

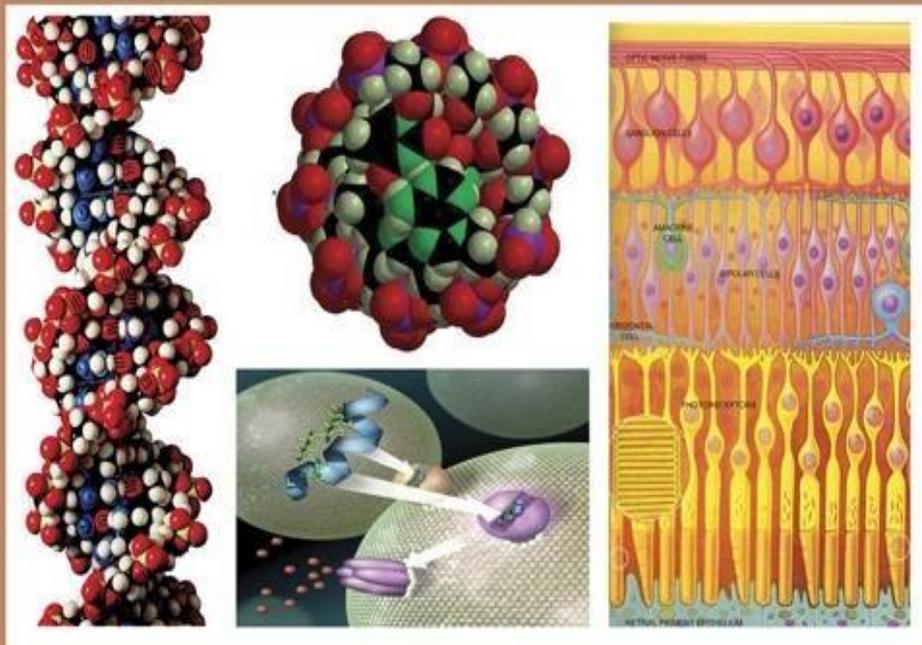


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EGYPTIAN ACADEMIC JOURNAL OF

BIOLOGICAL SCIENCES

PHYSIOLOGY & MOLECULAR BIOLOGY



ISSN
2090-0767

WWW.EAJBS.EG.NET

Vol. 15 No. 1 (2023)



**Risk Factors and Clinicopathological Features of Female Breast Cancer Patients:
A Retrospective Descriptive Study in Northwestern Algeria**

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ARTICLE INFO

Article History

Received:28/1/2023

Accepted:9/3/2023

Available:13/3/2023

Keywords:

Breast cancer, Risk factor, Clinicopathological features, Women, Algeria.

ABSTRACT

Background: Constituting the most frequent malignant tumor among women in Algeria, breast cancer represents a heterogeneous and multifactorial disease. The current study aimed to determine the risk factors and clinicopathological features of breast cancer in women from Sidi-Bel-Abbes region, Northwestern Algeria. **Patients and Methods:** A descriptive retrospective study was carried out by reviewing data from the medical records of patients who underwent a mastectomy at the level of the maternity hospital of Sidi-Bel-Abbes, in the period 2020-2022. **Results:** Based on 118 breast cancer patients' data records, the mean age at diagnosis was 52.92 ± 13.69 years. Patients with blood group O+ (38.1%) were the most affected. The majority of patients were married women (88.1%). The prevalent disease recorded in patients' medical history was hypertension (23.7%). Further, 45.8% of patients were premenopausal, and 12.7% were nulliparous. The mean age at menarche was 12.47 ± 0.73 years. The most common histological type was invasive ductal carcinoma (77.1%), SBR grade II was mainly found in 65.3% of cases, T2 was the main tumor size (64.4%), and 3.4% of patients had metastatic disease. The expression of estrogen receptors and progesterone receptors was respectively positive in 68.6% and 64.6% of cases. Luminal B was the predominant molecular subtype (55.1%). **Conclusion:** In our region, breast cancer is mainly diagnosed in younger and middle-aged women at an advanced stage, and numerous risk factors influence breast cancer occurrence. Therefore, Better identification of breast cancer risk factors and the biological mechanisms in which they are involved can be effective in improving breast cancer prevention.

