

RESEARCH ARTICLE

# Risk and Protective Factors Associated with Breast Cancer

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**Abstract: Objective:** To determine the risk factors according to age group, gynecological history, personal and family background, and the potential breast cancer protective factors of breast cancer patients who visited the gynecological clinic of the University Hospital of Caracas from January 2013 to December 2015 were determined. **Method:** Retrospective, descriptive, observational and cross-sectional studies. **Result:** 110 patients were female; the average age was 53 years and 3 months. The age of menarche is 12 years and 5 months. 77% were menopausal, with an average age of 48 years and 1 month, and only 5% received hormone replacement therapy. 92% were multiple pregnancies, and the first delivery age was 21 years and 5 months. Only 8% were ineffective and 33% had a history of abortion. 24% had a family history of primary or secondary breast cancer. 40% of women use hormonal contraceptives for an average of 21 months, and 72% of women breastfeed. **Conclusion:** Age, gender, personal and family background are consistent with international publications. In contrast, the use of oral contraceptives is not considered a risk factor, and breastfeeding is not considered a protective factor.

**Keywords:** Breast cancer, Risk factors, Protective factors

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## 1. Introduction

Cancer is one of the leading causes of morbidity and mortality worldwide. According to the World Health Organization (WHO), about 8.2 million people died of the disease in 2012. In the same year, the most common cancers in men were lung cancer, prostate cancer, colon and rectal cancer, liver cancer and gastric cancer, while in women, breast cancer, colon and rectal cancer, cervical cancer and gastric cancer<sup>[1]</sup>.

Because of its high morbidity and mortality, breast cancer is a global public health problem, which Venezuela cannot get rid of. Breast cancer has been the most common cancer in the UK since 1997. In 2012, it accounted for 30% of new cancers in women in this population<sup>[2,3]</sup>. In the United States, one in eight women (12%) will develop invasive breast cancer in their lifetime. By 2015, there were an estimated 231,840 new invasive cancer diagnoses and 60,290 in situ cancer diagnoses; in the same year, 40,290 people died due to the institution people<sup>[4]</sup>.

By 2012, there were more than 408,200 new cases (29%) of breast cancer and more than 92,000 deaths (15%), making it the largest cancer in the Americas and the second largest female cancer death toll. In Latin America and the Caribbean, 27% of new cancer cases and 15% of cancer deaths are caused by breast cancer<sup>[5]</sup>.

In 2012, there were 5,063 new cases of breast cancer in Venezuela (22.8%). The mortality rate from the same cause was 2,067 cases (18.25%), which was the first cause of cancer death among women in this population<sup>[6]</sup>.

The etiology of breast cancer is multifactorial. The identification of genetic and risk factors (such as environment and hormones) has attracted more and more attention and plays an important role in the prevention of breast cancer<sup>[7]</sup>. These risk factors increase the likelihood of tumorigenesis and will depend on the time of exposure to it or the genetic susceptibility of each individual. Therefore, these may affect the development of cancer, but most are not the direct cause of this disease<sup>[8]</sup>. Non-genetic factors include: over 65 years old is the most important risk factor, menarche before the age of 12, menopause after the age of 55, the first live birth after the age of 30, ineffectiveness, history of breast biopsy, atypical hyperplasia diagnosed by breast biopsy, obesity, alcohol consumption, hormone replacement therapy (HRT), and overexposure to radiation. Other possible risk factors include a high-fat and low-fiber diet, fruits and vegetables; little exercise. As for genetic factors, in addition to family history, there are other equally important genetic risk factors. BRCA1 and BRCA2 gene mutations have been found in hereditary breast and ovarian cancer. Less than 1% of breast cancers are associated with genetic syndromes: Cowden syndrome, Li-Fraumeni syndrome, Bloom syndrome, Peutz-Jeghers syndrome, Werner syndrome<sup>[9-11]</sup>. In numerous studies, the association between the use of oral contraceptives (OC) and abortion as a potential risk factor has not been determined<sup>[11,12]</sup>. On the other hand, breastfeeding may have a slight or moderate protective effect on the risk of breast cancer (20% reduction), or breastfeeding reduces the risk by 4.3% every 12 months, regardless of whether the tumor is positive or negative for estrogen receptor<sup>[11]</sup>.

Finally, there are several models for predicting breast cancer risk, two of which are the most famous. The most commonly used model was developed by Gail, which predicted the cumulative risk of breast cancer in the decades before the age of 90, while the Claus model was superior to the former in integrating broader family history information<sup>[13,14]</sup>.

