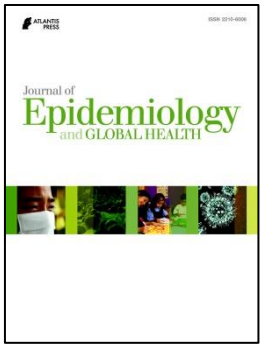

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# Factors associated with breast cancer in Puerto Rican women

Luisa Morales [a,b,*], Carolina Alvarez-Garriga [b], Jaime Matta [a], Carmen Ortiz [a], Yeidyly Vergne [b], Wanda Vargas [a], Heidi Acosta [b], Jonathan Ramírez [a], Julyann Perez-Mayoral [a], Manuel Bayona [b]

[a] *Department of Physiology and Pharmacology, Ponce School of Medicine and Health Sciences, P.O. Box 7004-388, Ponce 00732-7004, Puerto Rico*
[b] *Public Health Program, Ponce School of Medicine and Health Sciences, P.O. Box 7004-388, Ponce 00732-7004, Puerto Rico*

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**KEYWORDS**
Breast cancer;
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DNA repair capacity;
Receptor status

**Abstract** *Background:* Breast cancer (BC) is the most common cancer afflicting Puerto Rican women and accounts for more cancer-related deaths in this population than any other cancer.

*Methods:* Demographic, anthropometric, family history, and lifestyle data, as well as DNA repair capacity (DRC), were compared in 465 BC cases and 661 controls. Crude and multiple logistic regression-derived adjusted odds ratios were used as indicators of the associations between BC and the variables under study.

*Results:* A low DRC level, aging (>61 years), family history of BC, and low education level had statistically significant associations with increased BC risk. Endometriosis, full-term pregnancy at an earlier age, higher parity, hysterectomy before age 50, multivitamin and calcium intake, and longer duration of breastfeeding significantly decreased BC risk.

*Conclusions:* This study discusses the major risk factors for BC in Puerto Rico (PR). Because many of these findings represent modifiable risk factors, they can translate into public health initiatives to lower BC risk. In addition, the possibility of using DRC as a simple screening tool for BC risk is explored.
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## 1. Introduction

Worldwide, the malignancy that occurs most frequently in women is breast cancer (BC) [1]. In 2011, an estimated 230,480 new cases of invasive BC were expected to be diagnosed in women in the United States, along with 57,650 new cases of non-invasive (*in situ*) BC [2].

*Abbreviations*: BC; breast cancer; PR; Puerto Rico; BMI; body mass index; IRB; Institutional Review Board; DRC; DNA repair capacity; OR; odds ratio; MHT; menopause hormone therapy.

* Corresponding author at: Department of Physiology and Pharmacology, Ponce School of Medicine and Health Sciences, P.O. Box 7004-388, Ponce 00732-7004, Puerto Rico. Tel./fax: +1 787 259 7085.
*E-mail address:* lmorales@psm.edu (L. Morales).

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Hispanics are the fastest growing minority in the US, with 9% of the Hispanic population being Puerto Ricans [3]. Although mainland and island Puerto Ricans are included in the statistics of the US as part of the Hispanic group, differences in risk factors among mainland Puerto Ricans versus island Puerto Ricans have been found-most notably, lower BC incidence in the latter group [3,4]. Similarly, Nazario et al. estimated the lifetime risk of Puerto Rican women developing BC at 5.4% [5]; however, reported lifetime BC risk in the US is 2.3 times higher: 12.5% [6]. The incidence of BC among island Puerto Ricans has been increasing in recent years [4,5]; this warrants investigation.

BC is the most prevalent of all cancers in Puerto Rico (PR) and accounts for 30.3% of all female cancers [7]. BC also has the highest mortality of all cancers in this population [7,8]. The most recent data available through the Puerto Rico Cancer Registry state that between 2005 and 2009, 1725 new BC cases were reported in PR [7]. Thus, there is a need to pursue new ways to prevent, predict, identify, and mitigate the impact of BC in the Puerto Rican population.

