 ± 0.060	0.86
Weight (kg)	68.8 ± 13.4	68.9 ± 15.6	0.94
Waist (cm)	92.0 ± 11.5	92.0 ± 13.7	0.094
Hip (cm)	102.5 ± 10.9	102.6 ± 12.5	0.91
Subscapular Skfold (mm)	27.1 ± 10.7	29.8 ± 13.4	<0.001
Tricipital Skfold.(mm)	25.9 ± 9.2	28.7 ± 10.7	<0.0001
Bicipital Skfold (mm)	12.5 ± 6.1	15.2 ± 7.5	<0.0001
Supraspinal Skfold.(mm)	21.2 ± 9.6	23.0 ± 10.6	0.007
Abdominal Skfold. (mm)	51.5 ± 17.5	49.3 ± 19.3	0.07
Suprailliac Skfold.(mm)	53.6 ± 18.3	54.9 ± 20.4	0.33
Thigh Skfold. (mm)	40.9 ± 16.5	43.5 ± 18.8	0.03
Calf Skfold. (mm)	34.6 ± 10.7	38.5 ± 12.8	<0.0001
Relaxed Arm (cm)	29.2 ± 3.3	29.4 ± 4.1	0.52
Tense Arm (cm)	31.7 ± 3.5	31.8 ± 4.3	0.93
Calf (cm)	37.5 ± 4.8	37.3 ± 4.2	0.53
Wrist Diameter (mm)	49.7 ± 3.3	50.3 ± 3.4	0.01
Elbow Diameter (mm)	61.0 ± 4.1	62.0 ± 5.2	0.002
Knee Diameter (mm)	89.3 ± 8.0	89.2 ± 8.3	0.88
Calculations			
Body Mass Index (kg/m^2)	27.6 ± 5.2	27.6 ± 6.12	0.90
Fat fraction (%)	43.3 ± 7.6	43.9 ± 8.2	0.33
Muscle fraction (%)	22.9 ± 7.4	22.2 ± 8.1	0.18
Bone fraction (%)	12.9 ± 1.8	13.1 ± 4.3	0.93
Endomorphism	6.6 ± 1.8	7.03 ± 2.0	0.002
Mesomorphism	5.3 ± 1.6	5.3 ± 1.8	0.73
Ectomorphism	0.8 ± 0.9	0.9 ± 1.1	0.057

Mean values ± standard deviation.

Mean values of the anthropometric parameters showed that although height and weight were rather similar, as were waist and hip circumferences, significant differences between cases and controls were found for several skinfold thickness parameters (subscapular, tricipital, bicipital, supraspinal)(Table 2). Among the calculations, only Endomorphism was significantly different (p=0.002) and Ectomorphism was borderline associated (p=0.057), but fat fraction, muscle fraction, and the other parameters did not show significant differences.

In Table 3 the relative frequency of medical items associated to metabolic syndrome are presented by age groups. All of the analyzed items displayed an increasing trend along the ages (p for trend <0.001). Overweight/obesity was the most frequent pathology, involving 3 of each 4 subjects of ages 50 or more. Hypertension was also a very frequent pathology, involving 60% of women at ages 60 or more.

Table 4 shows the crude and adjusted odds ratios (ORs) of BC for each analyzed component among postmenopausal women. Slight changes took place when comparing both series of ORs, indicating that neither family history of cancer nor menstrual-reproductive variables modified substantially the risks. A personal history of diabetes was positively associated with the risk of BC (OR=1.92, 95% CI 1.04-3.52), while a high endomorphism (≥7.7) was also positively associated with

Table 3. Relative Frequency (%) of Metabolic Syndrome Components by Age Groups.