INTRODUCTION

Constituting one of the major public health issues in the world, breast cancer represents the most common malignant tumor and the main cause of cancer death in women worldwide, with an estimated 2.3 million new cases with 685,000 related deaths in 2020 (Sung *et al.*, 2021). In the last 24 years, breast cancer incidence rate has increased in Arab women (Saggu *et al.*, 2015). In Algeria, breast cancer continues to rise, accounting for approximately 2 460 533 new cases and 774 899 deaths in 2020 (International Agency for Research on Cancer, 2020).

Breast cancer is a complex and multifactorial disease, in which there are various factors such as age, reproductive, family history, lifestyle, environment and genetics can affect breast cancer development (Saggu *et al.*, 2015). Breast cancer prevalence is increasing every day due to changes in risk factors (Momenimovahed & Salehiniya, 2019). Nearly 1 in 8 women worldwide have a lifetime risk of developing breast cancer (Sun *et al.*, 2017).

In addition, breast cancer is a heterogeneous disease encompassing different types and multiple classifications that show considerable variation in morphological and molecular characteristics (Vuong *et al.*, 2014) and, thus, distinct clinical behavior and therapeutic responses (Feng *et al.*, 2018). Numerous prognostic factors play a principal role in breast cancer diagnosis and tumor behavior prediction (Tsang & Tse, 2020). Breast cancer's early diagnosis can lead to a good prognosis and a high survival rate; however, late diagnosis can lead to a poor prognosis and a short survival rate. In Algeria, the 5-year relative survival rate of breast cancer is below 40% but over 80% in North America and Japan (Sun *et al.*, 2017).

Therefore, the aim of the current study was to determine breast cancer risk factors and clinicopathological characteristics among women from the Northwestern region of Algeria. Further, to classify breast cancer into four molecular subtypes: luminal A, luminal

B, HER2+, and triple-negative breast cancer (TNBC), and to identify the distribution of these various molecular subtypes.

MATERIALS AND METHODS

Study Population:

A retrospective descriptive study was performed by reviewing data records of 118 female breast cancer patients who underwent mastectomy or tumorectomy at the level of surgery department of the maternity hospital of Sidi-Bel-Abbes region, Northwestern Algeria, during the period 2020-2022.

Data Collection:

Data were collected from the patients' medical files, including demographic data such as age, blood group, occupation, residence, and marital status; patient medical histories such as personal medical history, and family history of cancer; reproductive histories such as age at menarche, parity, menstrual cycle, and menopausal status; and clinicopathological characteristics such as American College of Radiology (ACR) classification, tumor side, histological type, Scarff-Bloom-Richardson (SBR) grade, Tumor-Node-Metastasis (TNM), Ki-67 proliferative index, estrogen receptors (ER), progesterone receptors (PR), and human epidermal growth factor 2 receptor (HER2) status.

Molecular Classification:

Breast cancer was classified into four molecular subtypes according to ER, PR, HER2, and Ki67 status as follows: Luminal A (ER+, PR+/-, HER2-, Ki-67<14%); Luminal B (ER+, PR+/-, HER2-/+, Ki-67≥14%); HER2+ (ER-, PR-, HER2+) and TNBC (ER-, PR-, HER2-). The HER2 status was scored from 0 to 3+ in which: scores 0 and 1+ were considered negative; 2+, indeterminate; and 3+, positive.

Statistical Analysis: All collected data were analyzed utilizing the SPSS 22.0 software (Statistical Package for the Social Sciences, IBM Corporation; Chicago, IL. August 2013) and were reported as frequencies and percentages for categorical variables and as means and standard deviations (SD) for continuous variables.