Limited published data exist regarding the epidemiology of BC in PR [5,7], and most information explores only incidence and mortality [5,7,8]. Due to the multiethnic composition of this population, which is an admixture of European, African, and Amerindian ethnic groups [9], it is important to study the risk factors that could make this population less susceptible to developing BC than other populations.

Because BC is a multifactorial disease that is a result of the interplay between genetic, epigenetic and lifestyle factors [10], the risk factors chosen in this study reflect all those domains. The modifiable risk factors under study represent risk factors that had been studied previously in other populations. In this study, the aim was to confirm their impact on the population of PR. This may be the first research to study those concurrently with genetic (receptor status) and epigenetic factors.

Regarding the latter, DNA repair capacity (DRC) was analyzed as a risk factor for BC. DRC is critical for maintaining genomic integrity, minimizing DNA mutations and replication errors [11]. Differences in DRC among individuals partially explain intrinsic sensitivities to mutagens and carcinogens [12]. Indeed, a number of studies have shown that low DRC correlates with higher cancer risk [13–15]. A recent study with the same cohort of women showed that, on an average, Puerto Rican women with BC have a 60% reduction in DRC compared with controls [15].

In this study, the association of all these potential risk factors for BC in Puerto Rican women was also evaluated. Elucidating these BC risk factors will provide increased opportunities for BC prevention and control [16].

## 2. Materials and methods

### 2.1. Case control selection

Participants comprised of 1126 adult female Puerto Rican residents, age 21 or older: 465 recently diagnosed BC cases and 661 without BC. Cases were patients who were: (1) recently diagnosed and histopathologically confirmed primary breast carcinomas; and (2) treatment-naïve — that is, they had not received chemotherapy, radiotherapy, or blood transfusions in the previous 5 years, as described by Matta et al., 2012 [15]. Patients with a prior history of cancer or with BC secondary to other cancer types were excluded. Controls were women (1) whose mammogram was negative within the previous 6 months; (2) who had undergone a clinical breast examination by a gynecologist or other physician; and (3) who had not received any blood transfusions within the previous 5 years. Patients were recruited as incident cases between 2006 and 2012 in collaborating private clinical practices, and controls were recruited concurrently. The sample obtained represented 83% of the 78 counties of PR.

### 2.2. Sample

The sample size was calculated utilizing CDC's Epi Info 7.0; it was found that the current sample would allow for a statistically significant odds ratio (OR) as low as 1.7 when the percent exposed among controls is 10% or higher (type I error = 0.05, type II error = 0.20; power 80%).

### 2.3. Data collection

Cases and controls completed a written informed consent, a HIPAA form, and participated in an interview based on a seven-page epidemiological questionnaire. Data gathered from the questionnaire included information on age, body mass index (BMI), family history of cancer, genetic, gynecological, hormonal, and environmental factors, selected nutritional variables including multivitamin and calcium intake, and other variables that could provide an estimate of BC risk. The selection of the potential predictors (exposures) under study

and the questions used were based on previously published research on BC.[1] This study was approved by the Institutional Review Board (IRB) of the Ponce School of Medicine and Health Sciences and by the IRBs of participating clinics that had such a body.

The research staff received proper training regarding NIH Guidelines for the Study of Human Subjects. A registered nurse interviewed each participant and drew a blood sample for assessing DRC (using a host-cell reactivation assay).

### 2.4. Host cell reactivation assay

The host cell reactivation assay was performed as described by Matta et al., 2012 [15].

### 2.5. Statistical analysis

Data analyses were performed using the SPSS® 17 statistical package (SPSS; Chicago, IL). BC cases and controls were compared with regard to the distribution of selected exposures such as age, BMI, family history of BC, irregular menses, breastfeeding practices, intake of vitamins and calcium supplements, and DRC level. DRC was categorized as low, medium, or high using tertiles from the whole sample. For the unadjusted analyses, cases were compared with controls in terms of the selected exposures (covariates). For categorical variables, the odds ratio (OR) was used as a measure of association, and the 95% confidence interval of the OR was utilized to assess the precision of this estimate. The two-tailed Fisher's exact test was calculated to measure the statistical significance of the crude OR [17]. A $P$ value $\leqslant 0.05$ indicated statistically significant results.