In view of the above, there are concerns about assessing and understanding the risk and protective factors of patients who attended the Breast Pathology consultation, the Gynecology and Obstetrics of the University Hospital of Caracas, so as to analyze whether they have behaviors similar to those reported in the international literature, and thereby enable us to improve and refine monitoring strategies and prevention measures, proportional to the individualized risk of each patient.

## 2. Objective

This is why the purpose of this study was to determine

the risk factors according to age group, gender, personal and family history, and to identify the potential protective factors for breast cancer in patients diagnosed with breast cancer who attended the consultation of Breast Pathology, of the Gynecology Service of the University Hospital of Caracas, from January 2013 to December 2015.

## 3. Method

This is a retrospective, descriptive, observational and cross-sectional study. The population consisted of all patients who attended the Breast Pathology consultation in the Gynecology Service of University Hospital of Caracas, from January 2013 to December 2015.

The sample consisted of all breast cancer patients who underwent the Breast Pathology consultation in the Gynecology Service of the University Hospital of Caracas, during the same period.

### 3.1. Inclusion criteria

The clinical history of all patients with histological diagnosis of breast cancer, regardless of stage, covered all study data.

### 3.2. Exclusion criteria

- 1) Patients with breast cancer without histological confirmation.
- 2) The clinical history does not include all study related data.
- 3) Pathological diagnosis of benign tumor.

### 3.3. Data acquisition

For this purpose, a recording tool was used, including patient identity, age, diagnosis, staging, gynecological and obstetric history, family history of breast cancer (grade I and grade II) and immunohistochemical results.

### 3.4. Statistical processing

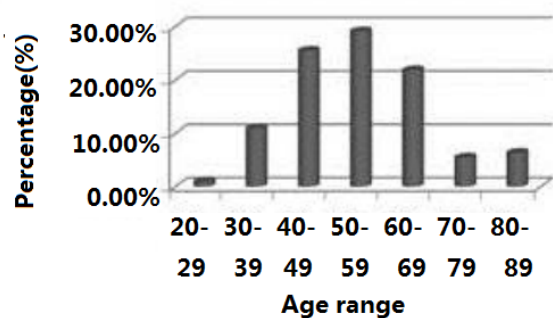
In order to describe the study population, descriptive statistical techniques and resources are used, such as: Number. Similarly, in different cases, calculate the statistical summary, which is called the sample average or data average. Contingency tables are also used to compare assumptions.

## 4. Results

In order to explore the risk factors and protective factors in patients diagnosed with breast cancer, we collected the clinical and family history data of 110 female patients with breast cancer treated by surgery in our service.

The patients in this group were between 29 and 86 years old, with an average age of 54 years and 3 months, and the proportion of patients between 40 and 69 years

old was the highest (**Figure 1**).



**Figure 1.** Distribution by age group.

The most common histological type of breast cancer was invasive ductal carcinoma, accounting for 78.25% ( $n = 86$ ), followed by ductal carcinoma in situ, accounting for 10.90% ( $n = 12$ ). The other histological types were invasive lobular carcinoma 5.50% ( $n = 6$ ) and invasive papillary carcinoma 2.70% ( $n = 3$ ). Invasive mucinous carcinoma, occult carcinoma and inflammatory carcinoma accounted for 0.90% respectively ( $n = 1$ ).

#### 4.1. Early clinical stage

The most common initial stage in the patients was stage IIA, representing 31.82% ( $n = 35$ ) of the case. The next most common initial stage was stage IIB, present in 18.18% ( $n = 20$ ) of cases. 8.18% ( $n = 9$ ) of the patients were initially diagnosed as stage 0, followed by stage IV, with 6.36% ( $n = 7$ ). 4.54% ( $n = 5$ ) of the cases could not be classified, which was consistent with the diagnosis of cTX and pTX. In the “not applicable” category, 4 cases were initially diagnosed as intracapsular papilloma and therefore could not be staged, because the staging in the study was based on the initial diagnosis, and it is well known that in this type of lesion, the staging was determined by surgical specimens.

