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Biology of risk factors in the origination of breast cancer and their role in early detection

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بِسْمِ اللَّهِ الرَّحْمَٰنِ الرَّحِيمِ

الَّذِي خَلَقَنِي فَهُوَ يَهْدِينِ (78) وَالَّذِي هُوَ يُطْعِمُنِي وَيَسْقِينِ (79) وَإِذَا مَرِضْتُ فَهُوَ يَشْفِينِ (80) وَالَّذِي يُمِيتُنِي ثُمَّ يُحْيِينِ (81) وَالَّذِي أَطْمَعُ أَنْ يَغْفِرَ لِي خَطِيئَتِي يَوْمَ الدِّينِ (82) .

سورة الشعراء

الأيات 78 – 82

Dedication

I am dedicating this thesis to my supportive and loving husband "*Saeef alnasar* "

To *my wonderful girls* which I hope to be an inspiring example to them.

I would like to thank *my parents* who taught me the value of hard work and for their encouragement and prays.

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In the name of Allah ,the beneficent and the merciful .

First thanks are to allah, the Almighty, on whom ultimately we depend for guidance and help.

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for his patience and feedback. I could not have undertaken this thesis without him where he generously provided knowledge and expertise. Additionally, this endeavor would not have been possible without the support from his advices and guidance .

I would like to thank my university that granted me this honor and provided me with all possible facilities to complete my studie.

Thanks to my supportive and loving husband Saeef alnasar and my wonder girls which I hope to be an inspiring example to them. Lastly, I would like to thank my parents for their encouragement and prays.

Finally, we wish to express my sincere thanks to any person who provides me with the needed facilitations to complete this work.

ABSTRACT

The current study attempts to shed light on the biological risk factors that may contribute to the emergence and development of breast cancer, while trying to find which factors are more related and effective to the emergence of breast cancer and to understand its mechanisms, so that we can early detection, treatment and limit the spread of the disease among women. The study focuses on various factors causing breast cancer includy body mass index, obesity, exposure to ionizing radiation, passive smoking, ABO blood types, diseas onset, signs or symptoms).

After obtaining approval to conduct the study by the Research and Ethics Committee of the University of Sabratha and the National Cancer Institute, Sabratha. Structured interviews were conducted on 80 breast cancer patients who joined the National Cancer Institute in Sabratha during the period from September 2020 to August 2021, and the data were tabulated in a questionnaire form, including " Measuring weights and lengths and taking blood data from records. The control group included 40 women who did not have any chronic diseases. All tests corresponding to the control group, such as measuring height and weight, and drawing blood samples, were applied; 3 ml of blood was drawn intravenously using sterile single-use syringes. It was then transferred to a sterile tube with EDTA. For complete blood profile and blood group determination. Data were analyzed using Graph Pad Prism version 8, and statistical significance values for differences between groups were calculated using multiple comparison with analysis of variance by one or two ways ANOVA, and the level of statistical significance was determined at ($P<0.05$).

The results showed that biological risk factors had a significant impact on the onset of the disease. Risk factors such as age, ABO, Rh factor, and reproductive characteristics recorded high significant values, confirming their dangerous effects on women and the development of the disease. The results also showed that the age group (40-50) years represented 41.25%, overweight 25-29.9 kg represented 30%, and blood types A and

O $^{+}$ve were 47.5% and 33.75%, respectively, which indicates the possibility that these groups are considered more susceptible to breast cancer , while other blood types (A^{-}, O^{-}, AB^{+}, AB^{-}, B^{-}, B^{+}) are at risk of breast cancer with a lower risk. The relationship of early menstruation was revealed and breast cancer; It was found that in high percentages among patients, while permanent menopause represented about 50% with highly significant analysis results (P>0.0037). The results of the number of births among patients was 77.5% As for the relationship between a previous history of breast cancer and previous exposure to therapeutic radiation, it represented high significant values (P<0.001), and the use of (black) hair dye and eating red meat recorded high rates, especially with older women. Analysis of vitamin D indicated a decrease in it among patients. Blood contents also recorded a decrease in white blood cells and hemoglobin, and the study recommends further studies for other regions of the country to confirm these results.

المستخلص

تحاول الدراسة الحالية القاء الضوء على عوامل الخطر البيولوجية التي قد تسهم في نشأة سرطان الثدي وتطوره ، مع محاولة ايجاد اي العوامل أكثر ارتباطاً و فعالية لنشوء سرطان الثدي وفهم آلياته، حتى نتمكن من الكشف المبكر والعلاج والحد من انتشار المرض ، و تركز الدراسة على العوامل المسببة لسرطان الثدي المختلفة (مؤشر كتلة الجسم ، السمنة ، التعرض للإشعاعات المؤينة ، التدخين السلبي ،فصائل الدم ABO ، وكيف يبدأ المرض والعلامات أو الأعراض). بعد الحصول على الموافقة لإجراء الدراسة من قبل لجنة البحوث والأخلاق بجامعة صبراتة والمعهد القومي لعلاج الأورام صبراتة، تم إجراء مقابلات منظمة على 80 مريضة بسرطان الثدي التحقوا بالمعهد القومي للسرطان بصبراتة خلال الفترة من سبتمبر 2020 إلى أغسطس 2021 ، تم تبويب البيانات في استمارة استبيان منها "قياس الاوزان والاطوال واخذ بيانات الدم من السجلات". المجموعة الضابطة شملت 40 سيدة ليس لديهم أي أمراض مزمنة، طبقت جميع الاختبارات للمجموعة الضابطة كقياس الطول والوزن وسحب عينات الدم ؛ بأخذ 3 مل من الدم عن طريق الوريد باستخدام محاقن معقمة تستخدم لمرة واحدة. ثم تم نقله إلى أنبوبة معقمة بها EDTA، لتعيين صورة الدم الكاملة والفصيلة. تم تحليل البيانات باستخدام برنامج Graph Pad Prism لإصدار 8، وحسبت قيم الدلالة الإحصائية للاختلافات بين المجموعات باستخدام المقارنة المتعددة مع تحليل التباين بواسطة اختبار ANOVA ذو الاتجاه الواحد وذو الاتجاهين بمستوى الدلالة الإحصائية عند ($P<0.05$) . أظهرت النتائج أن عوامل الخطر البيولوجية كان لها تأثير كبير في ظهور المرض . سجلت عوامل الخطر مثل العمر، ABO ،عامل Rh والخصائص الإنجابية قيما معنوية عالية أكدت آثارها الخطرة على النساء ونشوء المرض . كما أظهرت النتائج أن الفئة العمرية (40-50) تمثل 41.25% ، الوزن الزائد 25-29.9 كجم 30% ، فصيلة الدم A وve^{+} O كانت 47.5 % و33.75 % على التوالي مما يشير الى احتمالية اعتبار هذه الفصائل اكثر عرضة للإصابة بسرطان الثدي ، بينما فصائل الدم الأخرى (A^{-} ،O^{-}، AB^{+}، AB^{-}، B^{-}، B^{+}) معرضون لخطر الإصابة بسرطان الثدي مع خطر أقل . تم الكشف عن العلاقة بين الحيض المبكر وسرطان الثدي ؛ حيث وجد بنسب عالية بين المرضى ، بينما انقطاع الطمث الدائم مثل حوالي 50% مع نتائج تحليل ذات دلالة عالية ($P<0.0037$) . وكانت نتائج عدد الولادات بين المريضات 77.5%. أما عن علاقة التاريخ السابق للإصابة بسرطان الثدي ، والتعرض للإشعاعات العلاجية سابقا مثلت قيم معنوية عالية ($P<0.001$) ،وسجلت استخدام صبغة الشعر (السوداء) وتناول اللحوم الحمراء نسبا عالية خاصة مع المتقدمات بالعمر . وأشار تحليل فيتامين د إلى انخفاضه بين المرضى . كما سجلت محتويات الدم انخفاضا في كريات الدم البيضاء والهيموجلوبين ، وتوصي الدراسة إلى مزيد من الدراسات لمناطق اخري من البلاد لتأكيد هذه النتائج .

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Abbreviations

AC	Adriamycin and Cyclophamide
ANOVA	Analysis of Variance
BRCA1	Gene act as tumor suppressor gene
BRCA2	Gene act as tumor suppressor gene
BSE	Breast Self-Examination
BMI	Body Mass Index
CBC	The complete blood count
DALYs	The disability-adjusted life year
DNA	Deoxyribonucleic acid
DCIS	Ductal Carcinoma In Situ
FAC	Fluorouracil Adriamycin and Cyclophamide
Gap 1	Growth phase
Gap 2	Growth and preparation for cell divison
HB	Hemoglobin concentration
HPLC	High-performance liquid chromatography
HRT	Hormone treatment
IOM	International Organization for Migration
IDC/ILC	Invasive Breast Cancer
LN	Lymph node
M	Mean
M phase	Mitosis
NLR	Neutrophil-lymphocyte ratio
SD	Standard deviation
S phase	DNA synthesis
TNBC	Triple-negative breast cancer
VD	Vitamin D
WHO	World Health Organization
WBC	White Blood Cell

CHAPTER 1

INTRODUCTION

1. Introduction and Literature Review

1.1 Cancer

The term cancer is used when a tumor is malignant (cancerous), tumors are abnormal growth of tissue; it has the potential to cause harm and death. Generally, cancer is known as an abnormal growth of cells that are not function properly and spread to a different part of the body. Cancer is malignant because it can be locally invasive which harm near surrounding tissues and can be metastatic cancer that harms far tissues and organs. Cancer cells that do not spread are called "Benign tumors" (noncancerous) grow slowly and do not spread (Fares *et al*., 2020).

Cancer is a group of diseases, each one cause cells to grow out of control. They are classified according to the kind of fluid or tissue from which they originate and the location of the body where they developed. The following five broad categories indicate the classification of cancer: first, A Carcinoma is a cancer found in epithelial tissue that covers surfaces of organs, glands or body structures such as breasts, this type account for 80 – 90 % of all cancer cases. Second, Sarcoma that grows from connective tissues such as cartilage, fat, muscle, tendons and bones. Third, lymphoma that originates from lymphatic system whose function is to produce WBCs and clean body fluids such as brain and breast lymphoma. Fourth; Leukemia or blood cancer. Fifth, Myeloma grows in the plasma cells of bone marrow (Saini *et al*., 2020).

Cancer is a type of uncontrolled cell division, that can spread to other tissue or metastasize to distant organs through the blood or the lymphatic system (Dhanasekaran *et al*., 2022). cancer can arise in variety of tissues and organs (Baylin and Ohm., 2006). Although advances in detection and therapy, cancer is still a challenge for science (Brecqueville *et al*., 2012). As shown in figure 1, the first step of cancer formation is genetic

mutation, the “Initiation” phase “Initiators”, which cause or support the process of genetic mutations, include hormones, chemicals, radiation, infection and hypoxia (Siddiqui *et al*., 2015).

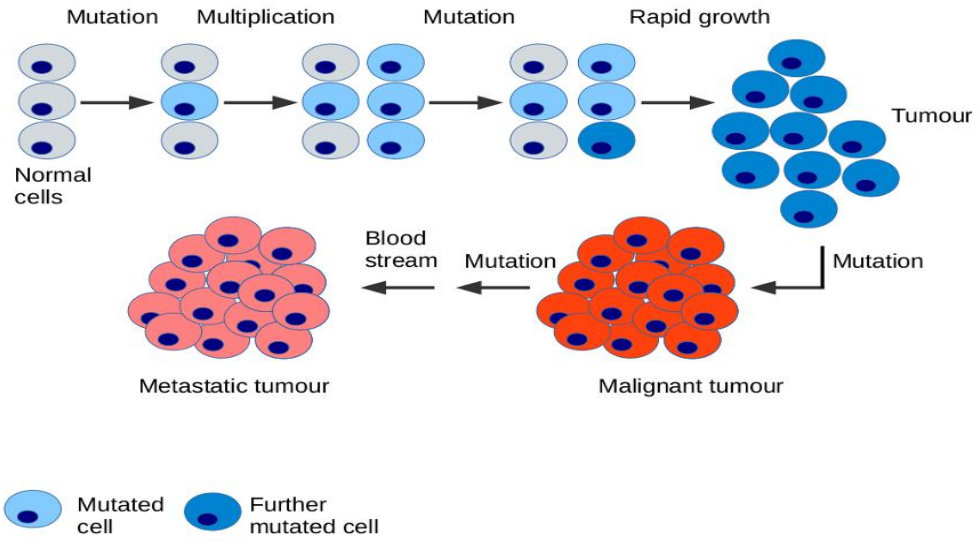


Figure 1.1 : Origin of cancer cell from normal cell .
(Siddiqui, 2015)

Gene mutations induce in pro-oncogenic genes such as (RAS), which are genes encode proteins that can cause cancer (or become oncogenic) when mutated (Downward *et al.*, 2003), (Finver *et al*., 1988). In the other hand other genes act as tumor suppressor genes such as
-(BRCA1), (BRCA2) and TP53 (Friedenson and Baker., 2007).
Generally, genetic aberrations are essential for cancer development (Narod *et al*., 1995). Mutated cells can stay in a dormant phase or become proliferative. The second step of cancer induction, is the “Promotion” phase, it has several steps known as hyperplasia (increase the cell number), dysplasia (cell phenotype change), in situ carcinoma (cancer cells) and finally invasive carcinoma (metastasis) (Lodish *et al*., 2000).
Cancer has six stages to appear as abnormal growth that avoid suppressor mechanisms, they occur in a sequence chain include sustaining of

proliferating signaling, evading growth suppressors, resisting cell death, enabling replicative immortality, inducing angiogenesis, and activated invasion and metastasis (Hanahan and Weinberg., 2011).

A genetic abnormality in somatic cells causes cancer by transforming them into uncontrollable cancer cells. They divide and expand at the wrong times and in the wrong places, resulting in tumors that can lead to secondary cancers**.** According to world health organization (WHO) statistics report 2021 about cancer in Libya Breast cancer (BC) population 6,871,287, number of new cases females all ages in 2020 is 1229, (31.4%) among all other female cancer types, and 16% among Libyan community cancer types. As well as female cancer deaths and 5-years prevalence were 9.7% and 104.22 per 100000 respectively (Macdonald *et al*., 2004). A normal and cancer cells are comparable as shown in figure1.2.

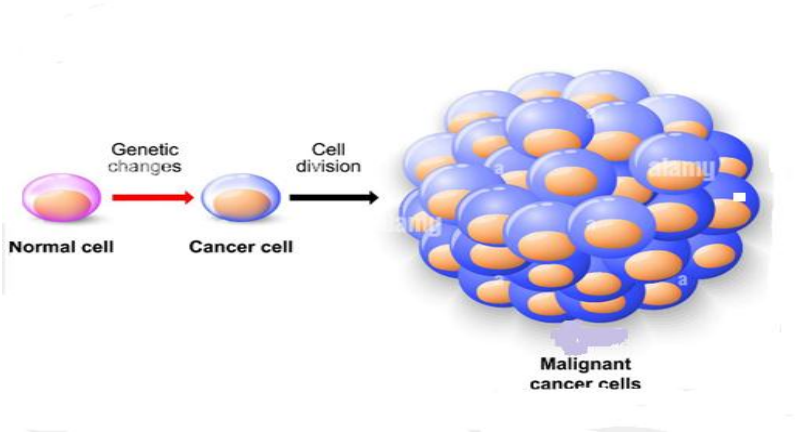


Figure 1.2 Normal and Cancer Cell Comparison of Cell

(Cooper and Hausman.,2007)

1.2 The stage of cancer development:

Cancer incidence and its development passes through several stages that can be summarized as follows:

1.2.1 Initiation stage:

When DNA is copied during cell division, a mutation occurs, resulting in a genetic flaw in the cell. Many studies have been pointed to that radiation, smoking, viruses, and environmental poisons are examples of mutagenic or carcinogenic substances. (Homo-Delarche *et al*., 1991).

1.2.2 Promotion stage:

A single simple mutation is not enough to cause cancer, but what happens is one mutation leads to a cascade of subsequent mutations, cancer develops. The more mutations (particularly mutations in genes governing cell development) and division (the cell was better able to survive and endure immune factors and became able to invade other tissues) over a period of time (Homo-Delarche *et al*.,1991).

1.2.3 Progression stage:

Cancer cells require oxygen and nutrients to grow and survive; it can easily grow, and it gets oxygen and nutrients from nearby blood vessels especially when being very small cancer. For this purpose; the cancer cells made their own blood network that is linked to the circulatory system. It may damage the endothelium membrane and dissolves the wall of target part with the help of protease enzyme, enters the circuit, and migrates to the Others, where they can attach themselves to healthy tissue and assume the place of healthy cells there, and cancer cells can give up their place (Coussens and Werb , 2002**)**The mutations in new cancer cells are higher than those in the original tumor. Spreading cancer is more difficult to treat and manage, as well as more hazardous and lethal than the original cancer (Homo-Delarche *et al*., 1991).

1.3 Types of Tumors

Tumors come in a variety of shapes and sizes, they are divided into two categories; benign and malignant. Benign tumors do not spread to other parts of the body and do not cause cancer, while malignant tumor can metastasis, where cancer cells spread from the tumor and enter the bloodstream or lymphatic system, where they travel to other regions of the body and eventually to distant locations. Some benign tumors can develop into malignant tumors over time. Malignant tumors develop in a series of phases over the course of several years. The sooner a tumor is discovered, the less probable it is to spread to other parts of the body. Over the last two decades, tremendous progress has been made in identifying the molecular events that occur as a result of a chemical reaction (Fares *et al*., 2020).

1.4 The stages of the cell life cycle and cancer:

The tumor is made up of a diverse collection of cells, some of which are growing and others of which are inactive, and each cell goes through a different growth phase, with the cell cycle separated into multiple phases (Figure3), specifically.

- Growth phase (Gap1) This phase accounts for 40% of the cell cycle, and it is at this time that the cell prepares for division and makes DNA components.
- DNA synthesis (S phase): during this phase of the cell cycle in which DNA is replicated, occurring between G_1 phase and G_2 phase.
- Growth and preparation for cell divison (Gap2) It lasts for 19% of the cycle's duration, during which RNA, proteins, and cellular components are required for division.
- Mitosis (M phase) : the mitotic phase of the cell cycle, which lasts only 2% of the time.

- G0 phase - an excretion phase in which the cell does not divide but continues to perform its other physiological functions such metabolism and secretion. This phase may be part of the G1 phase, in which the cell determines whether to differentiate or continue dividing (Meghan *et al*., 2011).

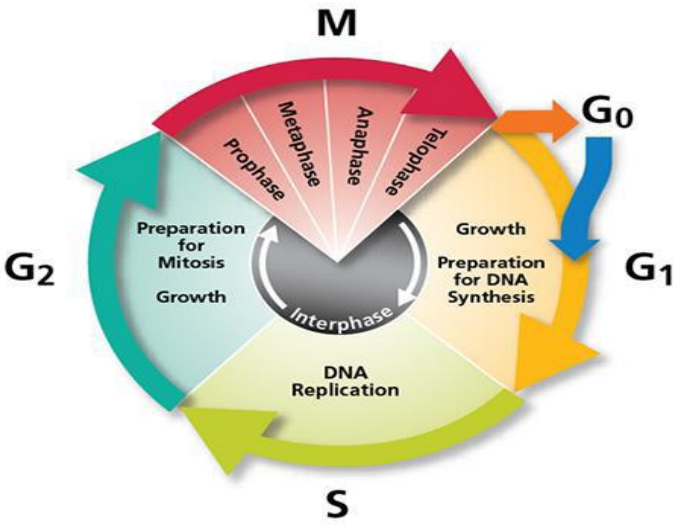


Figure 1.3 Cell life cycle phases
(Schafer.,1998)

1.5 Cancer characteristics

Despite the wide variety of cancers and the genes that cause them, they always have a number of characteristics:

Hanahan Weinberg defined distinct and common indications.

In the year 2000, six traits were identified that are related to survival and differentiation:

1- A cancer cell's growth signals are self-sufficient. Namely, Cancer cells do not need stimulation from external signals.

2- Anti-growth signals have no effect on cancer cells.

3- A cancer cell does not die in a predetermined manner. Apoptosis is evaded by eliminating the proteins that carry out the process.

4- A cancer cell's power to expand and multiply is limitless.

5- The cancer cell continues to build blood vessels until additional cancer cells are nourished.

6- The cancer cell spreads to other tissues and multiplies (Hanahan and Weinberg, 2011)**.**

1.6 Breast Anatomy

The female breast is a complex organ and made up of the nipple and areola on the outside, and milk ducts, lobes, lobules, lymph nodes, and vessels on the inside. Each breast has 15 to 20 sections, called lobes, which are arranged like the petals of a daisy. Each lobe has many smaller structures called lobules, which end in dozens of tiny bulbs that can produce milk. The lobes, lobules, and bulbs are all linked by thin tubes called ducts. The primary function of the female breasts is to produce breast milk and breastfeed a baby (Virginia A and Cirolla, 2017).

