EGYPTIAN ACADEMIC JOURNAL OF

BIOLOGICAL SCIENCES

PHYSIOLOGY & MOLECULARBIOLOGY

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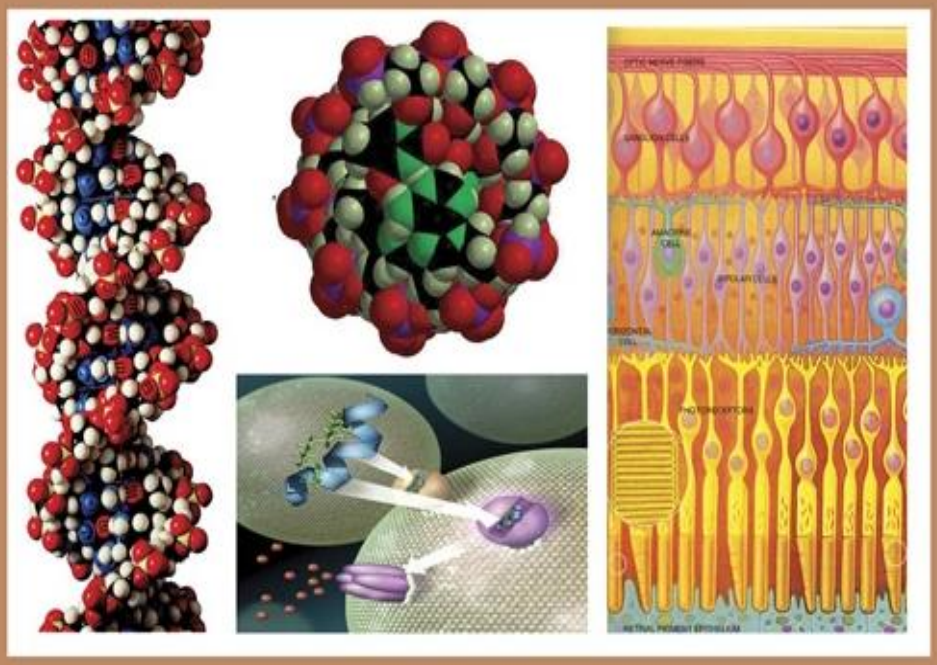

ISSN
2090-0767

WWW.EAJBS.EG.NET

Vol. 14 No. 1 (2022)

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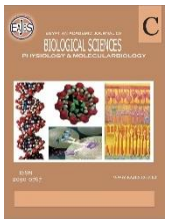
Citation: *Egypt.Acad.J.Biolog.Sci. (C.Physiology and Molecular biology) Vol. 14(1) pp435-449 (2022)*
DOI: 10.21608/EAJBSC.2022.241254

Egypt. Acad. J. Biolog. Sci., 14(1):435-449 (2022)

Egyptian Academic Journal of Biological Sciences
C. Physiology & Molecular Biology
ISSN 2090-0767
www.eajbsc.journals.ekb.eg



Epidemiological, Familial, and Biological Profile of Breast Cancer in a Population of Women in Oran

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ARTICLE INFO

Article History
Received:12/4/2022
Accepted:29/5/2022
Available:3/6/2022

Keywords:
Breast cancer, Epidemiology, Heredity, Risk factors, Biomarkers, Oran

ABSTRACT

Breast cancer (BC) is the most common cancer in women worldwide and in developed countries, with approximately two million new cases of cancer diagnosed in 2018, it is a real public health problem. and the major cause of morbidity and mortality worldwide. Breast oncogenesis remains poorly understood, it is a multifactorial pathology for which the prognosis and the response to treatment differ from one patient to another, all these parameters represent a major obstacle in the management of BC.Many epidemiological studies on risk factors have been performed, it turns out that KS is a heterogeneous disease with data strongly supporting different associations of risk factors. Improved biological tools have made it possible to individualize different subtypes of breast cancer, as well as established biomarkers, including hormone receptor (HR), estrogen receptor (ER), progesterone receptor (PR), human epidermal growth receptor-2 (HER-2), and Ki67 labeling index. The existence of familial forms of breast cancer has been known for a long time and the notion of familiarity or heredity of breast cancer is at the origin either of a genetic alteration, or due to the presence of breast cancer in the family.

The objective of our work is to identify the epidemiological, genetic and/or family and biological profile of breast cancer in women from western Algeria, in order to prevent the spread of this disease in Algeria and to be able to apply a diagnosis. early

To meet our objectives, we proceeded with a retrospective study carried out at the level of the departments, of anatomopathology, oncology, epidemiology and preventive medicine of the EHU Oran hospital.

INTRODUCTION

Breast cancer (KS) is the most common cancer in women worldwide and in developed countries, with approximately two million new cases of cancer diagnosed in 2018, representing 23% of all cancer types (Bray F. *et al.*, 2018), breast cancer is a real public health problem, it is the major cause of morbidity and mortality in the world causing approximately 2.3 million incident cases worldwide in 2020 Figure 1, and 9.6 million deaths in 2018. (Fig 1).

The trend is on the rise, according to estimates, there would be between 29 and 37 million cases by 2040. The WHO declares 10 million new cases per year, 50% of which are counted in developing countries with significant mortality since most patients present at a late stage. (Bray F. *et al.*, 2018).