RESULTS

1. Epidemiological Characteristics:

In the current study, a total of 118 female patients were diagnosed with breast cancer ranging from 27 to 108 years old, with a mean age of 52.92 ± 13.69 years. The most affected age group was 38-48, followed by the age group 49-59 years old, with a rate of 32.2% and 28.3%, respectively. Patients with blood group type O+ were the most affected by breast cancer, accounting for 38.1% of cases, followed by blood group type A+ (29.7%). A large majority of the studied population represented married women (88.1%), whereas about 10.2% were single. Most patients were housewives (69.5%) and lived in urban areas (82.2%). The most common diseases which were recorded in patients' personal medical history were hypertension (23.7%), diabetes (17.8%), thyroid disorders (10.2%), and benign breast diseases (8.5%). Moreover, 11 out of 118 cases (9.3%) had a family history of cancer. The reproductive history of 118 patients reported that the mean age at menarche was 12.47 ± 0.73 years (range, 12-17 years), with the majority of patients having the first menstrual period, menarche, at the age of 12 years old (61.9%); 63.6% of women had a regular menstrual cycle. However, 53.4% of cases were postmenopausal, a small proportion (12.7%) was nulliparous, and of 95 (80.5%) parous women, 73 (61.9%) had three or more children (**Table 1**).

2. Clinicopathological Features:

Table 2 summarizes the clinicopathological features of breast cancer

patients in our study. According to the American College of Radiology (ACR) classification, 48.3% of tumors were ACR5, highly suspicious of malignancy. All our patients were unilateral, and the left breast (58.5%) was more affected by cancer than the right (41.5%). The predominant histological type was invasive ductal carcinoma (77.1%), followed by invasive lobular carcinoma (12.7%). On the other hand, the SBR grade II (intermediate grade) was mainly found in 65.3% of cases, 28.8% of cases were SBR grade III (high grade), and 4.2% of cases were SBR grade I (low grade). According to TNM (Tumor Node Metastasis) classification, T2 (tumor measuring >2 but ≤ 5 cm) was the main tumor size in our results with a rate of 64.4%, followed by T1 (tumor measuring ≤ 2 cm), T4 and T3 (tumor measuring >5 cm) with 19.5%, 7.6% and 6.8% of cases, respectively. Positive lymph nodes, N1, N2, and N3, constituted respectively 24.6%, 17.8%, and 6.8% of cases. Patients with metastatic disease at diagnosis (M1) accounted for 3.4% of cases.

Further, based on medical data records, we found that the expression of ER and PR was respectively positive in 68.6% and 64.6% of all cases. HER-2 status was positive in 32.2% and negative in 55.1% of patients. A high proliferative index (Ki-67 $\geq 14\%$) was determined in 73.7% of cases. Luminal B (55.1%) was the predominant molecular subtype in our population, followed by luminal A (13.6%), triple-negative breast cancer (TNBC) (11.9%), and HER-2+ (8.5%).

Table 1. Epidemiological characteristics of 118 breast cancer patients

Variables	Number (%) or Mean \pm SD
Demographic data	
Age of patient	52.92 \pm 15.89
Age group at diagnosis, years	
27-37	13 (11.0)
38-48	38 (32.2)
49-59	31 (26.3)
60-70	22 (18.6)
71-81	11 (9.3)
>82	3 (2.5)
Blood group	
A+	35 (29.7)
B+	21 (17.8)
B-	1 (0.8)
AB+	6 (5.1)
O+	45 (38.1)
O-	9 (7.6)
Unknown	1 (0.8)
Marital status	
Married	104 (88.1)
Divorced	02 (1.7)
Single	12 (10.2)
Occupation	
Housewife	82 (69.5)
Employer	28 (23.7)
Retired	08 (6.8)
Residence	
Urban	97 (82.2)
Rural	21 (17.8)
Patient medical history	
Personal medical history	
Hypertension	28 (23.7)
Diabetes	21 (17.8)
Thyroid disorders	12 (10.2)
Benign breast diseases	10 (8.5)
Family history of cancer	
Yes	11 (9.3)
No	107 (90.7)
Reproductive History	
Mean age at menarche	12.47 \pm 0.73
Age at menarche, years	
12	73 (61.9)
13	37 (31.4)
≥ 14	8 (6.8)
Menstrual cycle	
Regular	75 (63.6)
Irregular	35 (29.7)
Unknown	8 (6.8)
Parity	
Nulliparous	15 (12.7)
Parous	95 (80.5)
1-2	22 (18.6)
≥ 3	73 (61.9)
Unknown	8 (6.8)
Menopausal status	
Postmenopausal	63 (53.4)
Premenopausal	54 (45.8)
Unknown	1 (0.8)