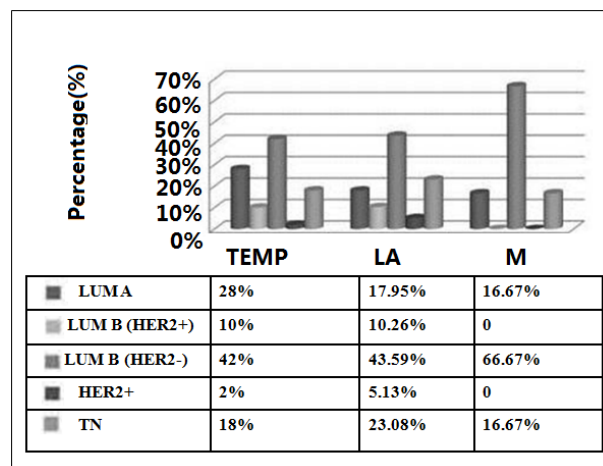
In conclusion, 54% ( $n = 59$ ) of breast cancer cases of the patients studied were in the early initial stage. Local progression was detected early in 35% ( $n = 38$ ), and only 6% ( $n = 7$ ) reported in a metastasis state.

#### 4.2. Molecular typing of breast cancer

After classifying each tumor according to the immunohistochemical results, it can be determined that the most common molecular subtype is lumen B (HER2-) (RE+; RP (<20%); Ki67 ( $\geq 14\%$ ), HER2-) accounted for 40% ( $n = 44$ ), followed by lumen subtype A (RE+; RP+ ( $\geq 20\%$ ); Ki67 (<14%); 20.91% ( $n = 23$ ). Another molecular type almost as common as lumen A is triple negative (RE-, RP-, Ki67 ( $\geq 14\%$ ); 18.18% ( $n = 20$ ). Among other molecular types initially diagnosed, we had lumen B (HER2+) (RE+; RP independent; Ki67 ( $\geq 14\%$ ); HER2+), 8.18% ( $n = 9$ ) and HER2+ (RE-, RP-, Ki67

( $\geq 14\%$ ); HER2+), 2.73% ( $n = 3$ ). In a small number of patients, immunohistochemical results were not reported in clinical history.

As can be seen from **Figure 2**, lumen B subtype (HER2-) is the most common in early, locally late and metastatic stages. HER2+ type accounts for a small proportion in the diagnosis stage.



**Figure 2.** Molecular distribution of P cell subtypes in breast cancer.

#### 4.3. History of female obesity

As a first feature in the gynecological history, we can mention that the average age of onset of menarche in women is 12 years and 5 months. The lowest age of onset of menarche was 9 years old (2 cases) and the highest was 16 years old (4 cases).

With regard to women of childbearing age, 77.27% ( $n = 85$ ) of the population is menopausal, and the remaining 22.72% ( $n = 25$ ) of the population is women of childbearing age. Among 85 postmenopausal patients, the average age of onset was 48 years and 1 month. Of the 85 patients, 6% ( $n = 5$ ) reached menopause after the age of 55 and 1% ( $n = 1$ ) reached menopause at the age of 26 (surgical menopause).

other relevant message is that only 5% ( $n = 4$ ) of 85 menopausal women received hormone therapy. The time of HRT was only 2 cases, 1 month and 2 months respectively. The average use time of THR is 1.5 months.

Of the patients studied, 92% ( $n = 100$ ) had a simple eutocic delivery, and the remaining 8% ( $n = 9$ ) were ineffective. The average number of deliveries in these patients was 3. The average age of first delivery was 21 years and 5 months. 72% of childbirth women breastfeed for an average of 10 months.

Of the 100 women who had experienced at least one delivery, 33% ( $n = 33$ ) reported a history of abortions, with an average of 1. The maximum number of abortions recorded per patient was 3.

Once reproductive life variables and at least one

euthyroid delivery were associated with early diagnosis of the disease, we found no statistically significant difference in the number of women in early clinical stages and whether they had at least one simple ataxia delivery ( $p = 0.3$ ). There was also no statistically significant difference in the number of women in early clinical stages and whether they reached menopause ( $p = 2.71$ ).

To determine whether breastfeeding was a protective factor for cancer patients, they were divided into early clinical stages (early, locally advanced and metastatic stage) and breastfeeding. However, there was no statistically significant correlation, indicating that the early diagnosis of breast cancer was not related to breastfeeding ( $X_{24.24} < X_{25.9}$ ).

Regarding the use of ACO, 57% ( $n = 62$ ) did not use ACO, and 3% ( $n = 3$ ) did not answer this question. On the other hand, 40% ( $n = 44$ ) of patients claimed to have used some kind of ACO for an average of 21 months. The maximum recording time of ACO is 240 months.

