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Thesis

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In: Biological science
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By:

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Entitled :

Toxicological factors and their association with histological types and immunohistochemical profiles of breast cancer(An epidemiological study in Tebessa).

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Dedication

To the dear one whose name I carry with pride,
To the one whom God adorned with dignity and reverence,
To the one who cleared thorns from my path and planted comfort instead,
To my father...
My father’s back didn’t bend from the weight he carried,
But it bent to carry me, he bowed for my sake.
I used to deny myself desires,
Yet he unveiled what I longed for.
Thank you for being my father!
To the one who taught me morals before I could learn them,
To the bridge that lifts me toward paradise,
To the unseen hand that cleared the obstacles from my path,
To the one whose prayers carried my name day and night...
My mother, my beloved and my inspiration.
And to those whom God blessed me with
To the source of my strength, my solid ground, the firm wall of my heart...
My brothers and sisters,
And to those who, when life became narrow, widened it with their steps,
And when I fell, were the first to lift me with their words,
To the one who walked with me in heart before the journey
My dearest friends,
I have folded a page of fatigue and recorded in my history a pride that will never be forgotten.
I no longer wonder what the features of success look like I saw them in my own eyes.
The clouds of exhaustion have faded, and the horizon smiled after the darkness of waiting.
Here are the steps that once stumbled they have now found their place at the peak of achievement.
Along the way, I breathed peace, joy, and gratitude.

HADFI CHAIMA

Dedication

To my family,

You have always been my refuge, my source of strength and inspiration. Thank you for your patience, your unwavering support, and above all, for the unconditional love you have given me throughout this journey. It is thanks to you that I was able to persevere and achieve my goals.

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I dedicate this thesis to you, the fruit of many hours of work, as a testimony of my gratitude and affection.

RAIS MOHAMED EL AKRAM

الملخص

يقع الثدي الأنثوي بين الضلعين الثاني والسادس، ويرتبط بعضلات الصدر الكبرى عبر أربطة كوبر، ويتكون من الجلد والدهون تحت الجلد ونسيج غدي منظم في 15 إلى 20 فصًا تتصل بالقنوات اللبنية، مع تمركز أغلب النسيج في الجزء العلوي الخارجي من الثدي. يُعد سرطان الثدي أكثر أنواع السرطان شيوعًا على مستوى العالم، وثاني أبرز أسباب الوفاة المرتبطة بالسرطان بين النساء، ومن المتوقع أن يُصيب نحو 3.2 مليون امرأة سنويًا بحلول عام 2050.

تتعدد العوامل المسببة والمساهمة في تطور هذا المرض، وتشمل العوامل الوراثية والهرمونية والبيئية بالإضافة إلى التاريخ العائلي. وينشأ سرطان الثدي نتيجة طفرات جينية، واضطرابات هرمونية، واختلالات في الإشارات الخلوية. ويتطور المرض من مراحل غير غازية إلى مراحل غازية، وتختلف أنواعه (مثل DCIS، IDC، ILC) في خصائصها وسلوكها. يعتمد اختيار العلاج على الخصائص البيولوجية للورم مثل حالة المستقبلات الهرمونية وHER2، بينما تحدد مرحلة المرض توقعات الشفاء ونوع العلاج. ويُعد النوع الثلاثي السلبي (TNBC) من أكثر الأنواع تحديًا بسبب قلة الخيارات العلاجية المستهدفة. وتسهم التقنيات الحديثة في تحديد البروفايل الجزيئي في تطوير خطط علاجية مخصصة أكثر دقة.

تتناول هذه الدراسة السمات المناعية النسيجية لسرطان الثدي، كونه أكثر أنواع السرطان شيوعًا بين النساء في تبسة، الجزائر. وقد شملت الدراسة تحليل البيانات الديموغرافية للمريضات ومعلوماتهن السريرية والمرضية، كما تم بحث العلاقة بين الأنماط الجزيئية المختلفة والخصائص السريرية المرضية. وتبين النتائج أن سرطان الثدي غالبًا ما يظهر في مرحلة منتصف العمر، كما أن النمط الجزيئي "Luminal B" هو الأكثر شيوعًا في هذه المنطقة. أما الأورام غير المصنفة، فغالبًا ما تكون أقل حدة في سلوكها السريري. وستُسهم نتائج هذه الدراسة في دعم جهود تبسة لوضع برامج فعالة للفحص المبكر وخطط للوقاية من السرطان.

الكلمات المفتاحية: سرطان الثدي، الأنماط الجزيئية، الكيمياء النسيجية المناعية، العلاج، بيولوجيا الأورام.

Abstract

The female breast, located between the 2nd and 6th ribs and attached to the pectoralis major by Cooper's ligaments, is composed of skin, subcutaneous fat, and glandular tissue organized into 15–20 lobes that drain into lactiferous ducts, with most tissue concentrated in the upper outer quadrant. Breast cancer, the most frequently diagnosed cancer globally and the second leading cause of cancer-related deaths in women, is expected to affect 3.2 million women annually by 2050. The etiology and risk factors of breast cancer, highlighting the interplay between genetics, hormones, environment, and family history. Breast cancer arises from genetic mutations, hormonal dysregulation, and disrupted cell signaling. Its progression involves transition from preinvasive to invasive stages, with subtypes (DCIS, IDC, ILC) differing in behavior. Tumor biology (HR/HER2 status) guides treatment, while staging determines prognosis and therapy. TNBC remains the most challenging subtype due to limited targeted options. Advances in molecular profiling continue to refine personalized treatment strategies.

This study examined the immunohistochemistry features of breast cancer, the most common cancer among women in Tebessa, Algeria. We examined patient demographics and clinical pathology. The relationship between molecular subgroups and clinicopathological characteristics was investigated. These findings demonstrate that breast cancer usually manifests in middle adulthood and that the luminal B subtype of the disease is more prevalent in this area of Algeria. Unclassifiable tumours had less aggressive clinical features. Tebessa will use the study's findings to create efficient screening programmes and cancer prevention plans.

Keywords: Breast cancer, Molecular subtypes, Immunohistochemistry, Treatment, and Tumor biology.

Résumé

Le sein féminin, situé entre les 2e et 6e côtes et attaché au grand pectoral par les ligaments de Cooper, est composé de peau, de graisse sous-cutanée et de tissu glandulaire organisés en 15 à 20 lobes qui s'écoulent dans les canaux lactifères, la plupart des tissus étant concentrés dans le quadrant externe supérieur. Le cancer du sein, le cancer le plus fréquemment diagnostiqué dans le monde et la deuxième cause de décès liés au cancer chez les femmes, devrait toucher 3,2 millions de femmes chaque année d'ici 2050. L'étiologie et les facteurs de risque du cancer du sein, mettant en évidence l'interaction entre la génétique, les hormones, l'environnement et les antécédents familiaux. Le cancer du sein résulte de mutations génétiques, d'un dérèglement hormonal et d'une perturbation de la signalisation cellulaire. Sa progression implique une transition des stades préinvasifs aux stades invasifs, avec des sous-types (CCIS, IDC, ILC) de comportement différent. La biologie tumorale (statut HR/HER2) guide le traitement, tandis que la stadification détermine le pronostic et le traitement. Le TNBC reste le sous-type le plus difficile en raison des options ciblées limitées. Les progrès du profilage moléculaire continuent d'affiner les stratégies de traitement personnalisées.

Cette étude a examiné les caractéristiques immunohistochimiques du cancer du sein, le cancer le plus fréquent chez les femmes à Tébessa, en Algérie. Nous avons examiné la démographie des patients et la pathologie clinique. La relation entre les sous-groupes moléculaires et les caractéristiques clinicopathologiques a été étudiée. Ces résultats démontrent que le cancer du sein se manifeste généralement au milieu de l'âge adulte et que le sous-type luminal B de la maladie est plus répandu dans cette région d'Algérie. Les tumeurs inclassables présentaient des caractéristiques cliniques moins agressives. Tébessa utilisera les résultats de l'étude pour créer des programmes de dépistage efficaces et des plans de prévention du cancer.

Mots clés : Cancer du sein, sous-types moléculaires, Immunohistochimie, Traitement et biologie tumorale.

List of abbreviations

3DCRT: 3D Conformal Radiation Therapy

ADCC: Antibody-Dependent Cellular Cytotoxicity

AJCC: American Joint Committee on Cancer

AICR: American Institute for Cancer Research

ATM: Ataxia Telangiectasia Mutated (gene)

BC: Breast Cancer

BRCA1/2: Breast Cancer Gene 1/2

BSE: Breast Self-Examination

CAD: Computer-Aided Detection

CEM: Contrast-Enhanced Mammography

COCs: Combined Oral Contraceptives

COVID: Coronavirus Disease

DAB: 3,3'-Diaminobenzidine (staining reagent)

DBT: Digital Breast Tomosynthesis

DCIS: Ductal Carcinoma In Situ

DCE-MRI: Dynamic Contrast-Enhanced MRI

DDR: DNA Damage Response

EGFR: Epidermal Growth Factor Receptor

EIS: Electrical Impedance Scanning

EPH: Établissement Public Hospitalier

ER: Estrogen Receptor

FFDM: Full-Field Digital Mammography

FIF: Field-in-Field (radiation technique)

HDI: Human Development Index

HE: Hematoxylin and Eosin (staining)

HER2: Human Epidermal Growth Factor Receptor 2

HR: Hormone Receptor

HRT: Hormone Replacement Therapy

HT: Helical Tomotherapy

IARC: International Agency for Research on Cancer

IBM: International Business Machines (software)

IDC : Invasive Ductal Carcinoma

IHC: Immunohistochemistry

ILC : Invasive Lobular Carcinoma

IMRT: Intensity-Modulated Radiation Therapy

IARC: International Agency for Research on Cancer

Ki-67: Proliferation Marker Protein

LOH: Loss of Heterozygosity

MG: Mammography

MRI: Magnetic Resonance Imaging

MRS: Magnetic Resonance Spectroscopy

NAD+: Nicotinamide Adenine Dinucleotide

NSABP: National Surgical Adjuvant Breast and Bowel Project

OARs: Organs at Risk (in radiotherapy)

PARP: Poly (ADP-Ribose) Polymerase (inhibitors)

PBS: Phosphate-Buffered Saline

PIK3CA: Phosphatidylinositol-4,5-Bisphosphate 3-Kinase Catalytic Subunit Alpha

POP: Progestin-Only Pills

PR: Progesterone Receptor

pT/pN/pM: Pathological Tumor/Node/Metastasis (staging)

SBR: Scarff-Bloom-Richardson (grading system)

SPSS: Statistical Package for the Social Sciences

TNBC: Triple-Negative Breast Cancer

TNM: Tumor, Node, Metastasis (staging system)

TP53: Tumor Protein 53

US: Ultrasound

VMAT: Volumetric Modulated Arc Therapy

WCRF: World Cancer Research Fund

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General introduction

General Introduction

Breast cancer represents a major societal and medical challenge as a leading cause of cancer-related morbidity and mortality worldwide. It is a heterogeneous disease characterized by the uncontrolled proliferation of malignant cells in breast tissue, driven by genetic, hormonal, and environmental factors. Globally, breast cancer accounts for 25% of all cancer cases in women, with over 2.3 million new diagnoses and 670,000 deaths annually ***(Kim et al., 2025).***

In Algeria, it is the most prevalent malignancy among women, constituting 43% of female cancers, with rising incidence rates linked to demographic and lifestyle changes ***(Nafaa et al., 2022).***

Among breast cancer subtypes, triple-negative breast cancer (TNBC) and HER2-enriched tumors are particularly aggressive, often diagnosed at advanced stages due to limited screening access and biological complexity. The disease's progression involves molecular alterations in genes like *BRCA1/2*, TP53, and PIK3CA, as well as hormonal dysregulation (e.g., estrogen/progesterone receptors). Despite advances in targeted therapies (e.g., HER2 inhibitors, PARP inhibitors), disparities in early detection and treatment efficacy persist, especially in low-resource settings.