Variable	Age Groups <30	30-39	40-49	50-59	60-69
Obesity	13.8	47.1	58.9	73.7	77.6
Hypertension	3.4	13.1	31.1	47.8	60.5
Dislypidemia	---	8.6	17.5	36.8	46.3
Diabetes	3.4	2.6	6.0	10.9	16.4
High Endomorphy	10.3	30.1	35.1	43.3	34.2
Hyperuricemia	---	0.7	4.0	7.1	12.1
Bile lithiasis	---	12.6	12.9	26.8	32.4

Table 4. Relative Frequency and Crude and Adjusted Odds Ratios (ORs) of Breast Cancer for Each Analyzed Component Among Postmenopausal Women

Variable	Relative frequency (%) Cases	Controls	ORs (95% CI) Crude OR	Adjusted OR
Obesity	70.9	75.1	0.80 (0.52-1.25)	0.77 (0.48-1.25)
Hypertension	57.0	47.0	1.37 (0.93-2.04)	1.49 (0.95-2.33)
Dislypidemia	30.3	41.2	0.66 (0.44-1.01)	0.59 (0.38-0.94)
Diabetes	17.0	9.6	1.93 (1.08-3.44)	1.92 (1.04-3.52)
High Endomorphy	45.7	32.9	1.71 (1.15-2.56)	1.76 (1.14-2.71)
Hyperuricemia	8.4	8.8	0.95 (0.47-1.94)	0.76 (0.36-1.64)
Bile lithiasis	29.9	24.1	1.34 (0.86-2.09)	1.10 (0.68-1.78)

* Adjusted by age, residence, family history of BC 1ºdegree, age at menarche, number of live births, age at first delivery and number of breastfeeding months.

Table 5. Breast Cancer Risks for Diabetes, Stratified by Menopausal Status

	All OR (95% CI)	Premenop. OR (95% CI)	Postmenop. OR (95% CI)
Crude	1.59 (0.99-2.53)	1.20 (0.73-2.54)	1.9* (1.08-3.44)
Adj	1.6* (1.00-2.69)	1.19 (0.50-2.89)	1.9* (1.04-3.52)
Hypertension			
No	1.16 (0.46-2.95)	0.92 (0.21-4.12)	1.08 (0.31-3.71)
Yes	1.58 (0.85-2.93)	1.08 (0.31-3.80)	1.93 (0.92-4.05)
Dislypidemia			
No	1.77 (0.87-3.61)	1.66 (0.49-5.61)	1.85 (0.74-4.62)
Yes	1.68 (0.78-3.63)	1.33 (0.21-8.34)	2.29 (0.90-5.82)
BMI.			
NW	0.83 (0.20-3.44)	1.00 (0.72-1.40)	3.60 (0.33-39.8)
OW	4.7* (1.89-11.6)	2.43 (0.42-14.1)	5.4* (1.77-16.6)
OB	1.14 (0.55-2.35)	3.00 (0.70-12.9)	0.84 (0.33-2.12)
Endomorphy			
Low	1.78 (0.81-3.93)	0.60 (0.14-2.53)	2.73 (0.96-7.79)
High	1.36 (0.70-2.63)	2.35 (0.67-8.20)	1.12 (0.49-2.55)
Fat/muscle ratio			
<1.5	1.98 (0.87-4.51)	2.46 (0.54-11.2)	0.85 (0.28-2.53)
≥1.5	1.56 (0.84-2.92)	0.85 (0.29-2.53)	2.01 (0.92-4.39)

*significant; Adj, Adjusted by age, residence, family history of BC 1ºdegree, age at menarche, number of live births, age at first delivery and number of breastfeeding months, *BMI*; body mass index, *NW*; normal weight, OW; overweight, OB; obese.

the risk of the disease (OR=1.76, 95% CI 1.14-2.71). Surprisingly, a history of any type of dislypidemia was negatively associated with BC in this sample (OR=0.59, 95% CI 0.38-0.94).

The crude and adjusted risks of BC for Diabetes, stratified by menopausal status are shown in Table 5. Statistical significant increased risks, not modified after adjustment for potential confounders were found only among postmenopausal women (adjusted OR= 1.92, 95% CI 1.04-3.52). This estimate was similar to those found in strata of postmenopausal women, as hypertension (OR=1.93), dislypidemia (OR=2.29) and high fat/muscle ratio (OR=2.01), although they not reach statistical significance. On the other hand, diabetes was strongly associated with BC risk in overweight postmenopausal women (OR=5.42, 95% CI 1.77-16.6), but lacked of association among obese ones (OR=0.84).