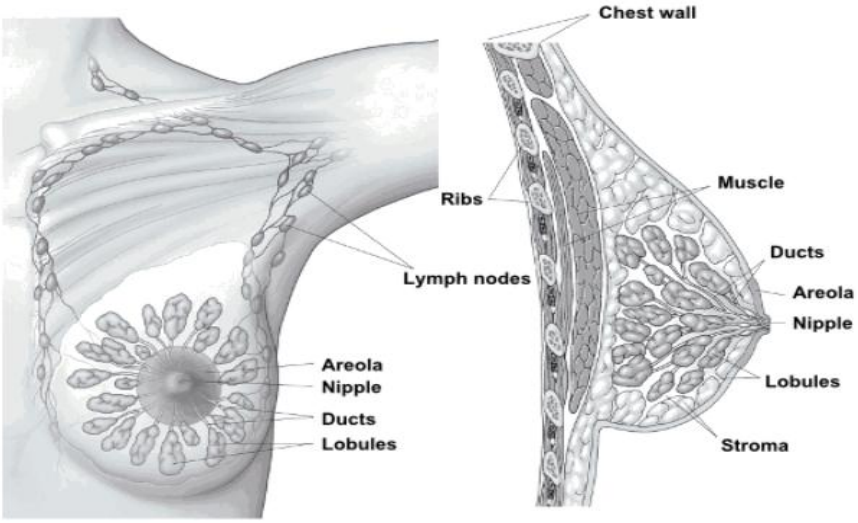


Figure 1.4 main parts of woman breast .

(Markarian and Holmes.,2022)

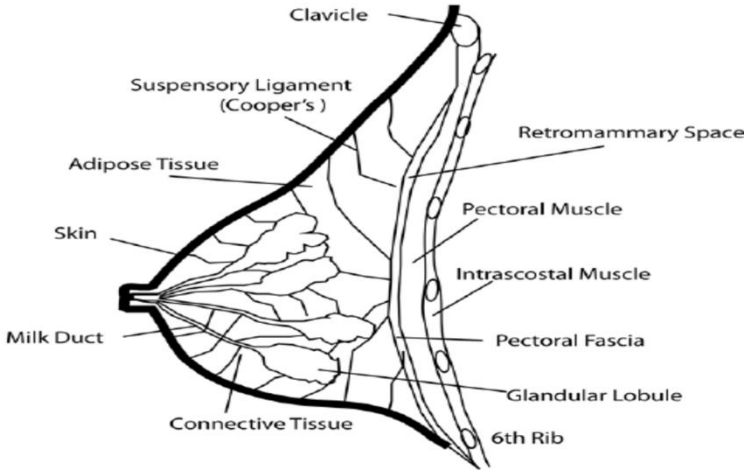


Figure 4-a Lateral view

A; Lateral view of the left axillary region

Breast Anatomy (Markarian and Holmes.,2022)

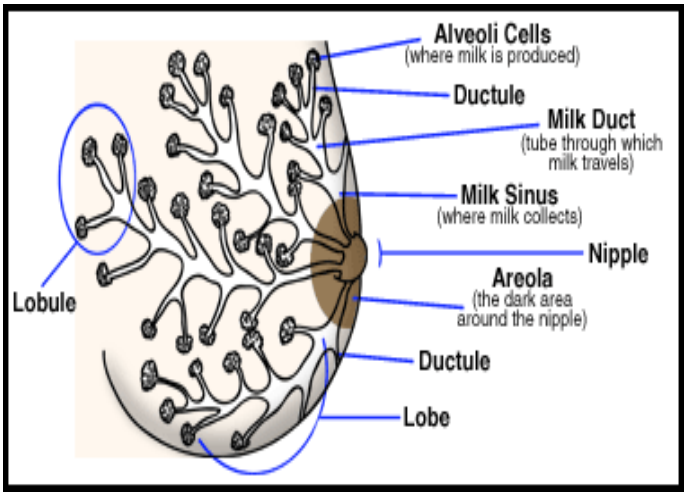


Figure 4-b anterior view

and **B;** anterior view of the left axillary region .

Breast Anatomy ((Markarian and Holmes.,2022)

1.7 Breast cancer (BC)

(BC) the most common cancer in women and the main cause of cancer death around the world. There are about 1.5 million new cases of BC

diagnosed annually with ratio of 12.5% for women BC (Zhang *et al*.,2021) **.**

Despite the observed global variations in the incidence of BC, but it considering is the most commonly diagnosed cancer (approximately 1.38 million) and the leading cause of cancer mortality among women (approximately 458,400) in both developing and developed countries (responsible for 23% of all new cancer cases and 14% of all cancer deaths (Kazan and Karalti, 2015).

The number of deaths from BC among women was estimated at about 522,000 deaths in 2012, as this disease was diagnosed among women in 140 out of 184 countries worldwide, accounting for one in every four cancer types in women, according to the International Agency for Research on Cancer (2013). BC is also the most frequent cancer among women in the Eastern Mediterranean region, as well as the main cause of cancer death worldwide (Oussama and Khatib, 2006).

It is worth noting that breast cancer naturally affects both sexes, male and female. According to the American Cancer Society, there are 232 000 new breast cancer cases (2000 of which were male BC) and 40 000 deaths in the United States in 2013(Shiovitz and Korde., 2015).

By reviewing the literature on BC in the Arab world, it was found that it represents 13-35% of all cancer cases in females, the average age is 50 years, and over 60% of cases being in an advanced stage of the disease (El Saghir *et al*., 2007).

Several studies have examined the rates of BC in different regions of the world, and the results indicate that it is the highest in Western and Northern Europe, Australia / New Zealand and North America . Average in South America, the Caribbean and North Africa; and lowest in sub-Saharan Africa and Asia, where the results concluded that 23% of all cancer cases and 14% of all cancer deaths (Jemal *et al*., 2010).

1.7.1 The role of lymph nodes in development of breast cancer

Breast cancer can spread to the lymph nodes from the armpits or toward the collarbone and form a lump or bulge there, even before the original breast tumor is large enough to be examined. Since the mechanism of action of breast cancer is not defined and understandable yet specifically, therefore it is recommended the gynecologist should examine the lymph nodes, which are increasing in size. That most types of breast cancer need 50-200 days to multiply, based on that, it is said that the tumor that is diagnosed at some point was the beginning of its growth in the body 5 years ago. Breast cancer may spread to other places in the body and lead to other symptoms. The most common first site of metastasis is often the lymph nodes under the arm, although there may be unpalatable carcinoma-bearing lymph nodes. Over time, cancer cells may spread to other organs, including the lungs, liver, brain, and bones, figure 1.7 shows commencing of breast cancer (Datta *et al*., 2017)

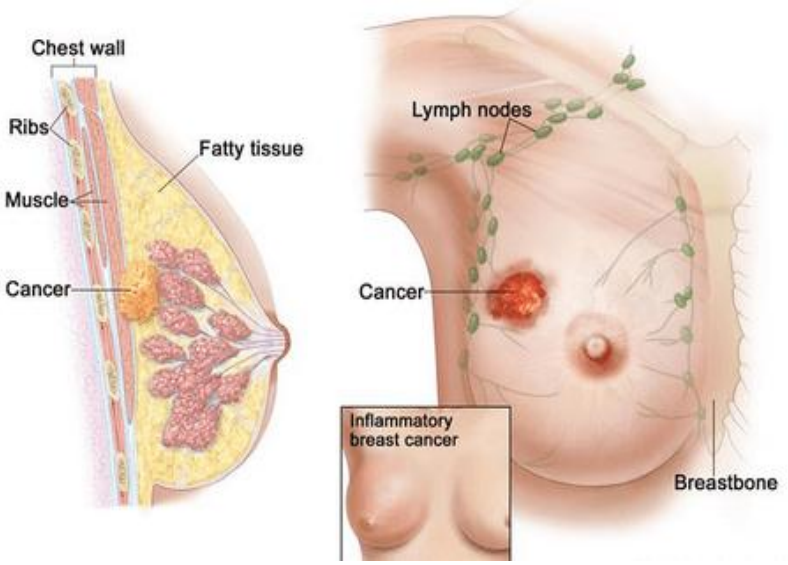


Figure 1.7.1 shows commencing of breast cancer and most common area start with. (Curigliano, 2018)

1.7.2 Breast Cancer Types

The uncontrolled proliferation of aberrant cells is a hallmark of BC. BC can be classified into two types: non-invasive breast cancer and invasive breast cancer. Non-invasive BC occurs when abnormal cells grow inside the lobules or milk ducts. This means that cancer cells in the breast or other sections of the body do not spread to other tissues. The cancer cells in invasive BC can start in the milk ducts or lobules, but they can move to other breast tissues or areas of the body (Davis and Hallerberg, 2010).

The inner lining of milk ducts or the lobules that provide milk to the ducts are where the majority of BC arise. Lobular carcinoma arises from lobules, while ductal carcinoma arises from ducts

BC comes in a variety of forms and is described in a variety of ways. The exact cells in the breast that are impacted determine the type of BC. The majority of BC are carcinomas, which are tumors that begin in the epithelial cells that line the organs and tissues in the body. Adenocarcinoma, which begins in cells in the ducts (milk ducts) or the lobules, is the most common type of carcinoma that forms in the breast (milk-producing glands). (Blaurock-Busch *et al*., 2014).

1.7.2.1 Ductal carcinoma in situ (DCIS)

Ductal carcinoma in situ (DCIS) is account for about 1 in every 5 new cases of breast cancer. It is the presence of abnormal cells inside a milk duct in the breast. Breast cancer in this stage can be cured in nearly all women. Intra ductal carcinoma, or stage 0 breast cancer, is another name for DCIS. DCIS is a type of breast cancer that is non-invasive or pre-invasive. This indicates that the cells that line the ducts have transformed into cancer cells, but they have not moved beyond the duct walls into the surrounding breast tissue (Corben *et al*., 2014).

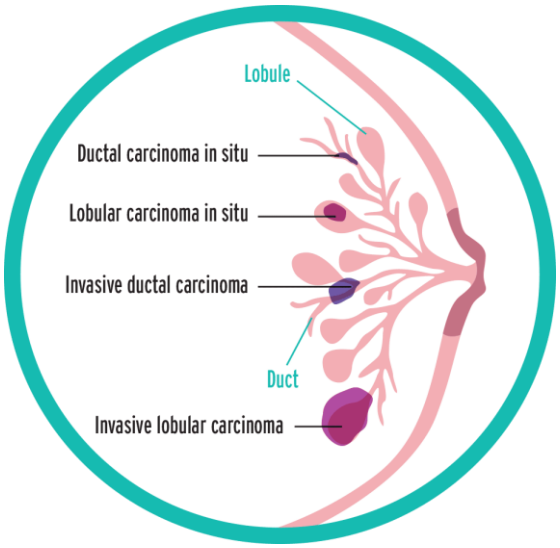


Figure 1.7.2.1 Ductal carcinoma in situ (Corben and Brogi., 2014)

1.7.2.2 Invasive Breast Cancer (IDC/ILC)

Invasive breast cancer is a type of breast cancer that has spread to the surrounding breast tissue. It is considering the most common type, although there are several varieties of invasive breast cancer. Invasive ductal carcinoma and invasive lobular carcinoma are the two most prevalent types (Arpino *et al*., 2004).

Invasive breast cancer also includes inflammatory breast cancer and triple breast cancer with a Triple Negative Status (TNBC) . It is representing for roughly 10-15% of all breast. The phrase triple-negative breast cancer refers to cancer cells that lack estrogen or progesterone receptors and produce insufficient amounts of the protein HER2. HER2 is a protein that helps breast cancer cells grow quickly. Women under the age of 40, who are African-American, or who have a BRCA1 mutation are more likely to get these diseases. Triple-negative breast cancer is distinct from other forms of invasive breast cancer in that it grows and spreads more quickly, has fewer treatment options, and has a poor prognosis (Arpino *et al*., 2004).

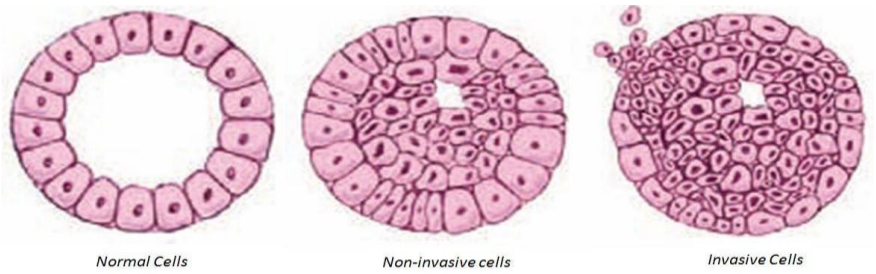


Figure 1.7.2.2 breast-cancer-invasive (Sharma *et al*., 2010)

1.7.2.3 Inflammatory Breast Cancer

Inflammatory breast cancer (IBC) is an uncommon type of breast cancer that accounts for approximately 1-5 percent of all cases. Although it is frequently a kind of invasive ductal carcinoma, it has symptoms, a prognosis, and therapy that are distinct from other types of breast cancer (Barkataki *et al*., 2018). IBC causes inflammation signs such as swelling and redness, but it is not caused by infection or injury. Cancer cells block lymph veins in the skin breast. causing the breast to seem "inflamed," resulting in IBC symptoms swelling, purple or red skin, and dimpling or thickening of the breast skin that looks and feels like an orange peel are some of the symptoms. Even if there is a lump, it may not be noticed.

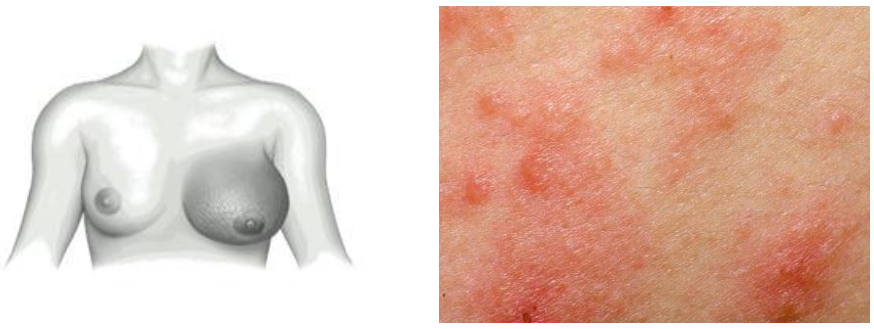


Figure 1.7.2.3: Inflammatory breast cancer, which often appears as an enlarged breast with red, thickened skin (Curigliano, 2018)

1.7.2.4 Breast Angiosarcoma

Angiosarcoma is a rare cancer that begins in the cells that lining the blood and lymph arteries. It is reported that It arises from the mammary stroma and is the most common sarcomatous malignancy in the mammary gland. It's frequently a side effect of earlier breast radiation treatment. It can happen 8-10 years after receiving breast radiation treatment (Patel *et al*., 2019).

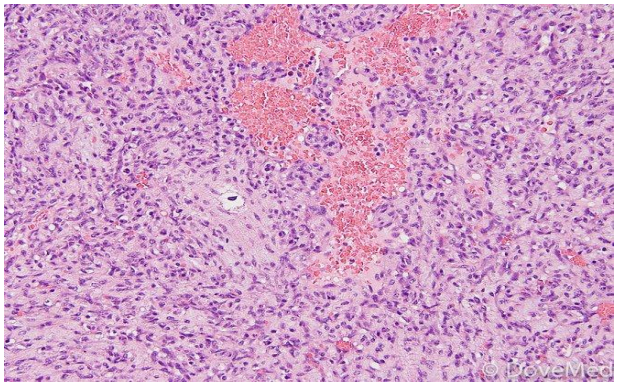


Figure 1.7.2.4 Breast Angiosarcoma (Nascimento, 2020)

1.7.2.5. Paget's Disease of the Breast

Also known as Paget's disease of the nipple, it is a type of breast Paget disease of the breast is a rare form of breast cancer that affects the nipple and areola skin (the dark circle around the nipple). Only one breast is usually affected by Paget illness. It's generally detected with either ductal carcinoma in situ (DCIS) or infiltrating ductal carcinoma in 80-90 percent of cases invasive breast cancer (Patel *et al*., 2019).

In addition, family history and age of women are the most two individual critical BC risk factors (Phillips *et al*., 2016). In low income societies BC were majority in young women with median age of 49 – 52 years whereas 63 years in high income countries (El Saghir *et al*., 2007). High BC mortality rates in developing countries are due to the late of detection (Farmer *et al*., 2010). Thus, the American cancer society recommended

that women should begin annual BC check around forties and discuss their family and medical history with a clinician, also they should be provided with information of BC (Oeffinger *et al*., 2015).

Early detection of BC lead to improve treatment, recovery and reduce both the complication and the risk of mortality (Barnard *et al*.,2015).

According to World Health Organization (WHO) statistics report 2021 about cancer in Libya BC revealed very important estimates, total population 6,871,287, number of new cases females all ages in 2020 is 1229, (31.4%) among all other female cancer types, and 16% among Libyan community cancer types. As well as female cancer deaths and 5-years prevalence were 9.7% and 104.22 per 100000 respectively **(**Saberian *et al*., 2021).

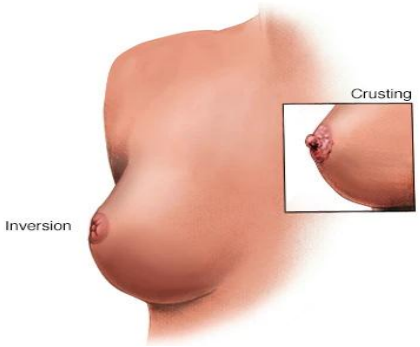


Figure 1.7.2.5 Paget's Disease of the Breast.

((Markarian and Holmes.,2022)

1.8 Stages of breast cancer

(Sopik and narod, 2018) defined staging of BC as the process where cancer spread within breast or to other parts of the body.

1- Early breast cancer

-Stage 0: Carcinoma in situ or disease that has not invaded the basement membrane.

-Stage I: Small primary tumor without lymph node involvement.

-Stage II: Involvement of regional lymph nodes.

2- Locally advanced breast cancer (Sopik *et al*., 2018)

-Stage III: Usually a large tumor with extensive nodal involvement in which node or tumor is fixed to the chest wall; also includes inflammatory breast cancer, which is rapidly progressive.

3- Advanced or metastatic breast cancer (Sopik and narod, 2018)

-Stage IV: Metastases in organs distant from the primary tumor.

1.9 Risk Factors For Breast Cancer

The earlier studies have been identified many risk factors for breast cancer and the most important of which are; Fewer births, a later age at first full-term pregnancy, not having breastfed, an early age at menarche, irregular menses, late menopause, the use of exogenous hormones (e.g., oral contraceptives), obesity, physical inactivity, and a family history of breast cancer are the most important of these factors (Canadian Cancer Society, 2014).

Common risk factors are unsuitable dietary and behavioral risks that cause 30% of cancer death (Coughlin and Ekwueme, 2009) .

Variation in female BC around the world were attributed to differences in socio demographic factors, reproductive patterns, lifestyle, and other hormonal factors (Jemal *et al*., 2010).

The high risk factor for a disease is important in evaluating and providing information about the pathogen; With a high probability when the patient carries this factor compared to the individual who does not carry such a factor for the disease, and therefore the term high risk factor for a breast cancer patient can often be defined as the person who is exposed to breast cancer at a high rate compared to other members of the community. Survey studies of family medical history, age of the patient and genetic factors give a great opportunity to assess the high risk of developing breast cancer (Borgquist *et al*., 2018).

A high number of breast cancer cases are diagnosed every year. Family history of breast cancer, age of menarche, duration of lactation, parity, age of menopause, diet and hormonal levels are known risk factors for the development of breast cancer. One of the major antigens in humans is the blood group antigens that are present on the surface of red blood cells membrane(RBC) and different epithelial cells and alteration of these blood group antigens is associated with cancer (Aly *et al*., 2014).

1.9.1 Breast cancer in the world

1.9.1.1 Breast cancer blood type risk factor

ABO blood groups in 166 Greek women were investigated. Results revealed that the ductal nature of breast cancer was (49.6%) in patients with blood group A and was least common in patients with blood group AB (3.6%) (Meo *et al*., 2017).

Classification of ABO blood types of the breast cancer patients were studied . The frequency results showed different percentages of ABO blood types where A^+ had a frequency of (40.8%), O^+ had a frequency of (28.9%), B^+ had a frequency of (14.5%), and AB^+ had a frequency of (9.2%), (Meo *et al*., 2017).

