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Breast Cancer in Young Patients: Same or Different Entity?

Gómez-Pedroso J, Iturralde P, Mancera MA, Studt D and Ubiergo M

Breast and Gynecologic High Specialty Group, Mexico

***Corresponding author:** Paola Iturralde Rosas Priego, Grupo de Alta Especialidad Ginecológica y Mamaria AC, Camino a Santa Teresa #1055- Torre de Especialidades quirúrgicas. Cons. #974. ext. 4974 Col. Héroes de Padierna México, DF. Del. Magdalena Contreras CP. 10700, Tel: 5555684888; Email: paola_iturralde@hotmail.com

Review Article

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Abstract

Overview

Breast cancer is the most common pathology in women of reproductive age; approximately 7% of breast carcinomas are diagnosed in women less than 40 years of age, corresponding to more than 40% of all malignant diseases diagnosed in this group. Genetic factors play a fundamental role in the genesis of the breast cancer in young patients. However, it is not easy to analyze them because their clinical usefulness is limited and there are multiple factors that must be considered. We conducted a retrospective study in which we included female patients of ages 40 years old or less, diagnosed with breast cancer at a private medical center during the period of January 2010 to July 2014.

The protocol of the study included a complete clinical study, radiological reports as mammography and/or ultrasound image, histopathological and immunohistochemistry reports. The study included 46 patients with an average age of presentation of 37.1 years, a standard deviation (SD) of ±3.02 years and a median of 38 years. There were also different percentages for the various variables such as tumor characteristics, risk factors, and treatment provided. Young patients with breast cancer should be treated and evaluated individually by a multidisciplinary staff, as this pathological entity shows specific characteristics that makes this group of patients difficult to treat and warrants special considerations.

Keywords: Histopathological; Women; Breast

Introduction

Breast cancer is responsible for 300,000 deaths a year in the world, representing 21% of all tumors in women [1,2]. In Mexico, this disease is a public health problem, constituting the first cause of cancer death in the female population over 25 years of age and is the gynecological cancer with the highest incidence in our country. In 2010, the Mexican National Institute of Statistics and Geography (INEGI) reported an increase in breast cancer of 13.3% in the period from 2000 to 2010. Although age is the most important risk factor for breast cancer and more than 65% of these neoplasms occur in women 50 years of age or older, thousands of young women are diagnosed each year with malignant breast disease [3]. On the other hand, individually, the probability that a woman with no history will develop breast cancer before age 50 is low; reporting that only 1 in 2,525 women will develop breast cancer at age of 30, and only 1 in 217 at age of 40, however it should be mentioned that more than 70% of breast cancer patients do not have any risk factor [4,5].

It is well established that breast cancer is the most common type of malignant tumor in women of reproductive age: approximately 7% of mammary carcinomas are diagnosed in women less than 40 years of age, which corresponds to more than 40% of all breast cancers. In women under the age of 35, breast cancer is extremely rare; these patients only represent 1.9% of all women with some malignant tumor of the breast. However they have a more aggressive presentation and are more difficult to treat, so an early diagnosis results in a better prognosis of the disease [6-8].

On the other hand, the incidence of in situ breast cancer has recently increased. This can be attributed to a significant increase in mammographic screening. However, when performing mammograms in younger age groups, in both Caucasian and African-American woman, adjusting this parameter for age, has been found that the incidence of cancer in women between 35 and 40 years old is less significant [9-11].

Genetic factors play a fundamental role in the genesis of breast cancer in young patients, directly affecting the rates of presentation worldwide and in different regions.[6] Genetic mutations in the BRCA1, BRCA2, P53 and PTEN genes have been widely recognized as trigger factors of this disease in young patients [8,12]. Mutations of the P53 gene are extremely rare and are responsible for mammary malignancy in patients with Li-Fraumeni syndrome and those with an age range of 20 to 40 years old. Several studies have shown a high prevalence of mutations in the BRCA1 and BRCA2 genes in young patients who develop malignant mammary tumors, for example: In the United Kingdom approximately 13% of mammary carcinomas in women under the age of 40 are attributable to mutations in the BRCA1 gene, while in the group older than 40, the causal percentage is only 2.2% [8,12,13].

There are some other genetic alterations of moderate penetrance that influence the genesis of breast cancer in young patients, such as alterations in the genes: CHEK2, ATM, NBS1, RAD50, BRIP1, and PALB2, which are associated with an increased risk of 2 to 4 times. Despite the above, there is insufficient evidence to recommend routine genetic screening for other genes besides BRCA 1 and 2 [6,8].