Continuous variables, including those related to age (oral contraceptive use, birth of first child, hysterectomy, and oophorectomy) were categorized. After using the Mantel and Haenszel stratified analysis to explore confounding and interactive effects among all variables in the study, multiple logistic regressions were used to measure the adjusted OR. Potential interactions with covariates such as age groups, menopause, and parity were further examined using multiple logistic regressions, adjusting for all confounders simultaneously [17]. No important effect modifications or statistically significant interactions were found during the analyses. To evaluate the association between BC and selected variables, the analysis was adjusted by age, BMI, family history of BC, menopause, number of children, alcohol use, smoking and vitamin use.

## 3. Results

A total of 465 BC cases and 661 controls were analyzed in the study. The mean age (±SD) of women with BC (range: 24—89 years) and controls (range: 21—87 years) was $56.4 \pm 12.6$ and $52.3 \pm 12.5$, respectively ($P < 0.001$). Table 1 includes the description of tumor characteristics among cases: 65.3% infiltrating ductal, 4.7% infiltrating lobular, 17.9% *in situ* ductal, 1.8% *in situ* lobular, and 9.8% mixed components. In terms of receptor status, 73.5% of the cases were estrogen receptor positive (ER+), 66.9% were progesterone receptor positive (PR+) and 76.8% were Her2 receptor negative (Her2−). In terms of ER and PR, a positive receptor status indicates better prognosis and more options of treatment available. A negative Her2 receptor status indicates a less aggressive cancer.

Table 2 includes the associations between BC and gynecological variables. Having a history of endometriosis decreased the risk of having BC by 39% ($P = 0.039$). Women who began menopause after age 50 had a 41% greater risk of having BC ($P = 0.023$), while, for women currently in menopause, no statistical significance was shown ($P = 0.278$). An inverse association between parity status and cancer risk was also observed. The adjusted odds ratio for $\geqslant 5$ children reached 0.42 ($P = 0.006$) versus nulliparous women. Also, in an analysis of parity on a continuous scale, it was found that the risk of BC decreased by 11% (OR = 0.89, $P = 0.003$) with each subsequent birth. Furthermore, women who had their children at a younger age, especially age 20—29, showed a 41% lower risk of developing BC (OR 0.59, $P = 0.011$). Oral contraceptives appeared to be associated with a 38% decreased risk of BC, if they were used after age 21 ($P = 0.048$). Hysterectomy (defined as the surgical removal of the uterus) on a continuous scale was not statistically significant. However, women who had a hysterectomy between the ages of 41 and 49 had a 56% lower risk of having BC ($P = 0.020$). That reduced risk appeared to decline by 1% with each year after hysterectomy ($P = 0.044$). In terms of menopause hormone therapy (MHT), it was found that BC postmenopausal cases were 26% less likely to have used MHT than

[1] Brinton's Women's Interview Study of Health; Ziegler's Asian-American BC Study; Tucker's Family Studies Questionnaire; Brown's Population Health Study; Schairer's BCDDP-Female Questionnaire; Hayes's Population Health Study; Anton-Culver's Familial Breast and Ovarian Cancer Study; and Doody's X-ray Technicians—Second Survey.

**Table 1** Description of tumor characteristics among case subjects with breast cancer (BC).

| Variable | BC cases *n* (%) |
|---|---|
| *Type of cancer* | |
| Infiltrating ductal | 280 (65.3) |
| Infiltrating lobular | 21 (4.9) |
| *In situ* ductal | 77 (17.9) |
| *In situ* lobular | 8 (1.9) |
| Mixed components | 43 (10.0) |
| Missing #36 | |
| *Receptor status* | |
| Estrogen | |
| Positive | 228 (73.5) |
| Negative | 82 (26.5) |
| Unknown #155 | |
| *Progesterone* | |
| Positive | 208 (66.9) |
| Negative | 103 (33.1) |
| Unknown#154 | |
| *Her2* | |
| Positive | 65 (23.2) |
| Negative | 215 (76.8) |
| Unknown #185 | |
| Triple negative | 41 (13.4) |
| *Grade* | |
| Well differentiated | 52 (14.6) |
| Moderately differentiated | 189 (52.9) |
| Poorly differentiated | 110 (30.8) |
| Unknown #114 | |

controls ($P = 0.001$). Women who breastfed for 6 months or more had a 36% lower risk of developing BC ($P = 0.057$; borderline significance).