A study was conducted to assess complete blood counts of the breast cancer patients to determine their prognostic values during the different courses of chemotherapy treatment. The mean age of breast cancer patients was 47.49±10.43. A decrease in mean value of Hb concentration was observed from12g/dl ±1.45 to 10.9g/dl ±1.54. Platelet count was observed to be increased as the treatment proceeds from first chemotherapy to fifth course of chemotherapy. A decreased pattern of number of total leukocyte and lymphocyte count was noted during chemotherapy treatment. No significant variation was observed for neutrophils, Eosinophil and monocyte count during the different courses of chemotherapy treatment. Conclusion: results suggested the prognostic

significance of the complete blood cell count in the disease monitoring and metastasis (Chauhan *et al*., 2016).

Whole blood analysis of BC patients treated with antineoplastic drugs Fluorouracil Adriamycin and Cyclophamide (FAC) and Adriamycin and Cyclophamide (AC) were investigated. The results indicated a moderate decrease in hemoglobin concentration, a large decrease in the number of red blood cells, and there were no significant differences between the antitumor chemotherapeutic agents. (Asif *et al*., 2017).

A study at the (PLA) General Hospital of China in Beijing, China was carried out to evaluate the primary predictions of blood analysis for breast cancer patients before treatment. Blood samples values of 162 patients, were scored for red blood cells and the ratio Neutro-Lymphoma Ratio (NLR) before treatment. The values of scored components were different according to age. these results confirm the importance of blood analysis for breast cancer early detection (Zhang *et al*., 2016).

1.9.1.2 Obesity and breast cancer

A study was carried out between in 2018 using a questionnaire on 105 BC women and 210 controls. Data were collected from the two main hospitals in Gaza strip. Statistical analysis identified the risk factors that lead to BC. Statistical analysis revealed that woman with Body Mass Index (BMI) more than or equal 30 kg/m2 are under risk of getting BC 2.9 times greater than those having BMI less than 29 kg/m2. The risk for women reaching menopause was greater among those reached menopause than among those did not reach menopause. The family history risk was more than two times higher than in case of the history of a free family of BC (Yassin *et al*., 2019).

Generally, it was reported that inverse relative risk between breast cancer and obesity or high BMI among individuals under the age of 49, Whereas a positive relative risk between breast cancer and obesity or high BMI

were found among individuals over 80 years. Several results indicated that menopause besides obesity or high BMI may represent a significant determinant risk of breast cancer (Kazan and Karalti, 2015).

1.9.1.3 Patient knowledge of breast cancer risk factors (awareness of risk factors)

Another study conducted among British women to examine knowledge and beliefs about breast cancer found that older women have a poorer understanding of symptoms and hazards, which may help to explain the substantial link between older age and delaying seeking help. Women aged 35 to 59 years were thought to be the most at risk of having breast cancer in the current group. BC is the leading cause of death among women in their forties and fifties. Older women and women who had never worked had a lower understanding of symptoms. Nipple eczema, changes in the form or size of the breast, and nipple retraction were less likely to be recognized as breast cancer signs by older women. It's possible that older women blame their ailments on the passage of time (Grunfeld *et al*., 2002).

In absolute terms, however, being older is the greatest risk factor for breast cancer. Over 70-year-old women account for roughly one-third of all breast cancer cases (Partridge *et al*., 2012).

1.9.1.4 Age at childbearing and it is relationship to disease

An international joint study of breast cancer and reproductive experience was conducted. In all areas analyzed there were A strong relationship between age at first birth and breast cancer risk. When first child occurs before the age of 18 there were a prediction of around one-third a breast cancer risk than women waiting until 35 years old or older. Several studies that found negative association between total parity and breast cancer risk was explained by the lower risk of breast cancer in young women, because they had first child early and likely to have high parity later. The etiological theories for age at first birth necessitates more studies of than those previously proposed to explain the link between breast cancer risk and reproductive experience (Macmahon *et al*., 1970)

1.9.1.5 The importance of early screening against breast cancer

A Palestinian questionnaire was distributed for 397 women aged from 30 to 60 years old . Results revealed more than (70%) of the participants had never used mammography, and (62%) had used physical Breast Self-Examination (BSE) due to socioeconomic demands (Cohen and Azaiza, 2010).

A questionnaire was used for 519 Jordanian women and indicated that (67%) knew and/or read about (BSE), however a low percent (7%) were do it monthly (Petro-Nustus and Mikhail, 2002).

A survey was conducted in the United Kingdom to assess knowledge of breast cancer and preventive measures, indications referred to the majority of breast cancer patients were unfamiliar with the subject of cancer and a lack of understanding its symptoms as an illness. Patient women considered a painless breast lump as a symptom of abnormalities, not malignancy, and also unaware of any non-lumpy breast symptoms (Karbani *et al*., 2011).

Similar results were scored in Iran that a lack of understanding breast cancer was a major reason for women breast cancer delay diagnosis and incidence (Montezeri *et al*., 2003).

1.9.1.6 Smoking and breast cancer

Factors associated with patient and doctor delay for breast symptoms diagnosis were studied among 180 Thai women. Results revealed that (17 %) of women delayed seeking consultation for more than 3 months, and (42%) was a doctor delay of more than 1 month. Statistics analysis showed that higher family income and smoking were a significant increase in patient delay, while previous breast symptoms, self-treatment, and travel time to the hospital were a significant increase in doctor delay (Poum *et al*., 2014).

1.9.1.7 Tobacco and breast cancer

Tobacco smoke contains more than 20 recognized carcinogens, which can be discovered in the breast fluid and tissue of smokers. The International Agency for Research on Cancer (IARC) considered the evidence to be inconclusive in recent evaluations of existing epidemiologic research, however the California Environmental Protection Agency and the Canadian study judged the evidence to be consistent with causality among younger, premenopausal women. According to the California Teachers Study, postmenopausal women are at an elevated risk as well (Hiatt and Brody., 2018).

1.9.1.8 Vitamin D and breast cancer

A relationship between low vitamin D levels and an increased risk of cancer is now widely established. Across-sectional investigation of VD levels and clinic-pathological features in 200 BC cases at the National Cancer Institute of Thailand was done during 2011-2012 to assess the influence of low VD on breast cancer progression. High-performance liquid chromatography (HPLC) was used to determine VD levels. The

average VD level was (23.06 ng /ml). VD levels were found to be high (32 ng /ml) in 7% of patients and low in (93%). VD deficiency was detected in the majority of individuals with advanced disease (P=0.036). Data indicated that low and reduced VD levels may be due to breast cancer growth and metastasis **(**Thanasitthichai *et al*., 2015**).**

1.9.1.9 Radiation and breast cancer

Ionizing radiation is an environmental factor that causes breast cancer. Japanese Survivors of the atomic bomb explosions were evidence of the developing breast cancer (Carmichael *et al*., 2003).

Radiation diagnostic medical methods, such as radiography, fluoroscopy, and computed tomography, are most common source of radiation exposure (IOM, 2012) . Efforts were done to significant reductions and control the use of medical diagnostic radiation (Hiatt and Brody, 2018).

1.9.2 Breast cancer in Libya

BC nical stage of breast cancer was (65.5%) of all patients, and it was more common among women with a diagnosis delay of more than 6 months (89.3%) than among women diagnosed within 3 months of onset of symptoms (23%; $p < 0.0001$). Large tumor size (T3 and T4; $p < 0.0001$) and positive lymph nodes (N2, N3; $p < 0.0001$) were both related with diagnosis delay. There were 23 patients had metastases at the time of diagnosis, and (91.3%) of them were some diagnosis delay more than six months (Ermiah *et al*., 2012).

Another study was carried out where data collected from Tripoli Medical Center in 2008. Patients groups were designed to represent (31%) less than 15 years old, (64.6%)represented 15-64 years, and (4.2%) were older than 64 years. BC was the highest among women cancer diseases (23.7%). Results revealed increasing cancer diseases in western Libya in relation to age. (Elzouki *et al*., 2018).

Data of registered Cancer patients (402 cases) were collected from Tobruk Medical Centre, Department of Histopathology during 2013 to 2020. Men and women patients were chosen randomly and represent (30.3%) (n= 122) and (69.6%) (n= 280) respectively. Results indicated that 49.0 ± 17.1 years old and the common cancers were breast and uterine for women (18.4%, n= 74, 15.9%, n= 64, respectively), while colorectal cancer, bladder cancer and thyroid cancer were common for men with percentages of (11.6%,), (8.2%,) and (8.0%) respectively (Jemal *et al*., 2010).

A BC study was carried out of 40 women to assess the relation between lipids and breast cancer at Benghazi's, Seventh of October Hospital. Their average height was 160.56 ± 5.89 cm, their weight was 71.36 ± 13.3 kg, and their BMI was 31.494 ± 5.53 Kg/m^2. Data indicated a positive relation between breast cancer and lipids (Kondredddy *et al*.**,** 2012).

A poll was carried out in Benghazi, Libya to evaluate women's knowledge, experience with BSE in 2013. The cluster approach was employed for sampling, 30 cluster groups were chosen, and 3000 women were targeted. Private interviews were done with 2,601 women, with an average age of 36.4 years and more than half of them being married. The findings revealed that just a small fraction of women is aware of the method of BSE, (48.1%) have never heard of it. Also, even among educated women, understanding of the self-examination test, as well as prevention and risk factors, were limited. The study suggested a priority awareness and early detection of risk factor breast cancer prevention in Benghazi (Ziuo *et al*., 2018).

1.11 Aims of the Study

This study aims to analyze the most important biological factors that cannot be changed such as gender - family history - age - hormonal factors - a decrease in the number of pregnancy periods of breastfeeding - age at marriage, in addition to other variable factors that were detailed in the supplementary questionnaire was applied to BC patients attending the Sabratha Cancer Center.

The objectives of the study can be identified in the following points:

1. Study of breast cancer biological risk factors .

2. Determine the type of blood group (A,B,AB,O) and the Rh factor (Rh) .

3.Compare between blood cell counts (CBC) before and after chemotherapy and determine the level vitamin D(VD) .

CHAPTER 2

SUBJECTS AND METHODS

2. Subjects and Methods

2.1.1 Study design and population

The present study was conducted on 80 breast cancer patients, attending the National Cancer Institute Sabratha . The study started in september 2020 until the end of August 2021) . The questionnaire was completed through personal interviews and measure weight and height , as well as determining the blood cells count (CBC),Hb concentration and percent of Nutro , lemphcytes , platelets of pre and post chemotherapy through from patient files as well as determining the blood group (ABO), Rh factore (Rh-,Rh^{+}) and also VD(VD) level and comparing it with the control group. This study was approved by the Research and Ethical Committee of Sabratha University and National Cancer Institute in Sabratha . Also, 40 healthy individuals without any chronic disease were recruited for the control group. Blood samples were collected by vein puncture, 3 ml of venous blood withdrawn from each participant in the study by using disposable syringes under aseptic technique; then transferred to a sterile EDTA tube, for complete blood.

Table 2.1 Patients group and control group numbers.

Category / Totals	First age Category (29-39)	Second age Category (40-50)	Third age Category (51-61)	Fourth age Category (62>)
Patients group	20	20	20	20
Control group	10	10	10	10

2.1.2 Determination of blood groups for control group.

Blood groups were carried out using open slide methods, where three drops of blood sample from a sterile finger prick were placed into three different locations on a clean glass slide followed by a drop of blood grouping reagents, anti-A, anti-B, and anti-D. The reagents and the blood drops were mixed using clean stick . After one minute, the test slide was checked for agglutination. If there is agglutination with anti-A reagent and agglutination with anti-D this means the blood group is A^+. If there is agglutination with anti-A reagent and no agglutination with anti-D this means the blood group is A^-. If there is agglutination with anti-B reagent and agglutination with anti-D this means the blood group is B^+. If there is agglutination with anti-B reagent and no agglutination with anti-D this means the blood group is B^-. If there is agglutination with both anti-A, anti-B, and anti-D this means the blood group is AB^+. If there is agglutination with anti-A and anti-B and no agglutination with anti-D this means the blood group is AB^-. If there is no agglutination with both anti-A and anti-B and only there is agglutination with anti-D this means the blood group is O^+. if there is no agglutination with all anti-A, anti-B or anti-D this means the blood group is O^-.

2.1.3 Questionnaire .

Data were collected through a personal interview for each women diagnosed with breast cancer in a questionnaire **(Appendix A)**. These data included age, blood type, family history, weight, height, age at menstruation, marital status, place of residence, red meat consumption , smoking, exposure to radiation and use of black hair dye.

2.3 Statistical analysis

Results are expressed as mean ± standard deviation. Statistical significance was tested by Unpaired Student’s. Dunnett's Multiple

Comparison Test with a one and two ways analysis of variance (ANOVA) was used for multiple comparisons. All date analyzed using GraphPad prism 8.0 software. The P values, for multiple group comparisons were adjusted using Bonferroni's method. All statistical tests were two-sided, and a statistical significance level was set at ($P < 0.05$).

CHAPTER 3

RESULTS

3.The results:

Early diagnosis and awareness of breast cancer risk factors are of great importance to save women worldwide. A several types of factors that increase the risk of breast cancer include biological origin such as family history and reproductive factors (pregnancy, fertility drugs, breastfeeding, hormonal birth control and postmenopausal hormones). Environmental origin factors such as (radiation exposure, environmental pollutants and occupational exposures). Other external risk factors include (tobacco use, obesity, physical activity, diet and alcohol consumption). This study has been designed to investigate the most important potential risk factors that increase incidence of the disease.

3.1. Distribution of control group and breast cancer patients according to age groups.

The mean age of breast cancer patients included in the current study was 33±14 years (29-62years old).

Data in (Table 3.1 & figure 3.1) show the distribution of patient women, were 80 chosen randomly and showed different numbers which related to each group. The most representative patient group was the category (40-50) years old with frequency of 33 cases and represented `(41.25%), (51-61) years with frequency of 14 cases , 21 and represented (26.25%), and the age group (62>) with frequency of 12 was represented (15%). A total of 24 women were chosen as control and represent the four age groups in equal numbers (each group has 6 healthy women) (table 3. 1 & figure 3.1).

Table 3.1: Distribution of control group and breast cancer patients according to age groups.

Control N=24			Patients N=80	
Age groups (Years)	**Frequency**	**Percent (%)**	**Frequency**	**Percent (%)**
(29-39)	6	25%	14	17.5%
(40-50)	6	25%	33	`41.25%
(51-61)	6	25%	21	26.25%
(62 >)	6	25%	12	15%
Sum	**24**	**100**	**80**	**100**

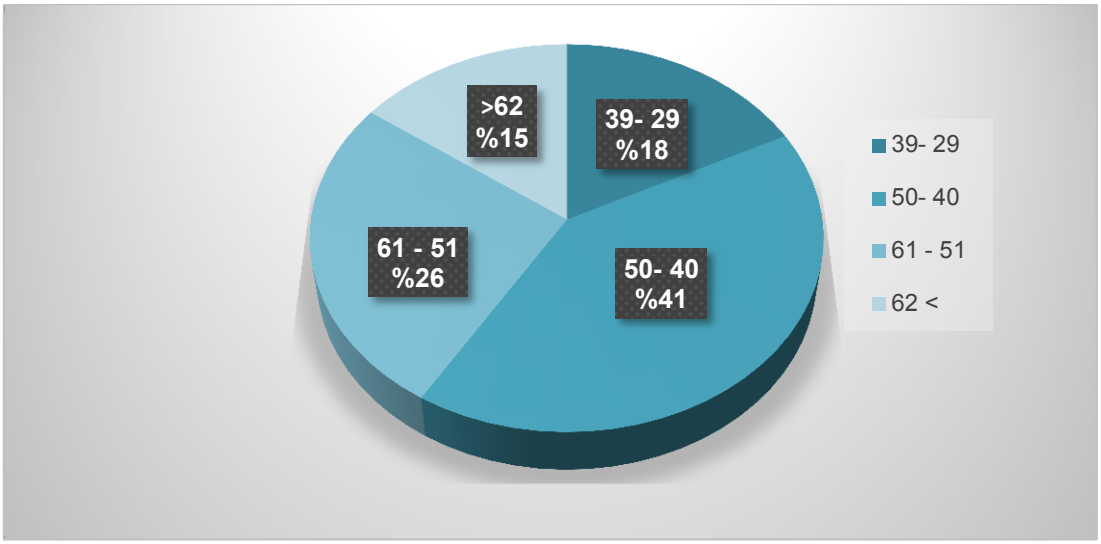


Figure 3.1: The percentage of breast cancer patients according to age. The study included 80 patients, the percentage was calculated for each age group as shown in the figure.

3.2. Distribution of control group and breast cancer patients according to body length.

Studies indicate the relationship of the body in terms of tall, weight, obesity, and hip circumference with the incidence of many diseases associated with obesity, such as type 2 diabetes, as well as carcinomas in general and breast cancer in particular. Measures of the frequency of patient height in (cm) were different among groups. The largest frequency

was registered to (157-162cm) height category group for 33 patients represent (41.5%). as well as the remaining patient groups were 150< 6 cases with 7.5%, (151-156cm) 16 cases with (20%), (163-168cm) 22 cases with 27.5% and (169-174cm) three cases with 3.75%.

Measures of the frequency of patient height in (cm) were different among groups for control and patients. The largest frequency was registered to (157-162cm) height category group for both control and patients represented (37.5%) with 9 healthy women and (41.5%)with 33 patients respectively (Table 3.2 & Figure 3.2).

Table 3.2: Distribution of control group and breast cancer patients according to body length.

Body length (CM)	Control N=24		Patients N=80	
GROUPS	**Frequency**	**Percent (%)**	**Frequency**	**Percent (%)**
150<	2	8.3	6	7.5%
151-156	4	16.6	16	20%
157-162	9	37.5	33	41.5%
163-168	6	25	22	27.5%
169-174	3	12.5	3	3.75%
Sum	**24**	**100**	**80**	**100**

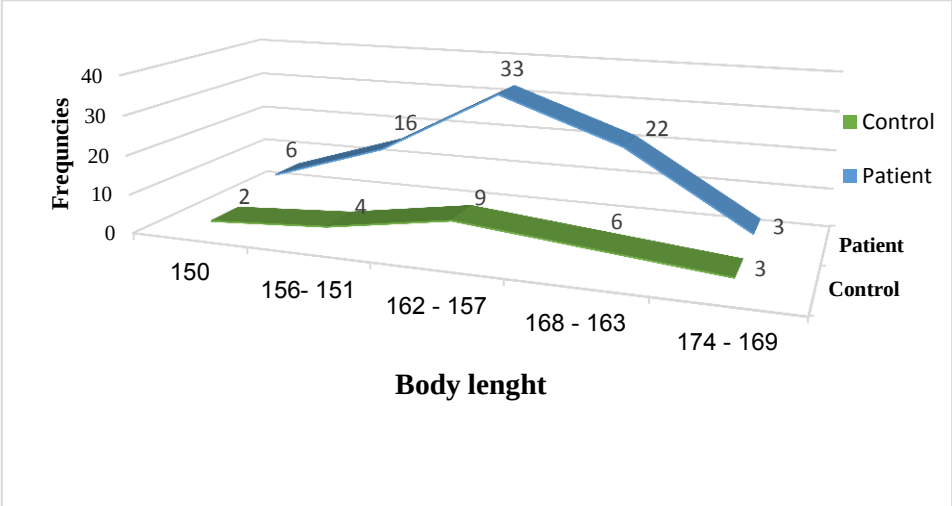


Figure 3.2: The frequency between the control and breast cancer patients according to height in (cm).

3.3. Distribution of control group and breast cancer patients according to body weight:

Data showed high body weight among women who their weight ranged from (73 - 83kg) were representing (33.3%) and (31.25%) for control and patients respectively. While the lowest 51 - 61 kg weight group represent (25%) and (27.5%) .The highest (95 >) weight group represent (8.3%) and (6.25%) for control and patients, both patient groups 62 – 72 and 84 – 94 kg were represented (23.75%) and (11.25%) respectively (Table 3.3 & Figure 3.3).