As for choosing the adequate treatment in this group of patients, it is still not entirely clear if they should receive a different management based entirely in age. This is due to the fact that breast cancer in young women is rare and has a frequent association with poor prognostic factors such as: BRCA gene mutations, high grade tumor differentiation, estrogen negative receptors and HER2 over-expression or even worse triple negative tumors that overshadow the prognosis.

It has been described that the age of presentation of the disease plays a key role in the risk of recurrence. Recent studies suggest that there are specific biological pathways in women under 45 years of age that, when compared to women over 65, have identified sets of genes related to cell signaling, survival, immune function and tumor pathogenesis, with notable differences depending on the age group. This suggests the need to treat young patients with breast cancer according to the corresponding individual subtype [14-17].

It is clear that there are still unidentified factors that contribute to an increased risk of recurrence in young patients. This must be considered at the moment of choosing the ideal treatment strategies for the patient, especially in reference to long term treatment [16].

To be able to carry out epidemiological and genetic studies that could explain the aforementioned differences related to the treatment and prognosis of this specific group of patients, it would be necessary to carry out a descriptive study on Mexican patients. At the time of this publication, such a study has not been performed in our country, although it would provide important information for the management of this disease. The objective of this paper is to describe the epidemiological, clinical, as well as additional specific screening (study) procedures, for potential breast cancer patients in the less than 40 years age group.

Material and Methods

A retrospective, cross-sectional and descriptive study was performed with breast cancer patients diagnosed during January 2010 to July 2014 by members of the Grupo de Alta Especialidad Ginecológica y Mamaria del Hospital Angeles Pedregal de la Ciudad de México (Group of Gynecological and Mammary High Specialty of the Angeles del Pedregal Hospital of Mexico City). The research protocol was carried out with informed consent of participation and under the review of the Hospital's ethics committee.

Patients diagnosed with breast cancer and under the age of 40 years were included in the study. The diagnosis of these patients was made through a complete study protocol that included clinical study, imaging study with mammography and ultrasound, histopathological and

immunohistochemistry studies. The inclusion criteria to be considered in the study were complete clinical record, with clinical evolution of the patient, as well as the final reports of all the studies carried out.

In order to carry out this study, various descriptive variables were included: age, parity, clinical presentation of onset, tumor size, histological lineage, estrogen receptors, progesterone receptors, overexpression of Her2-neu, as well as the treatment received. A systematic review of the files was performed to obtain the data.

Forty-six patients who met the inclusion criteria were included. The population analyzed in this study had an age range of 29-39 years, with an average age of presentation for breast cancer of 37.1 years, a standard deviation (SD) of ±3.02 years and a median of 38 years. As for the menarche, this population group had an average of age of occurrence of 12.6 years (SD ±1.2) and a median of 12 years. It is important to mention that at the time of the study none of the patients was in the menopause period, only 1 of the patients had a history of total hysterectomy, which was performed due to obstetric issues.

The study showed that 17.3% (8) of the patients had a hereditary family history of breast cancer in first degree. In the area of parity, 36.9% (17) were nuligesta, while the rest had one or more deeds, within this work it was not considered if the pregnancies reached term. Of the 39 patients who had at least one pregnancy, 51.2% (20) breastfed, while the rest of them differed.

Additionally, 34.7% (16) of the patients in this article reported the use of hormonal contraceptives in their clinical history, from 6 months to 5 years, with an average use of 2.5 years. The studied population had a BMI between the ranges of 19.2 - 35.3 kg/m^2, with an average of 24 kg/m^2 ± 3.4 kg/m^2. They were classified as follows 73.9% (34) were in a normal range, while 21.7% (10) were overweight, and only 4.3% (2) were considered obese. Approximately 35% of the study population (16) was identified as smokers.

Regarding the mastographic study, 100% (46) of the patients had a previous radiological study, and the population was distributed accordingly as follows: 69.5% (32) were classified as BIRADS 4, while 26 % (12) as 5, 2.1 (1) as 0 and 2.1% (1) as 6. All patients included in this study (46) underwent complementary ultrasound, which concurred with the category assigned to the mammogram. In the patient who had been cataloged as BIRADS 0, the USG lesion was reported as BIRADS 4. Only one patient in this study was subjected to Magnetic Resonance, leaving the report as BIRADS 4c.

The biopsy specimens were obtained with two different techniques: excisional and percutaneous with a cutting needle. Percutaneous biopsy was performed in 80.4% (37) of the patients; while in the remaining 19.6% (9) of the patients were subjected to an excisional biopsy.