Table 6. Relative Risks of Breast Cancer for Diabetes Combined with Other Components of Metabolic Syndrome Among Postmenopausal Women

Strata	Crude(95% CI)	Adjusted (95% CI)
Overweight	6.34 (2.27 – 17.7)	5.44 (1.84 – 16.1)
High FMR	7.27 (14.2 – 37.3)	7.85 (1.36 – 45.3)
Overweight + Hypertension	5.71 (1.66 – 19.7)	5.79 (1.52 – 22.0)
Overweight + High FMR	7.81 (2.01 – 30.3)	7.38 (1.75 – 31.2)
Overweight + Dislypidemia	9.33 (2.10 – 41.5)	10.6 (1.78 – 63.9)

* High FMR >=1.5 Adjusted by age, residence, family history of BC 1ºdegree, age at menarche, number of live births, age at first delivery and number of breastfeeding months.

Finally, Table 6 displays the relative risks of BC among postmenopausal women for diabetes combined with other components of metabolic syndrome (hypertension, dislypidemia, overweight, high fat/muscle ratio). All estimates of these combinations, being crude or adjusted, were statistically significant increases in risk. The highest risks for diabetes were found for postmenopausal women with overweight and dislypidemia (OR=9.33 and OR=10.6, crude and adjusted respectively), followed by those having a high fat/muscle ratio (adjusted OR=7.85).

Discussion

Our study gives support to the positive association of diabetes to the risk of postmenopausal BC, almost doubling it (OR=1.92). Other components of the metabolic syndrome, as hypertension and dislypidemia also displayed positive associations, slightly changing the estimates or not. BMI, on the contrary, showed that overweight (OR=5.42) was determinant –but not obesity (OR=0.84)— to the risk increase for diabetes among postmenopausal women. The analyses revealed that among obese women the frequency of diabetes is so high that this latter does not discriminate cases and controls in the studied population.

The analyzed Uruguayan sample should be recognized as a population subset with evident overweight and obesity (mean BMI =27.6 kg/m2, >40% fat fraction), corresponding also to a high meso-endomorphic pattern, two facts that were already reported (Ronco et al., 2008; Ronco et al., 2009a). The women belonging to low/mid social strata, although they could display some protective factors based on their usual reproductive pattern (early age for the first live birth, high number of full term pregnancies, long breastfeeding periods) have become

a high-risk group based on this fact and the diseases which are related to metabolic syndrome. Interestingly, the fraction with diabetes found among ages 60 and over was 16.4%, rather similar to the one accepted among elder BC patients (Schott et al., 2010). In view of the preceding arguments, it could be understandable why Uruguayan women belonging to the lowest socioeconomic classes could also be prone to developing cancer: they tend to be overweight or obese, have a sedentary lifestyle and display dietary patterns which are more typical of Western developed societies (Ronco et al., 2006, 2010c). Should their reproductive history be protective, it seems insufficient to antagonize their environmental/lifestyle risk factors, as we have recently described in a review (Ronco et al., 2010b).

A recent review on diabetes, metabolic syndrome and BC (Xue and Michels, 2007) reported that among all case-control studies in which the association between diabetes and risk of BC was addressed, results suggested that BC patients were more likely to have a history of diabetes, with odds ratios ranging from 1.10 to 2.15. On the other hand, among cohort studies, results indicated that women with a history of diabetes were more likely to develop BC, with hazard ratios ranging from 1.10 to 2.06. In both type of studies, around the half showed statistically significant increases in risk. Our results concerning diabetes reveal similar associations to the existing literature, from which diabetes is being considered as a probable independent risk factor (Grote et al., 2010). The history of diabetes seems to have enough statistical strength by itself, roughly doubling the risk whichever the analysis was. Taking into account different studied strata, it was also clear that the disease concerned mainly to postmenopausal women and specifically those bearing an overweight.