Table 3.3: Distribution control and patients according to body weight:

Weight (kg)	Control N=24		Patients N=80	
GROUP	**Frequency**	**(%)**	**Frequency**	**(%)**
51 - 61	6	25	22	27.5%
62 - 72	5	20.8	19	23.75%
73 - 83	8	33.4	25	31.25%
84 - 94	3	12.5	9	11.25%
95 >	2	8.3	5	6.25%
Sum	**24**	**100**	**80**	**100**

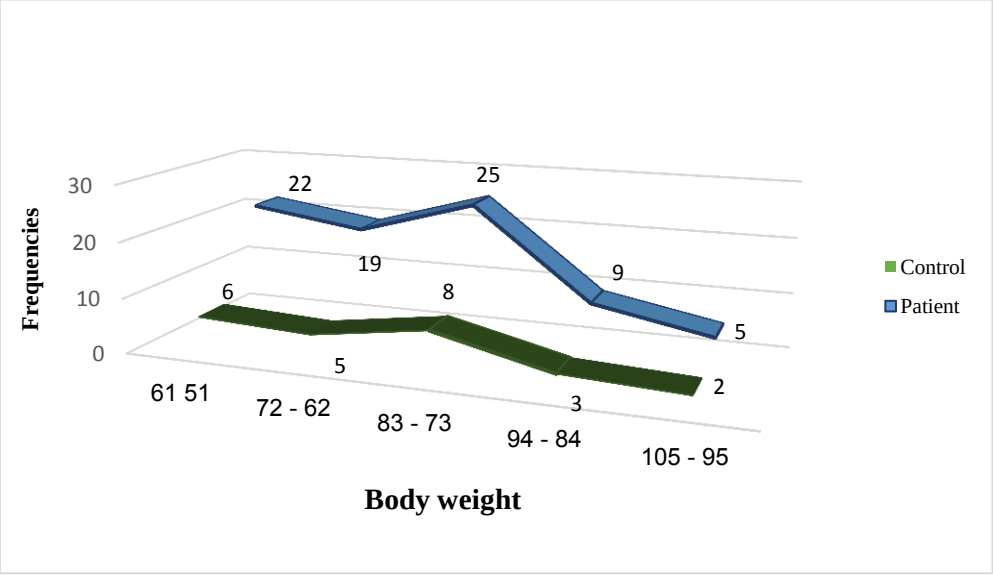


Figure 3.3: The frequency of breast cancer patients according to body weight.

3.4. Distribution of breast cancer patients according to the body mass index (BMI).

This results revealed approximately (75%) of patients have high BMI value, ranged from overweight 25 – 29.9 group to 40> group represent percentages of (30% -23.75% -16.25% - 6.25 %), respectively (Table 3.4 & Figure 3.4).

Table 3.4: Distribution of breast cancer patients according weight to the body mass index (BMI).

BMI Kg/m^2	Patients N=80	
GROUP	**Frequency**	**(%)**
Underweight 18.5 <	2	2.5%
Healthy weight 18.5 - 24.9	17	21.25%
Overweight 25 – 29.9	24	30%
Obesity 30 – 34.9	19	23.75%
Very high 35 – 39.9	13	16.25%
Massive weight 40>	5	6.25%
Sum	**80**	**100**

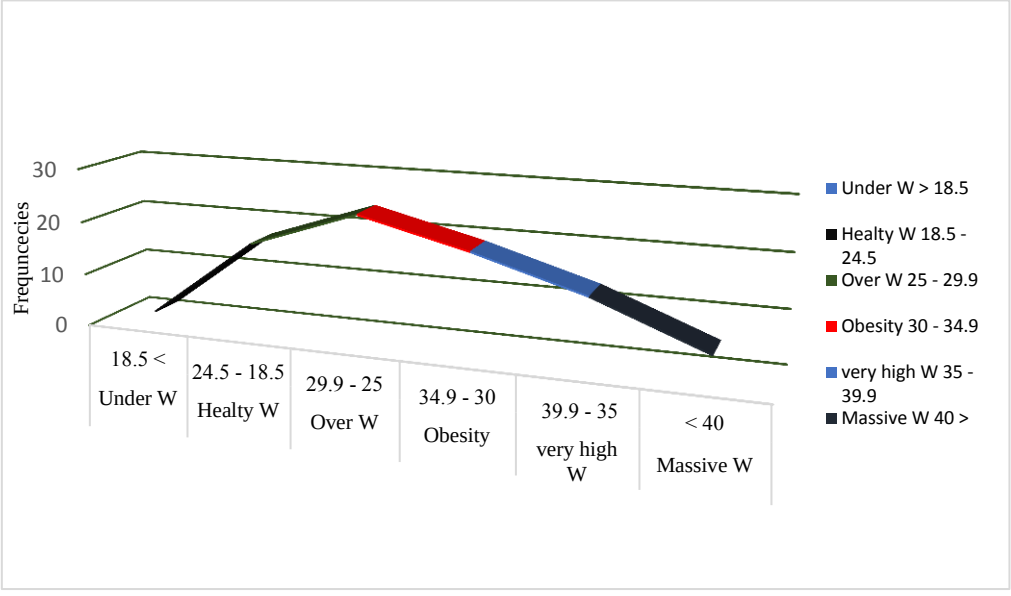


Figure 3.4: The frequency between the control and breast cancer patient according to BMI.

3.5. Distribution of control and breast cancer patients according to Rhesus Factor.

Patients Rhesus (Rh) positive blood group has high incidence of breast cancer (91.25%) and Rhesus negative has least association with breast cancer 8.75%. Control cases has (75%) Rh ve^{+} and 25 Rh ve^{-} (Table 3.5 & Figure 3.5), Statistical analysis was two-way ANOVA, Variance analysis revealed significant value of Rh factor interaction as a BC risk factor (P value > 0.0001) (Table 3.5 & Figure 3.5).

Table 3.5: Distribution of control group and breast cancer patients according to Rh Factor.

Control N=24			**Patients N=80**	
BLOOD GROUP	**Frequency**	**(%)**	**Frequency**	**(%)**
Rh^{+}	18	75%	73	91.25%
Rh^{-}	6	25%	7	8.75%
sum	**24**	**100**	**80**	**100**

******* P<0.0001 a statistically, high significant difference between control and patients
******* P<0.001 statistically high significant difference between control and patients.
P >0.9999 statistically not significant difference between control and patients.

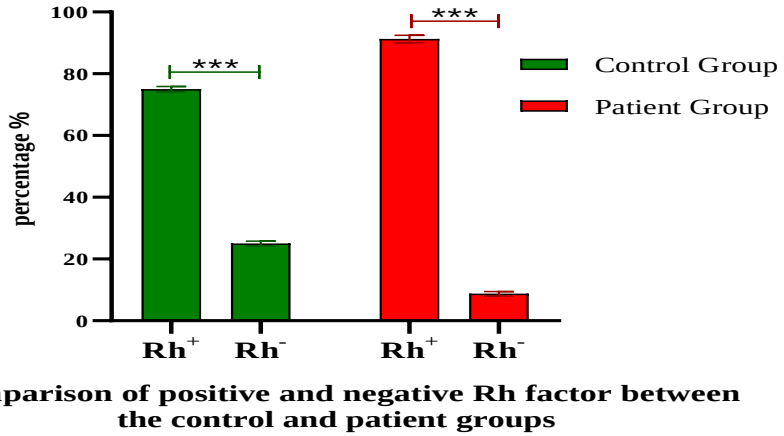


Figure 3.5: The percentage of both control and patients with breast cancer according to Rh Factor

3.6. Distribution of control group and breast cancer patients according to blood group (ABO).

Blood Group A (48.75%) has high incidence of breast cancer, blood group O has (37.5%), B (7.5%) and blood group AB has (6.25%) least incidence of breast cancer. Blood group A has highest and blood group AB has least association with breast cancer, blood groups showed a significant ($p<0.0001$) difference between healthy and breast cancer patients that, Statistical analysis was done two-way ANOVA, (Table 3.6 & Figure 3.6).

Table 3.6: Distribution and breast cancer patients according to blood group (ABO).

Control N=24			Patients N=80	
Blood group	**Frequency**	**(%)**	**Frequency**	**(%)**
A	10	41.6%	39	48.75%
B	3	12.5%	6	7.5%
AB	5	20.83%	5	6.25%
O	6	25%	30	37.5%
Sum	**24**	**100**	**80**	**100**

*P< 0.01 A statistically significant difference between control and patients for blood group
**P<0.0001 A statistically high significant difference between control and patients for blood group.

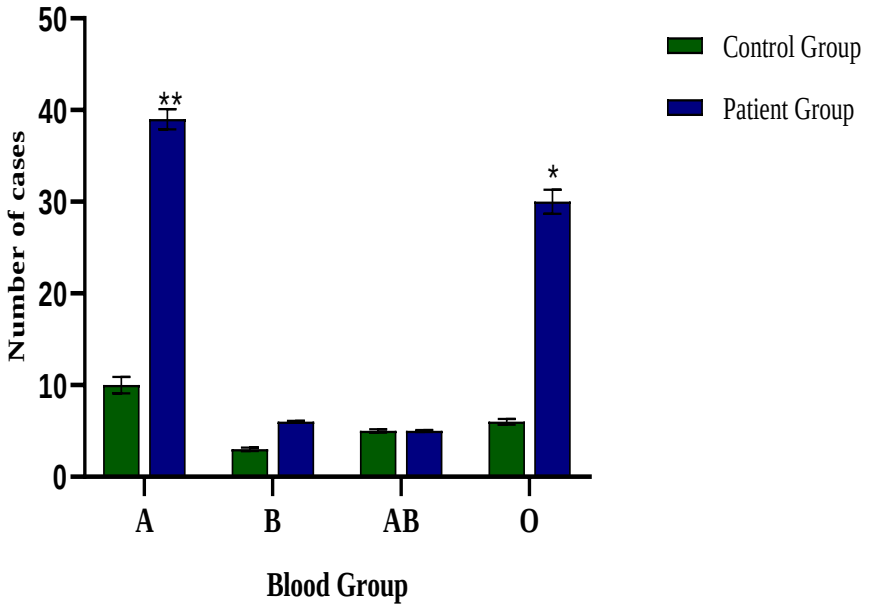


Figure 3.6: Distribution control and breast cancer patients according to ABO.

3.7. Distribution of control group and breast cancer patients according to the blood groups system (ABO) and Rhesus Factor (Rh).

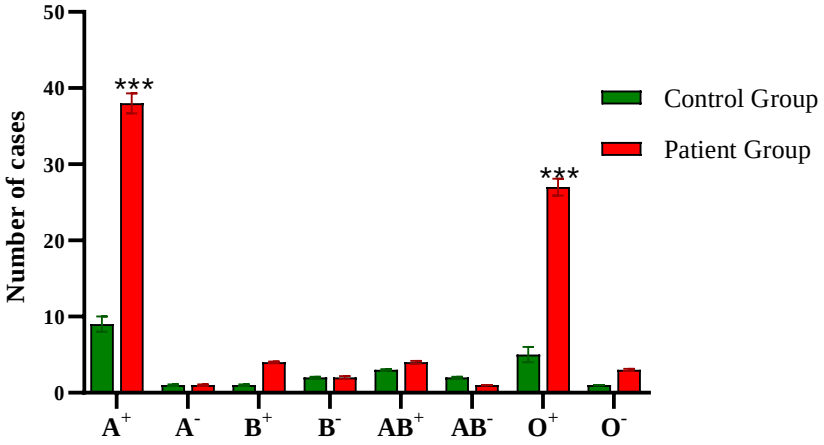
Blood groups A and O Rh $^{+}$ve represent (47.5%) and (33.75%) respectively have high risk of breast cancer, while other blood types AB and Rh ve- and ve^{+} ,A- , O- and + - B are at low risk of breast cancer . Researchers should carefully consider females with blood A and Rh ve^{+} and O Rh ve^{+} as these females are more tend to develop breast cancer. (Table 3.7) revealed significant correlation between Rh ve^{+} factor and blood groups A and O patients, blood groups and Rh showed very high incidence a significant ($p<0.0001$) difference between healthy and breast cancer patients that, respectively (Table 3.7 & Figure 3.7).

`

Table 3.7: Distribution healthy and patients according to blood group and Rh Factor.

Control N=24			Patients N=80	
Blood group	**Frequency**	**(%)**	**Frequency**	**(%)**
A^+	9	37.5%	38	47.5%
A-	1	4.16%	1	1.25%
B^+	1	4.16%	4	5%
B-	2	8.33%	2	2.5%
AB^+	3	12.5%	4	5%
AB-	2	8.33%	1	1.25%
O^+	5	20.83%	27	33.75%
O-	1	4.16%	3	3.75%
sum	**24**	**100**	**80**	**100**

**** P<0.0001 A statistically very high significant difference between control and patients



Frequency of breast cancer cases according to ABO/Rh factor compared to the control group

Figure 3.7: The frequency of control and breast cancer patients according to ABO/ Rh factor compared to the control group.

3.8 Distribution of breast cancer patients according to age category and blood group (ABO).

Table 3.8 reveals that risk of developing cancer is higher in blood groups A^+ and O^+ then a bit in AB^+, specially between age group (40-50) which represent(41.25%). Also, the same risk was found for the rest age classes

where blood group $A^{+,}$ O^{+} were common among patients, Variance analysis showed very high significant relations of blood group A^{+}, O^{+} and AB^{+} as breast cancer risk factors($P<0.0001$), Statistical analysis was conducted two-way ANOVA (Table 3.8 & Figure3.8).

Table 3.8: Distribution breast cancer patients according to Category blood groups (ABO).

Age group / ABO	Patients N=80								(%)
	A^{+}	A^{-}	B^{+}	B^{-}	AB^{+}	AB^{-}	O^{+}	O^{-}	
(29-39)	6	0	1	1	1	0	7	1	21.25%
(40-50)	18	1	2	1	3	1	6	1	41.25%
(51-61)	6	0	1	0	0	0	10	1	22.5%
(62>)	7	0	1	0	0	0	4	0	15%

*** P<0.0001 A statistically very high significant difference between control and patients
**p<0.001 A statistically high significant difference between control and patients.
*p<0.05 A statistically significant difference between control and patients.

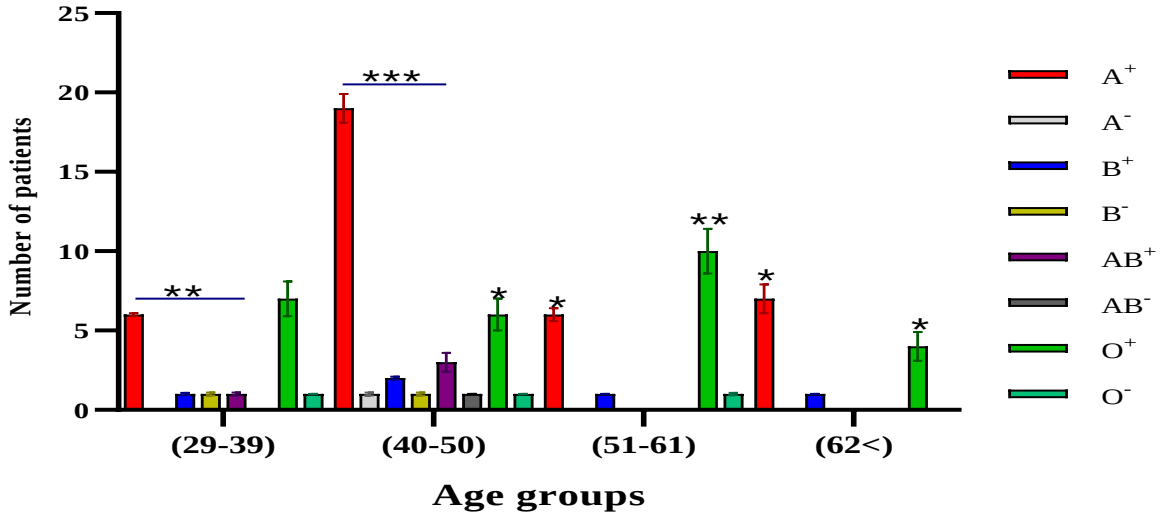


Figure 3.8: Distribution breast cancer patients according to category blood groups.

3.9. Distribution of control group and breast cancer patients according to the age at menarche.

Analysis of the results of the study sample showed a discrepancy in the age at the onset of menstruation, as the first age groups represented early menarche were (12<)(P< 0.002), (13-14)(P<0.01) represented frequency of 29 and 24 out of 80 patients, while the both groups (15-16) and more than 17 years were presented 18 and 9 frequencies respectively.

Table 3.9: Distribution of control group and breast cancer patients according to Age at menarche

Age at menstruation	Control N=24 Frequency	Patients N=80 Frequency	P value
12>	6	29	P<0.002
13-14	9	24	P<0.01
15-16	7	18	P<0.04
17<	2	9	P<0.05
Sum	**24**	**80**	**-**

***P <0.01 Variance high significant difference between control and patients.
* P <0.05 Variance significant difference between control and patients

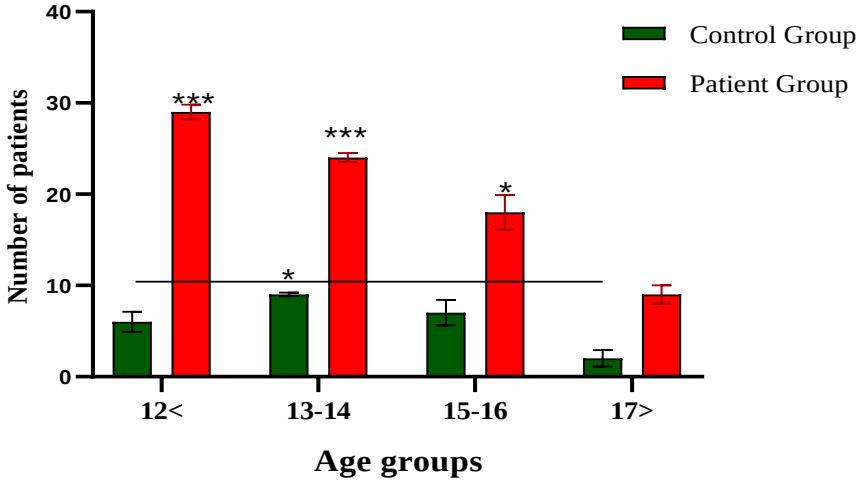


Figure 3.9: Distribution of control and breast cancer patients according to Age at menarche.

3.10. Distribution of control group and breast cancer patient's according to menopause status.

All menopause status was found among patients with different frequency 39, 27 and 14 which as percentage are (33.75%), (48.75%) and (17.5%) for Temporary, Permanent and Enduring types. Control group of study sample have showed only two menopause types, Permanent and Enduring where represent (41.6%) and (58.3%) (Table 3.10). The correlation between BC and menopause type was significant (Figure 3.10). Statistical analysis, menopause type showed a significant (P<0.0001) difference between healthy and breast cancer patients.

Table 3.10: Distribution of control group and breast cancer patients according to menopause type.

Menopause type	Control N=24 Frequency	Patients N=80 Frequency	P value
Temporary	0	27	P<0.01
Permanent	10	39	P<0.0037
Enduring	14	14	P<0.09
Sum	**24**	**80**	-

**P < 0. 01 statistically, high significant difference between control and patients.
*** P<0.003 statistically very high significant difference between control and patients

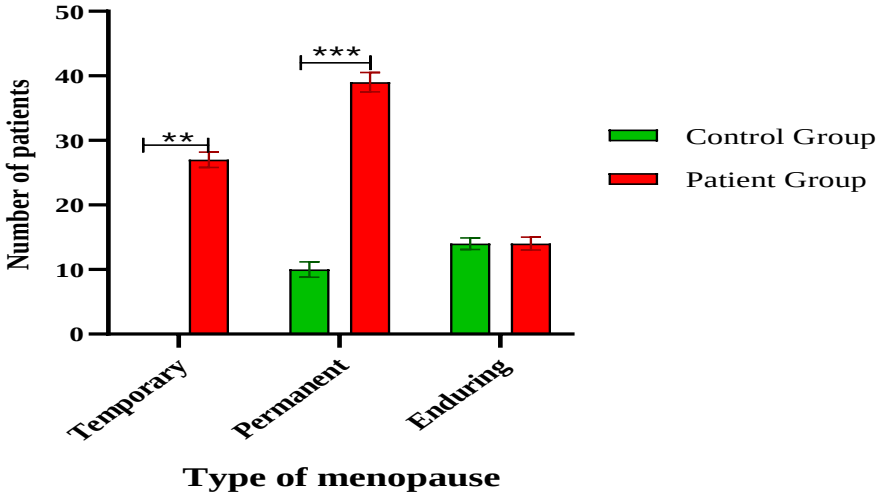


Figure 3.10 Distribution of control and breast cancer patients according to menopause type.

3.11. Distribution of control group and breast cancer patients according to residence.

The distribution of patients in rural was more than urban ones. Percentages were (37.5%) of urban and (62.5%) of rural for control group, while patient group were (42.5%) and (57.5%), respectively (Table 3.11 & Figure3.11).

Table 3.11: Distribution of control group and breast cancer patients of according to residence.