Objectives of This Study

This work aims to:

- Characterize the clinicopathological and immunohistochemical (IHC) profiles of breast cancer in Tebessa, Algeria, through a retrospective analysis of 155 cases (2018–2024).
- Evaluate the distribution of molecular subtypes (Luminal A/B, HER2+, TNBC) and their correlation with tumor grade, lymph node involvement, and metastatic potential.
- Identify regional epidemiological trends to inform localized screening and treatment strategies.

Methodology Overview

Part I: Bibliographic Review

Chapter I: Breast cancer epidemiology, anatomy, and risk factors (genetic, hormonal, environmental).

Chapter II: Tumor biology, including HR status, HER2 amplification, and TNBC pathogenesis.

Chapter III: Diagnostic and therapeutic advances (surgery, radiotherapy, immunotherapy).

Part II: Practical Study

Materials & Methods: IHC analysis of ER, PR, HER2, and Ki-67 in mastectomy specimens.

Results & Discussion: Statistical correlations between molecular subtypes and prognostic factors (e.g., tumor size, lymph node metastasis).

This study seeks to bridge gaps in regional data, offering insights to optimize Algeria's breast cancer management protocols. The findings may guide public health policies to improve early detection and reduce mortality rates.

Bibliographic Part

Chapter I

I. Introduction

1. Breast anatomy

The female breast is located on the anterior thoracic wall and is composed of skin, subcutaneous tissue, and breast tissue. It has anatomic boundaries from the second to sixth rib and is connected to the pectoralis major muscle by the suspensory ligaments of Cooper.

Cooper's suspensory ligaments secure the superficial fascia to the skin, while the retromammary bursa divides the breast tissue from the investing fascia.

The epithelial component, which is composed of stroma and epithelial parenchymal elements, makes up 10% to 15% of the breast volume. Each of its 15–20 lobes empties into a lactiferous duct.

The upper outer quadrant contains the majority of the breast, which is separated into four sections. The volume of adipose tissue between lobes, not the epithelial component itself, is responsible for the variation in breast size. ***(Pandya et al., 2011)***

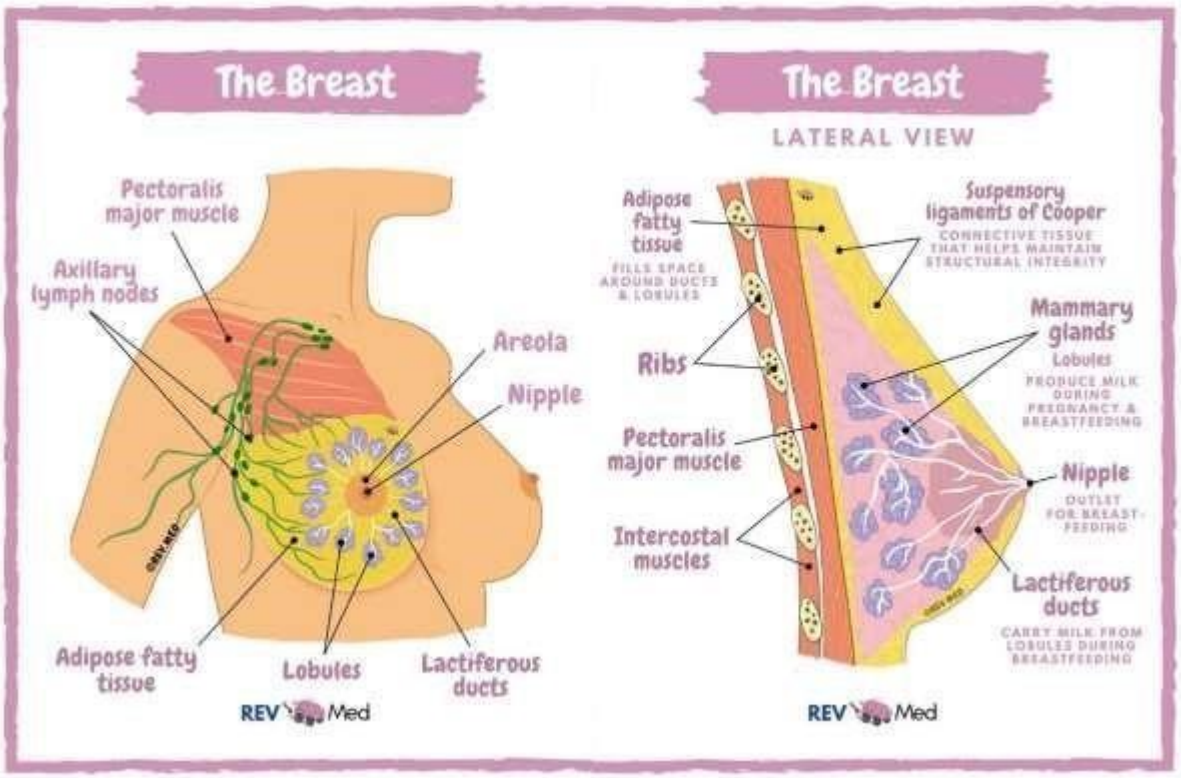


Figure01: the breast anatomy. ***(Pandya et al., 2011)***

2. Breast cancer definition

The second most common cause of cancer-related fatalities among women globally is breast cancer (BC), which is also the most common cause of cancer globally, with one in three women at risk of acquiring BC during their lifetime.

It is anticipated that 3.2 million new cases of female BC would occur globally by 2050. ***(Henriques et al., 2021)***

3. Epidemiology of breast cancer

3.1. Globally

Breast cancer is a prevalent malignant tumor, accounting for 10.4% of all cancers and the leading cause of death in women aged 20-50. Regional differences exist, with Asian countries like China and Japan showing lower mortality rates. Migration from low-mortality areas to higher-risk countries increases breast cancer incidence and mortality.

In the US, over 1.7 million new cancer cases are expected in 2019, with 271,000 being breast cancer, with 42,263 fatalities. Breast cancer, along with lung, colorectum, and lung cancer, accounts for 30% of all new cancer diagnoses in women. It remains the second leading cause of cancer death, after lung cancer and colorectal cancer.

Breast cancer incidence rates increased by 0.3-0.4% annually among non-Hispanic white and Hispanic women, 0.7-0.8% annually among black and American Indian/Alaska Native women, and 1.8% annually among Asian/Pacific Islander women between 2006 and 2015 as a result of the obesity epidemic and declining parity.

However, the survival rate is increasing to almost 90% for all stages of breast cancer. Because of the dramatic increase in lung cancer deaths brought on by the tobacco epidemic, the death rate from breast cancer fell by 40% between 1989 and 2016.

Socioeconomic status has a significant impact on cancer statistics worldwide; lower SES is associated with higher cancer mortality. 34% of cancer deaths among people aged 25 to 74 may be prevented by reducing socioeconomic disparities. ***(Iacoviello et al.,2020)*** .

In 2022, there were 2.3 million new cases and 670,000 deaths from breast cancer in women worldwide. Annual rates increased by 1–5% in half of the countries under analysis. Mortality rates decreased in 29 countries with exceptionally high Human Development Indexes (HDIs).

The 38% increase in new cases and 68% increase in mortality by 2050 will disproportionately impact low-HDI countries. Countries with low and medium HDI must continue to improve access to early diagnosis and treatment, as well as provide high-quality vital status and cancer data, in order to address disparities and monitor cancer reduction goals. ***(Kim et al.,2025)*** .

3.2. Regionally

The incidence of breast cancer has significantly increased in recent years both in Algeria and globally. In 2018, more than 2.1 million women worldwide were diagnosed with breast cancer, and approximately 627,000 deaths were documented. Algerian women are more likely to be affected by breast cancer than by other types of cancer. ***(Elbasyouni et al., 2021).***

Breast cancer is the most common cancer affecting women in Algeria, making up 43% of all female cancer cases. On average, between 2014 and 2018, about 65 out of every 100,000 women were diagnosed with breast cancer each year.

However, the numbers vary across the country — for example, the northern region of Sétif has one of the highest rates, with 108 cases per 100,000 women, while the southern region of Ouargla reports significantly fewer cases, around 45 per 100,000. What's even more alarming is that breast cancer is on the rise. Between 2014 and 2018, the number of cases increased by

32%, and if this trend continues, it's expected that by 2025, there will be 45% more new cases compared to 2014.

Breast cancer is also striking at a relatively young age in Algeria. Around 85% of cases are diagnosed in women under 60, and nearly a quarter — 23% — occur before the age of 40.

(Nafaa et al.,2022).

Chapter II

II. Etiology and risk factors

II.1. Genetic factors:

Genetic mutation is the term used to describe a changed gene. Certain gene alterations may increase the risk of developing a certain type of cancer. Gene mutations can be passed down from parents to their offspring. Only 5% to 10% of breast cancers are caused by genetic gene mutations.

Both the BRCA1 and BRCA2 genes for breast cancer are a normal part of human physiology. Because they seem to have a part in regulating the growth of cancer cells, these genes are known as tumor suppressors. The ability of the BRCA1 or BRCA2 genes to regulate the onset of cancer may be compromised by mutations in these genes. Such mutations are rare. About one in five people are impacted by them. Mutations in the BRCA gene can be inherited by both men and women from their parents.

Those who carry the gene mutation may pass it on to their children. A child has a 50% chance of inheriting the mutation if one or both parents have it in one of the two copies of the BRCA gene. A child has a 50% chance of not inheriting the gene mutation, according to this as well. According to studies, women who inherit mutations in the BRCA1 or BRCA2 genes have an 85% lifetime risk of developing breast cancer.

Furthermore, compared to other women, women with these genetic abnormalities have a higher chance of developing breast cancer earlier in life. Breast cancer in both breasts is more common in women who have a mutation in the BRCA gene.

They are more likely to get cancer in the other breast if they already have cancer in the first.

A woman can develop ovarian cancer at any age if she has a mutation in the BRCA gene.

(Obeagu et al.,2024).

II.2. Hormonal factors

Risk factors for the development of breast cancer have been compiled and integrated into comprehensive incidence models, including age, age at menarche, parity, and age at menopause.

Age or risk factors and age alone have typically been the focus of previous studies on risk factors for estrogen receptor (ER) status in patients with breast cancer. Many of these studies, nevertheless, did not categorize cancer patients according to their progesterone receptor (PR) and ER status. ***(Colditz et al., 2004).***

II.2.1. Estrogen

Both endogenous and exogenous estrogens are associated with an increased risk of breast cancer. The ovary normally produces endogenous estrogen in premenopausal women, and ovarian excision can reduce the risk of breast cancer. The main sources of exogenous estrogen are oral contraceptives and hormone replacement therapy (HRT).

Since oral contraceptives became widely used in the 1960s, their formulations have been improved to reduce side effects. However, the odds ratio is still higher than 1.5 among African, American and Iranian women. Nonetheless, there is no increased risk of breast cancer for women who stop using oral contraceptives for more than ten years.

Hormone replacement therapy (HRT) involves giving exogenous estrogen or other hormones to women who are menopausal or postmenopausal. Numerous studies suggest that using HRT may increase the risk of breast cancer.

The risk of breast cancer does, however, significantly decrease after two years of stopping HRT. The HR for a new breast tumor is 3.6, and survivors of breast cancer who used HRT also experienced a high recurrence rate. ***(Sun et al., 2017).***

II.2.2. Progestrone

A. Endogenous Progesterone Exposure:

There hasn't been much research done on the relationship between circulating progesterone levels and breast cancer risk. In a sample of postmenopausal women, there was no association between the incidence of breast cancer and prediagnostic progesterone levels. However, the investigation was hindered by low levels, large sample sizes, and inadequate sensitivity of the available tests.