In the Maghreb, data on BC are different from those in Europe, the incidence of this cancer is lower, the average age at diagnosis is younger and the size and stage of tumors are higher. In Algeria, breast cancer is the leading cause of death among women, the number of cases of breast cancer has increased considerably in recent years, with a standardized incidence rate of 55.8 per 100,000 inhabitants (Globocan 2020) by age of breast cancer, as well as the crude incidence rate of breast cancer in Algeria, is 57.8 per 100,000 (Globocan 2020).Still in Algeria and according to the figures reported by Globocan 2020, the prevalence rate of breast cancer, over a period of 5 years, is 179.2 per 100,000 inhabitants (Fig 2).

The cancer registry of Oran (western Algeria) reports a crude death rate from KS of 19.6 Breast cancer is a disease characterized by varied clinical behaviors and different biological characteristics, which makes the process of prediction and management more difficult (Elbasheer M.M.A. *et al.*, 2019). Advances in molecular technologies have revealed that breast cancer is not a single disease, but rather a group of conditions with distinct molecular profiles (Sotiriou C. *et al.*, 2009) mainly affecting women over 40 years of age. However, in our country more and more cases of breast cancer in young women are reported, recently in Oran cases of BC were found in young girls under 22 years old. (Registre du cancer d'Oran). per 100,000, and an age-standardized death rate from KS of 18.5 per 100,000 (Globocan 2020), (Fig.3).

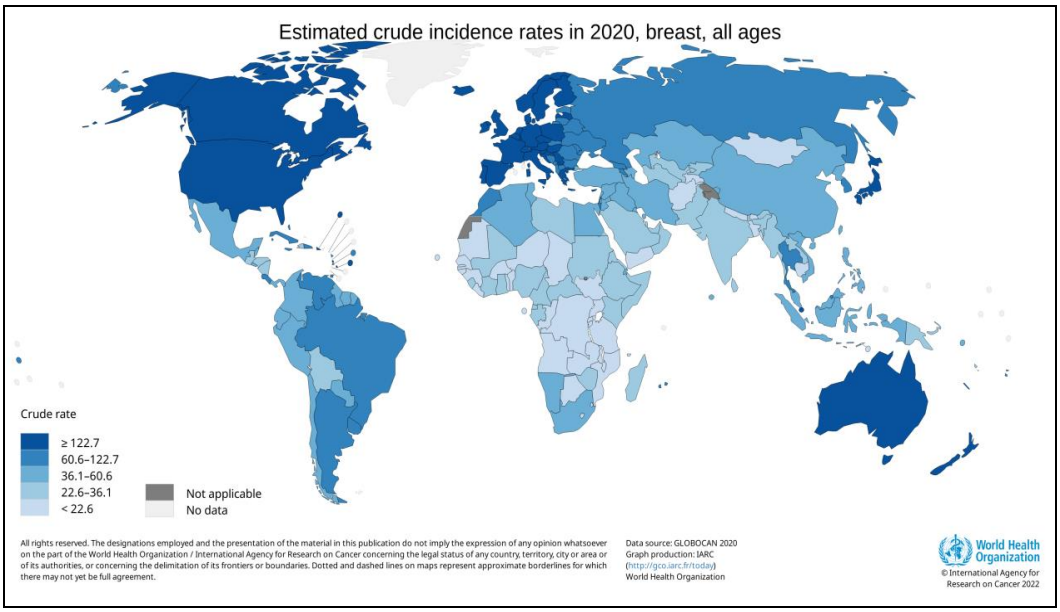

Fig1: Distribution of standardized incidence rate of breast cancer in the world and in Algeria. (Globocan 2020).

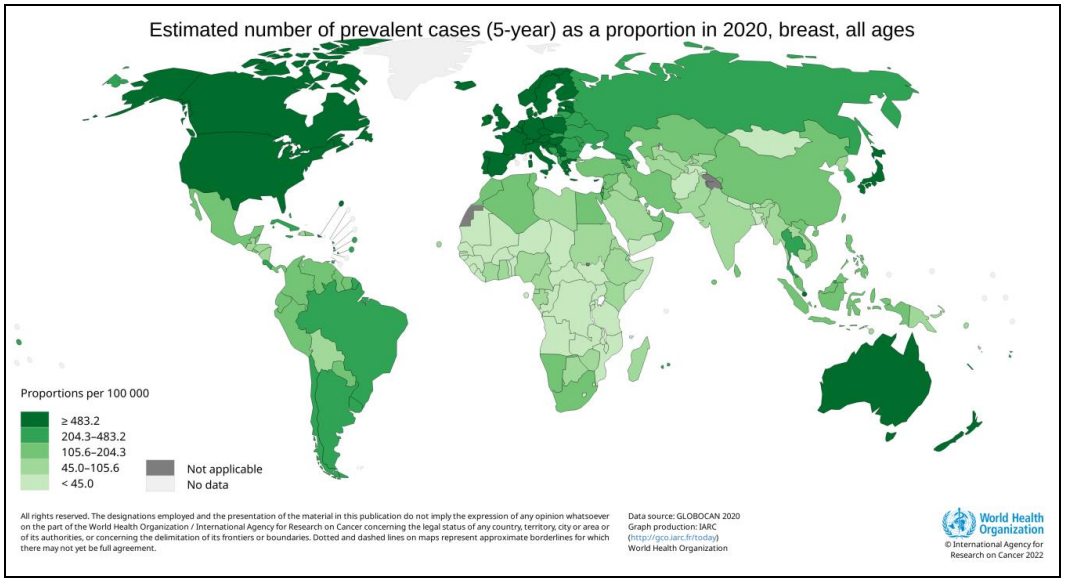

Fig. 2: Breast cancer prevalence rate in Algeria, over a period of 5 years (179.2 Per 100,000) (Globocan 2020).