Control N=24			Patients N=80	
Residence	**Frequency**	**(%)**	**Frequency**	**(%)**
Urban	9	37.5%	34	42.5%
Rural	15	62.5%	46	57.5%
Sum	**24**	**100**	**80**	**100**

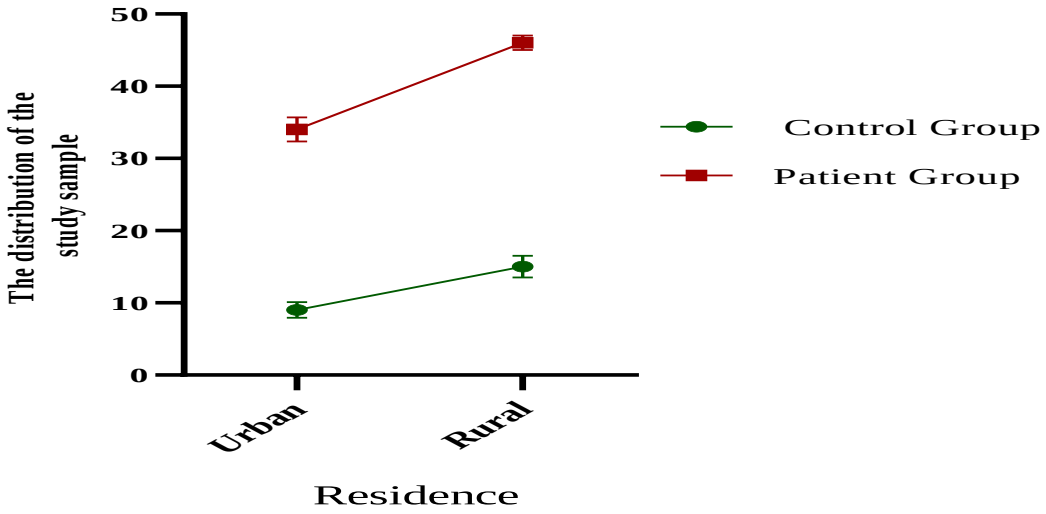


Figure 3.11: Distribution control and breast cancer patients according to residence

3.12. Distribution of control group and breast cancer patients according to social status.

Data showed that 50% of control was married, unmarried were 33.3% and widow was the least group with(16.6%). Married social status was the most group of patients with (77.5%), unmarried was (16.25%) and the widow was the lowest by (6.25%), representatives (Tab 3.12 & Fig 3.12).

Table 3.12. Distribution of control group and breast cancer patients according to social status .

Social status	Control N=24	Patients N=80	P value
	Frequency	Frequency	
Married	12 (50 %)	62 (77.5 %)	P<0.001
Unmarried	8 (33.3%)	13 (16.25 %)	P<0.01
Widow	4 (16.6%)	5 (6.25 %)	P<0.0826
Sum	**24**	**80**	**-**

*P < 0.0826 statistically significant difference between control and patients.
** P< 0.01 statistically high significant difference between control and patients

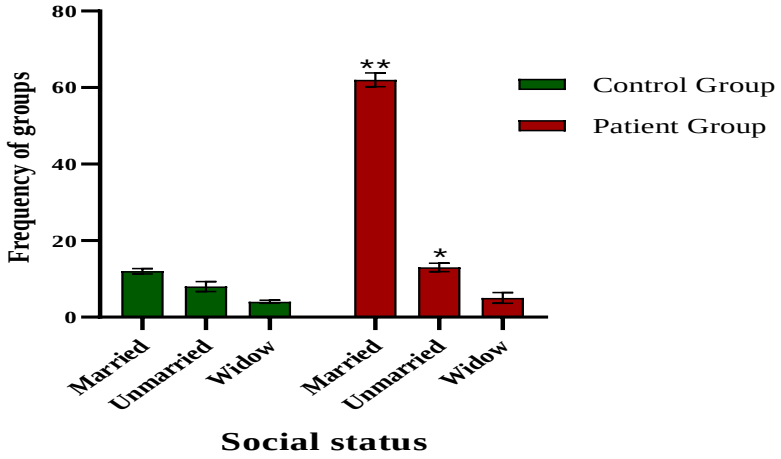


Figure 3.12: The frequency of control and breast cancer patients according to Social status.

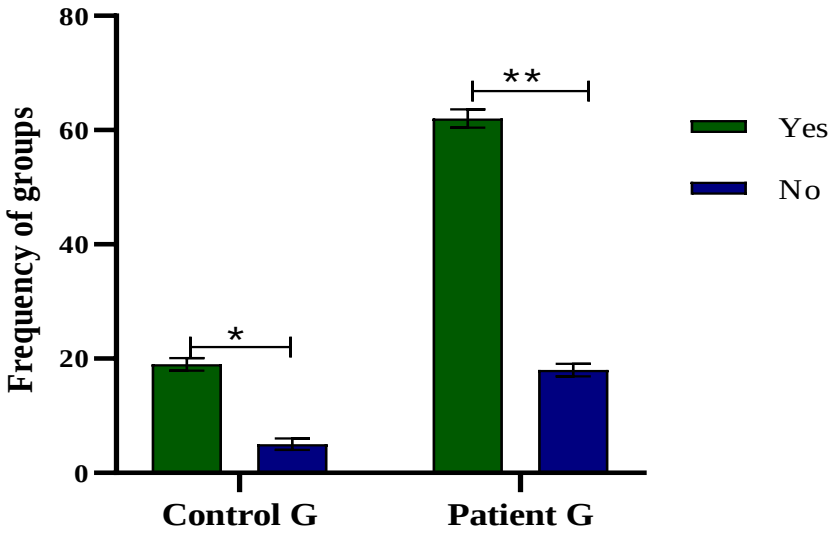
3.13. Distribution of control group and breast cancer patients according to having children.

Frequency of having children for patient group is 62 namely equal (77.5%) while have not children its frequency is 18 equal (22.5%). (Table 3.13 & Figure 3.13).

Table 3.13: Distribution of control group and breast cancer patients of according to having children.

Having children	Control N=24 Frequency	Patients N=80 Frequency	P value
Yes	16 (66.6%)	62 (77.5%)	P<0.020
No	8(33.3%)	18 (22.5%)	P<0.039
Sum	**24**	**80**	**-**

* P<0.039 statistically significant difference between control and patients
**p< 0.020 statistically significant difference between control and patients.



The relationship of breast cancer to the presence or absence of births, in both the control and the patients

Figure 3.13: The frequency control and breast cancer patients according to having children

3.14. Distribution of control group and breast cancer patients according to number of multiple births.

Multiple births frequencies were revealed differences among patients groups, while number of multiple births with frequency 47 women for multiple birth 1-5 was (58.75%) for patients none group was (22.5%) with frequency 18 women, the least percentage (18.75%) was the group of 6-10 with frequency 15 women (Table 3.14 & Figure 3.14).

Table 3.14: Distribution of control group and breast cancer patients according to number of multiple births.

Multiple births	Control N=24		Patients N=80	Percentage between group of patients (%)
	Frequency	(%)	Frequency	
None	8	33.3%	18	22.5%
1-5	4	16.6%	47	58.75%
6-10	12	50%	15	18.75%
sum	24	100	80	**100**

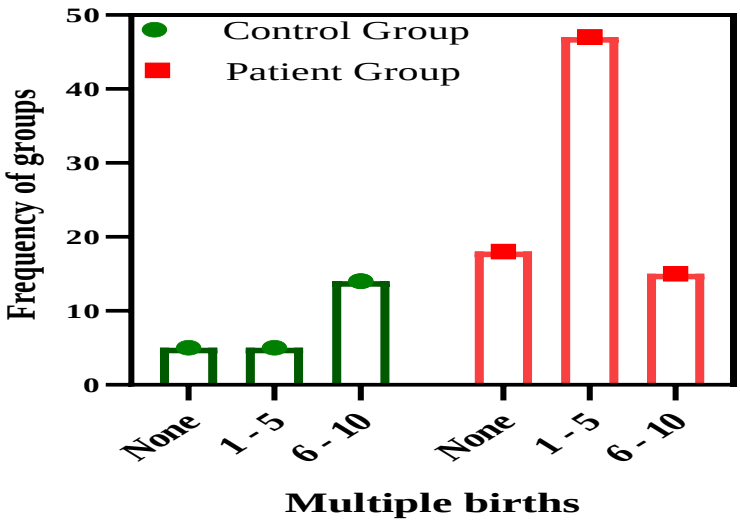


Figure 3.14: The frequency of control and breast cancer patients according to multiple births.

3.15. Distribution of control group and breast cancer patients according to marriage age.

Frequencies of marriage age were high to the age group 26 years old or less years and scored (70%) for 47 patient. The age group 27-37 years old frequency was 16 represented (23.88%) among patients. Frequency of 38 – 48 years old age group scored (4.47%) in patients. The age group 49-60 years old scored the lowest percentage (1.49%) for patient women representatives (Table3.15 & Figure 3.15).

Table 3.15. Distribution of control group and breast cancer patients according to marriage age.

	Control N=24		Patients N=67	
Marriage age	Frequency	(%)	Frequency	(%)
26>	12	50%	47	70.14%
27-37	7	29.1%	16	23.8%
38-48	3	12.5%	3	4.47%
49-60	2	8.33%	1	1.492%
sum	**24**	**100**	**67**	**100**

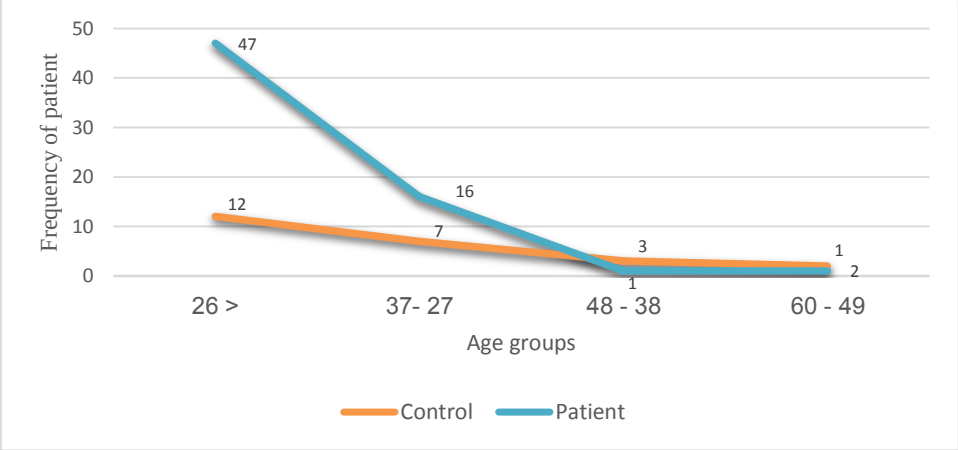


Figure 3.15: The frequency control and breast cancer patients according to marriage age.

3.16. Distribution of control group and breast cancer patients according to the age at lay a first birth.

The age at lay a first birth for patients were ranged from (1.6%) represent only one case to (66.1%) represent 41 patient, for age group27-37 and 49-60 years old. Age less than 26 years Frequencies was 18 women and represent (29%) at the first lay birth and for the age group 38-48 years old was (3.2%) represent two cases . (Table 3.16 & Figure 3.16).

Table 3.16: Distribution of control group and breast cancer patients according to the age at lay first birth.

The age at first birth	Control N=16		Patients N=62	
	Frequency	(%)	Frequency	(%)
26<	2	12.5%	18	29.0%
27-37	12	75%	41	66.1%
38-48	1	6.25%	2	3.2%
49-60	1	6.25%	1	1.6%
Sum	**16**	**100**	**62**	**100**

*P <0.01 Variance high significant difference between control and patients
**P <0.001 Variance high significant difference between control and patients.

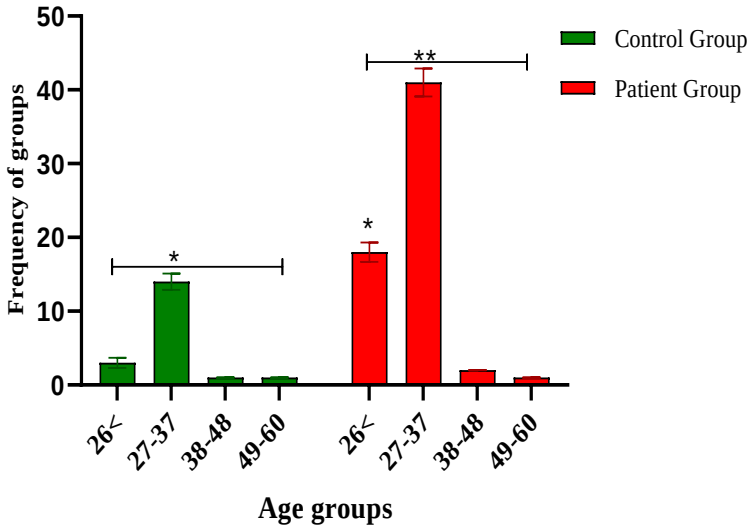


Figure 3.16: The frequency control and breast cancer patients according to the age at lay first birth.

3.17. Distribution of control and breast cancer patients according to type of lactation.

Lactation frequencies were calculated as percentages recorded for patients, the mix lactation in 49 patients (out of 62 patient women) and represented (79%) while the breast feeding 10 cases represented (16.1%), and formula feeding was (4.83%), with three cases. The control group, types were which were 9 cases (out of 16 healthy women) with (50%), 5 cases with (31.25%), and 3 cases with (18.75%) for the three types of lactation, respectively. Variance was very high with asignificant difference between control and patients P<0.0001, (Table 3.17 & Figer 3.17).

Table 3.17. Distribution healthy and breast cancer patients according to type of lactation.

Type of lactation	Control N=16		Patients N=62	
	Frequency	(%)	Frequency	(%)
Breast Feeding	8	50%	10	16.1%
Formula Feeding	5	31.25%	3	4.83%
Mixed	3	18.75%	49	79.0%
Sum	**16**	**100**	**62**	**100**

*** P<0.0001 Variance very high significant difference between control and patients.

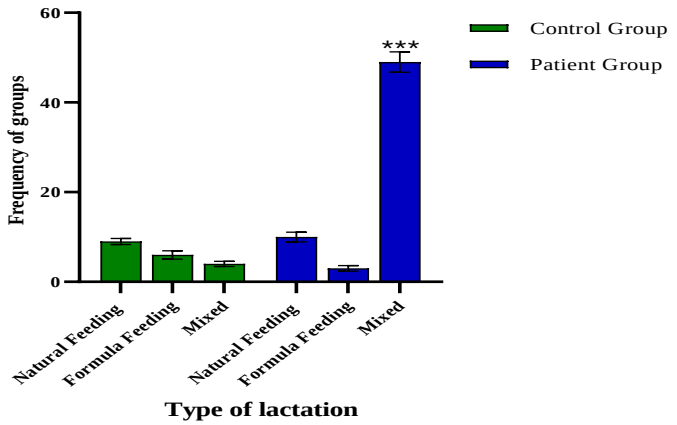


Figure 3.17: The frequency control and breast cancer patients according to the type of lactation.

3.18 Distribution of control group and breast cancer patients according to use of contraceptives .

By viewing and analyzing the questionnaire for the control group and patients, it was found that contraceptives were not related to the BC, as it was found that approximately (50%) used contraceptives and almost the same percentage did not use contraceptives, (Table 3.18 & Figure 3.18)

Table 3.18: Distribution of control group and breast cancer patients according to use of contraceptives.

Use of contraceptives	Control N=24		Patients N=67	
	Frequency	(%)	Frequency	(%)
yes	13	54.1%	34	50.7%
No	11	45.8%	33	49.2%
sum	**24**	**100**	**67**	**100**

P <0.19 Variance not significant difference between control and patients.

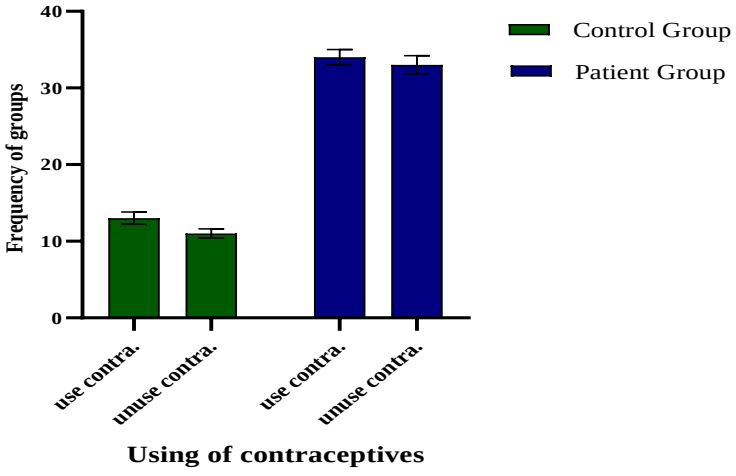


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Figure 3.18: The frequency control group and breast cancer patients according to use of contraceptives.

3.19. Distribution of breast cancer patients according to age at onset of symptoms

The current study showed that the age at the onset of symptoms for 38-48 years old was the highest among women that reached (43.8%) versus the age group less than 26 years old that was zero percent. The two age group 27-37 years old and more than 49 years old represented (23.7%) and (32.5%) (Table 3.19 & Figure 3.19**).**

Table 3.19: Distribution of breast cancer patients according to Age at onset of symptoms.

Patients N=80		
Age at onset of symptoms	**Frequency**	**(%)**
26<	0	0%
27-37	19	23.7%
38-48	35	43.8%
49>	26	32.5%
Sum	**80**	**100**

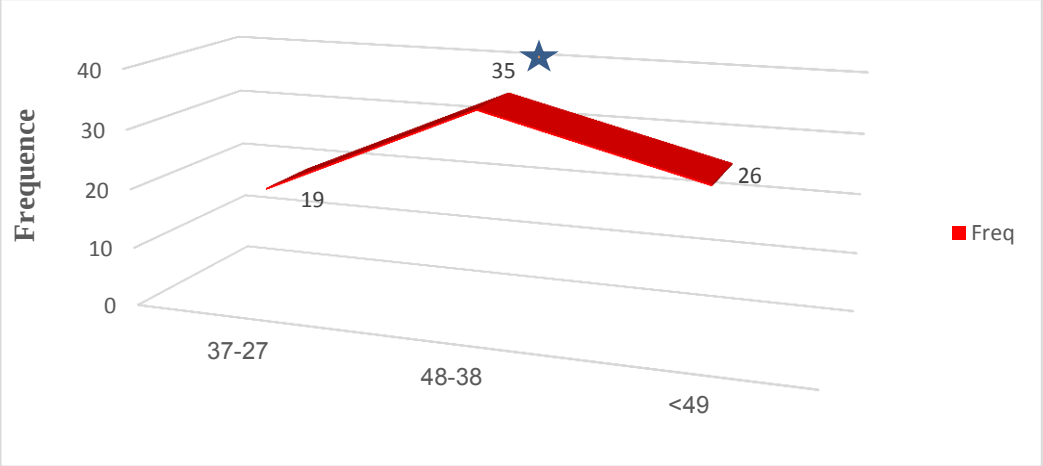

Figure 3.19: The Frequency of breast cancer patients according to Age at onset of symptoms.

3.20. Distribution of breast cancer patients according to the period of persistence of symptoms / year.

The results showed that the percentage of patients attending the National Cancer Institute in Sabratha, (45%) of them showed symptoms from 5 years old or less, and that the rates decrease with increasing years for patients, which the age group 6-10 years old was 26 women represented (32.5%) , 11-15 and 16-20 years old was15, 3 women represented (18.75%),(3.75%) as shown in the table below (Table 3.20 & Figure 3.20).

Table 3.20: Distribution breast cancer patients according to the period of persistence of symptoms / year.

Patients N=80		
The period of persistence of symptoms / year	**Frequency**	**(%)**
5≤	36	45%
6-10	26	32.5%
11-15	15	18.75%
16-20	3	3.75%
Sum	**80**	**100**

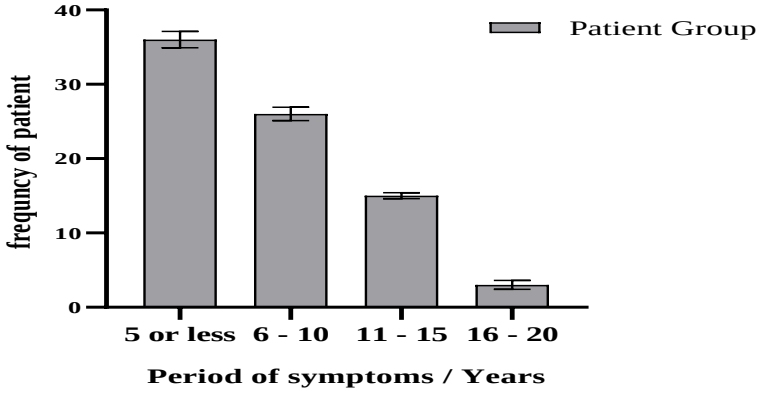

Figure 3.20: The Frequency of breast cancer patients according to the period of symptoms / year.