Almost a decade ago, a case-control study conducted in Italy reported an increased prevalence of type 2 diabetes mellitus, hypertension, and dislypidemia (abnormal serum cholesterol and/or triglycerides level) among BC cases compared with women with benign breast pathology or women with no breast pathology (Sinagra et al., 2002). Other study reported that the risk of postmenopausal BC was significantly increased for women with metabolic syndrome (OR = 1.75, 95% CI 1.37-2.22), for three or more components of metabolic syndrome (Rosato et al., 2011).

Regarding the BC risk, the worst possible scenario for the subset of our postmenopausal women with overweight is associated with the history of blood hypertension and any of the components of dislypidemia. Also considering the analysis of fat fraction, the estimates were higher for those women with high fat/muscle ratio (≥1.5 times), remarking that not only the amount but also the proportion of fat is important regarding the risks.

A high BMI in early ages is relevant to develop diabetes, and the studied population revealed high prevalence of overweight/obesity (47.1%) and high endomorphy (30.1%) just at ages 30-39, with trends parallel to age increase. After menopause, the suprarenal glands and adipocytes are major estrogen sources. If body fat is excessive there is an increased hormonal bioavailability. In addition, in the adipose tissue androgens which are gathered from the circulation are also transformed into estrogens through the action of the aromatase, in the process known as "androgen aromatization". In addition, obesity creates a doubly favorable environment for mammary carcinogenesis, since insulin requirements and androgen aromatization are stimulated and increased, the latter for producing more estrogens. Aromatization is stimulated bearing an excessive adipose mass, especially in the thighs, buttocks and abdominal-pelvic regions (gynoid obesity, sharing features with high endomorphism), with a high intake of Ω-6 polyunsaturated fatty acids (PUFAs) and having increased circulating glucocorticoids (McTernan et al., 2002)

A recent study suggested that the ratio of 2/16-α-hydroxyestrogen metabolites may be a marker for lifestyle influences on estrogen metabolism associated with westernization (Falk et al., 2005). In particular, body composition was associated with 2-α- and 16-α-OHestrone levels: while thicker skinfolds were associated with higher 16-α-OH levels, (Campbell et al., 2005) an increase in lean body mass was associated with an improvement in 2/16-α-OH estrogens ratio (Campbell et al., 2007). Women who metabolize a large proportion of their estrogens via the 16-α-hydroxylation pathway could be at a higher risk of BC (Cauley et al., 2003). It has been also suggested that women at higher risk for developing BC due to low 2/16-α-OHestrogens may reduce their risk by participating in lifestyle interventions such as exercise/calorie restriction (Westerlind and Williams, 2007).

The overabundance of insulin, called hyperinsulinemia, amplifies the bioavailability of Insulin-like Growth Factor I (IGF-I). IGF-I and insulin together have been shown to stimulate motility in human BC cell lines, an effect that could enhance migration and invasion (Macaulay, 1992; Sachdev and Yee, 2001). IGF-I signaling enhances estrogen receptor activation by inducing phosphorylation of the estrogen receptor, and IGF-I and estrogen have synergistic effects on the cell cycle signaling cascade and proliferation (Hamelers and Steenberg, 2003). Because the IGF-I system can be cross-activated by insulin, the synergic effects of IGF-I and estrogen may also play a role in the etiology of BC in the hyperinsulinemic state of type 2 diabetes (Chaudhuri et al., 1986, Guastamacchia et al., 2003). Recent experimental findings evidenced that Type 2 diabetes accelerates mammary gland development and carcinogenesis and that the insulin resistance and/or the IGF are major mediators of these effects (Novosyadlyy et al., 2010). If alterations of endogenous estrogen concentrations indeed play an important role in the association of type 2 diabetes with the risk of BC, this association is expected to be stronger for tumours that are estrogen receptor positive, which was confirmed in the Nurses Health Study (Michels et al., 2003).