Table 3 shows the association of BC with other selected variables. DRC as a continuous variable increased the risk of women developing BC by 1.54 times. Women with low DRC levels ($\leqslant$2.52%) had 17.3 times greater risk of developing BC in their lifetime. Women with medium DRC levels (2.53—5.36%) had 2.7 times greater risk of developing BC compared with those with high DRC levels ($\geqslant$5.37%). Both associations were statistically significant ($P < 0.001$). Women 41—60 years of age had 1.78 times greater risk of developing BC compared with women 21—40 years of age ($P = 0.036$).

The remainder of Table 3 lists modifiable risk factors and their impact on BC risk. Education level was an important risk factor for BC in the study population. Women with high school education (9—12th grade) showed a slight increase in BC risk of 1.3 times ($P = 0.086$), while those with only an elementary school education (1st—8th grade) had 3.4 times greater risk of having BC ($P = 0.003$). Regarding marital status, widows had 2.1 times greater risk of having BC ($P = 0.039$) than did married women, followed by those who were divorced, who were 2.6 times more likely to have BC ($P = 0.002$). Smokers had 1.58 times the risk of having BC ($P = 0.066$) than non-smokers. Those with a family history of BC had twice the risk ($P = 0.001$) of having BC in their lifetime. Women who had a family history of any other cancer (not BC) had a 35% greater risk of having BC ($P = 0.031$). No statistical association with BC was found regarding alcohol consumption and BMI.

Regarding vitamin consumption, 57.4% of women reported taking vitamins. The odds of currently taking vitamins was 50% lower in the BC cases ($P < 0.001$), while consumption of vitamins (5-year period) showed a decrease in BC risk by 40% ($P < 0.001$). In terms of multivitamin and calcium intake, BC patients had 30% and 50% less consumption than the control group, respectively ($P = 0.005$, $P < 0.001$, respectively).

## 4. Discussion

This study provides an overview of the major epidemiological factors for BC in PR using a sample of women that includes 465 BC cases and 661 controls. In this study, as in previous studies, it was shown that high DRC protects women against BC; a low DRC is a BC risk factor for the Puerto Rican population. Previous studies have indicated similar results of an association of DRC with BC risk [13,15] when analyzed as both a continuous and categorical variable [18]. A broad discussion on the usefulness of DRC level as a measure of BC risk was recently published by Matta et al., 2012 [15].

Another molecular factor described is hormone receptor status, which guides BC treatment choices and indicates disease prognosis. In general, PR+ and ER+ are indicators of a good prognosis [19] which, in this study, was of the majority of the sample. In this study population, 13.4% of the sample was triple negative (ER−, PR−, Her2−). Those patients carry the worst prognosis and have a high rate of relapse, especially within 3—5 years of initial treatment [20].

Reproductive factors were shown to modulate BC in the study population. This study found that having a diagnosis of endometriosis was protective against BC. This may be due to the way endometriosis is treated; long-term estrogen-suppressive pharmacological therapy decreases estrogen levels, thus reducing BC risk [21]. MHT was also shown to be important in modulating BC risk.