Epidemiologic studies have not evaluated the relationship between circulating progesterone metabolites and breast cancer risk in premenopausal or postmenopausal women. ***(Trabert et al., 2020).***

B. Exogenous Progesterone and Progestin Exposure:

The association between the use of progesterone or progestin alone and the risk of breast cancer is not well established. Even though premenopausal women use oral and parenteral progestinonly

formulations for contraception, the reproductive age group of contraceptive users has a low baseline risk of breast cancer, which limits clinical breast cancer data on the progestin-only effect.

Despite their widespread use, the majority of oral contraceptives (also known as combined oral contraceptives, or COCs) combine progestin and estrogen. Additionally, progestin-only tablets (POP) are available. They are primarily used as contraception for women for whom estrogen is contraindicated. COCs prevent ovulation, whereas POPs primarily prevent pregnancy by causing endometrial atrophy and thick, unfriendly cervical mucus.

In order to protect the uterus, postmenopausal women often take progestogens in addition to estrogen. The addition of a progestogen to estrogen in COCs or menopausal hormone therapy creates a complex and confusing situation because there is disagreement regarding the background effect of estrogen as well as the effects of dosage, delivery method, and treatment duration.

Additionally, giving a progestogen to a premenopausal woman may prevent ovulation; therefore, the direct effects of the progestogen on the breast and the indirect effects associated with anovulation are inseparable. ***(Trabert et al., 2020).***

II.3. Enveirmnental factors

II.3.1. Diet

The total amount of food consumed is referred to as a diet. The traditional and cultural decisions a person makes about what meals to eat are known as dietary habits. Among the many risk factors that are known to affect the risk and outcome of breast cancer, diet is regarded as one of the most important and modifiable.

A healthy lifestyle, which includes quitting smoking, exercising, eating a balanced diet, and maintaining a healthy weight, could have prevented 29% of cases of the 13 most common cancers, according to the most recent report from the American Institute for Cancer Research (AICR) and the World Cancer Research Fund International (WCRF).

Foods contain both preventive and potentially dangerous chemicals that can cause cancer. We can consider how certain foods (such as carbohydrates and saturated fat), important dietary markers (such as glycemic index and insulin load), and general dietary patterns (such as highfat versus plant-based diets) influence an individual's risk of breast cancer. ***(Seiler et al., 2018).***

II.3.2. Alcohol

Alcohol consumption is one of the primary risk factors for the global burden of disease and injuries. Alcohol is largely responsible for the burden of non-communicable diseases, including cancer.In 1987, the International Agency for Research on Cancer (IARC) declared alcohol to be carcinogenic, and in 2007, it was recognized that alcohol is a cause of breast cancer

The World Cancer Research Fund's Continuous Update Project also found compelling evidence that alcohol increases the risk of breast cancer.

The relationship between light drinking and breast cancer is still up for debate, despite the fact that the new IARC monograph did not establish a lower threshold for alcohol's influence on cancer. A revised analysis of alcohol and breast cancer is therefore necessary, with a focus on the effects of moderate consumption. ***(Shield et al., 2016).***

II.3.3. Radiation exposure

After discovering sufficient evidence that high levels of ionizing radiation exposure are linked to the development of breast cancer in humans, the IARC designated X- and γ-radiation as carcinogenic agents in 2000.

Studies of the Japanese population exposed to radiation during World War II revealed a statistically significant correlation between breast cancer risk in female survivors and exposure to atomic bombs. The risk was four times higher for women under the age of twenty at the time of the bombing.

Radiation increases the risk of breast cancer by altering normal cellular and intracellular processes and directly damaging DNA. Exposure to ionizing radiation may also contribute to the development of breast cancer by indirectly changing the way hormones or other chemical's function.

Recent genomic evidence suggests that women with specific gene mutations (e.g., ATM, TP53, and BRCA1/2) that may raise their risk of breast cancer may be particularly susceptible to the carcinogenic effects of ionizing radiation exposure. ***(Fenga, 2016).***

II.4. Family and personal history

More than 25% of all cases of breast cancer are related to family history. If a woman's mother or sibling has breast cancer, she is at a higher risk of getting it herself.

A UK cohort study involving more than 113,000 women found that people with one firstdegree cousin who has breast cancer are 1.75 times more likely to get the disease than people without any afflicted relatives.

In addition, women are at a 2.5-fold or greater risk if they have two or more first-degree relatives who have breast cancer.

The hereditary susceptibility to breast cancer is partially caused by mutations in genes associated with breast cancer, such as BRCA1 and BRCA2. ***(Sun et al., 2017).***

Although less than 15% of people with breast cancer have a family member with the disease, women who have close blood relatives with the disease are at a higher risk. For instance, having a mother, sister, or daughter with breast cancer roughly doubles a woman's risk of developing the disease, and having two first-degree relatives with the disease increases her risk by about three times.

Interestingly, women who have a father or brother with breast cancer are at a higher risk of getting the disease themselves. A woman who has cancer in one breast has a higher risk of developing cancer in the other breast or another part of the same breast. ***(Feng et al., 2018).***

Chapter III

III. Pathophysiology

III. 1. Development and progression of breast cancer

III.1.1. Function of Epigenetics and Genes

Our DNA is often the first place where breast cancer begins. Genetic mutations like BRCA1 or BRCA2 can occasionally be inherited, increasing a person's risk of getting cancer. In other instances, such as in the TP53 or PIK3CA genes, mutations are acquired over time. These alterations may result in aberrant behaviour and unchecked growth of breast cells. Normal breast cells gradually become cancerous as a result of the accumulation of these genetic and epigenetic changes.

Breast cells' progesterone receptors aid in growth regulation, but when this equilibrium is thrown off, cancer may result. ***(Fang et al., 2018).,(Xiong et al., 2025)***

III.1.2. Function of Hormones

Oestrogen, a vital hormone for women, regulates more than just reproduction. It also encourages breast cell growth and division. On the other hand, abnormalities in its internal signalling or high levels of oestrogen can be very detrimental. It has the potential to directly affect DNA, result in harmful changes, and open the door for cancer. Oestrogen and progesterone receptors in breast cells help regulate growth, but when this balance is upset, cancer may ensue. ***(Fang et al., 2018).,(Pesheva, 2023)***

III.1.3. Taking Over Typical Signals

Because they are cunning, cancer cells hijack regular cell communication networks. This frequently involves taking over the Wnt pathway, which is crucial for development, HER2 (a growth-promoting protein), and oestrogen receptor signalling in breast cancer. The HER2 gene is overactive in about 25% of breast cancers, which causes unchecked cell division and rapid tumour growth. ***(Fang et al., 2018).,(NBCF, 2025)***

III.1.4. Neighbourhood of the Tumour

Tumours don't grow by themselves. It interacts with blood vessels, immune cells, other cells, and even the metabolism of the body. The tumour microenvironment, which surrounds the cancer, is crucial to its growth, immune system evasion, and metastasis. ***(Xiong et al., 2025)***

III.1.5. Path of Breast Cancer

It takes time for breast cancer to appear. It usually starts with hyperplasia, which is just an increase in the number of normal cells. Some of those cells may then develop abnormal traits and become premalignant. Over time, these changes may lead to carcinoma in situ, a condition where cancer cells are present but stay inside the ducts or lobules of the breast.

Eventually, the cancer might become invasive, rupturing the boundaries of healthy tissue and spreading to nearby areas. Growth factors like HER2 and hormones like oestrogen and progesterone can promote the growth of the tumour**.** ***(Xiong, 2025)***

III. 2.Types of breast cancer

III.2.1. Ductal carcinoma in situ (DCIS)

The histologic progression of ductal carcinoma in situ, a group of preinvasive lesions that begin inside normal breast tissue, is atypical hyperplasia to invasive breast cancer. Even though the precise processes and early phases of breast carcinogenesis are still unknown, it appears that nearly all invasive breast cancers start as in situ carcinomas. The presence of similar chromosomal changes in ductal carcinoma in situ and synchronous, adjacent invasive tumours demonstrates their clonal, evolutionary connection.

Several clinicopathological and biologic features set ductal carcinoma in situ apart from other benign proliferative breast lesions as well as normal breast tissue. Chromosome abnormalities, with gain or loss at numerous loci, are caused by the progression of hyperplastic lesions from ductal carcinoma in situ to invasive breast cancer. For instance, loss of heterozygosity is seen in 35–40% of cases of atypical hyperplasia and more than 70% of high-grade ductal carcinomas in situ, whereas it is 0% in samples of normal breast tissue. Breast carcinogenesis is known to be associated with certain molecular markers. The oestrogen receptor, which is normally expressed by luminal breast epithelial cells, is present in over 70% of ductal carcinoma in situ lesions.

Atypical hyperplasia does not overexpress the HER2/neu proto-oncogene, but about half of all ductal carcinoma in situ lesions do.While normal or benign proliferative breast tissue almost never has a p53 tumor-suppressor gene mutation, about 25% of all ductal carcinoma in situ lesions do. In ductal carcinoma in situ, these molecular markers are usually expressed at a frequency comparable to that of invasive breast tumours. ***(Burstein, 2004)***

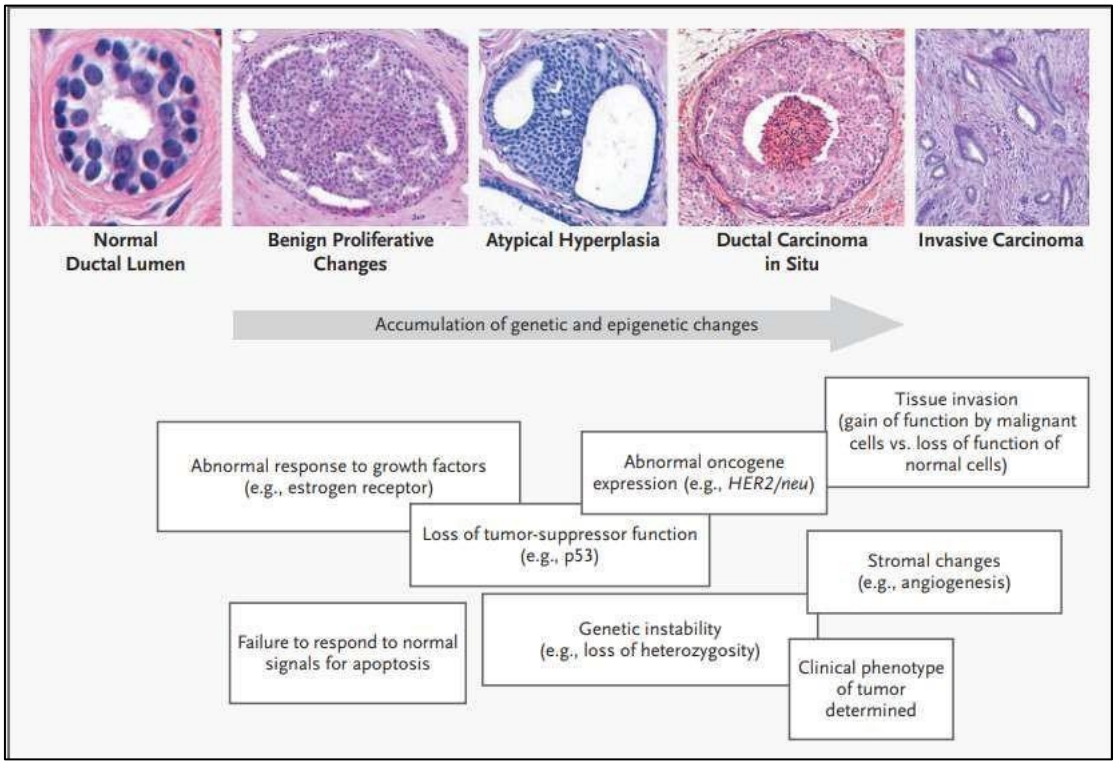


Figure02: Pathobiologic Events Associated with Ductal Carcinoma in Situ. ***(Burstein, 2004).***

III.2.2. Invasive ductal carcinoma (IDC)

Invasive ductal carcinoma (IDC), sometimes referred to as infiltrating ductal carcinoma, is the most common type of breast cancer. IDC is thought to be responsible for around 80% of all breast cancers, according to the American Cancer Society.