3.21. Distribution of breast cancer patients according to method of detection.

Breast self-examination (BSE) with frequency 64 women was the highest detection method that reached (80%) for the patients. Mammogram and Mammography methods were representing(15%) (12 cases) and (5%) (4 cases) respectively, (Table 3.21 & Fig 3.21).

Table 3.21: Distribution breast cancer patients of according to Detection method of detection .

Patients N=80		
Detection method	**Frequency**	**(%)**
BSE	64	80%
Mammogram	12	15%
Mammography	04	5%
Sum	**80**	**100**

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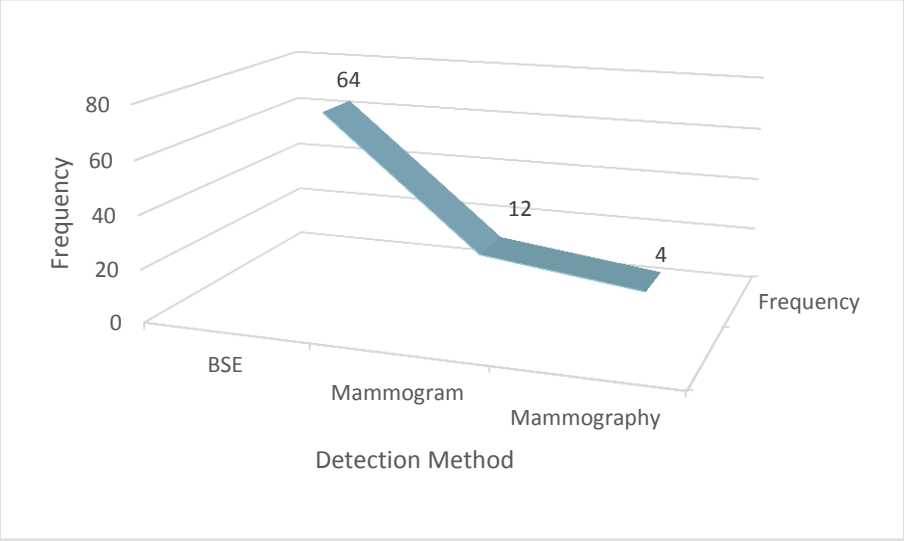


Figure 3.21: The Frequency of breast cancer patients according to method of Detection.

3.22. Distribution of breast cancer patients according to family history.

Family history was scored 29 women that represented (36.2%) among patient women while the more percentage was (63.7%) with 51cases among patient women that had no family history as risk factor of the disease, respectively (Table 3.22 & figure 3.22).

Table 3.22: Distribution of breast cancer patients according to family history

Patients N=80		
Family history	**Frequency**	**(%)**
No	51	63.7%
Yes	29	36.2%
Sum	**80**	**100**

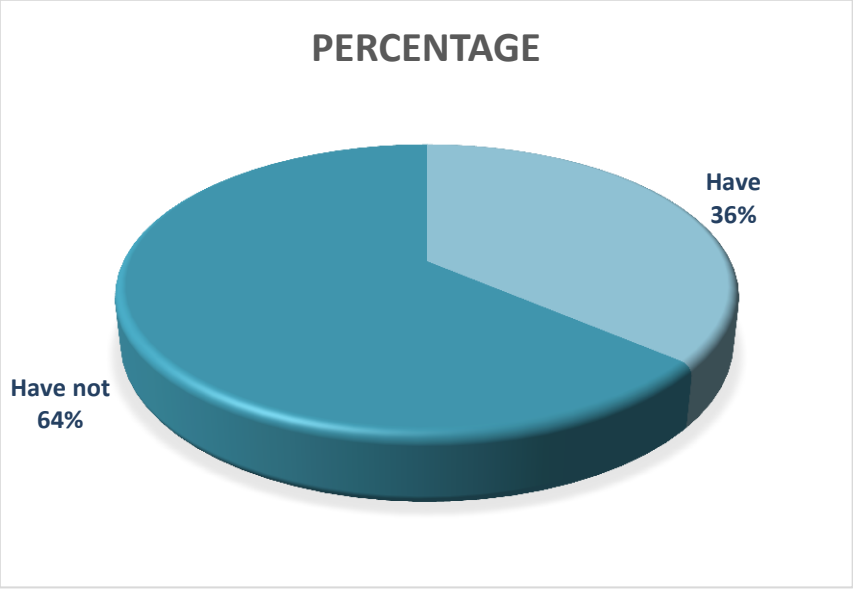


Figure 3.22: The percentage of breast cancer patients according to family history.

3.23. Distribution of breast cancer patients according to the degree of kinship

Kinship degree was (41.3%) for the first degree 12 out of 29 observed, while second degree was (58.6%) 17 cases respectively, (Table 3.23 & Figure 3.23).

Table 3.23 Distribution of patients according to the degree of kinship

Patient N=29		
Degree of kinship	**Frequency**	**(%)**
First degree	12	41.3%
Second degree	17	58.6%
Sum	**29**	**100**

*P<0.043 Variance significant difference between First degree and Second degree

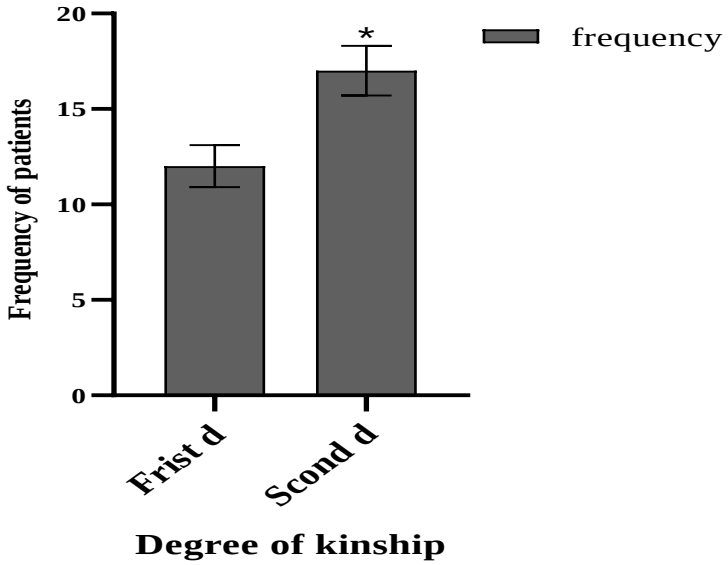


Figure 3.23: The Frequency of patients according to the degree of kinship.

3.24. Distribution of breast cancer patients according to first relationship Degree.

The patient cases included 12 women that represented (16.7%)first degree of mother relationship and (83.3%) due to sister relationship respectively, **(**Table 3.24& Figure 3.24).

Table 3.24: Distribution of patients according to their first-degree relationships degree.

Patients N=12		
First relationship degree	**Frequency**	**(%)**
Mother	2	16.6%
Sister	10	83.3%
Sum	**12**	**100**

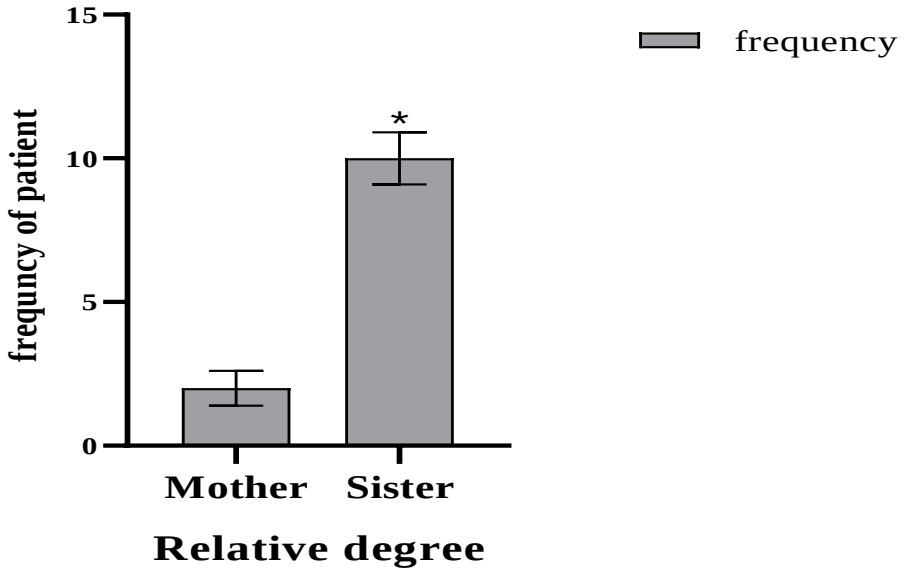


Figure 3.24: The Frequency of patients according to the first relationship degree.

3.25. Distribution of breast cancer patients according to second relationship degree.

The second relationship degree among 17 patient cases revealed equals percentages of (47.05%) for father and mother relationship. The same relationship degree via sister's daughter represented only (5.9%) (Table 3.25 Figure 25).

Table 3.25: Distribution of breast cancer patients according to second relationship degree .

Patient N=17		
Second relationship degree	**Frequency**	**(%)**
Aunt via father	8	47.05%
Aunt via mother	8	47.05%
Sister's daughter (niece)	1	5.8%
Sum	**17**	**100**

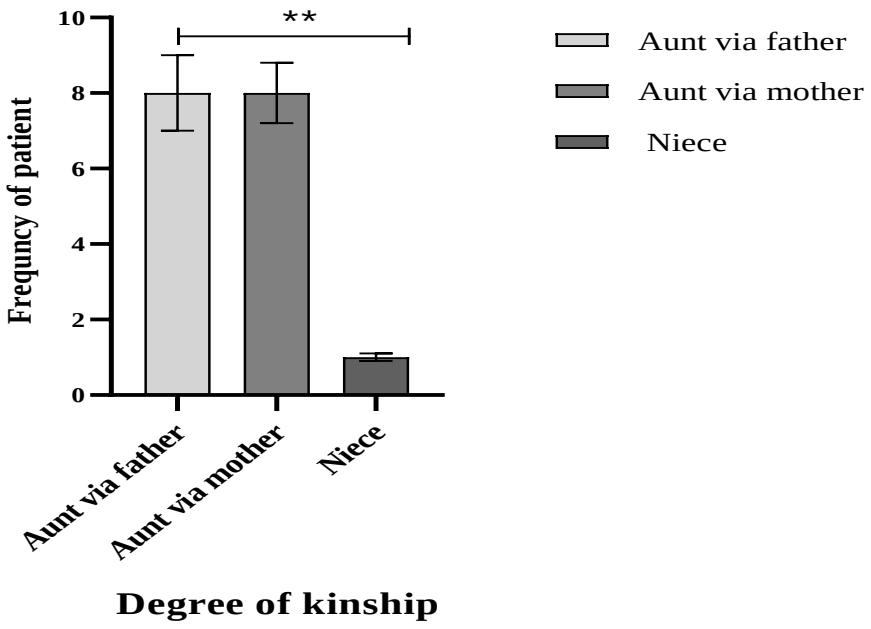


Figure 3.25: The Frequency of patients according to the second relationship degree.
results refer to statistically significant difference between them where P< 0.001.

3.26. Distribution of breast cancer patients according to the presence of other cancers with or without breast cancer.

By analyzing the questionnaire from all 80 cases, it was found that 78 cases represented(97.5%) answered that there were no other tumors and 2 cases represented (2.5%) said yes, respectively (Table 3.26& Figure 26)

Table 3.26: Distribution of patients according to the presence of other cancers with breast cancer.

Patient N=80		
Other cancers with breast cancer.	**Frequency**	**(%)**
Yes	2	2.5%
No	78	97.5%
Sum	**80**	**100**

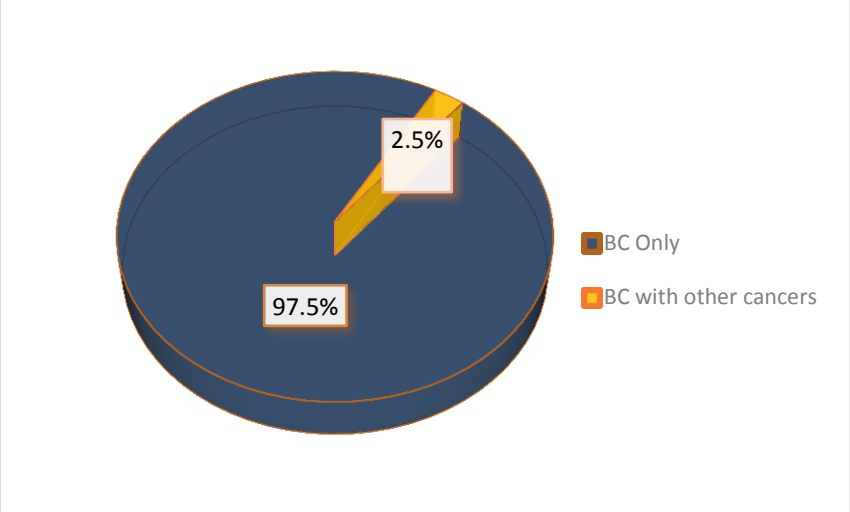


Figure 3.26 : The percentage of patients according to the presence of other cancers with breast cancer.

3.27 Distribution of breast cancer patients according to vitamin D test analysis.

Analyzing the questionnaire form for 80 cases about whether they had taken a vitamin D(VD) check before the disease, the data were (47.5%) yes and (52.5%) no, respectively (Table 3.27 & Figure 3.27).

Table 3.27: Distribution of breast cancer patients according to vitamin D test analysis.

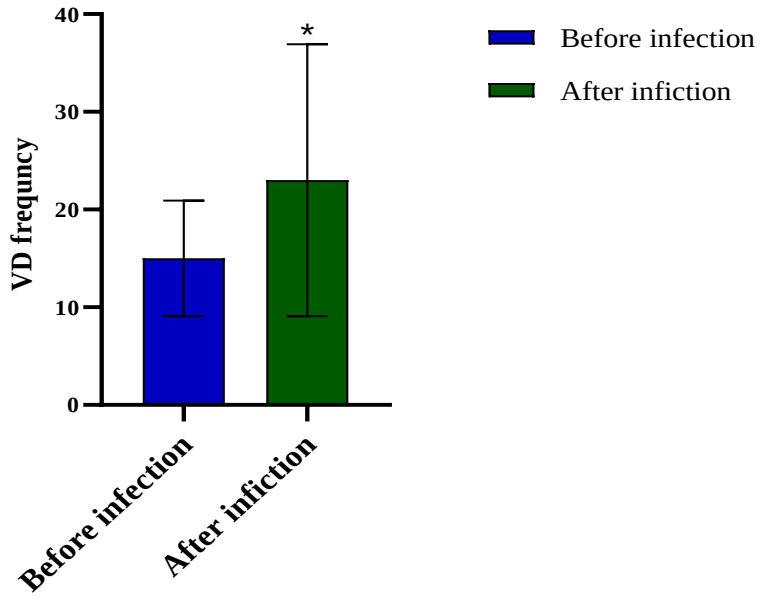
Vitamin D Test N=80		
Test of the vitamin in the past	**Frequency**	**(%)**
Yes	38	47.5%
No	42	52.5%
Sum	**80**	**100**

3.28. Distribution of breast cancer patients according to vitamin D analysis before and after incidance .

It is become knows that a deficiency in vitamin D is associated with tumor progression and metastasis in breast cancer. The results of the follow-up records of the patients were that ,vitamin D analysis before and after BC incidence was (39.5%) represented 15 women before incidence and (60.5%), represented 23 women after BC incidence respectively (Table 3.28 &Figure 3.28).

Table 3.28: Distribution of breast cancer patients according to vitamin D analysis before and after incidence disease.

Patient N=38		
Vitamin D analysis	**Frequency**	**(%)**
Before	15	39.5
After	23	60.5
Sum	**38**	**100**



Vitamin D procedure before and after BC Infection

Figure 3.28: The Frequency of patients according to Vitamin D analysis before and after incidence.

3.29. Distribution of breast cancer patients according to periodic Vitamin D analysis.

There is no evidence that vitamin D enhancement will reduce the risk of breast cancer recurrence, but it may be recommended for the general health of the patient. Our survey results of the periodic vitamin D analysis for the infected showed that (43.8%) of the patients did the periodic analysis, while (56.2%) did not follow up the periodic analysis (Table 3.29 & Figure 3.29).

Table 3.29: Distribution of breast cancer patients according to periodic Vitamin D analysis.

Patients N=80		
Update Vitamin D analysis	**Frequency**	**(%)**
Frequency of examination periodically	35	43.8
Frequencies of not conducting the examination periodically	45	56.2
Sum	**80**	**100**

P<0.07 One sample t test shows not significant

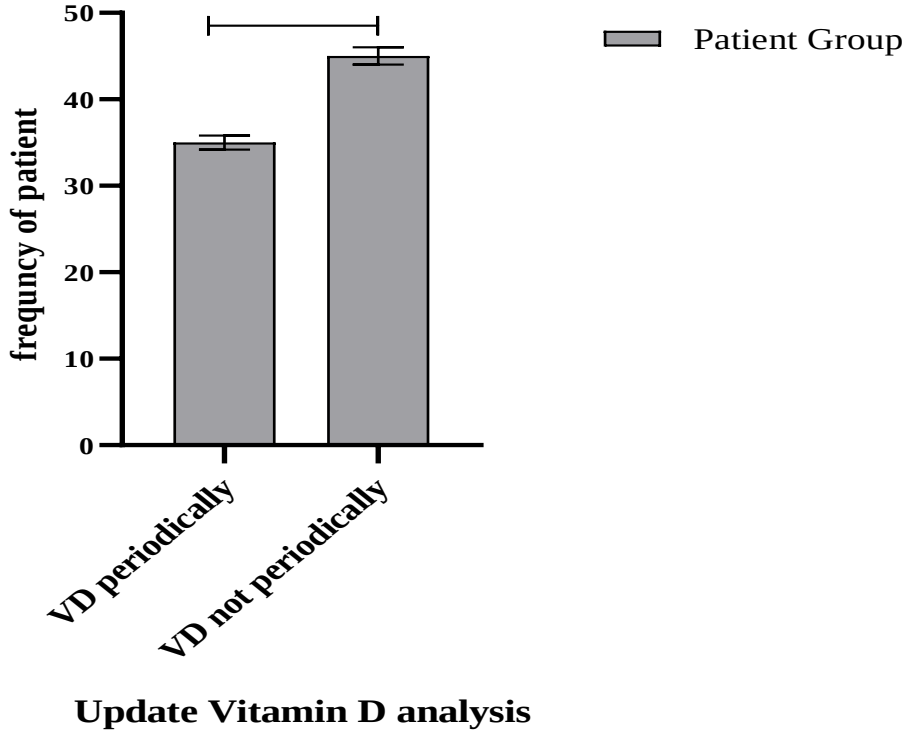


Figure 3.29: Analysis data of breast cancer patients who follow up on vitamin D test periodically

3.30. Distribution of control group and breast cancer patients according to vitamin D rate.

Generally, (30ng gram) per milliliter (ng/ml) of vitamin D (VD) is accepted as an optimal value, although in some contexts, it is recommended to raise it above 36 and up to (40ng/ml). Therefore, insufficient levels are considered if it does not reach (30ng/ml) of VD and it is considered a severe deficiency when it does not get (10ng/ml) of VD, the mean level of vitamin D in blood is between (20ng/ml) (adequate) to (50ng/ml) (high). Surveyed patient women and control revealed different levels of this vitamin. Control group rate lower than (3ng/ml) was (0%), (4-10 ng/ml) (6 cases) (30%),(11-17ng/ml) was (4 cases) (20%), (18-24 ng/ml) rate showed (4 cases)(20%) and (2 cases to each of the last three groups)(10%) was scored for the three rates groups (25-31, 32-38 and 39-44 ng/ml . Patient women revealed high percentage (9 cases) 45% for the 4-10ng/ml) rate group, and the three rate groups (3<, 11-17 and 18-24 ng/ml) scored (15% ,20% and 20%) respectively, while the last three rate groups scored 0%, respectively. This result showed low level of vitamin D for more (80%) of patients (Table 3.30 & Figure 3.30).