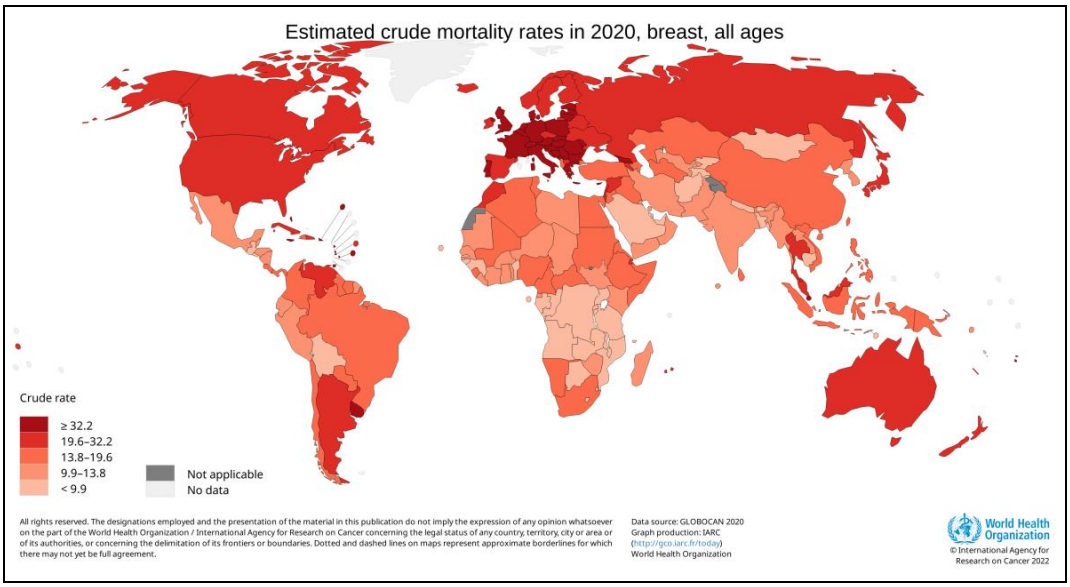

Fig.3: reports a crude death rate from BC of 19.6 per 100,000, (Globocan 2020).

Numerous epidemiological studies on risk factors have been performed and proved that BC is a heterogeneous disease with data strongly supporting different associations of risk factors such as parity and genetic susceptibility loci. A family history of breast cancer increases the risk of developing breast cancer, these are important risk factors (Ford *et al.*, 1998). Certain inherited "high penetrance" genetic mutations strongly increase the risk of breast cancer. The most important of these are present in the BRCA1, BRCA2 and PALB2 genes (Marie Eliade *et al.*, 2017). As well as hormone receptor status and other clinical/pathological features (Almer J.R. *et al.*, 2011), (Xiaohong R. *et al.*, 2011),

Breast cancer remains a heterogeneous disease, its etiology is not completely elucidated, others factors are involved, such as hormonal factors. In the era of precision medicine, the availability of high-quality tumor biomarker assays with proven analytical validity and clinical utility becomes essential. For example, estrogen receptor (ER) and HER2 content are strong

predictors for anti-estrogen therapies (McGuire WL. *et al.,* 1975, Davies C. *et al.,* 2011), and anti-estrogen therapies. HER2, respectively (Fehrenbacher L. *et al.,* 2020).Improved biological tools have made it possible to individualize different subtypes of breast cancer, as well as established biomarkers, including hormone receptors (HR), estrogen receptor (ER), progesterone receptor (PR), human epidermal growth receptor-2 (HER-2), and Ki67 labeling, classify breast cancer into four subtypes: HER2-enriched, triple-negative (TN), and Luminal A types and B (Goldhirsch A., *et al.,* 2013; Cancer Genome Atlas N, 2012). Approximately 70-80% of all breast cancers are HR-positive, which includes estrogen receptor (ER) expression and/or progesterone receptor (PR) on tumor cells. The majority of HR-positive breast cancers are HER2-negative.

Therefore, early-stage BC, with HR-positive, and HER2-negative is an important public health concern. As well as the Ki67 marker, which is a nuclear indicator of cell proliferation. Many studies show that the expression and level of Ki67 is an indicator of breast cancer and a useful prognostic factor for patients with Luminal B and nodal type breast cancer (Fasching PA. *et al.,* 2011, Nishimura R. *et al.,* 2014), (Criscitiello C *et al.,* 2014), (Smith I. *et al.,* 2020).