In relation to the tumor characteristics by location, 44.6% (21) of the tumors were lodged in the right breast, while 55.4% (26) in the left breast, in this section, 47 tumors were counted, because bilaterality was found in 1 of the patients. Of the 21 tumors found in the right breast, 90.5% (19) of them were found in the upper external quadrant, while the remaining 9.5% (2) were found in the internal inferior quadrant and retroareolar. As mentioned earlier in the left breast 26 tumors were found, which were distributed as follows according to the quadrants: 19.2% (5) in the internal lower quadrant, the remaining 21 corresponding to 80.8% were located in the upper external quadrant. According to the tumor dimensions, 34% (16) of this population had a tumor less than 2 cm in its major axis, while in 61.7% (29) tumors measured between 2 and 5 cm, 4.3% (2) remaining showed tumors greater than 5 cm.

According to the histological lineage, 74.4% (35) corresponded to infiltrating ductal carcinoma, 17% (8) to ductal in situ, 4.2% (2) infiltrating lobular, 2.1% (1) to medullary and finally 1 patient reported lymphoma mammary, reason why this last one was not considered in the following exposed categories.

When classified on the Nottingham scale, 63.1% (29) corresponded to Grade III, while 30.5% (14) was classified as Grade II and 6.4% (3) as Grade I. The lymphovascular permeation was present in the 76.5% (36) of the specimens studied.

Regarding immunohistochemistry, 63.1% (29) of the tumors did not present overexpression of the Her2/neu receptor, while 40% (17) were distributed with Positivity 2+ in 4 (23.5%) patients (performed FISH) and positivity 3 + in 13 (76.5%). For estrogen receptors 30.4% (14) of the tumors were negative, while for progesterone 39.1% (18) were also negative. In relation to Ki67, the ranges of variability were 5-100%, with a median of 30%, 69.5% (32) of these tumors had this marker above 14%, which directly impacts the patient's prognosis.

The population studied in this study was subjected to various therapeutic procedures, 65.2% (30) underwent

modified radical mastectomy, while 19.5% (9) were taken to quadrantectomy, of these patients 3 underwent axillary radical dissection; all the patients who underwent conservative surgery were taken to radiotherapy as part of their treatment. The procedure that was performed with less frequency was the simple mastectomy, which was carried out in 15.3% (7) of the patients. The average number of days of in-hospital stay was 2.8 ±1.6, with a median of 3 (range 1-10 days). In this group, only one patient with a serious complication was found who suffered from a deep vein thrombosis in the left limb pelvic.

Discussion

The young patient suffering from breast cancer faces not only a life-threatening disease, but also a debilitating treatment, in addition to the latent concern of an increased risk of local and systemic recurrence. This is because tumors in these patients regularly have a more aggressive biological behavior and are diagnosed in advanced stages, so an integral approach should be the goal for every doctor in contact with these patients.

In women of 15 to 40 years of age, breast cancer is one of the most frequently diagnosed malignant neoplasms, with approximately 14% of all cancers in this age group, and 7% of all diagnosed breast cancers [6,8]. Several international studies have reported an increase in the presentation of breast cancer in the group of women aged 25 to 40 years, with rates increasing by 1 to 3% in both European and American women [8]. Bodmer, et al. reported that there was a substantial increase in breast cancer in young patients in Switzerland from 1996 to 2009 [18].

Multiple hypotheses have been proposed regarding the increase in the incidence of this pathology. The delay of the first gestation, the low parity, the estrogenic window, avoiding breastfeeding, together with an increase in the BMI secondary to an increase in fat intake, tobacco and alcohol consumption, are some of the factors proposed for the genesis of this phenomenon. Family history is of vital importance in this group of patients, since most of the time there is a genetic risk factor such as the mutation of: BRCA1, BRCA2 and P53, however its presence is not enough to directly impact the presentation or not of the disease [6,12,13,19]. In our study we were able to show that although not the majority, but a significant proportion of the population had a first-degree familiar with breast cancer, in addition to almost all of them, these patients had at least 1 or 2 risk factors of the mentioned. It is important to note that 25% of the 46 patients studied were either overweight or obese by international standards. Additionally, approximately 35% of the patients studied were identified as regular smokers.