**Table 2** Association of breast cancer (BC) with gynecological variables.

| Variable | BC cases | Controls | Crude OR (95% CI) | Adjusted OR[a] (95% CI) | *P* value |
|---|---|---|---|---|---|
| *Pregnancy* | | | | | |
| Yes | 397 | 552 | 1.12 (0.8, 1.7) | 1.04 (0.7, 1.4) | 0.824 |
| No | 68 | 109 | | | |
| *Breast feeding total* | | | | | |
| Never | 276 | 362 | Referent | Referent | |
| 0—5 months | 138 | 244 | 0.82 (0.5, 1.2) | 0.76 (0.5, 1.2) | 0.244 |
| ⩾6 months | 51 | 55 | 0.61 (0.4, 0.9) | 0.64 (0.4, 1.0) | 0.057 |
| *Parity status* | | | | | |
| Nulliparous | 68 | 109 | Referent | Referent | |
| 1—2 children | 185 | 321 | 0.25 (0.1, 0.5) | 0.36 (0.2, 0.7) | 0.003 |
| 3—4 children | 159 | 201 | 0.24 (0.1, 0.4) | 0.34 (0.2, 0.6) | 0.001 |
| ⩾5 children | 44 | 18 | 0.32 (0.2, 0.6) | 0.42 (0.2, 0.8) | 0.006 |
| # Missing (21) | | | | | |
| *Age at first live birth* | | | | | |
| ⩽19 | 82 | 88 | 1.14 (0.8—1.6) | 0.59 (0.4, 0.9) | 0.011 |
| 20—29 | 242 | 365 | 0.76 (0.5—1.2) | 0.63 (0.4, 1.0) | 0.075 |
| ⩾30 | 63 | 85 | Referent | Referent | |
| # Missing (201) | | | | | |
| *Menarche* | | | | | |
| ⩽12 | 245 | 378 | 0.85 (0.7, 1.1) | 0.88 (0.7, 1.2) | 0.372 |
| ⩾13 | 216 | 282 | | | |
| # Missing (5) | | | | | |
| *Endometriosis* | | | | | |
| Yes | 26 | 68 | 0.52 (0.3, 0.8) | 0.61 (0.3, 1.0) | 0.039 |
| No | 438 | 590 | | | |
| # Missing (4) | | | | | |
| *Age oophorectomy* | | | | | |
| ⩽40 | 35 | 54 | 0.84 (0.4, 1.7) | 0.79 (0.3, 1.5) | 0.283 |
| 41—49 | 37 | 53 | 1.12 (0.5, 2.5) | 0.95 (0.3, 1.9) | 0.635 |
| ⩾50 | 20 | 26 | Referent | Referent | |
| # Missing (901) | | | | | |
| *Menopause* | | | | | |
| Yes | 357 | 429 | 1.76 (1.4, 2.3) | 1.30 (0.8, 1.9) | 0.278 |
| No | 108 | 232 | | | |
| *Menopause age* | | | | | |
| >50 | 201 | 208 | 1.47 (1.1, 1.9) | 1.41 (1.1, 1.9) | 0.023 |
| ⩽49 | 155 | 236 | | | |
| # Missing (326) | | | | | |
| *MHT (estrogen-only)* | | | | | |
| Yes | 100 | 182 | 0.72 (0.6—0.9) | 0.74 (0.6—0.9) | 0.001 |
| No | 357 | 467 | | | |
| # Missing (20) | | | | | |
| *Age hysterectomy* | | | | | |
| ⩽40 | 43 | 67 | 0.52 (0.5, 0.9) | 0.44 (0.2, 0.8) | 0.020 |
| 41—49 | 45 | 69 | 0.53 (0.3—1.0) | 0.45 (0.2—0.9) | 0.023 |
| ⩾50 | 31 | 25 | Referent | Referent | |
| # Missing (846) | | | | | |

(*continued on next page*)

**Table 2** (*Continued*)

| | | | | | |
|---|---|---|---|---|---|
| Oral contraceptives | | | | | |
| Yes | 224 | 357 | 0.77 (0.6, 0.9) | 0.78 (0.6, 0.9) | 0.053 |
| No | 238 | 292 | | | |
| # Missing (15) | | | | | |
| *Age oral contraceptives* | | | | | |
| <20 | 41 | 88 | 0.72 (0.5, 1.1) | 0.62 (0.4, 0.9) | 0.048 |
| ⩾21 | 168 | 259 | | | |
| # Missing (570) | | | | | |

*Abbreviations:* BC, breast cancer; CI, confidence interval; OR, odds ratio; MHT, menopause hormone therapy.
[a] Adjusted by age, BMI, family history of breast cancer, menopause, number of children, alcohol use, smoking, vitamin use.