An invasive cancer has spread to the surrounding breast tissues. The tubes that carry milk from the lobules to the nipple are called milk ducts, and if a cancer is ductal, it started there. A carcinoma is any type of cancer that begins in the skin or other tissues that cover the lining of internal organs, such as breast tissue. ***(BC.org, 2025).***

- **Subtypes of invasive ductal carcinoma**

  - **Tubular carcinomas of the breast:** Tubular carcinomas make up less than 2% of all breast cancers. Under a microscope, the cells of a tubular carcinoma look like tubes. These tumours are typically low-grade. The majority of tubular carcinomas are hormone receptor-positive and HER2-negative.

  - **Medullary carcinomas of the breast:** Less than 5% of all breast cancers are medullary carcinomas. Because the tumour is a soft, fleshy mass that resembles the medulla, a region of the

brain, it is known as "medullary" carcinoma. Triple-negative (progesterone receptor-negative, oestrogen receptor-negative, and HER2-negative) medullary carcinomas are frequently found. However, medullary carcinoma does not grow rapidly and typically does not migrate to the lymph nodes beyond the breast, in contrast to the majority of triple-negative breast tumours, which are more aggressive.

- **Mucinous carcinomas of the breast:** Mucinous carcinomas, sometimes referred to as colloid carcinomas, account for less than 2% of all breast tumours. The cancer is referred to as "mucinous" carcinoma because it produces mucin, a substance that occurs naturally and is necessary for the formation of mucus. Mucinous carcinomas are usually low-grade and do not spread to other lymph nodes. Most mucinous carcinomas are hormone receptor-positive and HER2-negative.

- **Papillary carcinomas of the breast:** Papillary carcinomas make up less than 1% of all breast cancers. Under a microscope, the cells have projections known as "papules" that resemble fingers. Most papillary carcinomas are small, hormone receptor-positive, and HER2-negative.

- **Cribriform carcinomas of the breast:** Cribriform carcinomas make up less than 1% of all breast cancer cases. In invasive cribriform carcinoma, the cancer cells invade the stroma, the connective tissues of the breast, and create nest-like structures between the ducts and lobules. The distinctive holes between the cancer cells give the tumour a Swiss cheese-like appearance. Most invasive cribriform carcinomas are low grade. ***(BC.org, 2025)***

III.2.3. Invasive lobular carcinoma (ILC)

Invasive lobular carcinomas (ILCs) account for 8–14% of all breast tumours. For unknown reasons, the incidence of this type of breast cancer is increasing, especially in postmenopausal women, according to data from a recent epidemiologic study. The morphologic features of ductal carcinoma and lobular carcinoma differ. After infiltrating the stroma in single file, ILC is characterised by small, spherical cells with a bland appearance and little cytoplasm that surround benign breast tissues in a particular manner.

Infiltration typically doesn't destroy anatomical structures or result in a significant connective tissue reaction. Lobular carcinomas often do not develop into distinct masses that are easily recognised by mammography or palpation due to their distinct development pattern and biology. This could make early detection and breast conservation methods more difficult. Lobular carcinomas may be substantially more likely to exhibit bilaterality as well as multifocal and multicentric distribution. Unusual patterns of involvement in metastatic dissemination have been reported. ***(Arpino et al., 2004).***

III. 3. Tumor biology

III.3.1. HR status

In both observational studies and randomised trials, it has been demonstrated that women with breast cancer who have tumours that test positive for the oestrogen receptor (ER) and/or progesterone receptor (PR) live longer than those whose tumours test negative for both hormone receptors.

In large studies with more than a decade of follow-up, like the National Surgical Adjuvant Breast and Bowel Project and the San Antonio trial, hormone receptors have been associated with a 10% survival advantage.

The survival curves of patients with ER-positive (ER+)/PR+ tumours converge because of late recurrences, while patients with ER+ tumours lose their early survival advantage over time, according to some researchers. In patients with breast cancer, hormone receptor status is associated with age, race, socioeconomic status, and stage of the disease. Therefore, even though hormone receptor status is taken into account when choosing a course of treatment, the benefits of having a tumour that is hormone receptor-positive may not be entirely attributable to treatment**. *(Grann et al., 2005).***

III.3.2. HER2 status

Human epidermal growth factor receptor 2 (HER2) is overexpressed in 15–20% of cases of breast cancer, making it a significant predictor and prognostic factor. One of the most important clinical decision-making steps for prognostication and treatment regimen selection is determining its state. To determine HER2 status, transcriptomics or immunohistochemistry (IHC) by in-situ hybridization (ISH) are employed; however, these techniques have additional costs and tissue burden, and they are prone to analytical variability in terms of scoring biases resulting from manual observation**. *(Lu et al., 2022)***

Located on chromosome 17q, the human epidermal growth factor receptor 2 (HER-2, HER-2/neu, c-erbB-2) gene was first discovered by Weinberg and associates in 1984. It codes for a transmembrane tyrosine kinase receptor protein that is a member of the HER family and is also referred to as the epidermal growth factor receptor (EGFR). Signal transduction is the main way that this receptor family aids in communication between cells and between cells and the stroma. It involves ligands or external growth factors influencing the transcription of various genes by phosphorylating or dephosphorylating a variety of transmembrane proteins and intracellular signalling intermediates, many of which have enzymatic activity. Signal propagation occurs when the enzymatic activity of one protein triggers the enzymatic activity of the protein that follows in the pathway.

Both morphology-based and molecular-based methods have been used to evaluate the HER2/neu status in clinical samples of breast cancer. Changes in HER-2 expression at the gene, message, or protein level have been associated with a worse prognosis in the vast majority of cases of breast cancer, whether they are lymph node-positive or lymph node-negative**. *(Ross et al., 2009).***

III.3.3. Triple negative status

Triple-negative breast cancer (TNBC) has a higher risk of distant recurrence and mortality than other BC subtypes. Treatment options are limited because TNBCs lack human epidermal growth factor 2 (HER2) and the hormone receptor (HR). Due to the absence or low expression of HR and HER2, TNBC is not responsive to endocrine therapy or targeted anti-HER2 medication therapy. TNBC is now the most frequently diagnosed cancer type globally, with 2.26 million new cases reported in 2020.

Unifocal, invasive ductal carcinomas account for about 90% of TNBC tumours; the remaining 50% are medullary, secretory, apocrine/histiocytoid, adenoid cystic, metaplastic, invasive lobular, and carcinomas arising in microglandular adenosis. ***(Kumar et al.,2016).***

III. 4. Tumor staging and grading

In 1959, the tumour, node, and metastasis (TNM) cancer staging system was standardised by the American Joint Committee for Cancer Staging and End-Results Reporting, which is currently the American Joint Committee on Cancer (AJCC). Clinical practitioners can now standardise treatment and assess treatment results across many institutions thanks to the 1977 publication of the first edition of the AJCC Staging Manual. Since then, the handbook has been updated periodically to take into account developments in clinical practices and industry technology.

Before the AJCC Staging Manual's eighth edition was adopted in 2018, a strictly anatomic staging approach was employed. The original tumour (T) size, nodal (N) involvement, and metastasis (M) are all determined using clinical and pathological examinations. Advances in tumour biology and prognostic biological markers, including HER2/neu, Ki-67, the oestrogen receptor (ER), and the progesterone receptor (PR), have helped clinicians understand why patients with identical stages had significantly different outcomes. The most recent version of the staging system combines anatomic staging with prognostic staging, which uses factors like hormone receptors, oncogene expression, tumour grade, and multigene testing. ***(Zhu et al., 2021).***

III.4.1 Clinical anatomic staging

A. Primary Tumor (pT):

pTX: Primary tumor cannot be assessed.
pT0: No evidence of primary tumor.
pTis: Carcinoma in situ (non-invasive cancer).
pT1: Tumor ≤2 cm in greatest dimension.
pT1mi: Tumor ≤1 mm.

pT1a: Tumor >1 mm but ≤5 mm.
pT1b: Tumor >5 mm but ≤10 mm.
pT1c: Tumor >10 mm but ≤20 mm.
pT2: Tumor >2 cm but ≤5 cm.
pT3: Tumor >5 cm.
pT4:Tumor of any size with direct extension to chest wall or skin

B. Regional Lymph Nodes (pN):

pNX: Regional lymph nodes cannot be assessed.
pN0: No regional lymph node metastasis.
pN0(i-): No isolated tumor cells.

pN0(i+): Isolated tumor cells ≤0.2 mm.
pN1: Metastases to 1–3 axillary lymph nodes.
pN2: Metastases to 4–9 axillary lymph nodes or clinically apparent internal mammary nodes. pN3: Metastases to ≥10 axillary nodes, infraclavicular nodes, or clinically apparent internal mammary nodes.

C. Distant Metastasis (pM):

pMX: Distant metastasis cannot be assessed.
pM0: No distant metastasis.
pM1: Distant metastasis present. ***(Zhu et al., 2021).***

III.4.2 Tumor grade

In addition to other variables like proliferative index, hormone receptor expression, and gene expression profiles, the AJCC 8th edition manual emphasises that grade is a crucial evaluation of tumour differentiation, which is a crucial prognostic tool. Scarff, Bloom, and Richardson's histologic grading

approach and the Nottingham group's standardisation determine the tumour grade used in the staging manual. The prognosis for high-grade or poorly differentiated tumours is worse than that of low-grade or well-differentiated tumours, regardless of hormone therapy or chemotherapy. Moreover, histologic grade is a useful predictive indicator that is independent of tumour size and the number of positive lymph nodes, according to the National Cancer Institute's Survey, Epidemiology, and End Results Programme. ***(Zhu et al., 2021).***

III. 4.3. Stages of breast cancer

A. Stage 0: Also known as ductal carcinoma in situ (DCIS), this stage is characterised by cells that are restricted to a duct and have not spread to nearby tissues.

B. Stage 1: The tumour is up to 2 cm wide and has not yet spread to any lymph nodes.

C. Stage 2: The tumour has started to spread to nearby nodes and has a diameter of 2 cm.

D. Stage 3: The tumour may have spread to specific lymph nodes and may have a diameter of up to 5 cm.

E. Stage 4: the cancer has spread to distant organs such as the liver, lungs, brain, or bones. ***(Effiong et al., 2022)***

Chapter IV

IV. CLINICAL PRESENTATION

IV.1. Signs and symptoms

A. Lumps: The most common indication of breast cancer is a lump in the breast or underarm. A monthly breast self-examination (BSE) is a great way to learn about the size, texture, cyclical changes, and skin condition of the breasts. Breast swelling or lumps (mass) and swelling in the armpit (lymph nodes) are common warning signs of breast cancer. ***(Sharma et al., 2010).***

B. Nipple discharge: Breast discharge is the first symptom experienced by 3 to 9 percent of patients who visit a breast cancer clinic. Most patients are referred under the cancer criteria because breast discharge has historically been considered an indication of breast cancer. Even though nipple discharge may be the first symptom, a breast tumour or abnormal mammography may also be present in many cases. The breast discharge was deemed abnormal if it was bloodstained, serosanguinous, serous, or clear. It was believed that green or white discharge was physiological and harmless. Each patient with nipple discharge underwent a triple evaluation consisting of a clinical examination of the breast, cytology, and mammography or ultrasound imaging.