As other case-control studies, our work has limitations and strengths. A major limitation is related to the sample size; it would be desirable to analyze a larger one, in order to have enough statistical power for certain results. On the other hand, both cases and controls belong to a very homogeneous base subpopulation: they were matched by age frequency and they also proceeded from the same

healthcare system, showing similarities concerning socio-demographic variables. To be quoted also among the strengths, we selected as controls women with normal breasts according to mammography, not only without cancer; thus, if benign breast diseases had any association with the analyzed dietary items, we avoided the possibility of biasing results due to this. The inclusion of detailed anthropometric measurements and calculations as body composition and somatotype instead of using only the BMI or waist-to-hip ratio can be considered also a strength. Finally, a high participation was achieved (around 98% of the incident cases below 70 years old during the study period): selection and recall bias appear to be unlikely. Although it is not possible to avoid completely any bias, we think that results were not chance findings. Anyway, we need caution in the interpretation of results, since generalizability is limited due to the population features: they have mainly low educational level and belong to low socioeconomic strata.

In conclusion, we can state that: First, a personal history of diabetes was strongly associated with overweight and it tended to increase the risk of BC. Second, a high-risk subset of BC arose from the analyses. This subset was composed by postmenopausal, diabetic and overweight women, who in addition display a personal history of blood hypertension and/or dislypidemias and/or a high endomorphism. Finally, the results give elements with potentiality to define high-risk subjects, for primary as well as for secondary prevention, since this pathologic pattern related to the metabolic syndrome is usually not taken into account for BC prevention. As an example of this, the ages with the highest prevalence of metabolic factors fall out of the range considered for screening and early detection programmes, but those ages involve a large fraction of the diagnosed BC cases.

References

Agnoli C, Berrino F, Abagnato CA, et al (2010). Metabolic syndrome and postmenopausal breast cancer in the ORDET cohort: a nested case-control study. *Nutr Metab Cardiovasc Dis*, **20**, 41.

American College of Radiology (1998). *Breast imaging reporting and data system* (BI-RADS). 3rd ed., American College of Radiology, Reston, VA.

Bjørge T, Lukanova A, Jonsson H, et al (2010). Metabolic syndrome and breast cancer in the me-can (metabolic syndrome and cancer) project. *Cancer Epidemiol Biomarkers Prev*, **19**, 1737-45.

Bray F, Mc Carron P, Parkin DM (2004). The changing global patterns of female breast cancer incidence and mortality. *Breast Cancer Res*, **6**, 229-39.

Breslow NE, Day NE (1980). *Statistical methods in cancer research*. Vol. 1. The analysis of case-control studies. IARC Sci.Publ. 32. IARC, Lyon.

Campagnoli C, Pasanisi P, Peris C, et al (2008). Insulin-like Growth Factor-I and Breast Cancer: Epidemiological and Clinical Data. In: Pasqualini JR (ed) Breast Cancer: Prognosis, Treatment and Prevention. 2nd ed. Informa Healthcare, New York.

Campbell KL, Westerlind KC, Harber VJ, Friedenreich CM, Courneya KS (2005). Associations between aerobic fitness and estrogen metabolites in premenopausal women. *Med Sci Sports Exerc*, **37**, 585–92.

Campbell KL, Westerlind KC, Harber VJ, et al (2007). Effects of aerobic exercise training on estrogen metabolism in premenopausal women: a randomized controlled trial. *Cancer Epidemiol Biomarkers Prev*, **16**, 731–9.

Capasso I, Esposito E, Pentimalli F, et al (2011). Metabolic syndrome affects breast cancer risk in postmenopausal women: National Cancer Institute of Naples experience. *Cancer Biol Ther*, **10**, 1240-3.

Carter JEL (2002). *The Heath-Carter anthropometric somatotype– Instruction Manual*. Surrey, Canada, TeP and Rosscraft.

Cauley JA, Zmuda JM, Danielson ME, et al (2003). Estrogen metabolites and the risk of breast cancer in older women. *Epidemiology*, **14**, 740-4.