Almost all women in this study who had a history of MHT treatment reported the use of estrogen-only MHT (98.6%) because it is the most popular MHT treatment that Puerto Rican physicians prescribe. The findings of MHT being a potential protective factor for BC need to be studied further; the literature indicates that increased risk of BC contributable to MHT treatment is due to a formulation that combines estrogen with progestin [22]. The use of estrogen-only MHT has a less clear effect on BC risk [23]. Elevated estrogen levels found in women with both ovaries and those going through late menopause are at least partly responsible for those women having BC some time in their lives.

In addition, this study showed that women who had a hysterectomy and/or an oophorectomy had lower odds of having BC. It was also found that women who have a hysterectomy at an advanced age have an increased risk of BC. This association could be explained by a longer lifetime exposure to estrogens and other hormones that have been found to be associated with BC [24].

An increased number of pregnancies and a younger age at a full-term pregnancy decreased the risk of BC. Changes in gene expression have been observed in breast tissue of parous women compared with nulliparous women [25], thus providing a rationale for pregnancy-related protection against BC.

The protective effect found in breastfeeding women did not reach statistical significance due to the reduced number of women who reported breastfeeding for a prolonged period of time (⩾6 months). This finding is particularly important because of the cultural decline in the prevalence of breastfeeding in Puerto Rican women [26]. Breastfeeding, like some endometriosis treatments, decreases estrogen levels, thus helping to decrease the risk of BC in premenopausal women. A longer duration of breastfeeding delays reestablishment of ovulation after pregnancy, thus decreasing the cumulative ovulatory menstrual cycles.

Having a family history of BC and/or any type of cancer increases the odds of a woman having BC. Relatives share genes, lifestyles, and environmental factors that collectively may influence their health and their risk of developing BC.

Higher education was associated with decreased BC risk; women who stopped their education at a relatively low level (i.e., elementary school) were at higher risk for BC when compared with those who had at least an associate degree [27]. This association is controversial because some studies attribute a high educational level to high risk of BC [27], while others present the opposite [28].

Changes in social and lifestyle patterns due to widowhood or divorce appear to have an impact on BC risk [29], and these results support that: both widows and divorcees had higher odds of having BC compared with married women. Widows tend to be older women (aging is a risk factor in BC) and more prone to depression and stress caused by the loss of a spouse.

An increased risk in BC in Puerto Rican women who smoke cigarettes was also observed. A number of studies have suggested that smoking increases the risk of BC [2], but this relationship is still controversial. Further studies are required to confirm this finding in the population studied.

The odds of having BC increased with age [2]. It was found that in this population, women between the ages of 40 and 61 years of age should be screened more frequently for BC.

In agreement with other publications [30], this study found that BC risk increases as BMI increases. However, our results did not reach statistical significance. That may be due to the similarity in BMI among cases and controls, mean BMI (±SD) of 27.9 ± 5.5 and controls 27.3 ± 5.0 ($P = 0.081$), 66%

**Table 3** Association of breast cancer with DRC, family history of cancer and breast cancer, obesity, lifestyle, marital status and level of education.