Table 2. Clinicopathological features of 118 breast cancer patients

Variables	Number (%)
ACR classification	
ACR2	5 (4.2)
ACR3	17 (14.4)
ACR4	35 (29.7)
ACR5	57 (48.3)
Unknown	4 (3.4)
Tumor location	
Right breast	49 (41.5)
Left breast	69 (58.5)
Histological types	
Invasive ductal carcinoma	91 (77.1)
Invasive lobular carcinoma	15 (12.7)
Mixed invasive ductal and lobular carcinoma	4 (3.4)
Micropapillary carcinoma	3 (2.5)
Other	5 (4.2)
Tumor size	
T1	23 (19.5)
T2	76 (64.4)
T3	8 (6.8)
T4	9 (7.6)
Unknown	2 (1.7)
Lymph nodes	
N0	51 (43.2)
N1	29 (24.6)
N2	21 (17.8)
N3	8 (6.8)
Nx	7 (5.9)
Unknown	2 (1.7)
Metastasis	
M0	22 (18.6)
M1	4 (3.4)
Mx	90 (76.3)
Unknown	2 (1.7)
SBK grade	
I	5 (4.2)
II	77 (65.3)
III	34 (28.8)
Unknown	2 (1.7)
Estrogen receptors status	
Negative	24 (20.3)
Positive	81 (68.6)
Unknown	13 (11.0)
Progesterone receptors status	
Negative	29 (24.6)
Positive	76 (64.4)
Unknown	13 (11.0)
HER-2 status	
Negative	65 (55.1)
Positive	38 (32.2)
Unknown	15 (12.7)
Ki-67	
Ki-67 < 14%	18 (15.3)
Ki-67 \geq 14%	87 (73.7)
Unknown	13 (11.0)
Molecular subtypes	
Luminal A	16 (13.6)
Luminal B	65 (55.1)
HER2+	10 (8.5)
TNBC	14 (11.9)
Unknown	13 (11.0)

DISCUSSION

We conducted the present study to determine the epidemiological and clinicopathological characteristics of breast cancer among women to elucidate potential risk factors for breast cancer in Algeria.

1. Epidemiological Characteristics:

1.1. Demographic Data:

Age represents an important risk factor for breast cancer. Our results showed that breast cancer mainly appears in younger and middle-aged women with a mean age at diagnosis of 52.92 years, the most affected age group was 38-48 years with 32.2%. These results are similar to the previous studies done in Algeria (Elbasyouni *et al.*, 2021), Africa

(Brahim *et al.*, 2021; Gnanamuttupulle *et al.*, 2021), Arab and Asian countries (Abdel-Razeq *et al.*, 2020; Lim *et al.*, 2022). While breast cancer in Western countries occurs in older women like in the United States (Sisti *et al.*, 2020). Many studies indicated that younger age poses an adverse risk factor (Hinyard *et al.*, 2017; Tao *et al.*, 2015).

In our retrospective study, we observed that 38.1% of patients had blood group type O+, followed by blood group type A+ (29.7%). In contrast, the results of a review study showed that a higher risk of developing breast cancer was related to women with blood group A and Rhesus positive, while women with blood group AB

and Rhesus negative have a lower risk of developing breast cancer (Meo *et al.*, 2017). In addition, many researchers found no association between the blood group and breast cancer (Momenimovahed & Salehiniya, 2019).