C. Changes in breast shape or size: Breast cancer can change the shape, feel, or appearance of your breasts. Breast cancer can change the shape, feel, or appearance of your breasts. ***(Richards et al., 2007).***

IV. 2. Diagnostic methods

a. Mammography: Mammography (MG) is a common method for diagnosing and detecting breast cancer (BC), and early detection can reduce death rates by 30% to 40%. However, only 4–10% of BC patients are given a positive diagnosis. Current techniques like digital breast tomosynthesis (DBT) and contrast-enhanced mammography (CEM) have higher diagnostic specificity and accuracy than fullfield digital mammography (FFDM). MG and its derivatives are now essential for BC screening and diagnosis due to the increased instrument sensitivity brought about by computer-aided detection (CAD). However, MG may not be suitable for everyone because it involves risky contrast agents and X-rays and is only recommended for those under 40. Advances in AI and sensor technology could automate the detection and analysis of BC.

b. Ultrasound: Ultrasound (US) is a safe and efficient diagnostic method for analysing tumour morphology and tissue variations. Three-dimensional imaging, such as colour Doppler US, which provides helpful clinical information for distinguishing between benign and malignant tumours, replaced early grayscale imaging. In 1998, Krouskop founded Elastic US, which has improved the accuracy of breast cancer diagnosis. Tissue homogeneity, high contrast

resolution, and reduced speckle are the results of a new US image-processing technique called MicroPure. Despite its advantages, such as low contrast agents and suitability for all ages, the US has disadvantages, such as requiring professional operation and having a lower resolution than CT. Intelligent US detection will reduce errors caused by amateur judgements, leading to more accurate diagnostic results in the future.

c. **MRI:** Magnetic resonance imaging (MRI) is a useful tool for early detection of familial breast cancer (BC), regardless of age, density, or risk status. A technique known as MRDW helps distinguish between benign and malignant tumours by showing water movement. In terms of resolution and specificity, dynamic contrast-enhanced MRI (DCE-MRI) performs better than MRI alone, with a 98% positive predictive value. MRI can also improve diagnostic rates by determining BC risk and guiding treatment. Magnetic resonance spectroscopy (MRS) is one non-invasive method for assessing BC risk. ***(He et al., 2020).***

d. **Biopsy:** A noninvasive technique for extracting tumor-derived materials from bodily fluids such as blood, urine, saliva, stools, or cerebrospinal fluid is liquid biopsy. It provides longitudinal monitoring, overcomes tumour heterogeneity, and may be used for prognosis, treatment response prediction, and early cancer detection. Liquid biopsy is now a feasible substitute for traditional tumour biopsies due to recent developments in sensitive assays. ***(Tay et al., 2021).***

IV.3. Screening programs and early detection

The majority of studies on breast cancer diagnosis have focused on mammography, ultrasound, and magnetic resonance imaging (MRI). These techniques are known to be the most successful. However, their shortcomings—like the difficulty in diagnosing cancer in remote and rural areas—have led to the development of alternative technologies, such as electronic palpation, thermal imaging (thermography), and electrical impedance scanning (EIS). ***(Mashekova et al., 2021).***

Chapter V

V. Treatment options

1. Surgery

Surgery is the recommended treatment for most cases of early-stage breast cancer. It is used as a curative treatment option when appropriate, in combination with radiation, chemotherapy, or hormone therapies. The National Surgical Adjuvant Breast and Bowel Project (NSABP) was one of the first studies to examine surgical options for treating breast cancer. ***(Admoun et al., 2021).***

a. **Lumpectomy:** This approach to breast-conserving surgery has two major issues. First, removed lumpectomy specimens quickly deform and lose their surface orientation with respect to the lumpectomy cavity, where the tumour may still be. When specimens are handled and sectioned, they may reveal tumours that are not at the margin but are mistakenly attributed to it, leading to falsely positive results. Second, a large tumour in the breast could still be present even if the margins on the lumpectomy specimen are deemed "negative," which could result in false-negative margin values. Rates of local recurrence after lumpectomy without radiotherapy highlight the proportion of breasts with clinically significant remaining tumour after routine lumpectomy surgery.

The local recurrence rate at 20 years was 39.2% without radiation and 14.3% with radiation in the National Surgical Adjuvant Breast and Bowel Project (NSABP) B06 study. One At 15 years, the local recurrence rates for DCIS ranged from 15.1 to 35.1% without radiation and from 7.1 to 17.5% with radiation. ***(Smith et al., 2023).***

b. **Mastectomy:** The National Cancer Institute recognises four main types of breast removal surgery as therapeutic and preventative measures. These include total (or simple) mastectomy, partial mastectomy, radical mastectomy, and modified radical mastectomy. Two variants of these procedures that are used to achieve better results for subsequent breast reconstruction are subcutaneous mastectomy and total skinsparing mastectomy. Each affected individual has a unique surgical procedure, often chosen based on the stage of the cancer and/or the desired cosmetic result.

During a mastectomy, the tumour, surrounding breast tissue, and the lining over the chest muscles behind the tumour are all removed. A complete mastectomy involves the removal of all breast tissue except the pectoralis muscle. There are three types of mastectomy: nipple-sparing, skin-sparing, and traditional. The type of operation depends on the tumor's size and location. With a modified radical mastectomy and lymph node dissection, breast reconstruction can be performed right away or later. Examples of cosmetic procedures that remove as much breast

tissue as possible without removing the nipple/areola complex and the skin covering it are subcutaneous and total skin-sparing mastectomies. ***(Loukas et al., 2011).***

2. **Radiation therapy:** Because of the different sizes and shapes of the breast and chest wall, as well as setup repeatability and respiratory motion, planning radiotherapy for patients with breast cancer can be technically difficult. The heart, lungs, and contralateral breast (CB) are examples of spare organs at risk (OARs) that must be prioritised in order to prevent long-term problems and attain desired cosmetic results. Radiation therapy techniques that have been proposed for patients with breast cancer include helical tomotherapy (HT), intensity modulated radiation therapy (IMRT), volumetric modulated arc therapy (VMAT), hybrid technique, 3-dimensional conformal radiation therapy (3DCRT) with or without wedges or field-in-field (FIF) method, and Tomo direct. ***(Balaji et al., 2016).***

3. **Chemotherapy:** Because of the different sizes and shapes of the breast and chest wall, as well as setup repeatability and respiratory motion, planning radiotherapy for patients with breast cancer can be technically difficult. The heart, lungs, and contralateral breast (CB) are examples of spare organs at risk (OARs) that must be prioritised in order to prevent long-term problems and attain desired cosmetic results. Radiation therapy techniques that have been proposed for patients with breast cancer include helical tomotherapy (HT), intensity modulated radiation therapy (IMRT), volumetric modulated arc therapy (VMAT), hybrid technique, 3-dimensional conformal radiation therapy (3DCRT) with or without wedges or field-in-field (FIF) method, and Tomo direct***.(Hassan et al., 2010).***

4. Endocrine therapy

a. **Tamoxifen:** Tamoxifen is an antagonist of ERs in the brain and breast tissues and an oestrogen agonist on the liver, uterus, and bone. Several BC chemoprevention trials have been reported. ***(Lumachi et al., 2011).***

The introduction of the anti-oestrogen tamoxifen in the early 1970s marked a major breakthrough in the treatment of breast cancer. More than 30 years later, tamoxifen has shown promise in the treatment of ductal carcinoma in situ (DCIS), early and advanced breast cancer, and the chemoprevention of breast cancer in high-risk premenopausal and postmenopausal women. Actually, tamoxifen is the benchmark used to assess more recent endocrine therapies. ***(Clemons et al., 2002).***

b. **Aromatase inhibitors:** More than a century has passed since oophorectomy was first shown to cause advanced breast cancer to regress, and oestrogen deprivation remains a vital therapeutic approach. The main hormone implicated in the development and spread of breast tumours is

oestrogen. Tamoxifen inhibits the development of breast tumours by competitively opposing oestrogen at its receptor site. Its actions are complex, though, and it also has partial estrogenagonist effects. These partial agonist effects can be beneficial since they may help postmenopausal women prevent bone demineralisation, even though they are associated with an increased risk of thromboembolism and uterine cancer. They may also play a role in the development of tamoxifen resistance. ***(Smith et al., 2003).***

5. Target therapy

a. **HER2 inhibitors:** Single-epitope monoclonal antibodies, such as pertuzumab, margetuximab, and trastuzumab, bind to HER2 at a single extracellular domain. These medications can cause antibody-dependent cellular cytotoxicity, block downstream signalling pathways, or, in the case of pertuzumab, prevent receptor dimerization in order to combat tumours. Two antibody–drug conjugates that target HER2, trastuzumab emtansine and trastuzumab deruxtecan, may also have antitumor effects via these pathways. However, by releasing a highly cytotoxic chemical close to HER2-positive cancer cells, these medications also demonstrate targeted cytotoxicity. Conversely, small-molecule inhibitors such as neratinib, afatinib, and lapatinib are designed to bind to the intracellular tyrosine-kinase domain of HER2 and prevent the activation of the PI3K pathway. A fourth class of drugs, known as bispecific antibodies, like ZW25, target multiple HER2 extracellular regions. These medications may theoretically provide a greater degree of HER2 inactivation than that attained with single agents, despite the fact that there are currently only early phase trials available for clinical data. The acronym for antibody-dependent cytotoxicity of cells is ADCC. ***(Oh et al., 2020).***

b. **PARP inhibitors:** Deficits in DNA repair and damage are two of the primary features of cancer pathophysiology. The five main DDR pathways are used by healthy cells to defend against DNA damage and maintain genomic integrity. Base excision repair corrects single-strand breaks, nucleotide excision repair corrects damage that distorts helices, and mismatch repair corrects replication errors. The sister chromatid can be used as a template, or the more error-prone homologous recombination repair (HRR) route can be used to repair double-strand breaks. prone, template-independent non-homologous end-joining process. At least 450 proteins are thought to be involved in DDR pathways, including PARP1 and PARP2. PARP enzymes are essential to the base excision repair mechanism. After PARP1 attaches itself to the damaged DNA strand, nicotinamide adenine dinucleotide (NAD+) can attach to its active site. The process of PARylation, which entails the transfer of ADP-ribose moieties from NAD+ to target proteins, recruits effectors for single-strand DNA repair. When PARP1 autoPARylates, it is

liberated from DNA and transforms back into a catalytically inactive form. ***(Cortesi et al., 2021).***

6. Immunotherapy

The advancement of immune therapy to a more central and relevant position in breast cancer remains a top goal, given the potential for high response persistence that can be attained—sometimes uniquely so—with immune therapy of advanced cancer. Immunotherapy for breast cancer will be most successful if it is developed in collaboration with scientists studying other significant facets of the illness. A significant obstacle to the development of immunotherapy for patients with metastatic breast cancer is moving past PD-1/PD-L1 blockage alone and the empirical combination of other medications with PD-1/PD-L1. A deeper understanding of the immunobiology of breast cancer is believed to be necessary for the ultimate clinical success of these treatments. ***(Vonderheide et al., 2017).***

Practical Part

V. Introduction

Breast cancer constitutes a major global health issue, comprising 23% of all malignancies in females. In 2012, approximately 1.7 million new cases were detected, and their occurrence continues to escalate alarmingly. In Algeria, breast cancer is the most common malignancy among women, with more than 14,000 new cases documented each year.

This underscores the pressing want for thorough disease characterization to enhance treatment options and elevate patient outcomes. Breast cancer is a multifaceted and heterogeneous illness marked by the accumulation of several molecular changes.

We conducted a cross-sectional, descriptive, analytical, retrospective study on 155 patients with immunohistochemical features of breast cancer , diagnosed in the pathology laboratory of EPH Bouguerra Boularas in Bekkaria (Tebessa) over a period of 60 months, from January 2018 to December 2024, Because of the laboratory's shutdown owing to the COVID epidemic, we account for the absence of data for 2020 and 2021. Clinical pathology and patient demographics were analyzed. It was determined which molecular subgroups existed and examined how they related to clinicopathological traits.