| Variable | BC cases | Controls | Crude OR (95% CI) | Adjusted OR[a] (95% CI) | *P* value |
|---|---|---|---|---|---|
| *DRC*[b] | | | | | |
| Low <2.52 | 279 | 101 | 14.86 (10.3—21.4) | 17.32 (12.2—26.7) | <0.001 |
| Medium 2.53—5.36 | 122 | 252 | 2.44 (1.7—3.4) | 2.7 (1.8—4.0) | <0.001 |
| High > 5.37 | 61 | 306 | Referent | Referent | |
| # Missing (5) | | | | | |
| *Age* | | | | | |
| 21—40 | 53 | 118 | Referent | Referent | |
| 41—60 | 238 | 376 | 2.32 (1.6—3.3) | 1.78 (1.0—3.0) | 0.036 |
| 61+ | 174 | 167 | 1.65 (1.3—2.1) | 1.41 (1.0—1.9) | 0.024 |
| *BMI* | | | | | |
| Up to 24.99 | 327 | 422 | 1.26 (0.9—1.7) | 1.06 (0.8—1.4) | 0.788 |
| ⩾25 | 142 | 231 | | | |
| # Missing (4) | | | | | |
| *Smoke (more than 100 cigarettes in a lifetime)* | | | | | |
| Yes | 58 | 59 | 1.44 (0.9—2.1) | 1.58 (0.9—2.5) | 0.066 |
| No | 405 | 594 | | | |
| # Missing (10) | | | | | |
| *Alcohol* | | | | | |
| Yes | 68 | 113 | 0.82 (0.6—1.1) | 0.99 (0.6—1.3) | 0.556 |
| No | 394 | 538 | | | |
| # Missing (13) | | | | | |
| *Current vitamin consumption* | | | | | |
| Yes | 228 | 418 | 0.55 (0.4—0.7) | 0.55 (0.4—0.7) | <0.001 |
| No | 227 | 229 | | | |
| # Missing (24) | | | | | |
| *Vitamins last 5 years* | | | | | |
| Yes | 247 | 440 | 0.57 (0.4—0.7) | 0.58 (0.4—0.8) | <0.001 |

(*continued on next page*)

**Table 3** (*Continued*)

| | | | | | |
|---|---|---|---|---|---|
| No | 208 | 210 | | | |
| # Missing (21) | | | | | |
| *Multivitamins* | | | | | |
| Yes | 134 | 256 | 0.64 (0.5—0.8) | 0.65 (0.5—0.9) | 0.005 |
| No | 320 | 393 | | | |
| # Missing (23) | | | | | |
| *Calcium* | | | | | |
| Yes | 86 | 181 | 0.60 (0.5—0.8) | 0.52 (0.4—0.7) | <0.001 |
| No | 368 | 467 | | | |
| # Missing (24) | | | | | |
| *Marital status* | | | | | |
| Married | 227 | 435 | Referent | Referent | |
| Divorced | 103 | 116 | 3.59 (2.1—5.8) | 2.57 (1.4—4.4) | 0.002 |
| Single | 54 | 79 | 2.11 (1.2—3.6) | 1.36 (0.7—2.6) | 0.421 |
| Widow | 46 | 24 | 2.74 (1.5—5.0) | 2.08 (1.1—4.0) | 0.039 |
| # Missing (42) | | | | | |
| *Education* | | | | | |
| 1—8 | 31 | 10 | 5.77 (2.9—11.7) | 3.38 (1.5—7.5) | 0.003 |
| 9—12 | 146 | 174 | 1.72 (1.3—2.2) | 1.33 (0.9—.9) | 0.086 |
| *Associate or higher* | | | | | |
| Degree | 218 | 445 | Referent | Referent | |
| # Missing (102) | | | | | |
| *Family history of cancer (not BC)* | | | | | |
| Yes | 305 | 384 | 1.37 (1.1—1.8) | 1.35 (1.0—1.8) | 0.031 |
| No | 160 | 277 | | | |
| *BC history in any family member* | | | | | |
| Yes | 134 | 121 | 1.81 (1.4—2.4) | 2.00 (1.4—2.7) | <0.001 |
| No | 331 | 540 | | | |

*Abbreviations:* BC, breast cancer; CI, confidence interval; DRC, DNA repair capacity; BMI, body mass index.

[a] Adjusted by age, BMI, family history of breast cancer, menopause, number of children, alcohol use, smoking, vitamin use.

[b] DRC low (up to 2.50%), medium (2.51—5.50%), and high (5.51% and higher).

of the sample studied reported being overweight or obese. This may be due to self-reported weight and height, which could potentially increase random error and variability, leading to an underestimation of the real association.