Housewives and married women were the most affected, with 69.5% and 88.1%, respectively. Igiraneza *et al.* have reported that breast cancer screening is more common among married women than single women due to the higher awareness of the responsibility to stay healthy and live long to support their children, and thus being married would have a positive effect on self-examination and ultrasound (Igiraneza *et al.*, 2021).

Further, Breast cancer was more frequently diagnosed in women living in urban areas than in rural areas, which can be explained by the differences in diet, lifestyle, and environmental factors; living in urban areas is associated with a higher risk of developing breast cancer (Momenimovahed & Salehiniya, 2019). Urban women adopt a westernized lifestyle, which leads to an increased frequency of obesity and risk of breast cancer (Kantelhardt *et al.*, 2015; Tao *et al.*, 2015), while some studies explained the low proportion of patients living in rural areas by the absence of screening equipment, unqualified health workers, the lower level of education, and unawareness of breast cancer screening (Balekouzou *et al.*, 2016; Igiraneza *et al.*, 2021).

1.2. Patient Medical History:

Hypertension, diabetes, and thyroid disorders were reported in 23.7%, 17.8%, and 10.2% of cases, respectively. A meta-analysis of 30 studies demonstrated that hypertension is associated with a 15% increased risk of breast cancer, especially among postmenopausal women (H. Han *et al.*, 2017). Another meta-analysis of 13 prospective studies reported that hypertension is associated with a 7% higher risk of total breast cancer (Seretis *et al.*, 2019). This association has been explained by several mechanisms, including apoptosis blocking, adipose tissue-related hypoxia, and chronic

inflammation (H. Han *et al.*, 2017 ; Seretis *et al.*, 2019).

Diabetes can affect the incidence of breast cancer by interfering with biological mechanisms or through its effects on screening and treatment. In postmenopausal women and those with body mass index (BMI) higher than 26kg/m², diabetes is associated with the risk of breast cancer progression. A meta-analysis study identified that women with diabetes are at a 20% increased risk of developing breast cancer, especially those with type II diabetes (Momenimovahed & Salehiniya, 2019).

Thyroid disorders such as hyperthyroidism, hypothyroidism, autoimmune thyroiditis, and nodular goiter have been associated with breast cancer (Yalagachin *et al.*, 2020). A meta-analysis result reported that autoimmune thyroiditis, goiter, and Graves' disease were positively correlated with an increased risk of breast cancer (M. Han *et al.*, 2022). Another study identified hypothyroidism as a potential breast cancer prognostic factor which is associated with poor outcomes of patients (Elgebaly *et al.*, 2022); also, hyperthyroidism is associated with high incidence and aggressiveness of breast cancer (Liu *et al.*, 2019). This relationship between breast cancer and thyroid disorders has been explained by the presence of thyroid antibodies and thyroid-stimulating hormone (TSH) receptors on the breast. The presence of thyroid receptors on the breast induced the activation of the Mitogen-activated protein kinase (MAPK) pathway and upregulation of the anti-apoptotic gene via the carcinogenic potential of thyroid hormones, which promotes breast cancer cell proliferation (Liu *et al.*, 2019; Yalagachin *et al.*, 2020).

Moreover, 8.5% of patients had a personal history of benign breast diseases. Benign tumors and proliferative lesions without or with atypia in the breast can increase the risk of malignancy, thus proliferative lesions with atypia, especially atypical ductal hyperplasia and atypical lobular hyperplasia, will increase breast cancer risk 4-5fold (Akram *et al.*, 2017; Feng

et al., 2018). However, another study concluded that the relationship between benign breast disorders and breast cancer leans on the disease's histological classification and family history of breast cancer (Momenimovahed & Salehiniya, 2019).