In Algeria, the analysis of KS risk factors shows that primary prevention is not yet possible. It is secondary prevention that is adopted and continues to prove its worth when cancer is diagnosed and treated at an early stage. The improvement of biological tools as well as scientific advances in our country has made it possible to individualize different prognostic subtypes of breast cancer and to develop predictive tools for different treatments.

The objective of our work is to identify the hereditary and or family and biological profile of breast cancer in women from western Algeria; this study was based on epidemiological, biological and anatomopathologic data, in order to make highlight the correlation that may exist with the various parameters listed.

MATERIALS AND METHODS

Main Objective:

Determine the hereditary/familial profile and variables of KS. Describe the epidemiological profile of the patients. Identify the different risk factors. Describe the biological variables of patients with KS.
In this study we included all patients with BC, the exclusion criteria were patients with a breast abnormality without cytological and/or histological confirmation of malignancy as well as incomplete records.

Protocol and Data Collection:

To meet our objectives, we proceeded with a retrospective and exhaustive study carried out at the level of different departments of the EHU Oran hospital, such as anatomopathology department, oncology department and epidemiology and preventive medicine department.

This work was carried out on tumor samples as well as on patient records. Tumor samples were obtained with the consent of the patients according to the protocol (for the use of surgical tissues and medical records) previously approved by the ethics committee. Patients were informed of the study procedures and informed consent was written and signed by all patients. A questionnaire covering several clinical, pathological and socioeconomic criteria was carried out for the purposes of this study. (Annex 1). This study was conducted in two parts:

1-The variables studied are age, occupation, family history of BC, age of menarche and menopause, parity, contraceptive use and smoking. As well as parameters and epidemiological factors and personal characteristics of patients and factors related to reproductive life.

2- The second part of the work concerned the biological factors, anatomopathological and clinical variables, we looked for the circumstances of the disease discovery, the symptoms, the signs of loco-regional and metastatic extension, the tumor localization according to the breast affected, and stage of

disease according to the American Joint Committee on Cancer (Emily Z. Keunga and Jeffrey E.2018) classification and staging for TNM breast cancer. The data was collected from the consultation of the medical files of the patients within the Oncology Department of the EHU. Oran.

All histopathology slides were analyzed independently by two trained pathologists and a consensus diagnosis was obtained. All cases of malignancy, tumor size, histological type and tumor grade were noted.

The study covered 450 biopsies fixed at the level of the anatomopathology laboratory and 150 cases of BC treated and recorded at the level of the oncology department over a period of three years (2017-2019), data collection was carried out by using a questionnaire containing all the variables that made it possible to meet all our set objectives.

Statistical Analysis:

Coding of the Variables: The variables coding was carried out to standardize the information and facilitate their use in the computer tool. Data entry and analysis were carried out using the EPI info version 6 software. The descriptive analysis focused on the calculation of percentages for qualitative variables and the calculation of the average with its standard deviation for quantitative variables. The results are presented in the form of tables or graphs treated on the Excel 3 software, then discussed in comparison to knowledge already collected on the subject.

Techniques Used:

For the diagnosis and to obtain the results of our research, we used histology, immunohistochemistry as well as a large epidemiological study highlighting the family and or hereditary characteristics, in a questionnaire grouping together several criteria. (Annex 1).

-The histological study was used for histological characterization and histoprognostic grading SBR: Scarff-Bloom and Richardson classification according to the method of Contesso *et al.*, 1987) and Singletary *et al.*, 2002).

-Concerning the study of immunohistochemistry we used RP, HER2, Ki-67 antibodies to detect antigens in order to determine the stage of the tumor by either membrane or nuclear labeling.

RESULTS

In our study, we were confronted to problems such as a lack of information on the files. Thus, our study focused on only 141 files meeting the desired profile.

The results obtained show that all our patients underwent either a total mastectomy, a lumpectomy, or a mastectomy and oophorectomy.

Our results are presented in two parts to meet our prefixed objectives.

1-First Parts:

a-Study the epidemiological profile of women with BC and the different risk factors.

b- Describe the type of family relationship between personal and family history and KS.

Of the 141 files studied, we reported an average age of 52 ± 2.1 years over an age group of 45-49 years (24%) and a range of 54 years. The youngest woman recorded is 29 years old (Fig. 4). The upper limit is 84 years (Table 1). 48% of cases are married, and 44% are single. Among these patients, 104 are sedentary housewives and 37 women have a job (Table 2). For the status of menarche, we found 4 women with early menarche, 66 normal and 23 late menarches (Table 3). 48 cases with gestational age <35 years. Regarding reproductive life, 61 women have an irregular cycle, 80 with a normal cycle of 28 days. More than half of the women are menopausal 84 = 59.5% and 57 are not, i.e. 40.5%. Concerning contraception, we found 121 women (85.8%) who use contraception. The results of breastfeeding show that 85 women did not breastfeed their children, i.e. 60.3%, against 56 women, i.e. 39.7%, who breastfed their babies correctly (Table 4).

Table 1: Age characteristics of the cases studied (2017-2019).