This work seeks to fill this vacuum by offering a comprehensive review of the immunohistochemistry profile of breast tumors in Tebessa, Algeria also to facilitate the formulation of efficient screening programs and cancer management strategies.

W.Materials

Our study focused on 155 patients:

To carry out this work, we used a data collection sheet to gather the following information:

record number, patient gender, and age at diagnosis. Clinical characteristics encompass tumor dimensions, Scarff-Bloom Richardson (SBR) classification, lymph node involvement, metastatic status, and immunohistochemical (IHC) profile. The IHC profile involved evaluating estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2) status.

Our study material consists of: 155 surgical specimens (mastectomy).

These samples were mainly sent to us by the department of pathological anatomy and cytology. Based on this series, we conducted a retrospective study spanning from January 2018 to December 2024.

X. Methods

1. Data entry, analysis, and judgment criteria:

A descriptive analysis of the characteristics of the disease focused on the following variables:

Patient gender, and age at diagnosis. Clinical characteristics encompass tumor dimensions, Scarff-Bloom Richardson (SBR) classification, lymph node involvement, metastatic status, and immunohistochemical (IHC) profile.

These data were collected, coded, entered into Microsoft Office Excel 2013, and then analyzed using IBM SPSS 20 software for Windows 2010.

This statistical analysis only considered the available data, so the missing data were excluded from our analysis.

This study allowed us to specify the most affected age groups, assess the predominant histological types, the grade, the macroscopic appearance, and the IHC profile.

Generally speaking, the anatomo-pathological analysis is divided into three main stages:

- The macroscopic study.
- The microscopic study.
- The immunohistochemical study.

✓ **The macroscopic study:**

The macroscopic examination is essential to determine the choice of the sample to be examined.

The macroscopic handling of mastectomy specimens aims to obtain information regarding the morphological, topographical, and prognostic aspects useful for diagnosis and treatment.



Figure03: macroscopic appearance of a right mastectomy

- ✓ **The microscopic study:**

The observation of the colored slides was carried out using an optical microscope.

Stages of technique:

- Fixation: The purpose of fixation is to prevent the premature dehydration of cells and especially the putrefaction of tissues. In the lab, we use a 10% diluted formalin solution because it allows for good immunohistochemical and molecular biology studies.

- Dehydration: The tissue sample is fixed, then progressively dehydrated through successive passages in increasingly concentrated alcoholic solutions until all the water (from the tissues and the fixation medium) has been removed and the sample is fully impregnated with absolute alcohol. The alcohol is then replaced by an organic solvent in which both alcohol and paraffin can dissolve (paraffin is not soluble in alcohol).

- Inclusion in heated paraffin: The sample is then immersed in paraffin heated to a temperature just above its melting point, as it is solid at room temperature.

- Cooling: Once the sample is well impregnated, it is left to cool in a mold filled with paraffin that solidifies.

- Making cuts: As it cools, the fragment, soaked in paraffin, becomes embedded in a solid block from which 5-micron thick sections are obtained using a microtome equipped with a razor.

- The staining of sections with Hematoxylin-Eosin (HE): Stain with hematoxylin for 5 to 7 minutes (staining the nuclei blue or black). Rinse with running water and then with distilled water. Stain in a 1% eosin solution for 2 minutes (staining the cytoplasm pink). Quickly rinse with running water and dehydrate in 100° alcohol. Quickly pass through the alcohols (Methanol – Ethanol) for clarification.

- Assembly of the blades: The mounting of the blades involves permanently protecting them with a glass lamella glued using a transparent synthetic product that polymerizes in the air, called EUKIT.

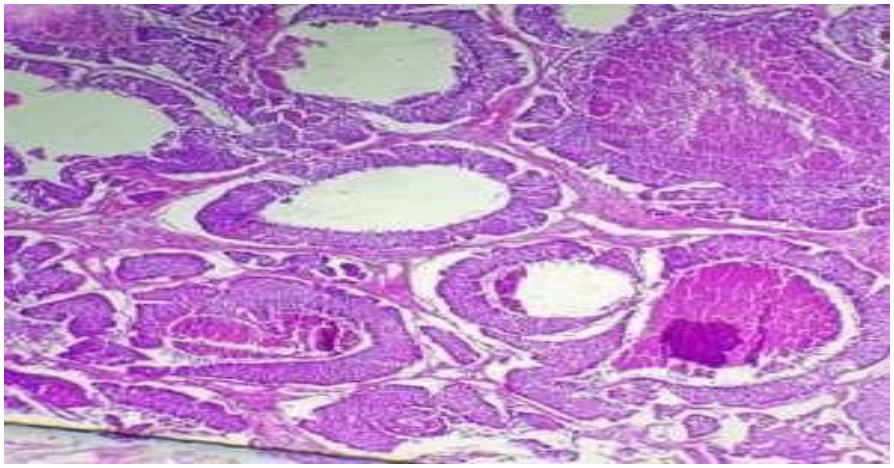


Figure04: the slide under the optical microscope

✓ **The immunohistochemical study:**

The most useful markers in breast pathology are Ki67, HER2, and hormone receptors (ER, PR).

Stages of technique:

- Fixation - Paraffin Embedding: The type of fixator, time, and duration of fixation are crucial for immunohistochemistry studies. The fixation should be done in a sufficient volume, with the fixator being as close to the operating room as possible. The ideal fixation time is 24 hours. Longer fixation prolongs protéolysis, causing loss of immunohistochemical signal, while shorter fixation improves reproducibility.
- Adherence of the cuts: The sections must be spread on slides coated with a high-performance adhesive (silanized slides, pre-treated glass slides) and dried for at least one hour at 56-58°C and/or overnight at 37°C. The fineness of the cuts (2-3 microns) promotes better adhesion.

- Deparaffinization and rehydration: Deparaffinization involves incubating the slides in an oven at 37°C for 24 hours. Then their passage through a series of baths containing xylene, alcohol at decreasing concentrations decreasing and distilled water to eliminate the remaining paraffin, rehydrate, and thoroughly clean the tissues.

- Antigen unmasking (Antigen restoration by heat): Antigen retrieval is performed by heating the slides in a retrieval solution (boiling citrate buffer at pH=6) in a pressure cooker, microwave oven, autoclave, incubator, water bath, or steam cooking device; for 30 to 40 minutes at 95-99°C. The purpose of this step is to break the molecular bonds created by the fixative and thus restore the antigenic determinants that were masked by formalin fixation. Each laboratory must calibrate its antigen retrieval time.
- Blocking of endogenous peroxidases: The slides are placed at room temperature in a humid chamber. They are then covered for 5 minutes with peroxidase blocking reagents (solution containing hydrogen peroxide H2O2) to block the activity of endogenous peroxidases present in the cells and thus reduce background noise. The slides are then rinsed with distilled water, and placed in a bath containing washing buffer; PBS for 5 minutes to eliminate H2O2. We delineate the areas where we will apply the primary antibody with a DAKO pen that prevents the diffusion of the antibodies.
- Primary antibody (Negative control reagent): We apply enough primary antibody solution to cover the sample and we incubate for 30 minutes in a humid chamber to prevent tissue dehydration. We drain the slides and place them in a basket. We pass them through 2 PBS wash baths for 5 minutes each.
- Secondary antibody (Visualization reagent): We apply the secondary antibody (biotinylated antibody) and let it incubate for 30 minutes at room temperature. We cover the slides with a tray so they don't dry out. We drain the slides and place them in a basket to rinse them in 2 baths of PBS.
- Revealing systems (DAB chromogenic substrate solution): Revealing systems (mainly avidin-biotin or streptavidin-biotin systems), enzymatic markers (horseradish peroxidase and, less commonly, alkaline phosphatase), and chromogens (for peroxidase, diaminobenzidine or amino-ethyl-carbazole) that are commonly used yield good results.
- The advantage of diaminobenzidine is that it produces markings that deteriorate little during storage. We apply a solution of the DAB (3,3'-diaminobenzidine tetrahydrochloride) chromogenic substrate for peroxidase of 3,3-diaminobenzidine, Dako) for 10 minutes. DAB is the chromogenic substrate for peroxidase, which marks the antigenantibody interaction site in brown. We rinse with distilled water and drain the slides.

- Counter-coloration: The counterstaining should be minimal, sufficient to visualize all the nuclei and not too strong to prevent the appreciation of weak markings. It is performed with Mayer's hematoxylin for 1 to 5 minutes, which intensely colors the nuclei
a bluish-violet but also the cytoplasms and supporting tissues to a lesser extent. The slides are rinsed with distilled water and then passed through an alcohol bath followed by xylene to decolorize the cytoplasms and connective tissues.
- Blade assembly: The slide-lamella assembly is performed in the same way as previously described in the histological study.

Y. Results

A retrospective analysis was performed on female breast cancer cases recorded at the PHE from January 2018 to December 2024. Initially, 220 cases were recognized. To concentrate on invasive illness, eight cases of in situ breast cancer (3.63% of the total) were omitted. Additionally, 47 cases were omitted due to the absence of immunohistochemistry (IHC) data, culminating in a final research group of 155 patients with invasive breast cancer. Data on age at diagnosis was accessible for 155 patients, with ages spanning from 29 to 81 years, yielding a mean age of 51.54 years (± 12.90) and a median age of 51 years.

Histological examination identified ductal carcinoma (DC) as the predominant subtype, comprising 82.2% of the research cohort. Invasive lobular carcinoma (LC) ranked as the second most prevalent kind, accounting for 9.6% of cases. Infrequent subtypes comprised medullary (1.9%) and papillary (0.6%) carcinomas. A fraction of 4.5% was identified as different histological categories. In 69% of instances, tumor size surpassed 2 cm. The predominant classification of tumors was grade II (49.0%) as per the SBR grading system, followed by grade I (28.0%) and grade III (21.7%). Lymph node involvement was noted in 64.5% of patients with established nodal status, whereas 2.6% of patients with confirmed metastatic status exhibited distant metastases.

Immunohistochemical analysis indicated that 32.9% of tumors were hormone receptor-positive (HR+, ER+, and/or PR+), 26.5% were hormone receptor-negative (HR-, ER+, and/or PR+), 19.4% were triple-negative (ER-, PR-, HER2-), 16.8% were HER2-enriched (ER-, PR-, HER2+), and 4.5% were unclassifiable.

Breast cancer cases were classified into four distinct molecular subtypes—Luminal A, Luminal B, Triple Negative breast cancer (TNBC), and HER2-enriched—using immunohistochemical markers (ER, PR, and HER2). Table 2 presents the distribution of these subtypes. Luminal B was the most common subtype, comprising 32.9%, followed by Luminal A at 26.5%, TNBC at 19.4%, HER2-enriched at 16.8%,

and unclassifiable at 4.5%. Statistical analysis indicated that no significant association was found between molecular subtypes and sex (p=0.726) or age range (p=0.124). A statistically significant relationship exists between molecular subtypes and histological type (p = 0.002) . The Luminal A subtype exhibited the highest prevalence of ductal carcinoma at 25.8%, compared to Luminal B at 23.9%, Triple Negative at 16.8%, and HER2 at 12.9%. The Luminal A and Luminal B subtypes demonstrated the highest rates of invasive lobular carcinoma relative to other subtypes.

No significant difference in mean tumor size was observed across molecular subtypes (p=0.329). Molecular subtypes exhibited significant differences in histological grade (p=0.000), with Luminal A and Luminal B subtypes showing the highest proportion of advanced histological grade (grade II) relative to the other subtypes .All molecular subtypes exhibited a moderate occurrence of vascular emboli . No significant differences were noted among subtypes concerning vascular emboli status (p = 0.786) . However, Luminal A and Luminal B subtypes exhibited a greater prevalence of vascular emboli than the other subtypes. No significant differences in lymph node involvement at diagnosis for carcinoma in situ were observed among molecular subtypes (p = 0.634; p = 0.731) . The Luminal A and Luminal B subtypes exhibited the highest proportion of positive lymph nodes . Significant differences in metastasis status were observed among molecular subtypes (p = 0.000) . Nonetheless, Luminal A cases demonstrated the highest percentage of metastases at 32.9%, in comparison to other subtypes . The pathological stage demonstrated a significant correlation with molecular subtypes (p<0.0001) .