In addition, a family history of cancer was identified in 11 of our patients (9.3%). It is an important breast cancer risk factor; thereby, women may have an increased risk of developing breast cancer if some members of their family had a certain type of cancer. Less than 15% of women diagnosed with breast cancer have a family member diagnosed with this disease (Feng *et al.*, 2018). Women with a positive breast cancer family history are 2–4 times more likely to develop this disease, especially females who had mutated BRCA1 or BRCA2 genes, and the risk increases if the relative was affected at an early age and/or had bilateral cancer (Akram *et al.*, 2017).

1.3. Reproductive Factors:

In the current study, the majority of patients had their menarche at the age of 12 years (61.9%) and a regular menstrual cycle (63.6%). Numerous studies showed that early menarche is associated with a higher risk of breast cancer occurrence, due to a longer period of exposure to estrogen activity (Kamińska *et al.*, 2015). This exposure is considerable when menstrual cycles are regular (Nkondjock & Ghadirian, 2005). Each delay of menarche by one year or two years reduces the risk of occurrence of breast cancer by 5% or 10%, respectively (Kamińska *et al.*, 2015; Sun *et al.*, 2017). In addition, in women who had menarche that occurred before the age of 12 years, estrogen expression in each menstrual cycle is higher than in women whose menarche appeared after the age of 13 years (Kamińska *et al.*, 2015).

Further, 45.8% of patients were premenopausal. Women will have more menstrual cycles if they go through menopause later, especially after age 55, and also have a prolonged lifetime exposure to estrogen and progesterone with a higher risk of breast cancer compared to women who had

menopause before 45 years of age. Each 1-year delay in menopause increases the risk of breast cancer by 3% (Feng *et al.*, 2018; Nkondjock & Ghadirian, 2005; Sun *et al.*, 2017).

Furthermore, 15 out of 118 cases (12.7%) were nulliparous, and the majority of our patients were parous women (80.5%), of which 61.9% had three or more children. High parities were related to an increased risk of developing breast cancer among women younger than 45 years and a decreased risk among individuals older than 45 years in African-American women (Momenimovahed & Salehiniya, 2019). Some other studies also found that breast cancer risk was associated with higher parity among young women but not older women, and having more than five full-term pregnancies are associated with an increased risk of breast cancer (Chollet-Hinton *et al.*, 2016; Momenimovahed & Salehiniya, 2019).

2. Clinical and Pathological Features:

The clinicopathological results of our patients showed that 48.3% of tumors were highly suspicious of malignancy (ACR5), according to the American College of Radiology classification. Our results were lower than those found in Morocco (72.5%) (Bakkach *et al.*, 2017).

In our patients, the most common histological type was invasive ductal carcinoma with 77.1% of cases, followed by invasive lobular carcinoma (12.7%), these findings are reported in the literature (Bansal *et al.*, 2017; Mighri *et al.*, 2022; Soliman & Yussif, 2016). The left breast was the main affected side with 58.5%, which is consistent with the results of (Balekouzou *et al.*, 2016; Elobaid *et al.*, 2021).

In our study, we observed that grade II was the most frequent histological grade with 65.6% of cases, followed by grade III (28.8%) and (4.2%) grade I. These results are in accordance with those observed in Iraq, Angola, Tunisia, and the Republic of Congo (Abood, 2018; Lopes *et al.*, 2015; Mighri *et al.*, 2022; Moudiongui Mboundou Malanda *et al.*, 2021).

Further, T2 was the main tumor size with

64.4% of cases; 49.2% of patients had lymph node involvement, and 3.4% of cases were diagnosed with distant metastasis, which means breast cancer was diagnosed at an advanced stage in our region. It could be caused by the absence of breast cancer screening awareness and diagnostic facilities. These results are similar to those reported in Saudi Arabia, India, and the United Arab Emirates (Al-Thoubaity, 2020; Bansal *et al.*, 2017; Elobaid *et al.*, 2021).

The histological grade with breast cancer TNM classification, which includes the tumor size, lymph node involvement, and metastasis, are important prognostic factors for determining the prognosis and the need for systemic treatment in breast cancer patients (Abood, 2018; Al-Thoubaity, 2020).