Chaudhuri PK, Chaudhuri B, Patel N (1986). Modulation of estrogen receptor by insulin and its biologic significance. *Arch Surg*, **121**, 1322–5.

Connolly BS, Barnett C, Vogt KN, et al (2002). A meta-analysis of published literature on waist-to-hip ratio and risk of breast cancer. *Nutr Cancer*, **44**, 127–38.

De Rose EH, Pigatto E, Celi R (1984). *Kinanthropometry, physical education and sport training*. SEED, Brasilia. (in Portuguese)

De Stéfani E, Ronco AL, Mendilaharsu M, Guidobono M, Deneo-Pellegrini H (1997a). Meat intake, heterocyclic amines, and risk of breast cancer: a case-control study in Uruguay. *Cancer Epidemiol Biomark Prev*, **6**, 573-81.

De Stéfani E, Correa P, Ronco A, et al (1997b). Dietary fiber and risk of breast cancer. *Nutr Cancer*, **28**, 14 9.

De Stéfani E, Deneo-Pellegrini H, Mendilaharsu M, Ronco AL (1998). Essential fatty acids and breast cancer: a case-control study in Uruguay. *Int J Cancer*, **76**, 491-4.

Falk RT, Fears T, Xu X, et al (2005). Urinary estrogen metabolites and their ratio among Asian American women. *Cancer Epidemiol Biomarkers Prev*, **14**, 221–6.

Faulkner J (1968). Physiology of swimming and diving. In Falls H: *Exercise Physiology*. Academic Press, Baltimore.

Feig SA (1999). Role and evaluation of mammography and other imaging methods for breast cancer detection, diagnosis, and staging. *Semin Nucl Med*, **29**, 3–15.

Ferlay J, Shin HR, Bray F, et al (2010). GLOBOCAN 2008. *Cancer Incidence and Mortality Worldwide*: IARC CancerBase No.10. Lyon, France: International Agency for Research on Cancer. Available at: http://globocan.iarc.fr. [Accessed 17.08.2010].

Food and Agricultural Organization (2010). http://faostat.fao.org/site/610/Desktop Default.aspx? PageID=610#ancor [Accessed 30.04.10].

Freund E (1885). Diagnosis des Carcinomas. *Wiener Medizinische*, **B1**, 268 (in German).

Furberg AS, Veierod MB, Wilsgaard T, Bernstein L, Thune I (2004). Serum high-density lipoprotein cholesterol, metabolic profile, and breast cancer risk. *J Natl Cancer Inst*, **96**, 1152–60.

Glicksman AS, Rawson RW (1956). Diabetes and altered carbohydrate metabolism in patients with cancer. *Cancer*, **9**, 1127–34.

Goodwin PJ, Ennis M, Pritchard KI, et al (2002). Fasting insulin and outcome in early-stage breast cancer: results of a prospective cohort study. *J Clin Oncol*, **20**, 42–51.

Grote VA, Becker S, Kaaks R (2010). Diabetes mellitus type 2 - an independent risk factor for cancer? *Exp Clin Endocrinol Diabetes*, **118**, 4-8.

Guastamacchia E, Resta F, Mangia A, et al (2003). Breast cancer: biological characteristics in postmenopausal type 2 diabetic women. Identification of therapeutic targets. *Curr Drug Targets Immune Endocr Metabol Disord*, **3**, 205–9.

Hamelers IH, Steenbergh PH (2003). Interactions between estrogen and insulin-like growth factor signaling pathways in