To determine whether oral contraceptives were a risk factor for cancer patients, these patients were classified according to the initial stage (divided into early, locally advanced and metastatic) and whether the patients had used ACO or not. However, no statistically significant relationship was found, indicating that the initial stage was not related to the use of ACO ( $X_{24.2} < X_{25.9}$ ).

#### 4.4. Personal and family history of breast and ovarian cancer

In terms of personal history, only 4.5% ( $n = 5$ ) of women had breast cancer. Of the 5 patients, 3 were diagnosed as early (2 stage 0 and 1 stage IA), and the other 2 patients had metastasis (stage IV).

Among the top three patients, only one patient had a family history (Grade I and Grade II), especially breast cancer. Like the other two patients (stage IV), only one patient had a family history (Grade II), but in this case, the patient had colon cancer.

In addition, of the 110 patients, 24% ( $n = 27$ ) of family members had a relative who suffered or had suffered from cancer. The most common cancer among family members was breast cancer, in 41% of cases. Of the 27 women, 33% ( $n = 9$ ) had first-degree relatives with or having cancer, 52% ( $n = 14$ ) had second-degree relatives, and 15% ( $n = 4$ ) had first-degree and second-degree relatives with or having cancer.

It is important to emphasize the type of cancer suffered by the patient's family members and classify them according to the degree of kinship. In this analysis, we should not ignore the fact that four patients have relatives of grade I and grade II who either have cancer or have cancer.

Among the 13 patients with a history of cancer in their first grade relatives, the most common cancer was

breast cancer, accounting for 84.6% ( $n = 11$ ). In these 11 cases, 72% ( $n = 8$ ) of the affected family members were sisters. Ovarian cancer accounted for 8%, pancreatic cancer and colon cancer accounted for 3.7% respectively.

We can mention that the probability of at least one grade I relative suffering from cancer is 0.1, that is, in 1% of cancer patients, one grade I relative has or has suffered from cancer.

Among the 18 patients with a history of cancer in their grade II relatives, breast cancer was the most common, accounting for 66.6% ( $n = 12$ ). In these 12 cases, 85% ( $n = 10$ ) of the affected family members were aunts. Among the second-degree relatives associated with a cancer patient, seven relatives (five cousins and two aunts) had cancer or cancer. Ovarian cancer accounted for 30.5% and colon cancer for 2.9%.

In addition, the probability of having at least one level II relative of the patient with cancer is 0.16, that is, in 1.6% of cases, one level II relative of the treated patient has or has had cancer.

## 5. Discussion

Breast cancer is one of the most common cancers among women in developed and developing countries. The etiology is multifactorial, and it is well known that there are many variables that increase the risk of breast cancer. Gender, genetic, environmental and dietary factors have been widely studied as triggers for this entity, so timely identification and action should be taken. Our results show that the behavior of China's population is similar to the literature at home and abroad.

All 110 patients were female; invasive ductal carcinoma accounted for 75.4%. Early clinical stage accounted for 54%, and lumen B subtype (HER2-) accounted for 40%.

The most important known risk factor for breast cancer is age over 65. In this study, we determined that the average age of the study patients was 54 years and 3 months, which was related to the results of Ozmen *et al.*<sup>[15]</sup> and a meta-analysis of 117 epidemiological studies in 2012<sup>[16]</sup>. Olaya *et al.*<sup>[17]</sup>, in Bogota, Colombia, indicated determined the average age of 50 years in its sample, which is very similar to the report of Hernández *et al.*<sup>[18]</sup> In Venezuela, the average age is 47.20 years. This is also related to the publication of the previous issue of the Yearbook of morbidity and mortality of MPPS, with the highest prevalence for this entity ranged in ages between the ages of 45 and 64<sup>[6]</sup>.