Variable	Total	Mean	Standard Deviation	Range	Mode
Age (years)	132 cas	52 ± 2.1 ans	11.9	54 (29-83)	45-49(18,2%)

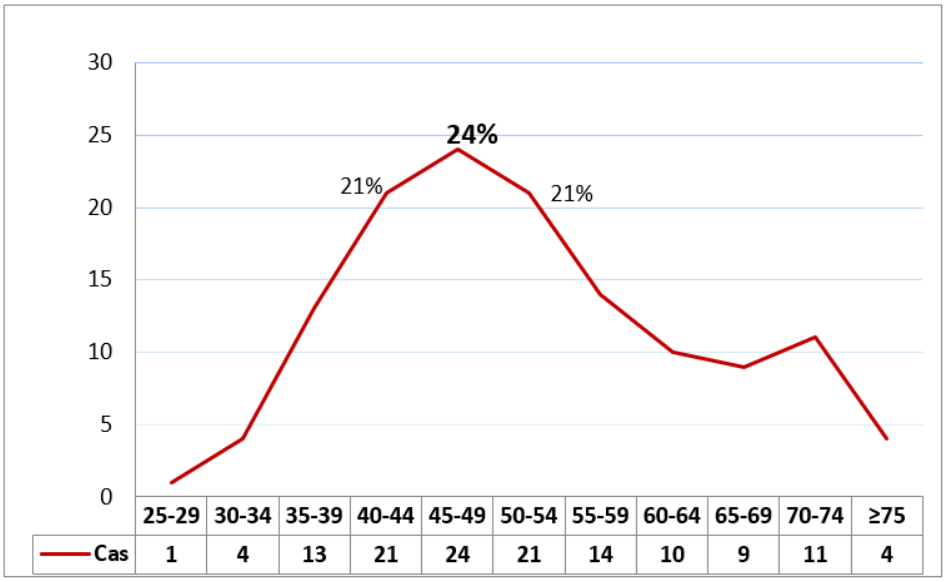

Fig.4: Distribution of cases by age 2017-2019

Table 2: Breakdown of cases by marital status (2017-2019).

Etat civil Marital status	Cases	Frequency (%),
Married	68	48
Single	62	44
Divorcee	7	5
Widow	4	3
Total	141	100

Table 3: Frequency of cases by type of menarche EHUO (2017-2019).

Type of menarche	Cases	Fréquency (%)
Early menarche	4	4,3
Normal menarche	66	71
Late menarche	23	24,7
Total	93	100

Table 4: Risk factors related to EHUO reproductive life (2017-2019).

Risk factor	Present/regular	Absent / Irregular
Job	37(27)	104 (73)
Cycle type	80 (56,7)	61 (43,3)
Contraception	121(85,8)	20 (14,2)
Menopause	84 (59,5)	57 (40,5)
Feeding with milk	56 (39,7)	85 (60, 3)

2- The second part of the study is reserved for the study of personal and family history of cancer and benign tumors

The results obtained through the answers to the questionnaires by the patients in order to bring out the theme sought show that out of 141 patients, 51 (36%) of them have at least one parent with cancer of all types compared to 90 patients, i.e. 64%. have no case of BC reported in the family, 60 patients (42%) have a personal history of benign breast tumour, of which 81 or 58% have no personal history, 31 patient (22%) had a family history of breast cancer against 110 without a family history (Table 5 &Fig.5).

Table 5: Study of personal and family history of cancer EHUO 2017-2019

Antécédents	Présents Nbre (%)	Absents Nbre (%)
Antécédents familiaux du cancer	51(36)	90(64)
Antécédents personnels de tumeur bénigne	60(42)	81(58)
Antécédent familial du cancer du Sein	31(22)	110(78)

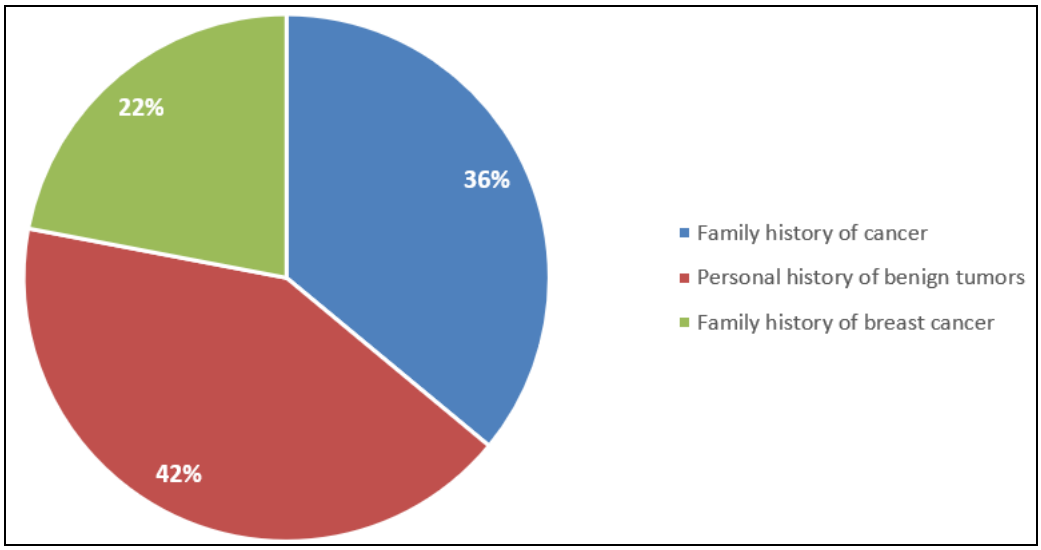

Fig 5: Study of personal and family history of cancer EHU.Oran 2017-2019

Table (6) shows that of the 141 cases included in the investigation, we found 16 cases with a first degree relative with cancer, 15 cases with a second degree relative and 11 cases with at least one third degree relative who has cancer, these results clearly bring out the family notion.