Furthermore, we noted that ER, PR, and HER-2 positivity presented in 68.6%, 64.4%, and 32.2% of cases, respectively. Our results are similar to those observed in Eastern Morocco and Egypt (Elidrissi Errahhali *et al.*, 2017; Soliman & Yussif, 2016). In addition, ER, PR and HER-2 are used in clinical practice as prognostic factors of patient outcome and predictive biomarkers of response to treatment (Vuong *et al.*, 2014).

The findings of our study showed that 73.7% of cases had a high proliferation index ($Ki-67 \geq 14$). Our results were higher than those reported in Egypt (34%) (Soliman & Yussif, 2016). Ki-67 index is a crucial biomarker of tumor proliferation, aggressiveness, and prediction of tumor responsiveness to adjuvant systemic treatments such as chemotherapy and aromatase inhibitors (Barnard *et al.*, 2015; Tashima *et al.*, 2015), thereby a cut-off of 14% point for the Ki-67 index was recommended to distinguish between luminal A and B type cancers (Tashima *et al.*, 2015). Based on immunohistochemical data collected from medical records, breast cancer cases were classified into four molecular subtypes. The distribution of these subtypes showed that luminal B was predominant with 55.1% of cases, followed by luminal A, TNBC, and HER2+ with a rate of 13.6%, 11.9%, and 8.5%, respectively. These results

are in accordance with those reported in Tunisia (Mighri *et al.*, 2022). In contrast, other studies found that luminal A was the most prevalent subtype, followed by TNBC, luminal B, and HER2+ (Al-Thoubaity, 2020, p.; Moudiongui Mboundou Malanda *et al.*, 2021; Soliman & Yussif, 2016).

Luminal A tumors are low-grade, slow growing, and have the best prognosis of all molecular subtypes (Feng *et al.*, 2018). Luminal B tumors tend to be a higher grade and have a worse prognosis than luminal A. Clinically, luminal A cancers benefit from hormone therapy, whereas luminal B tumors may be candidates for additional chemotherapy (Tsang & Tse, 2020).

HER2+ subtypes are characterized by overexpression of HER2 gene, high grade, aggressive phenotype, and high risk of recurrence, generally worse prognosis. Nevertheless, HER2+ tumors have a favorable response to anti-HER2-targeted therapies, such as trastuzumab, pertuzumab, lapatinib, and T-DM1 or ado-trastuzumab emtansine (Feng *et al.*, 2018; Tsang & Tse, 2020).

TNBC is characterized by aggressive behavior, high grade, and poor outcomes than other types of breast cancer. The incidence of TNBC is generally higher among women younger than 40 years, African-American women, and patients with mutated BRCA1. TNBC has been treated by conventional chemotherapy until the approval of the PARP inhibitor Olaparib for BRCA1 and BRCA2 mutation carriers, who are more likely to develop TNBC (Feng *et al.*, 2018; Tao *et al.*, 2015; Tsang & Tse, 2020).

These subtypes vary in prognosis, clinical behavior, and treatment response. Thus, they have different tumoral biology.

CONCLUSION

The present study showed that breast cancer is mainly diagnosed in younger and middle-aged women at an advanced stage and is characterized by aggressive behavior, which predicts a poor prognosis in our region. This could be due to insufficient public breast cancer awareness and barriers to health services. In addition, the results of our study

showed that various risk factors, such as age, family history, reproductive history, and benign breast diseases, can affect breast cancer incidence. Patients with hypertension, diabetes, and/or thyroid disorders should pay particular attention to their health and be more aware of breast cancer risk occurrence. Thus, better identification of breast cancer risk factors and the biological mechanisms in which they are involved can be effective in improving breast cancer prevention and early detection.

Acknowledgments: We would like to thank all the staff at the Obstetric and Gynecologic Hospital of Sidi-Bel-Abbes for their invaluable support and guidance.

Ethics Approval: The local Ethics Committee of University Hospital has approved our study.

Conflict of interest: The authors declare no conflicts of interest.

Funding: Not applicable.

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