Table 3.30: Distribution of study cases according to Vitamin D rate

Control N=20			**Patients N=20**	
Vitamin D range ng/mL	**Frequency**	**(%)**	**Frequency**	**(%)**
3<	0	0	3	15%
4-10	6	30	9	45%
11-17	4	20	4	20%
18-24	4	20	4	20%
25-31	2	10	0	0%
32-38	2	10	0	0%
39-44	2	10	0	0%

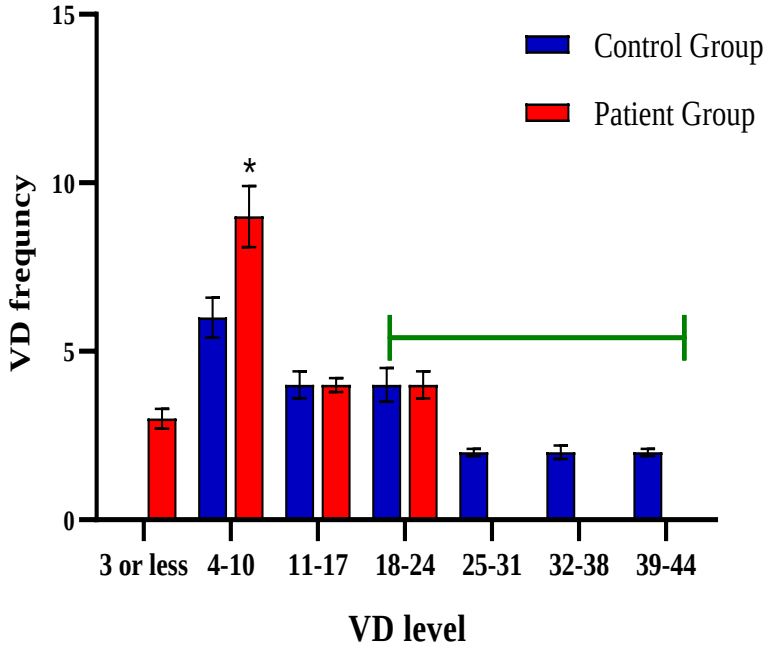


Figure 3.30: The Frequency of patients according to Vitamin D rate.

3.31. Distribution of breast cancer patients according to the simultaneous of breast cancer with other diseases.

Results showed 22 women that represent (27.5%) of patients had other disease and 58 women that represent (72.5%) were had not, respectively (Table 3.31 & Figure 3.31).

Table 3.31: Distribution of breast cancer patients according to the simultaneous of breast cancer with other diseases.

Patients N=80		
Whether BC is simultaneous with other diseases?	**Frequency**	**(%)**
Yes	22	27.5%
No	58	72.5%
Sum	**80**	**100**

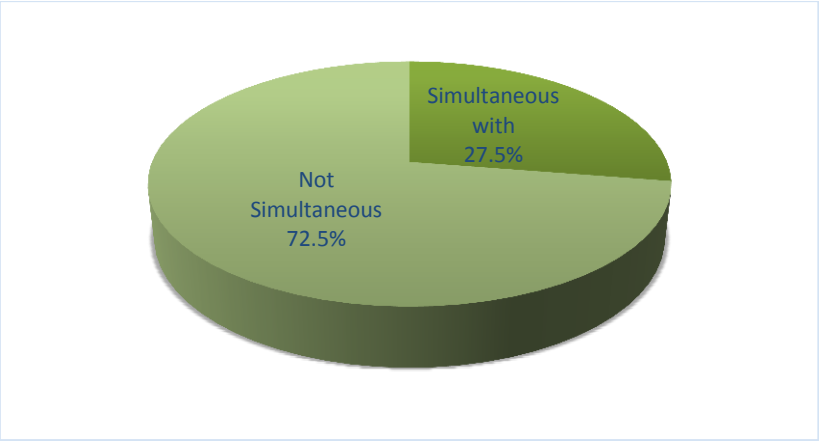


Figure 3.31: The Frequency of patients according to other diseases before BC incidence

3.32. Distribution of patients according to have other medicines before.

This question aimed to discover of concern intake other medicines as a risk factor to BC incidence and was included with the previous question about the other diseases. Results showed 22 women that represent (27.5%) of patients had different disease medicine and 58 women that represent (72.5%) were had not, respectively (Table 3.32 &Figure3.32).

Table 3.32: Distribution of breast cancer patients according to have other medicines before .

Patients N=80		
Have you had Other medicines before?	**Frequency**	**(%)**
Yes	22	27.5
No	58	72.5
Sum	**80**	**100**

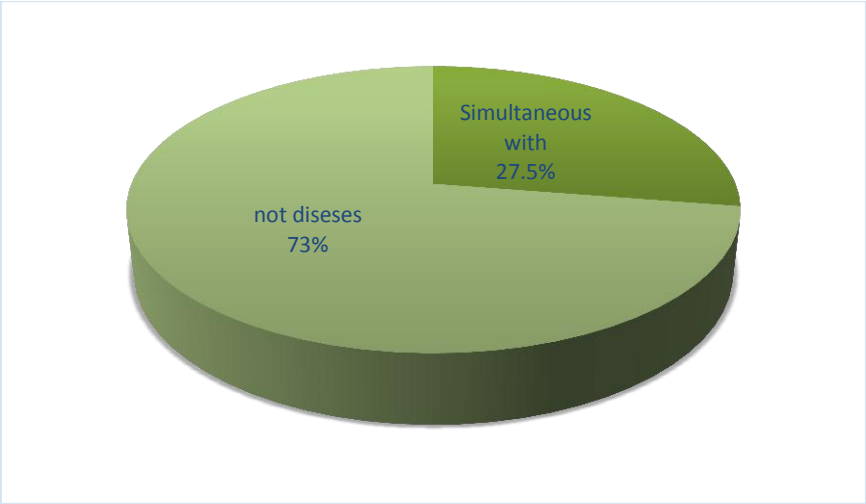


Figure 3.32: The Frequency of patients according to have other medicines before.

3.33. Distribution of patients according to radiation exposure.

Previous studies indicated the relationship between BC with exposure to radiation, and through the results obtained, it was found that (33.75%) that scored 27 women were exposed among patients, while 53 women that represent (66.25%) did not expose to radiation, respectively (Table 3.33).

Table 3.33: Distribution of breast cancer patients according to radiation exposure.

Patient N=80		
Patient exposed to radiation before	**Frequency**	**(%)**
Yes	27	33.75%
No	53	66.25%
Sum	**80**	**100**

3.34. Detecting the presence of breast redness and swelling/ tumor.

Redness skin and tumor in the nipple area of the breast was surveyed. Of the all 80 there is not any patient had such change .

Table 3.34: Distribution of breast cancer patients according to breast redness and tumor.

Patient N=80		
Observing redness or tumor	**Frequency**	**(%)**
Yes	0	0%
No	80	100%
Sum	**80**	**100**

3.35: Distribution of patients according to breast Clear lump.

Collected data surveyed were showed 95% of patients have aclear lumps and only 5% has not, respectively.

Table 3.35: Distribution of study cases according to breast clear lump

Patient N=80		
Apperance of clear lump	**Frequency**	**(%)**
Yes	76	95
No	4	5
Sum	**80**	**100**

3.36. The extent of using black hair dye among patients before BC incidance

Participants who used black hair dye, representing (25%), answered that they had stained their hair black before BC, and (75%) of them reported that they had not used stain either before (Table 3.36.a).

Using black dye according to age shows that the percentages were high (6 cases) for age group 40-50 years for and (9 cases) for age group 41-51 years that represented (30%) and 45% respectively. The age group 29-39

and 62 > represented the low percent that scored (15%) (3 cases) and 10% (2 cases) respectively (table 3.36.b).

Table 3. 36.a): Distribution of breast cancer patients according to use black hair stain before BC incidence.

Patients N=80		
Black hair stain use	Frequency	**(%)**
Yes	20	25%
No	60	75%
Sum	**80**	**100**

Table 3. 36.b): Using black stain according to age.

Patients N=20		
Age while using black dye	**Frequency**	**(%)**
29-39	3	15%
40-50	6	30%
41-51	9	45%
62>	2	10%
Sum	**20**	**100**

3.37. Analysis of the patients according to meat consumption.

The sample of the study consisted of 80 patients with breast cancer, and about the type of meat that they consumed the most, it was found that red meat was the most consumed type, recording 56.25%, and white meat came second with a percentage of 38.75%. Likewise, fish consumption was the lowest species by 5% with the frequencies of 45, 31 and 4 women respectively (Table 3.37 & Figure37).

Table 3.37: Distribution of breast cancer patients according to meat consumption.

Patients N=80		
The most consumed meat type	**Frequency**	**(%)**
Red meat	*45	56.25%
White	31	38.75%
Fish	4	5%
Sum	**80**	**100**

*P<0.01

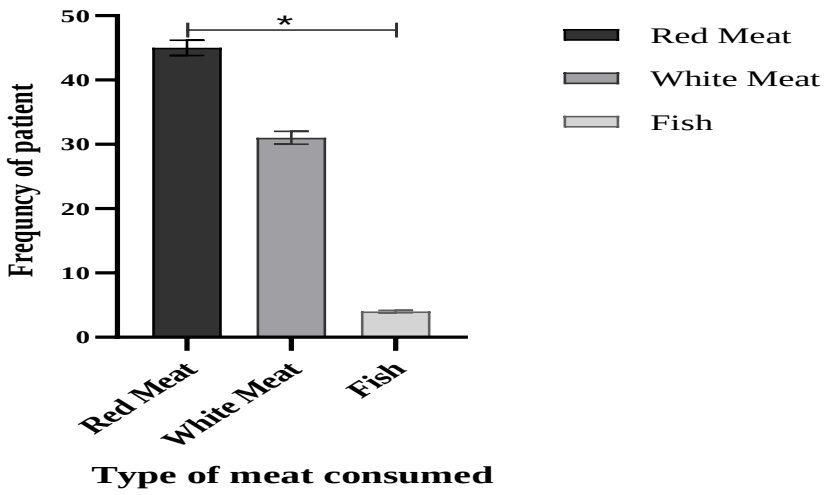


Figure 3.37: The Frequency of patients according to the most consumed meat type.

3.38. Consumption precentage of red meat per week by the patients.

Through the results obtained, about the extent of red meat consumption on a daily basis or intermittently, the current study found that (68.8%) with 31 frequency of the patients that red meat daily, and that (13.3%) with a frequency of 6 of the patients eat red meat 3 times a

week, and (11.1%) with a frequency of 5 eat red meat once a week, while approximately (6.7%) with a frequency of 3 eat it at intervals.

Table 3.38: Distribution of breast cancer patients according to range of red meat consumption.

Patients N=45		
Range of red meat consumption	**Frequency**	**(%)**
Daily	31	68.8%
3 times a week	6	13.3%
Once a week	5	11.1%
Rarely	3	6.66%
Sum	**45**	**100**

**P<0.001

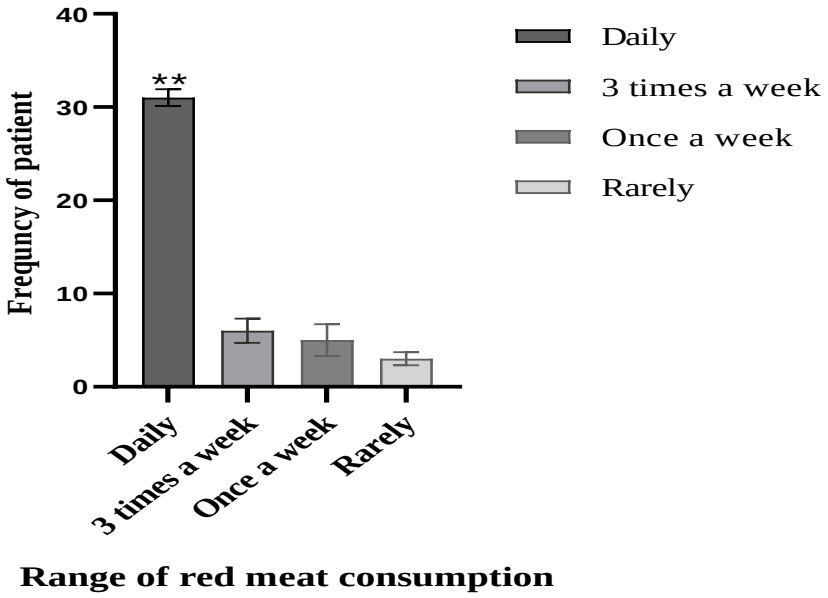


Figure 3.38: The Frequency of patients according to range of red meat consumption

3.39. Distribution of patients according to exposure to negative smoking.

The data related to passive smoking was surveyed and the results revealed that(57.5%) of the female patients were exposed to passive smoking with frequency 46 and (42.5%) were not exposed to smoking (Table 3.39 & Figure 39).

Table 3.39: Distribution of breast cancer patients according to negative smoking

Patients N=80		
Negative smoking state	**Frequency**	**(%)**
Yes	46	57.5%
No	34	42.5%
Sum	**80**	**100**

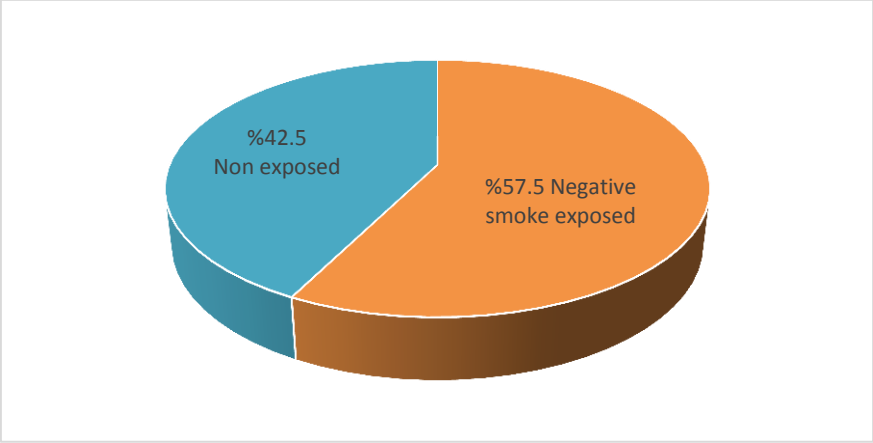


Figure 3.39: The Frequency of patients according to negative smoking exposure.

3.40. Blood contents value for patient sample before chemotherapy.

The normal average was observed for the most samples (7/12) patient women before chemotherapy (Table 3.41), while decrease in mean value of HB concentration was observed from (14 -17) Hb g/dl to 10 g/dl. Averages were observed for WBC count, LYM % and PLT count at

values 18.7±1.6 10ˆ3/ul , 49.45±3.3/mmˆ3 , and 428± 32/ul , respectively (Table 3.40& Figure 3.40).

Table 3.40: Average blood contents of patients sample before chemotherapy.

Range / Count	WBC count (4 -10) 10ˆ3/ul		Hb g/dl (14 -17)		LYM % x/mmˆ3 (14 - 44)		NEUT# x/mmˆ3 (1.9-8 #)	
	Freq.	Mean ±SD	Freq.	Mean ±SD	Freq.	Mean ±SD	Freq.	Mean ±SD
Less than average	2	3.35±1.33	2	13.6±1.2	0	0	2	1.15±0.9
Normal range	7	6.45±1.3	10	14.9±2.04	10	29.58±1.9	9	4.26±1.4
Above average	3	18.7±1.6	0	0	2	49.45±3.3	1	9.5±0.7
Total	12		12		12		12	

***P<0.01**

****P<0.001**

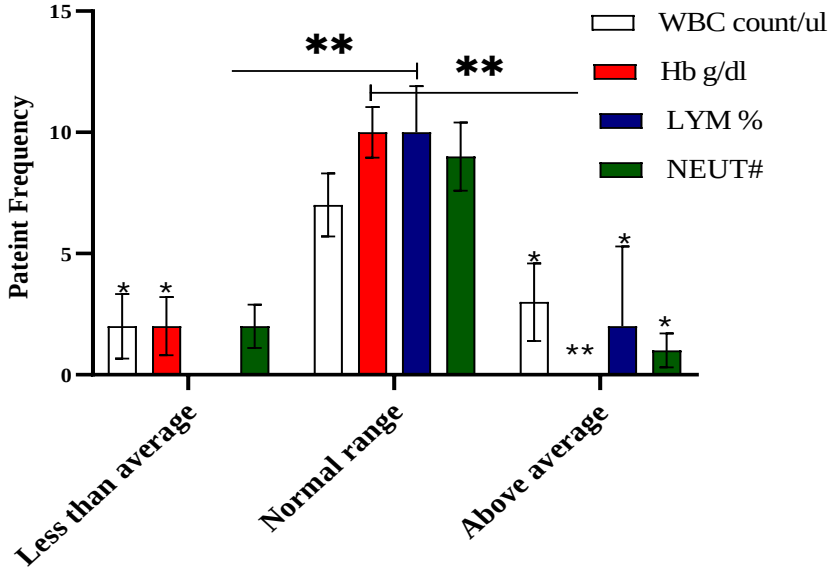


Figure 3.40: The Frequency of patients according to Patient sample before Chemotherapy.

3.41. Blood contents value for patient sample after chemotherapy.

After chemotherapy as revealed in Table 3.42 normal range was observed for the most cases. Above average was found for 2 cases with LYM value of (48.65%) and one case for PLT that its value was (656)10ˆ3/ul, respectively (table 3.41 & figure 41).

Table 3.41 Average blood contents of patients sample after chemotherapy.

Count / Range	WBC count (4 -10) (x 10₃/µL)		HB g/dl (14 -17)		LYM % x/mmˆ3 (14 - 44)		NEUT# x/mmˆ3 (1.9-8 #)	
	Freq.	**Mean ±SD**	**Freq.**	**Mean ±SD**	**Freq.**	**Mean ±SD**	**Freq.**	**Mean ±SD**
Less than average	1	3.9±0.01	1	11.6±0.03	0	0	2	1.2±0.8
Normal range	11	5.88±0.6	11	14.0±0.7	10	29.2±1.21	10	3.25±0.9
Above average	0	0	0	0	2	48.65±2.0	0	0
Total	12		12		12		12	

***P<0.01 **P<0.001**

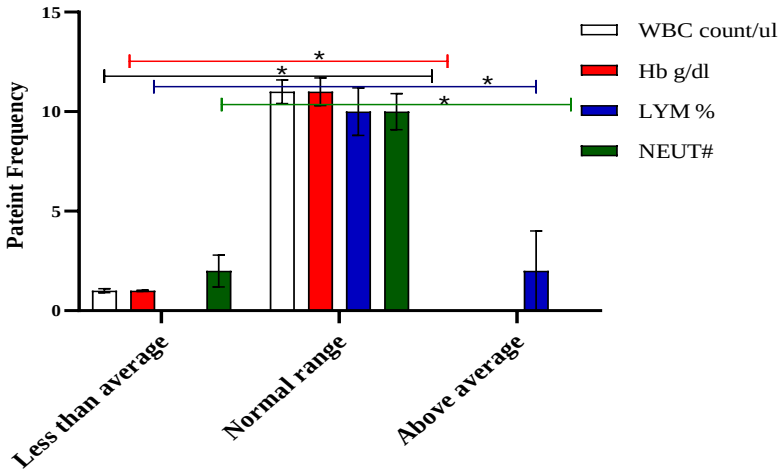


Figure 3.41: The Frequency of patients according to patient sample after chemotherapy.

3.42. Averages of the patients sample before and after Chemotherapy.

It is clear from the (Table 3.42) that before treatment, most cases (with a recurrence of 9 cases out of 12 cases) were normal, while 3 cases were above the normal average rate. After treatment, the normal return was recorded in 10 cases out of 12 cases, one case was above the rate, and one case was below the rate, which indicates the effectiveness of chemotherapy.

Table 3.42: PLT investigation of a random sample of breast cancer patients before and after chemotherapy

Count / Range	Mean of PLT before chemotherapy		Mean of PLT after chemotherapy	
	Freq.	Mean ±SD	Freq.	Mean ±SD
Less than average	0	0	1	125 ± 0.2
Normal range	9	271.4 ± 28	10	248.1 ± 0.3
Above average	3	428 ± 32	1	656 ± 0.8
Total	12		12	

*P<0.01
**P<0.001

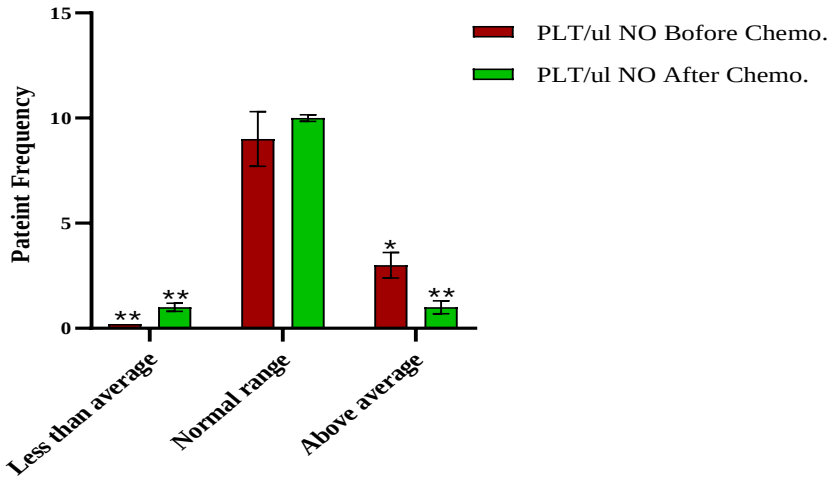


Figure 3.42. Platelet count values for all cases (Patient sample) before and after Chemotherapy.