## 5. Public health relevance

Despite the fact that BC is the #1 cancer in Puerto Rican women, limited research has been done regarding its treatment and prevention on the island. This study is the first to use a large cohort of women to identify important protective and risk factors for this population. Because some of these risk factors are modifiable, the knowledge gained from this study has practical applications in terms of modifying public health policy for further BC prevention. State public policy regarding cancer control is influenced by the Puerto Rico Cancer Registry. However, the Registry currently only collects epidemiological data; it does not analyze or publish population studies.

Thus, this study provides additional critical data required for a more effective BC control plan. Some of the findings can help public health personnel target high-risk populations, like those with low levels of education, and create programs to help young women adopt healthier lifestyles/habits that will decrease their risk of BC. Education and outreach to help women implement simple, low-cost risk reduction strategies, including breastfeeding, exercise, and use of multivitamins and calcium (as reported by Vergne et al., 2013 [31]) can change the face of BC statistics in PR and can possibly provide the basis for risk-reduction models for other populations. In addition, the possibility of widespread use of a simple, non-invasive blood test for DRC is appealing, as currently no such screening test is available.

## 6. Limitations

Because of the case-control nature of the study, the temporal and causal associations could not be determined; however, that was minimized because incident cases were recruited in this study. Another limitation in this study could be recall bias; however, an attempt was made to minimize this limitation by relying on recall of current exposures. Selection bias is also a frequent problem in this type of study, but the selection procedures minimized it. Control subjects consist of women recruited from the same locations from which the cases were recruited; if those controls were to develop BC eventually, they would almost certainly be treated in the same clinics from which the cases were recruited [32]. Thus, the selection procedures reduced the bias that otherwise may have been caused by differences in the mode of selecting BC patients and control participants [17]. The two main criteria for selecting all controls were that all participants within the last 6 months prior to enrollment [15] had been examined by their primary physicians (normal clinical breast examination) and had undergone a mammogram that produced negative results. Those criteria reduced the possibility of the existence of undiagnosed BC among the controls [27]. It is possible that some of the associations (around 5%) and their statistical significance levels are artifactual due to a potentially inflated type I error. This problem is especially important for weak associations. Therefore, weak and borderline significant associations should be interpreted with caution as they may not be associated with the outcomes under study. Further studies on the Puerto Rican population are needed to confirm these results.

## 7. Conclusions

This study provides an overview of the major risk factors for BC in PR. These results support that family history of cancer or BC, low level of education and aging increase the risk of developing BC. However, this study shows a decreased risk in women with endometriosis, full-term pregnancy at an earlier age, higher parity, and longer duration of breastfeeding.

BC pathobiology is multifactorial and many risk factors have been published. While efforts continue for finding a cure for BC, researchers should concurrently intensify efforts in providing early interventions: implementing programs to mitigate modifiable risk factors, and utilizing knowledge of genetic susceptibly to identify high-risk women to perform earlier BC screening, and diagnosing BC at an earlier stage. All these efforts should be targets for public health interventions.

## Competing interests

The authors declare that they do not have competing interests.

## Disclosure

All authors have read and approved the final article.

## Author contributions

*Accountability:* Matta and Bayona had full access to all of the data in the study and assume responsibility for the integrity of the data and the accuracy of the data analysis.

*Concept and study design:* Matta, Bayona.

*Acquisition of data:* Morales, Vargas.

*Analysis and interpretation of data:* Bayona, Morales, Alvarez-Garriga, Ramírez.

*Drafting of the manuscript:* Morales, Alvarez-Garriga, Bayona, Matta.

*Critical revision of the manuscript for important intellectual content:* Alvarez-Garriga, Bayona, Matta, Morales, Ramírez, Ortiz, Vergne, Acosta, Perez-Mayoral.

*Statistical analysis:* Bayona, Morales, Alvarez-Garriga.

*Acquisition of funding:* Matta.

*Study supervision:* Bayona, Matta.

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