The results of the study of diagnostic and biological variables report that the majority of women underwent mastectomies and lymph node dissection with a predominance of left breast 51.1% and 44.7% for the right breast for the bilateral form we found 4.3% of cases (Table 7).

Results of the distribution of the cases studied according to the radiological results (mammography). Most patients discovered their cancer by chance following a self-examination or a breast discharge, which led them to consult the Oncology department, where examinations such as ultrasound, X-ray, ray, and mammography were prescribed

Table (8) represents most of our patient results that are classified by the ACR system.

Table 6: Study of the degree of parental bond EHUO 2017-2019

Degree	Yes (Nbre %)
1st degree	16 (11,3)
2nd degree	15(10,6)
3rd degree	11(7,80)
Total	114

Table 7: Distribution of cases by affected breast EHUO 2017-2019

Breast	Cases	Frequency (%)
Right breast	63	44,7
Left breast	72	51,1
Bilateral	6	4,3
Total	141	100

Table 8: Radiological results ACR, mammography EHUO 2017-2019

ACR	Cases	Frequency (%)
ACR1	5	7
ACR2	7	10
ACR3	12	16
ACR4	18	25
ACR5	31	42
Total	73	100

Results of The Histological Study:

The results of the histological study showed a high rate of Grade II, i.e. 54.3%, followed by grade III with a rate of 44.7%, without any grade I tumor was reported (Table 9). There are 57 cases of the non-metastatic stage (Mo), 10 metastatic cases (M1) and 67 not determined. Reactive adenitis was found in 15 cases, 62 non-reactive and 64 undetermined cases. Regarding the histological type, most tumors were non-specific infiltrating carcinomas (Fig. 6), there are 47% invasive ductal carcinoma, 4% ductal carcinoma in situ and 2% lobular (Fig 7).

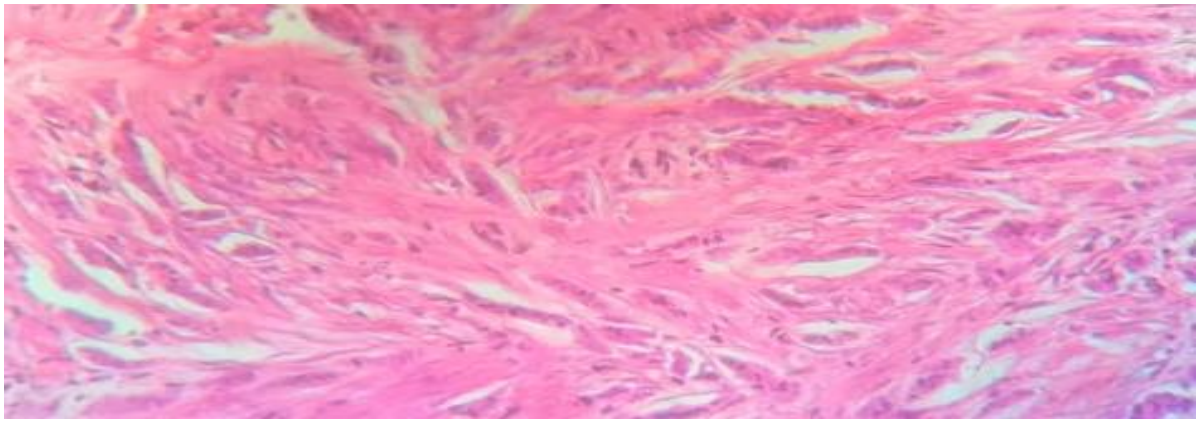

Fig. 6: Infiltrating carcinoma of non-specific type stained by the hematoxylin-eosin method (Gr10x40).

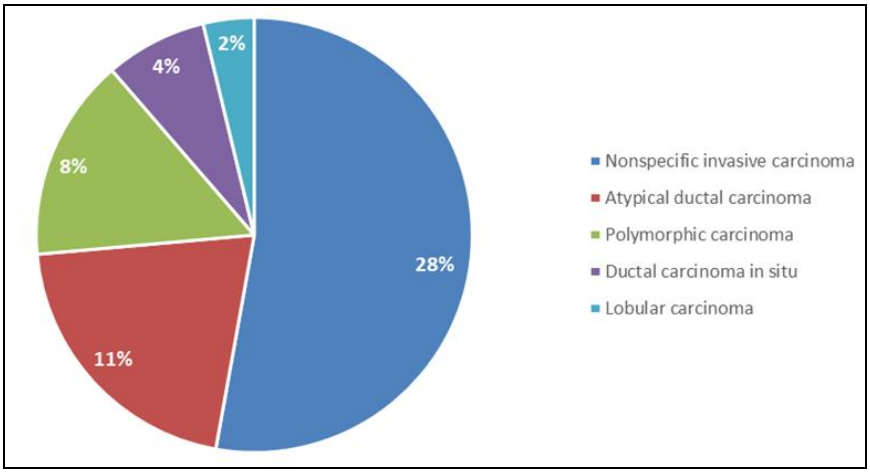

Fig. 7: The different histological types of cases encountered at the EHUO

The results of the immunohistochemistry study: Widely used in anatomopathology for the detection of tumor cells, we studied the markers HER2, KI67, and RH which are indices of tumor proliferation. For RE marking, 44 tumors are negative, and 41 are not. For RP, 48 are negative and 65 positive. HER2 marker 71 negative tumours, 9 intermediate and 41 positives. The KI-67 gives us 33 negative results and 65 positives (Fig. 8 &Table 9).