All the results are made as graphs (histograms) :

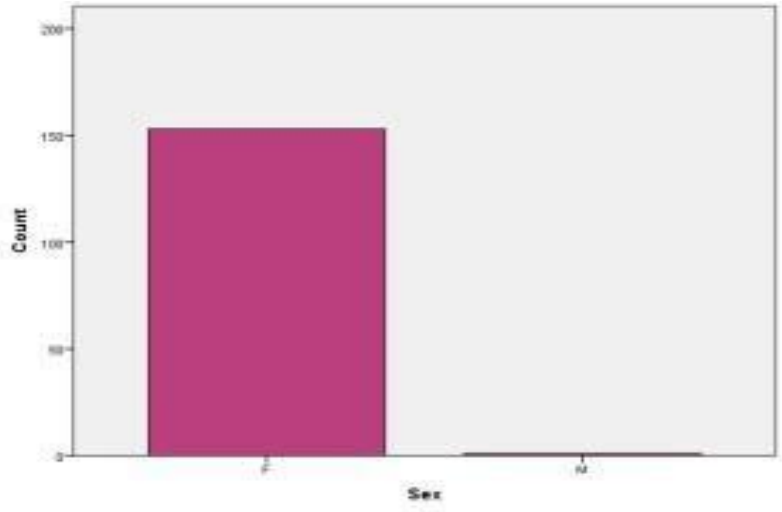


Fig 01: Count by sex

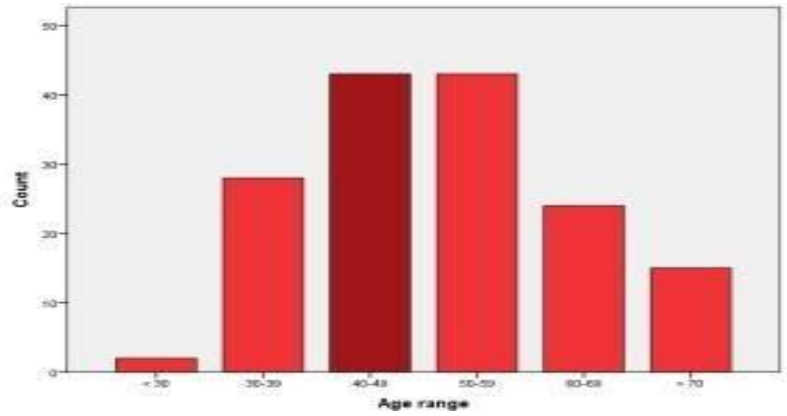


Fig 02: Count by Age range

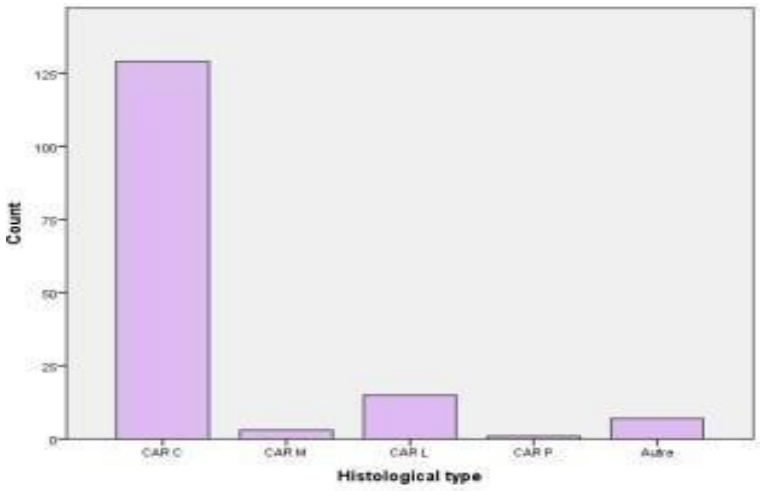


Fig 03: Count by histological type

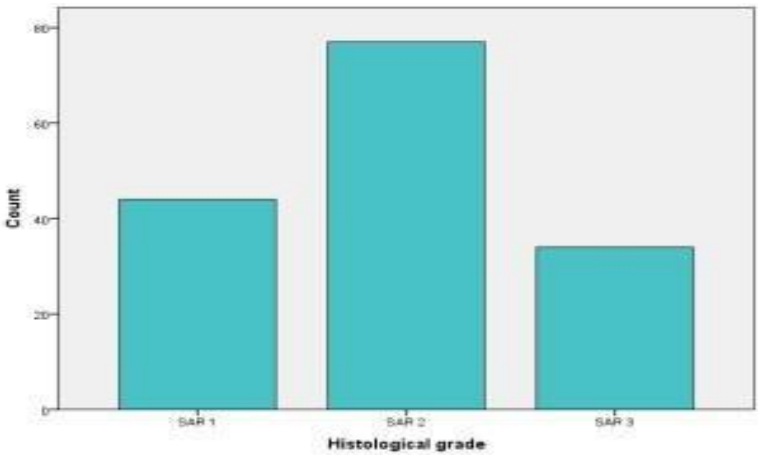


Fig 04: Count by histological grade

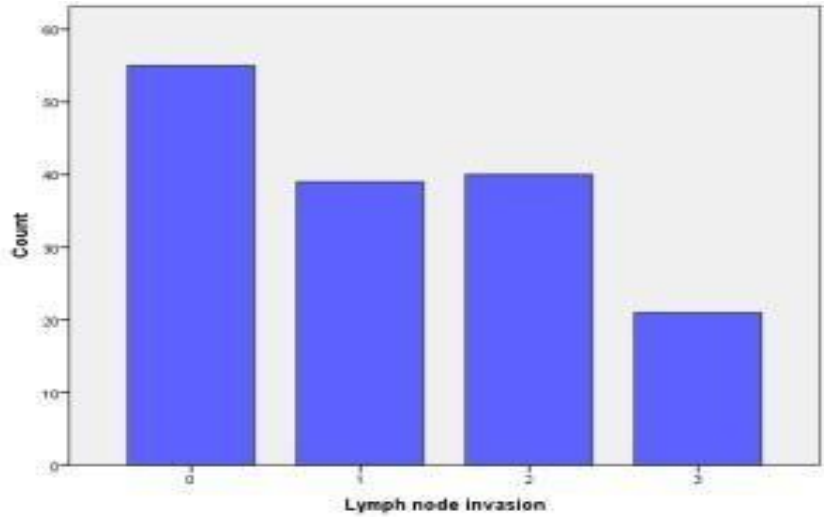


Fig 05: Count by lymph node invasion

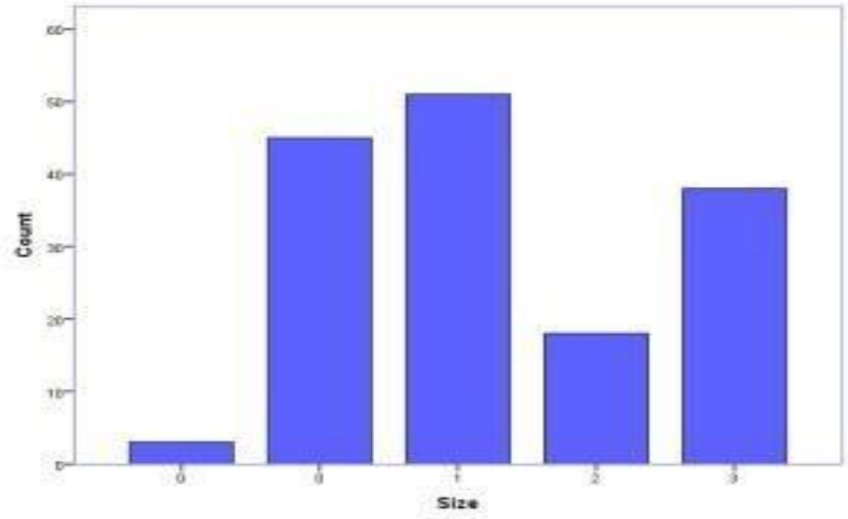
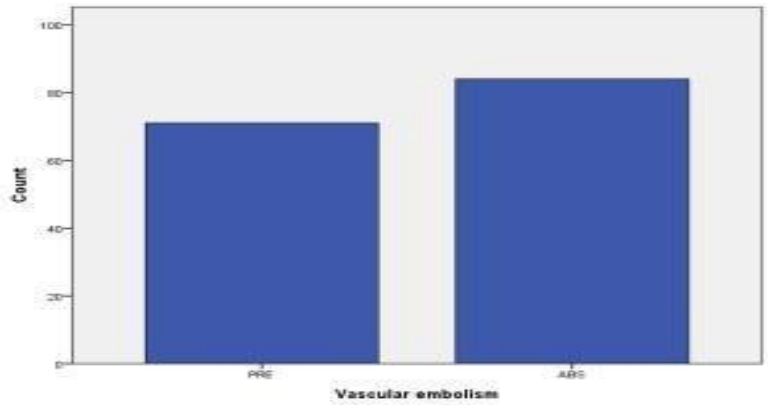