It is well known that menarche before the age of 12 increases the RR by 1.3 times as much as breast cancer<sup>[10]</sup>. The average menarche age of these women was 12 years and 5 months, which was similar to that of the study population such as Hernandez *et al.*<sup>[18]</sup> In Venezuela, this was 12.76 years old. Sarah *et al.* and Badar *et al.* published similar results<sup>[19,20]</sup>. Likewise,



Titus *et al.*<sup>[21]</sup> demonstrated that menarche after age of 15 or older reduces the risk of breast cancer. When analyzing menopause data, 77% of the population was menopause, and the average age of onset was 48 years and 1 month. Similar results were obtained by Olaya *et al.* in Colombia and Hernandez *et al.* in Venezuela, where the average age at menopause was 48 years and 47.76 years, respectively, as well as that of Turani *et al.* and Surakasula *et al.*<sup>[17,18,22,23]</sup>. However, in one population of Denmark, Ewertz *et al.*<sup>[24]</sup> reported that menopause at the age of 54 was one of the most important risk factors. Late menopause after the age of 55 increased the RR by 1.2 and 1.5 times<sup>[10]</sup>. Only 5% of these menopausal women received HRT, with an average use time of 1.5 months. Although this data was not relevant in this study, it was important to remember that estrogen and progesterone HRT for 5 years or more has a RR of 1.3 times in breast carcinogenesis<sup>[10]</sup>.

92% of patients reported one or more pregnancies, with an average of 3 deliveries, and the average age of the first delivery was 21 years and 5 months. 8% is invalid. The first live birth and ineffectiveness after the age of 30 are well-known risk factors for breast cancer, with a RR of 1.7–1.9, similar to the article published by Ortiz *et al.*, in Mexico, the age of first delivery is after the age of 30<sup>[9,10,25]</sup>. In Chile, Atalah *et al.*<sup>[26]</sup> determined that multiparity had a protective effect with risk reduction 0.66 (95% CI 0.44–0.99). Compared with the international literature and publishing industry, the behavior of our people was different; however, when compared to the population of Hernandez *et al.*<sup>[18]</sup>, it is homogeneous. In Venezuela, the age of the first child is 22.25 years. On the other hand, 33% had a history of abortion, with an average of 1 case. Concerns about the side effects of abortion are based on the theory that full-term pregnancy can prevent breast cancer by inducing complete differentiation of breast cells. Although abortion increases the risk of spreading in the first three months of pregnancy, if it prevents complete differentiation in the second trimester of pregnancy. Many studies have failed to determine whether there is a correlation between spontaneous or induced abortion and breast cancer<sup>[11]</sup>.

Personal history of invasive or in situ breast cancer has a RR = 6.8–17.3, and family history increased RR = 11<sup>[11]</sup>. 4.5% of women had previously suffered from breast cancer, and 24% had a family history of grade I or grade II breast cancer. In Pakistan, Nisar *et al.*<sup>[27]</sup> and Badar *et al.*<sup>[20]</sup> found that the family history of breast cancer was 34% and 16.9% (27.20%) respectively. Olaya *et al.*<sup>[17]</sup>, when assessing the family history of the study group, found that the data increased the risk of breast cancer by 10.39 times. Likewise, the study also found that in 1% of cases, breast cancer patients have a grade I relative who has or has had cancer, and 1.6% of them

have a grade II relative who also has cancer.

With regard to the use of ACO, 40% reported that they had used ACO at some time in their lives, with an average time of 21 months. It is difficult to link this data with other publications because in order to determine the risk, the type of ACO and hormone load or specific formula must be determined, which is why there are differences in studies seeking links between the use of ACO. It is well known that long-term use of HA before early pregnancy and the first full-term pregnancy seems to have a certain impact on the occurrence of the disease because they act on breast tissue with low differentiation<sup>[12]</sup>. Kahlenborn *et al.*<sup>[28]</sup>, in a meta-analysis published in 2006, concluded that the association between oral contraceptives and breast cancer risk was greater among women who used oral contraceptives four years or more before their first full-term pregnancy. To determine whether the use of ACO is a risk factor for cancer patients, we classified patients according to two initial diagnostic criteria (groped with early, locally advanced and metastatic stages), and whether patients use ACO or not. Through the hypothesis comparison tests, we conclude that it is not a risk factor in our population.

The literature suggests that breastfeeding may have a slight or moderate protective effect. The analysis of available data around the world concludes that breastfeeding will reduce the risk of breast cancer by 4.3% and may reduce the cumulative incidence at the age of 70 by more than 50%<sup>[11]</sup>. In our study, breastfeeding was not a protective factor for breast cancer; this is consistent with the article published by Tessaro *et al.* and Michels *et al.*<sup>[29,30]</sup>.

Age, gender, personal and family background are consistent with international publications. In contrast, ACO use is not considered a risk factor, and breastfeeding is not considered a protective factor.

## Conflict of interest

The authors declare that they have no conflict of interest.

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