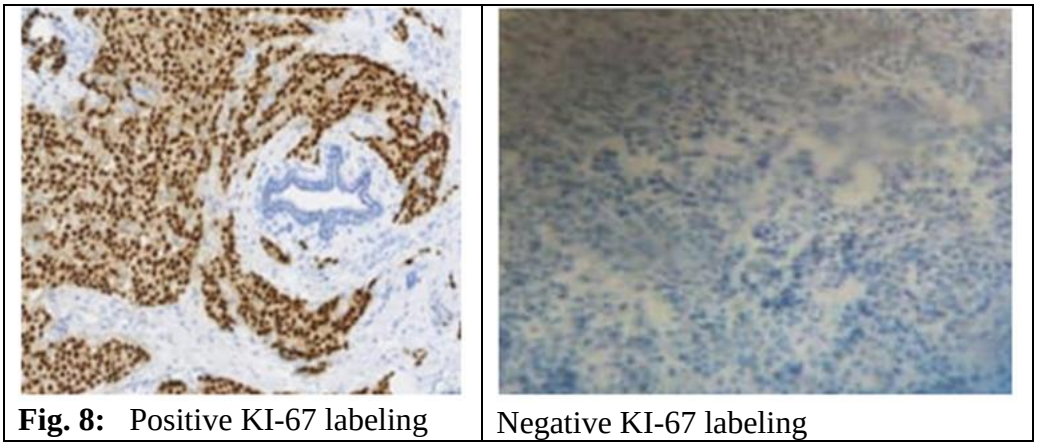

Fig. 8: Positive KI-67 labeling Negative KI-67 labeling

Table 9: Distribution of cases according to biological characteristics

RE receiver		
Negative	44	38
Positive	70	62
Total	114	100
RP		
Negative	48	41.4
Positive	68	58.6
Total	116	100
HER2		
Status	Cases	Frequency (%)
Negative	71	58.7
Intermédiaire	9	7.4
Positive	41	34
Total	121	100
KI67		
Négative	33	33.7
positive	65	66.3
Total	98	100

DISCUSSION

The etiology of breast cancer is multifactorial and complex. it is a heterogeneous tumor with different histological types, recent expression studies by immunohistochemistry on "microarray" tissue have made it possible to identify histological subtypes (basal and luminal), thus allowing new classifications for different patient populations and different anatomoclinical forms of the disease. However, to date, many risk factors for breast cancer have been identified (Key, Verkasalo and Banks, 2001; Andreas Pettersson, *et al.,* 2014). This is consistent with our results which show that in our study several factors emerge such as age and stress (case of depressed widowed women with dependent children) also the average age at diagnosis was 52 ± 2.1 years. An age range of 45-49 years (24%) and a range of 54 years. The youngest woman is 29 years old, these figures may be due to the fact that our sample was not large. In developed countries, the average age at diagnosis is higher, varying from 62.3 to 63.3 years, we also find a significant frequency of single women in our sampling, i.e. 44% of cases, this is a reported risk factor. in literature. Among these patients, 104 women are housewives, which explains their physical inactivity, one of the risk factors reported in the occurrence of BC. As for the status of the menarche, we found 4 women with early menarche versus 23 late, this is consistent with the literature (Cogliano *et al.,* 2011). Hormonal factors are clearly linked to the risk of breast cancer.

The fact of having one or more late pregnancies, lack or little breastfeeding or not having had a pregnancy was traditionally considered a risk factor (Key, Verkasalo and Banks, 2001). Justified by 85 of our patients who have not breastfed their babies.

For the results related to the genetic and or family factor, the literature reports that different genetic factors can play a role in the risk of developing BC, the best known are the mutations of the BRCA1 and BRCA2 genes which generate a very high risk of breast cancer. breast. A family history of first-degree breast cancer increases cancer risk (Collaborative Group on Hormonal Factors in Breast Cancer, 2001). studies have shown that women with two or more relatives with a history of breast cancer had a 2.5 times greater risk (95% CI 1.83–3.47) of developing breast cancer (Brewer HR, *et al.*, 2017). All these data suggest that family history of breast cancer should be treated as one of the most important screening factors in the prevention of breast cancer, our results are in perfect agreement with this literature where we have 51 patients with any cancer in their family, and 31 have at least one family member who has or has died of breast cancer. These results correspond to our theme.

A personal history of benign breast disease also increases the risk of breast cancer (Key, Verkasalo and Banks, 2001; Santen and Masnel, 2005). This is in agreement with our results where we find 60 patients with a personal history of benign breast tumour, 16 patients with an affected first-degree relative, 15 with a degree and 11 with a third degree.