Fig 06: Count by tumor size



07: Count by vascular embolism

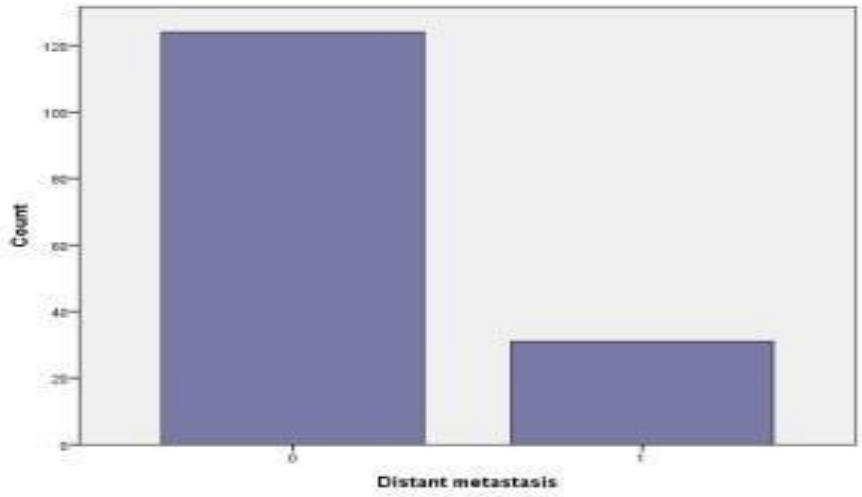


Fig 08: Count by distant metastasis

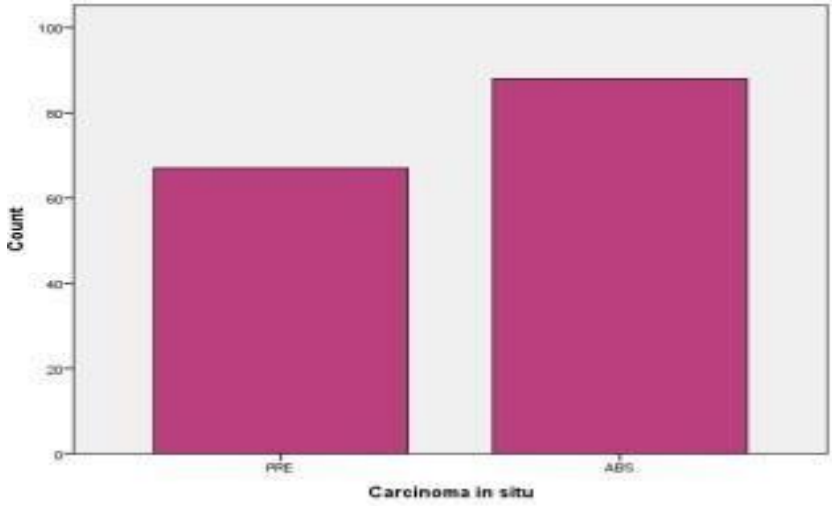


Fig 09: Count by carcinoma in situ

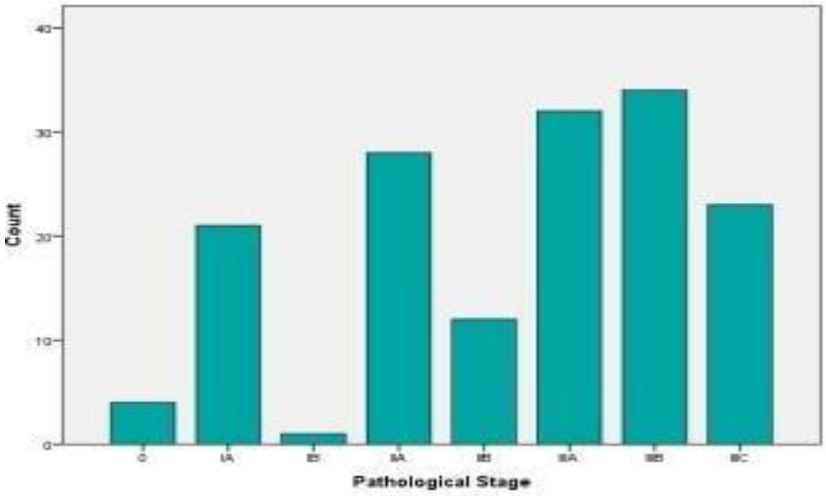


Fig 10: count by pathological stage

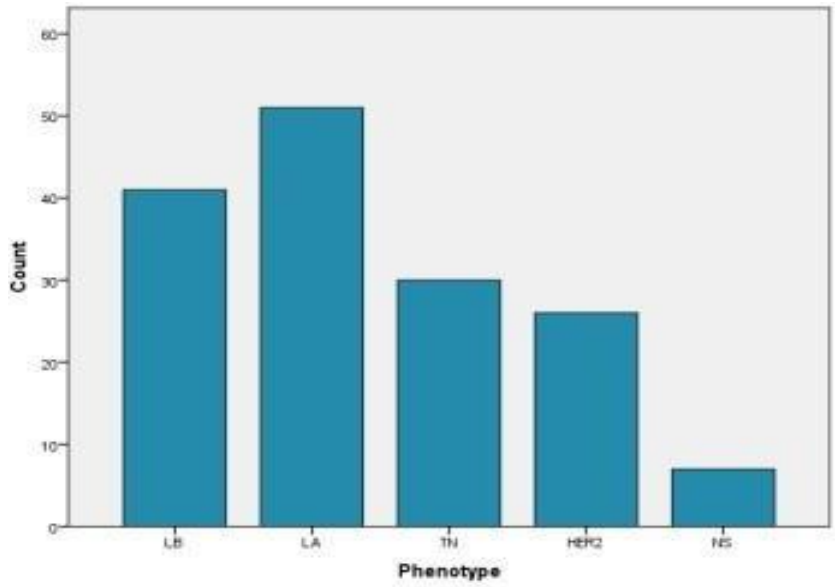


Fig 11: count by phenotype

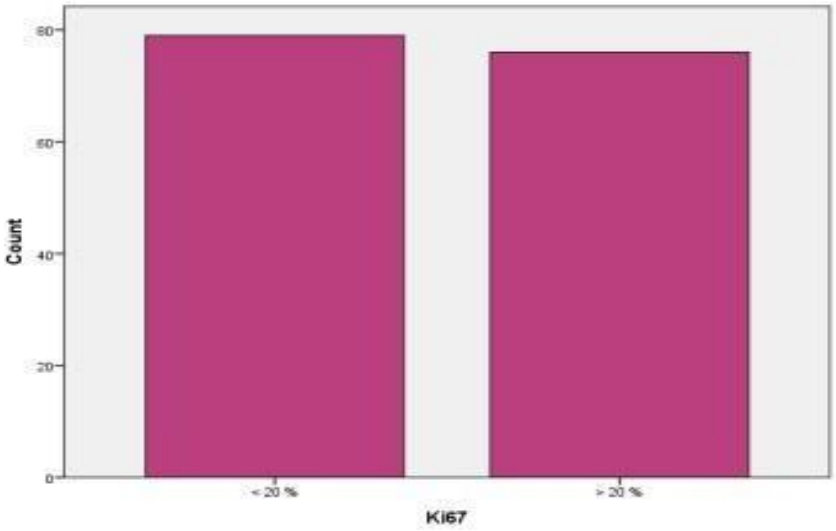


Fig 12: count by Ki67

Z. Discussion

Breast cancer continues to be a primary cause of mortality in women worldwide. The complex and heterogeneous nature, shaped by various clinical, pathological, and biological factors, highlights the necessity for thorough characterization within specific populations. This study examines 155 breast cancer cases in Tebessa, marking the first analysis of its kind in the wilaya. The majority of participants were female, with ages ranging from 29 to 81 years. The average age is 51.54 years (± 12.90), with a median of 51 years. This finding is consistent with reports from various Western countries as well as select Arab and Asian nations. In contrast, North African countries and Pakistan tend for breast cancer to manifest at a younger age . Further investigation is necessary to clarify the roles of genetic and environmental factors. Early-onset breast cancer is frequently linked to heightened aggressiveness and diminished treatment responsiveness , underscoring the significance of this observation.

Ductal carcinoma emerged as the predominant histological type, aligning with findings from prior studies . Lobular carcinoma accounted for 15.3% of cases, a proportion comparable to that in Morocco and the USA, which is 15% .

The findings demonstrate no significant variation in mean tumor size among the various molecular subtypes. This finding aligns with several prior studies. A study published in indicates that the luminal A subtype demonstrates notable differences in prognosis and molecular profile; however, it does not report significant variations in tumor size among these subtypes. A review of breast cancer molecular subtypes in France highlights variations in epidemiology and management yet does not report significant differences in tumor size .

The majority of tumors were classified as grade II (49.7%), followed by grade I at 28.4% and grade III at 21.9%. This contrasts with a prior study conducted in Fez, which indicated a similar proportion of grade II tumors (54.7%) and a higher prevalence of grade III tumors (30.7%) . Lymph node involvement occurred in 64.5% of cases, while 19.7% of patients exhibited distant metastases. The reported figures exceed those from Fez (53% and 17.5%, respectively) and those from developed countries with established screening programs . This discrepancy highlights the necessity for efficient breast cancer screening in Tebessa to enable early detection and enhance prognosis.

Luminal B constituted the most common molecular subtype at 32.9%, succeeded by Luminal A at 26.5%, triple-negative breast cancer (TNBC) at 19.4%, HER2-enriched at 16.8%, and unclassifiable at 4.5%. The distribution closely resembles global patterns, with Luminal A being the predominant subtype in Western Algeria . Variations were observed. The prevalence of Luminal A was lower than that observed in European countries yet higher than in other North African nations, Sub-Saharan Africa, China, and among

Black, Hispanic, and Asian American populations . The findings indicate that although broad patterns are present, there are notable regional and ethnic variations in the distribution of molecular subtypes.

Histological grade varied significantly among subtypes, with Luminal B and unclassifiable tumors showing the lowest percentage of grade III tumors, consistent with their generally less aggressive nature . Luminal B tumors exhibited a more aggressive profile compared to Luminal A, characterized by a higher proportion of grade. Luminal A exhibited the highest proportion of grade III tumors and an average age, reflecting its aggressive characteristics . Nevertheless, it exhibited the greatest prevalence of positive lymph nodes and vascular emboli . HER2 demonstrated the highest prevalence of medullary carcinoma.

The molecular subtypes of breast cancer showed no statistically significant differences regarding tumor size, vascular emboli status, lymph node involvement, or metastasis. A significant variation was observed regarding the histological type. The Luminal A subtype aligns with findings from previous studies conducted in various populations . Distant metastasis demonstrated a significant correlation with molecular subtypes, with Luminal B breast cancer exhibiting the highest prevalence, while other types showed the lowest prevalence, aligning with previous studies .

Luminal A breast cancer exhibited the highest percentage of histological grade III tumors, along with the average age. These findings corroborate existing literature that indicates this subtype is more prevalent among average women and is generally more aggressive . Furthermore, in this cohort, Luminal A breast cancer was predominantly linked to ductal carcinoma, a histological type characterized by an average histological grade and rare lymph node metastases, aligning with previous research .

In the comparison of Luminal A and Luminal B breast cancer subtypes, both demonstrated a comparable histological type proportion, with ductal carcinoma at 25.8% for Luminal A and 23.9% for Luminal B. In contrast, Luminal A tumors exhibited a higher histological grade III rate (9.7% compared to 1.3%), an increased presence of vascular emboli (15.5% versus 12.9%), and a lower incidence of distant metastases (0.0% versus 19.4%). The findings indicate that in Tebessa, Luminal A breast cancers are generally more aggressive than Luminal B subtypes.

The study of those variables is related to risk factors, and these factors are divided into: genetic, hormonal, environmental factors, family and personal history of breast cancer.

Genetic mutations, particularly in the BRCA1 and BRCA2 genes, can increase the risk of breast cancer, even though inherited mutations account for only 5–10% of cases. These genes' capacity to inhibit tumour growth and regulate cell division is impacted by mutations. Mutations are rare but have a 50% chance of being passed on to children. In their lifetime, up to 85% of women with BRCA mutations will get breast cancer, usually in both breasts and at a younger age.

Additionally, ovarian cancer is more likely to strike these women.

Age, parity, and the ages at menarche and menopause are all considered hormonal risk factors. A higher risk of breast cancer is associated with both endogenous (natural) and exogenous (medication-based) oestrogens. Hormone replacement therapy (HRT) and oral contraceptives are examples of exogenous sources. Long-term HRT still considerably raises the risk of breast cancer, even though newer contraceptive formulations carry fewer risks. However, this risk may decrease after two years of stopping HRT.

It's unclear what part synthetic or natural progesterone plays. Studies on their association with breast cancer are conflicting, although some formulations are used as part of HRT or as contraception. Risk assessment is made more difficult by the interaction between progesterone and oestrogen.

One modifiable risk factor for breast cancer is a poor diet. Risk is increased by eating a lot of alcohol, processed carbohydrates, and fats, as well as by eating few fruits and vegetables. Approximately 29% of common cancers could be avoided with a healthy lifestyle.

Alcohol: Alcohol is known to cause cancer and increases the risk of breast cancer. Even moderate drinking may be detrimental, but more research is needed to establish a safe threshold.

Radiation Exposure: Breast cancer has been linked to high doses of ionising radiation, such as those from atomic bombs or medical imaging. Particularly vulnerable are women with particular gene mutations (e.g., ATM, TP53, or BRCA1/2). Radiation can alter hormones and harm DNA.

Breast cancer risk is greatly increased by a family history of the disease. Women are more vulnerable if they have first-degree relatives with the illness, such as mothers or sisters, particularly if several relatives are afflicted. Gene mutations that are inherited, like BRCA1/2, are frequently linked to this familial risk.

Conclusion

This study presents a comprehensive analysis of breast cancer in Tebessa, highlighting multiple areas of concern. Tumors are frequently presented as large, high-grade entities, commonly associated with significant lymph node involvement and distant metastases. These findings likely reflect a delayed diagnosis and restricted access to timely treatment. The observation that breast cancer manifests at an average age in this population underscores the necessity for early detection and intervention. Luminal A and Luminal B tumors demonstrate a more favorable clinical trajectory relative to other subtypes, characterized by moderate size, histological grade II, and later-stage diagnosis (IIIA and IIIB).

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