human breast tumor cells. *Endocr Relat Cancer*, **10**, 331– 45.
Hanley AJ, Festa A, D'Agostino Jr RB, et al (2004). Metabolic and inflammation variable clusters and prediction of type 2 diabetes: factor analysis using directly measured insulin sensitivity. *Diabetes*, **53**, 1773–81.
Hirose K, Toyama T, Iwata H, et al (2003). Insulin, insulin-like growth factor-I and breast cancer risk in Japanese women. *Asian Pac J Cancer Prev*, **4**, 239–46.
Jaumandreu S, Varas X, Mezzera J, et al (2001). Cytologic diagnosis in palpable nodules of the breast. *Arch Ginecol Obstet*, **39**, 148-53 (in Spanish).
Larsson SC, Mantzoros CS, Wolk A (2007). Diabetes mellitus and risk of breast cancer: a meta-analysis. *Int J Cancer*, **121**, 856-62.
Macaulay VM (1992). Insulin-like growth factors and cancer. *Br J Cancer*, **65**, 311–20.
McTernan PG, Anderson LA, Anwar AJ, et al (2002). Glucocorticoid regulation of p450 aromatase activity in human adipose tissue: gender and site differences. *J Clin Endocrinol Metab*, **87**, 1327–36.
Maiti B, Kundranda MN, Spiro TP, Daw HA (2010). The association of metabolic syndrome with triple-negative breast cancer. *Breast Cancer Res Treat*, **121**, 479-83.
Michels KB, Solomon CG, Hu FB, et al (2003). Type 2 diabetes and subsequent incidence of breast cancer in the Nurses' Health Study. *Diabetes Care*, **26**, 1752-8.
Muck BR, Trotnow S, Hommel G (1975). Cancer of the breast, diabetes and pathological glucose tolerance. *Arch Gynakol*, **220**, 73–81.
Muti P, Quattrin T, Grant BJ, et al (2002). Fasting glucose is a risk factor for breast cancer: a prospective study. *Cancer Epidemiol Biomarkers Prev*, **11**, 1361–8.
Novosyadlyy R, Lann DE, Vijayakumar A, et al (2010). Insulin-mediated acceleration of breast cancer development and progression in a nonobese model of type 2 diabetes. *Cancer Res*, **70**, 741-51.
Parkin DM, Whelan SL, Ferlay J, et al (2002). *Cancer incidence in five continents, vol 8*. IARC Scientific Publications No. 155, IARC, Lyon.
Pasanisi P, Berrino F, De Petris M, et al (2006). Metabolic syndrome as a prognostic factor for breast cancer recurrences. *Int J Cancer*, **119**, 236–8.
Potischman N, McCulloch CE, Byers T, et al (1991). Associations between breast cancer, plasma triglycerides, and cholesterol. *Nutr Cancer*, **15**, 205–15.
Reaven GM (1988). Banting lecture 1988. Role of insulin resistance in human disease. *Diabetes*, **37**, 1595–607.
Rock CL, Demark-Wahnefried W (2002). Can lifestyle modification increase survival in women diagnosed with breast cancer? *J Nutr*, **132**, 3504–7S.
Ronco AL, De Stéfani E, Mendilaharsu M, Deneo-Pellegrini H (1996). Meat, fat and the risk of breast cancer: a case-control study from Uruguay. *Int J Cancer*, **65**, 328-31.
Ronco AL, De Stéfani E, Boffetta P, et al (1999). Vegetables, fruits, and related nutrients and risk of breast cancer: a case control study in Uruguay. *Nutr Cancer*, **35**, 111-9.
Ronco AL, De Stéfani E, Dáttoli R (2002). Dairy foods and risk of breast cancer: a case-control study in Montevideo, Uruguay. *Eur J Cancer Prev*, **11**, 457-63.
Ronco AL, De Stéfani E, Fabra A (2003). White meat intake and the risk of breast cancer: a case-control study in Montevideo, Uruguay. *Nutr Res*, **23**, 151-62.
Ronco AL, De Stéfani E, Boffetta P, et al (2006). Food patterns and risk of breast cancer: A factor analysis study in Uruguay. *Int J Cancer*, **19**, 1672-8.