The surgical results are mastectomy and lymph node dissections performed, the majority of cases being left mastectomy and only 6 patients who received a bilateral mastectomy, also in line with the literature. The histological study gives us a fairly low proportion of lobular cancers 2%, i.e. 3 patients, with a dominance of infiltrating ductal carcinoma (47% i.e. 66 patients) which also corresponds to the findings made in studies on young women (Kollias J. *et al.*,1997).

We note in particular that the grade II SBR (Scarff Bloom and Richardson) is more frequent than and absence of grade I. most with a TNM of type T1N1M0 with also some metastatic cases.

Immunochemical labeling gives us a majority of positive labeling with regard to ER, RP HER2, and KI67.

We faced problems with patients who shamed self-reporting of family history considering it a taboo, which may have introduced errors into the database

Conclusion :

Globally, BC poses a major threat to public health. Breast oncogenesis remains poorly understood, it is a multifactorial pathology for which the prognosis and the response to treatment differ from one patient to another. All these parameters represent a major obstacle in the management of the disease.

The existence of familial forms of breast cancer has been known for a long time and the notion of familiarity or heredity of breast cancer is at the origin either of a genetic mutation or due to the presence of breast cancer in the family. Scientific research has highlighted several genes predisposing to breast cancer.

The mutation of these genes confers a significant risk of developing breast cancer in female carriers. The identification of key genes in the process of mammary oncogenesis may also lead to the identification of new therapeutic targets for new anti-cancer weapons.

Most anti-cancer drugs have low therapeutic indices due to their toxicity to healthy tissues. Additionally, drug resistance is a recurring problem, highlighting the need for alternative strategies that can selectively and efficiently kill the malignant cell population without affecting normal cells.

Recently, researchers identified the anti-apoptotic clone AAC-11 as an anti-cancer therapeutic target (Anastassia Mikhailova et Poyet JL. *et al.,* 2020). Indeed the AAC-11 protein is overexpressed in KS and allows the survival of cancer cells under metabolic stress conditions, its overexpression is associated with a poor prognosis of KS (Kim JW *et al.,* 2000, Koci L *et al.,* 2012)), Wang Z, *et al.,* 2010) this protein can become a powerful prognostic marker, and also for early diagnosis for better management of KS. The inhibition of some of this protein gives it an anti-cancer therapeutic role.

Finally and in order to prevent the spread of breast cancer in Algeria, early diagnosis remains the best way.

Acknowledgments

The authors would like to thank all those who authorized and participated in the success of this survey, the department heads who opened their doors and contributed in a very transparent way, the study participants for their cooperation, the time granted, their sincere answers and their help during the data collection.

Conflicts of Interest

The authors declare that they have no conflicts of interest. This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Annexe-1- Epidemiology Service-Medical Oncology Service-Anatomopathology Service (EHUO). A. Personal characteristics

Questionnaire : File N° :	**Registration**
A. Personal characteristics	
• Full name:	
• Date and place of birth:.....	
• Age:..... Sexe: F1 M2 Marital status: Married 1, Single 2, Divorced 3, Widowed4	
• Consanguinity yes 1 no 0	
• Level of education: Illiterate 1, Primary 2, Average 3, Secondary 4, Superior5	
• Current occupation.....Exercise durationI____I	
• Previous occupation..... Exercise durationI____I	
B. Reproductive life	
• Age at menarche I___ I duration of the cycle..... Age at first marriage: I____I	
• contraception: yes 1 no 0Mode: Oral 1, IUD 2, spermicides 3, Condoms 4, other methods	
• Type of pill: Normodose:1, Minidose:2, Microdose:3	
• Age of onset: I____I Drinking duration I____I, Continuous 1, Discontinuous 2	
• Age of first pregnancy I____I Number of pregnancies I____I	
• TSH: yes 1, no 0	
• Menopause: Yes 1, No 0 Age menopause I_____I	
• Notion of oophorectomy: yes 1, no 0	
• Maternal breastfeeding yes 1, no 0 Breastfeeding duration (in months)	
C. Family history	
• Family history of cancer yes 1 no 0 Location:	
• Relatives link.....	
• Personal history of benign breast tumor yes 1no 0	
• History of malignant breast tumor in the family: yes 1 no 0	
• Affected relative: Mother 1 Sister 2 Niece 3 Paternal aunt 4 Maternal aunts 5, Paternal uncle 6, Uncle	
• Maternal 7 Cousin 8 Maternal grandmother 11 GM Paternal 12 Degree: 1, 2,3	
D. Diagnostic	
• Age discovery of breast cancer:..... Circumstance discovered: Mass 1 Nodule 2 Discharge 3	
• Affected breast: Right 1 Left 2 bilateral 3	
• Diagnosis: Clinical 1, Cytopunction 2, Radiological 3, Other 4	
• Date of diagnosis /____ /____/_____/FNA result/	
• Tumor size:.....Existence of metastases: yes 1 no	
• Mammography result:.....	
E. Biological assessment and immunohistochemistry	
• Histopathological type:.....	
• Lymph nodes: yes 1, no 0 Site..... Classification: T N M	
• Distant metastases: yes 1, no 0 Location:.....	
• Hormone receptors: HER2.....RE.....RP.....KI67.....	

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