The majority of young women with breast cancer present with palpable masses because these women do not go regularly to mammary screenings unless they themselves know that they have a high risk to develop this pathology. This situation is the basis for patients to present high-grade and advanced-stage tumors. The suspicious masses are studied using the usual radiological methods such as mammography, ultrasound and even, in some patients, magnetic resonance; knowing that each of them has advantages and disadvantages [3,7,12]. For example, magnetic resonance has a low specificity, although a very high sensitivity, which is similar to that of ultrasound in this type of patients; while mammography only reaches 87.4% effectiveness due to the variability in mammary density [15]. According to the guidelines of the American Cancer Society, breast density is not a sufficient reason for performing magnetic resonance imaging as a first-line radiological study due to cost and low accessibility [15]. According to the above, in this study, all of the patients had adequate radiological screening, as they had breast ultrasound and mammography. Only one of the patients underwent magnetic resonance imaging as a complementary study.

The biological spectrum of the tumors presented in young women, are totally different from those suffered by women with the same characteristics but older; because the first ones have completely unfavorable parameters.

Pourzand, et al. conducted a study between 2008 and 2010 that included 105 women with breast cancer, dividing the population of women into two groups, the first with women <40 years of age and the second with women >40 years of age. This author found that most of the tumors of the patients in the first arm had positive progesterone receptors and a high tumor grade, which translated into more aggressive neoplasms and with a poor prognosis. The author also found that these patients had a lower estrogen receptor positivity rate, higher Her2/neu expression, as well as a lower disease-free interval [20].

Regarding the population in the present study, there was a high incidence of adverse biological factors described previously, molecular and histopathological. It is noteworthy that the vast majority of tumors studied had dimensions ranging between 2 and 5 cm, corresponding to categories T2 and T3, according to the

TNM classification of breast cancer, as well as a high tumor grade and the presence of lymphovascular permeation. All of these results support the concept that tumors developed in young women are biologically different from those of older women, tend to be more aggressive and with unfavorable biological markers.

The treatment of breast cancer by mastectomy or conservative surgery followed by radiotherapy is the current option for focal control of the disease in young women [21]. However, due to the difficulty of leaving free margins as well as the intraductal component and the inherent aggressiveness of these tumors, these patients have a 9 times greater risk of recurrence, which is why in most cases, an adjuvant treatment such as chemotherapy and hormone therapy must be considered. In women with positive hormone receptors and favorable parameters, 10 years of tamoxifen are considered, with or without ovarian suppression as the ideal therapy. Chemotherapy alone has not shown good results in these patients [15,21].

A balance must be maintained between adjuvant therapy and the long-term sequela of these, as the possible impact of anticancer treatments on fertility or ovarian function is of great importance to the young patient, as several studies suggest that approximately 50% of young women with breast cancer consider pregnancy after treatment. Chemotherapeutic drugs and those that suppress ovarian function can induce amenorrhea and even a permanent menopausal state. The risk of induced infertility depends directly on the age of the patient and the intensity of the treatment, this can be seen reflected in the fact that women under 35 years of age that are subjected to adjuvant therapy, have approximately a 15% risk of suffering a permanent menopausal state, while older women risk 40% [22-24].

Breast cancer survivors should be evaluated and treated holistically, as cancer alters not only the biology of the patient, but also affects the psychological and sexual aspects of the patient's life. There are a large number of references in the literature that these groups of patients experience a wide variety of negative emotions such as depression, anxiety, concern for their physical appearance, sense of loss of femininity and decreased sexual desire. This can have negative consequences in their interpersonal relationships leading to conflicts, fractures and even loss of the relationship. It is therefore very important that these patients receive support and treatment from a group of specialists such as psychologists or sexologists [25].

Conclusions

Breast cancer is rare in young women; however, it is an entity that is apparently increasing due to changes in lifestyle and often associated with a genetic component. The diagnosis in this group of patients is difficult because the clinical manifestations occur until the tumor is in advanced stages, because this age group is not contemplated for routine screening.

Tumors that occur in these patients usually have a higher incidence of unfavorable biomarkers, as well as strains and adverse histological factors; which results in these tumors delivering a worse prognosis for the patient, as well as a higher risk of local and systemic recurrence. Therefore, detection by self-exploration is recommended from a younger age and in case of any suspicion of the disease, the patient should be referred to competent health services to rule out malignancy.

The appropriate treatment for these women is long-term, although surgery continues to be the cornerstone, adjuvant treatments have become important, and however these tend to have serious and even permanent adverse effects. The monitoring of this disease is physically and emotionally debilitating for patients, most of them will face a life-long situation that will directly impact their life plans. This is why the treatment of these patients is a challenge, which must be carried out in a multidisciplinary manner and considering the integral environment of these patients.

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