Ronco AL, Silveira S, De Stéfani E, Deneo-Pellegrini H, Mendilaharsu M (2007). Factores socioculturales y psicológicos y cáncer de mama: un estudio caso-control en Montevideo, Uruguay. *Biomedicina*, **3**, 6-17.
Ronco AL, Mendoza B, Varas X, et al (2008). Somatotype and risk of breast cancer: a case-control study in Uruguay. *Braz J Epidemiol*, **11**, 215-27.
Ronco AL, Boeing H, De Stéfani E, et al (2009a). A case-control study on fat to muscle ratio and risk of breast cancer. *Nutr Cancer*, **61**, 466-74.
Ronco AL, Stoll M, De Stéfani E et al (2009b). Rh factor, family history and risk of breast cancer: a case-control study in Uruguay. *Cancer Det Prev*, **32**, 277-85.
Ronco AL, De Stéfani E, Aune D, et al (2010a). Nutrient patterns and risk of breast cancer in Uruguay. *Asian Pac J Cancer Prev*, **11**, 519-24.
Ronco AL, De Stéfani E, Stoll M (2010b). Hormonal and metabolic modulation through nutrition: towards a primary prevention of breast cancer. *The Breast*, **19**, 322-32.
Ronco AL, De Stéfani E, Deneo-Pellegrini H, et al (2010c). Dietary patterns and risk of ductal carcinoma of the breast: a factor analysis in Uruguay. *Asian Pac J Cancer Prev*, **11**, 1187-93.
Ronco AL, De Stéfani E (2010d). Diabetes, overweight and risk of breast cancer: a case-control study in Uruguay. *Proceedings of the XVI World Congress of the Senologic International Society*. Valencia, Spain, October 20-22nd, 2010.
Rosato V, Bosetti C, Talamini R, et al (2011). Metabolic syndrome and the risk of breast cancer in postmenopausal women. *Ann Oncol,* **22**, 2687-92.
Sachdev D, Yee D (2001). The IGF system and breast cancer. *Endocr Relat Cancer*, **8**, 197-209.
Schott S, Schneeweiss A, Sohn C (2010). Breast cancer and diabetes mellitus. *Exp Clin Endocrinol Diabetes*, 118, 673-7.
Sinagra D, Amato C, Scarpilta AM, et al (2002). Metabolic syndrome and breast cancer risk. *Eur Rev Med Pharmacol Sci*, **6**, 55-9.
Soler M, Chatenoud L, Negri E, et al (1999). Hypertension and hormone related neoplasms in women. *Hypertension*, **34**, 320-5.
Tsugane S, Inoue M (2010). Insulin resistance and cancer: epidemiological evidence. *Cancer Sci*, **101**, 1073-9.
United Nations Organization (2009), Human development index rankings. Available at: http://hdr.undp.org/en/statistics/. [accessed 27.04.10].
U.S. Census Bureau (2010). International data base, http://www.census.gov/ipc/www/idb/ country.php [accessed 30.04.10].
Varas X, Leborgne F, Leborgne JH (1992). Non palpable, probably benign lesions: role of follow-up mammography. *Radiology*, **184**, 1409-14.
Verheus M, Peeters PH, Rinaldi S, et al (2006). Serum C-peptide levels and breast cancer risk: results from the European Prospective Investigation into Cancer and Nutrition (EPIC). *Int J Cancer*, **119**, 659-67.
Vona-Davis L, Howard-McNatt M, Rose DP (2007). Adiposity, type 2 diabetes and the metabolic syndrome in breast cancer. *Obes Rev*, **8**, 395-408.
Warburg O (1930). The metabolism of tumors. Constable Press, London.
Westerlind KC, Williams NI (2007). Effect of energy deficiency on estrogen metabolism in premenopausal women. *Med Sci Sports Exerc*, **39**, 1090-7.
Wilson AM, Ryan MC, Boyle AJ (2006). The novel role of C-reactive protein in cardiovascular disease: risk marker or pathogen. *Int J Cardiol*, **106**, 291-7.
World Cancer Research Fund/American Institute for Cancer Research (2007). Food, nutrition, physical activity, and the prevention of cancer: a global perspective. AICR, Washington DC.
Xue F, Michels KB (2007). Diabetes, metabolic syndrome, and breast cancer: a review of the current evidence. *Am J Clin Nutr*, **86**, 823-35.