CHAPTER 4

DISCUSSION

4.1 Discussion

The current study dealt with one of the deadliest cancers, which is breast cancer. The study sample included 80 patient women and 40 healthy women. Through reviewing the literature, it was possible to collect most of the risk factors potentially related to breast cancer, such as obesity, family history, genetic predisposition, diet, and lifestyle. This study attempted to shed light on all of the factors mentioned and others. However, there is an important risk factor which had not get a sufficient study in previous studies; Therefore, the current study focused specifically on it, which is the relationship of breast cancer to blood groups and the Rh factor.

Principally; The current study discusses all risk factors. First, studying the age at incidence and the average age of women with breast cancer (BC). Age is one of the main factors in the incidence of cancer. The results showed that their average age is 33 ± 14 years, and their ages range from (29-62) years and above (Sujatha and Jenilin, 2016). As the incidence of BC is highly related to age where the results of the study showed that the majority of patients were from the age groups (40-50) and (51-61) years, with a rate of (41.25%) and (26.25%). This result was similar to the study (Tice *et al*., 2015) that was conducted in Japan and China and showed that higher the incidence of breast cancer in the age group (45-50) years. And with the study (Brewer *et al*., 2017), which showed that the highest incidence of breast cancer was (44.6%) in the age group more than (60 <), (42.4%) in the age group (45-59) years. As for Indian women, the rate is lower in the age group (45-50) years and increases in older ages (Ferlayx *et al*., 2010), and also with the study (Siegel *et al*., 2017) that showed most deaths related to BC in America are among women over the age of 40 and 60 years with a rate of (99.3%) and 71.2%. Chen and others

in 2016 in china confirmed that women aged 40 to 49 years and 60 to 69 years exhibited significantly (Chen, *et al.*, 2016).

In terms of family history, this study found that nearly a quarter of the study sample of breast cancer cases had a family history of the disease, whose mothers or sisters had it. Family history was recorded (36.2%) among patient (Inoue and Fry, 2015). In contrast the more percentage was (63.7%) among patients that had no family history as risk factor of the disease.

Kinship degree was (41.3%) for the first degree, while second degree was (58.6%) for patient women respectively, A woman's breast cancer risk is increased if she has a first-degree relative with breast cancer at a young age or if she has multiple relatives with breast cancer (Claus *et al*., 1990). Approximately (5–10%) of breast cancers are thought to be hereditary (Bogdanova *et al*., 2013). Some others perceive that close related by mother or sister less correlation unless depending on age, namely; having a mother, sister or daughter (first degree relative) diagnosed with breast cancer approximately doubles the risk of breast cancer. This risk is higher when more close relatives have breast cancer, or if a relative developed breast cancer under the age of 50. But most women who have a close relative with breast cancer will never develop it (Gail *et al.*, 1989).

It may be noted that the results of studies on this relationship fluctuate between the first and second degrees of breast cancer probability, and our results tend to agree with the following study; cohort study of over 113,000 women in the UK demonstrated that women with one first-degree relative with breast cancer have a 1.75-fold higher risk of developing this disease than women without any affected relatives. Moreover, the risk becomes 2.5-fold or higher in women with two or

more first-degree relatives with breast cancer (Brewer *et al*., 2017). These findings are consistent with our results.

The second relationship degree among 17 patient cases revealed equal percentages of (47.05%) for father and mother relationship. The same relationship Degree via Sister's daughter represented only (5.9%), The results that reported on the risks caused by a family history of breast cancer in a second degree relative were generally lower than the risk associated with having an affected first-degree relative (Teare *et al*., 1994). It is believed that (10>%) of breast cancers are genetically determined (Armaou *et al*., 2009). The risk of developing breast cancer increases twice in women whose closest relative (mother, sister) has been treated for BC malignant tumor and by three to six times if the two closest relatives have been treated (Nardin *et al*., 2020.).

This study also showed that most of the cases were positive for the Rh^+ factor which represented a (91.25%), while the negative Rh^- factor among patients represented (8.75%). The analysis revealed a significant value for Rh correlation as a BC risk factor (P<0.0001). These results are consistent with several studies showed that the highest incidence of breast cancer was among Rh^+ patients with a percentage of (97.1%) (Flavarjani *et al*., 2014), (93.4%) (Stamatakos *et al*., 2009, Shiryazdi *et al*., 2015), (%89) (Yu *et al*., 2012), (88 %) (Urun *et al*., 2012 ،Meo *et al*., 2017), (82%) (Cihan, 2014). The increase in the incidence of the disease among those who carry Rh-positive factor, may interpret that a person with the Rh-positive factor will not make anti-Rh antibodies. Those with Rh negative factor will produce the antibodies. In addition, the highest incidence of breast cancer was (48.75%) in patients with blood group (A), which is the highest incidence compared to healthy subjects (41.6%) at a probability (P<0.0001)، The incidance rate among patients with blood group O) was (37.5%) compared to healthy subjects (25%), and the lowest infection rate

among patients with blood group (AB) was (6.25%) compared to healthy subjects (20.83%). These results are consistent with several studies showed that the highest incidence of breast cancer was among those with blood group (A) was (47.6%) (Stamatakos *et al*., 2009), (45.88%) (Meo *et al*., 2017), (44%) (Yu *et al*., 2012), (42.4%) (Akhtar *et al*., 2010). Then those with blood type (O) by (39%) (Sujatha and Jenilin, 2016). (32%) (Urun *et al*., 2012), (31.69%) (Meo *et al*., 2017). And that the lowest incidence rate was in breast cancer patients with blood type (AB) at a rate of (4-9%) (Payandeh *et al*., 2015), (Shara *et al*., 2013) (Aly *et al*., 2014). The study also found that blood groups O^+, A^+ (47.5% and 37.75%) respectively, and other blood groups AB^+, AB^- , O^- and B^- were at low levels.

The absence and presence of blood group antigens can increase cellular motility and facilitate the interaction between cancer cells (Prakash *et al*., 2016), people with type A blood have less response to antibodies against cancer cells, which makes them more susceptible to BC (Prakash *et al*., 2016).

One of the objectives of the study is to reveal the possibility of a relationship between height, weight, and incidence with this disease. The results indicated that the most frequent occurrence of body length cases is (157-162) (157-162) cm for both control and patients represent (37.5%) and (41.5%) respectively, our results are consistent with the previous study that there was appositive association between women height and breast cancer risk (vatten, 1990).

Control and patients weight was represent percentages of 33.3% and (31.25%) for the weight group73 - 83 kg, respectively. Also, the highest 95> weight group represented (8.3%) and (6.25%) for control and patients. The lowest 51 - 61 weight group represents (25%) and(27.5%)

for both control and patient, healthy body weight of breast cancer was surviving more after BC incidence (Touzani *et al*., 2020).

The current study examined the relationship between body height, weight, and body mass Index what leads to obesity, the relationship of these changes to breast cancer. No data were reported investigating the interaction between body weight and body length on BC, while BMI studies can be used better to clear this relationship. This study found about (75%) of patients have high BMI ranged from overweight to obesity convincing evidence relates being overweight to the risk of several types of cancer which responsible for a large percentage of premature mortality (Manson *et al*., 1995). The international agency for research on cancer found association between excess body weight and reported that it was a sufficient evidence for a causal link with breast and other cancer diseases (IARC, 2002).

The age of the female at the onset of menstruation may be another risk factor for this type of cancer. The current study showed that (88%) of patients revealed high values to age at menarche with early age groups (12<. 13-14. and 15-16) years old respectively similar values were with control group percentages scored (25%, 37.5% and 29.16%). High significance analysis values were outcomes (P<0.0001). Factors related to a woman's hormonal status seem to have a huge impact on the risk of developing breast cancer. The results of many studies indicate that the risk of developing breast cancer increases in proportion to the time of exposure to estrogen, which prolongs early menarche, late menopause, the age of birth of the first child and the number of children born (Lima *et al*., 2021, Torre *et al*., 2017 and Sisti *et al*., 2016).

It seems there is important relationship between BC and menopause type was significant. Results indicated Breast cancer constituted about 65% of all patient were permanent menopause or close to this status 48.75% and

17.5% and 33.75% for temporary menopause type that was 33.75%, while control women revealed only two types that were enduring and represent 41.6% and 58.3%. The previous studies demonstrated that BC risk factors were doubled each decade until the menopause then the increase slow down or remain stable. However, BC is common among postmenopausal women (Mcpherson *et al*., 2000, Visser *et al*., 2004 and Kelsey *et al*., 1993, and Collaborative Group on Hormonal Factors in Breast Cancer ,2012) found that Women who have had more menstrual cycles because they started menstruating before the age of 12 and/or went through menopause after age 55 have a slightly higher risk of developing breast cancer. The increased risk may be due to longer lifetime exposure to reproductive hormones.

Patients in rural cities was distributed more than urban ones, they reached (57.5% vs. 42.5%) respectively. Similar results were found to control where rural women were more than urban ones **(**WHO, 2015) was reported that although breast cancer is thought to be a disease of the developed world, almost (50%) of BC cases and (58%) of deaths occur in less developed countries. (Faronbi and Abolade, 2012) found that Socio-demographic profile showed different personal information of the participants. It revealed that most of them came from village and their knowledge about different treatment facilities was very poor. Others came from city or semi-town, and their knowledge about breast and cervical cancer is not satisfactory.

Samuel Oppong 2021 studied marital status to explore the awareness, risk factors, and self-reported screening practices of breast cancer among female and found only (16%) of participants were married and about (1%) was widow and divorced while unmarried represented about 83%. This study results showed high percentages of married women among patients that reached (77.5%), while unmarried and widow were 16.25 % and

6.25 % respectively. Married control women were 50% while unmarried were 33.3% and the remain were widow and divorced.

Having multiple births or not may be related to breast cancer. Some evidence indicates that mothers who have given birth to five or more children have half the breast cancer risk of women who have not given birth. This may be explained by the reduced risk associated with a higher number of births may be limited to hormone receptor positive breast cancer. Frequency of have children was scored high percentages with control and patient women that reached to 79.16% and 77.5% respectively. Have children are important in the development of breast cancer and attributed to genetic factors, the use of hormone replacement therapy, improper diet, and the resulting obesity (Smolarz *et al*., 2022).

Frequencies of Childbearing times represented differences for class 1-5 between control and patient that were (26.3%) and 75.8% respectively. Also differences between control and patients were observed for class 1-6 Childbearing times which represented (73.6%) and 24.1% respectively. The protective role of parity increases proportionately with the number of children and the early age at first birth. Thus, a first pregnancy before 30 years reduces the risk by (25%) compared to a woman who has not had children (Ewertz *et al*., 1990).

Patient marriage age was (70%) for the age group 26 or less years, (23.88 %) The class (27–37,4.47%) of age class (38–48 and 1.49%) to the age class 49-60 years old. control women represented (50%, 29.1%, 12.5%) and (8.33%) to previous age groups respectively. This results showed differences with previous studies that reported that women who have their first full term pregnancy before age 30 have an average risk of breast cancer decreased by 25% compared to nulliparous women (Layde *et al*.,

1989), and thus, the protective effect of multiparty seems to increase proportionally the number of births (Hinkula *et al*., 2001).

(Mervels *et al*., 2011) showed that the risk of breast cancer is high when the first delivery is late and it seems to decrease if the first delivery is before 30 years old . Findings in this regard are in line with the results of former research.

Mix Breastfeeding among patients reached (79.0%), while natural and artificial were (16.1%) and (4.83%). Control women represented (47.3%), (31.5%) and (21.0%) Natural Artificial and Mix Breastfeeding respectively**.**

The incidence of the malignancy is still low in Africa compared to the incidence in Europe. This has largely been attributed to a protective reproductive history including late menarche, early menopause, high parity with prolonged breastfeeding, irregular menses, and fewer ovulatory cycles A (Fregene and Newman ,2005).

With respect to have contraceptives and risk of breast cancer in women, findings of the present study indicated that patients scored (50.7%) that had contraceptives, while (49.3%) had not. The relationship between hormonal contraceptive use and breast cancer risk demonstrated that long-term use of hormonal contraception adversely affects the relative risk of breast cancer. This risk was estimated at 1.20 and 1.24. It was higher the longer the subjects took hormonal contraception (1.09 for hormonal contraception used for less than a year vs. 1.38 for women taking contraception for more than 10 years) (Collaborative, 1996 and Morch, *et al*., 2017). In addition, this study showed that the relative risk of developing breast cancer was elevated for at least 5 years after the end of hormonal contraception in women who took it for a long time (≥5 years). This trend was not noticed in women who used hormonal contraception for a short time (less than 5 years) (Morch *et al*., 2017). The relative risk

of developing breast cancer was also increased regardless of the type of contraception taken (Collaborative1996). This result was consistent with our results.

With respect to Onset symptoms for age and risk of breast cancer in women, findings of the present study indicated that age group 38-48 was the highest among that reached (43.8%) versus the age group less than 26 years old that was zero percent. The two age groups 27-37 and more than 49 years represented 23.7% and 32.5%. Earlier studies have generally relied on the use of mean age or unadjusted age distribution of breast cancer to infer that the age at the onset of breast cancer is lower among arab women (Najjar and beasson, 2010) found that the mean age at diagnosis was 48 years old , almost a decade younger compared with that among western women. In a large series of breast cancer cases from Lebanon, the mean age was 49.8 years old, with (50%) of the women presenting at ages less than 50 years old (El Saghir et al., 2002). The age of the onset of breast cancer in the arab world is controversial. This results were significantly associated with developing of breast cancer among women more than 26 years.

Compared 80 breast cancer patients that have other tumors, the scored percentage gave (2.5%) not related. There are many benign breast disease alterations identified which were associated with increased breast cancer risk. The risk of developing breast cancer in women with usual hyperplasia is increased (50-100%), whereas atypical hyperplasia of the breast increases risk 4-5-fold (Komen *et al*., 2017), or 1.5-2% per year (Sharko *et al*., 2011). The risk of breast cancer development in patients with LCIS (Lobular Carcinoma in Situ) is 2% per year, compared to the risk in otherwise healthy women of < 0.4% per year (King *et al*., 2015).

Women with atypical hyperplasia or LCIS have a greater than 30% lifetime risk of developing breast cancer (Hartmann *et al*., 2014). disease

increases risk for women diagnosed with atypical hyperplasia (Degnim *et al*., 2016) and the lack of clarity regarding which with atypical hyperplasia and LCIS will develop to breast cancer is a problem. Our results showed 97.5 % of patients have not any tumors before BC, and that represented a significant challenge to concern previous tumors have risk factors to BC patients and consistent with previous study (King *et al*., 2015).

Results showed 27.5% of patients had companied other disease and 72.5% were had not, Aging is one of the most important risk factors of breast cancer, because the incidence of breast cancer is highly related to the increasing age. In 2016, approximately 99.3% and 71.2% of all breast cancer-associated deaths in America were reported in women over the age of 40 and 60, respectively (Siegel *et al*., 2017). Diabetes has been consistently associated with a little increased risk of cancer (Giovannucci *et al*., 2010). Evidence has also linked the risk of cancer with cardiovascular disease markers (Wannamethee *et al*., 1993) for example, blood pressure, heart rate, (Jouven *et al*., 2011) total cholesterol level, (Kitahara *et al*., 2011) chronic kidney disease, Stengel B. 2010 and gouty arthritis marker (uric acid) (Fini *et al*., 2012). As chronic diseases are typically clustered, it is necessary to study them simultaneously to elucidate their independent and joint impact on cancer risk, but few data are available on this topic.

Hormone treatment (HRT) involves the administration of exogenous estrogen or other hormones for the menopausal or postmenopausal women. A number of studies have shown that the use of HRT can increase the breast cancer risk. Results from a million women in study at the UK reported a relative risk (RR) of 1.66 between current users of HRT and those who never used it (Beral *et al*., 2003).

An important diagnostic sign is redness skin and tumor emerge in the nipple area or the breast was surveyed. No any of the all 80 patient women were observed such change. Common symptoms of breast cancer are redness or scariness of the nipple or breast skin, or a discharge are also symptoms (Rondanina *et al*., 2017). According to all the researchers the signs and symptoms were demonstrated in cancer patient and these signs has help to reduce the mortality rate of women across the world. This study no one of patients observed such signs, maybe due to poor knowledge of the symptoms of breast cancer. Data surveyed was showed (95%) of patient women have the classic symptom for breast cancer was a lump found in the breast or armpit and only (5%) have not. This result agrees with findings of (Lauridsen *et al*., 2000). It appears that breast lump also has a role in the possibility of originate this disease. Coleman in (2017) reported that Breast lump was the most common symptom, recorded in about four-fifths of all women (83%).The next most commonly reported presenting symptoms were nipple abnormalities (7%), breast pain (6%), and breast skin abnormalities (2%).This results consistent with previous studies (Coleman *et al*., 2017).

Using black hair dye is also a major risk factor. The results from the current study showed that (25%) of patients used black dye before developing BC. Permanent hair dye products typically consist of intermediates (aromatic amines and other compounds) which can form chemical reactions in the presence of oxidants. Exposure to intermediates is much higher than that to the reaction product during the dyeing process. (IARC, 2010), (ACS, 2019) has classified some chemicals that were used in hair dyes as reasonably anticipated to be human carcinogens. Breast cancer, are among some cancers most frequently investigated in relation to hair dye use (Takkouche *et al*., 2005). Relative risk of overall hematopoietic cancer (especially among people who use permanent, dark

hair dye (Towle *et al*., 2017). The observation of higher risk among women who were presumed to use dark colored permanent hair dye was need warrants cautious interpretation. This finding is based on a limited number of women, so sufficient information to concern different types of dark dyes than other colours as causes of cancer needs to more studies (Anagnostopoulos *et al.,* 2000). Interestedly, some studies were reported that the null evidence on higher risk of bladder cancer among personal users of hair dyes with any hair colors reported by prior meta-analyses, (Turati *et al.,* 2014) but is inconsistent with the previously reported elevated risk of bladder cancer among dark colored dye users (Turati et al., 2014) and the reported null finding for breast cancer among any colored dye users (Takkouche *et al.,* 2005). Patient women were used the black dye during different age group . The percentages were high for 40-50 and 41-51 age group that represented (33.3%) and (42.9%) respectively. The age group 29-39 and 62 > represented the lower percentages that scored (14.3%) and (9.5%) respectively**.** Black women are more likely than white women to be diagnosed with breast cancer at earlier ages (Richardson *et al.,* 2016) and (Brandt *et al*., 2015). Previous epidemiologic research on hair products has largely been inconclusive, focusing primarily on the relationship between adult use of hair dye use and breast cancer risk, largely in populations that were not racially/ ethnically diverse (Green *et al*., 1987). This results showed approximately (85%) of adult use dye among patients and consistent with previous findings.

Red meat consummation despite its unacceptable effects in the case of excessive consumption, as its percentage among patients in this study reached 68.8% among surveyed patient 3 times a week, white meat represented 38.75% and while fish represented 5% of consumption for patient groups. Study of Anderson 2018 found that red meat

consumption increased the risk of invasive breast cancer, whereas poultry consumption was associated with reduced risk, particularly for postmenopausal invasive breast cancer. (Anderson et al., 2018) reported no association between red meat consumption and breast cancer risk, whereas (Farvid *et al.,* 2018) reported significant positive associations between red meat consumption and BC risk. An association between red meat and breast cancer may be due to dietary heme iron, fat, and N-glycolylneuraminic acid as these compounds found in red meat are indicated to possibly increase tumor formation. (Wu *et al.,* 2016). Another plausible explanation for this association may be the carcinogenic byproducts resulting from the high-heat cooking practices of meat such as polycyclic aromatic hydrocarbons and heterocyclic amines (Wu *et al.,* 2016). In contrast, it observed a significant inverse association between poultry consumption and risk of breast cancer in the present study. Many studies found non-significant associations between poultry and breast cancer risk (Missmer *et al.,* 2002) and non-significant inverse associations (Dai *et al.,* 2002) whereas a few studies found significant inverse associations of poultry and white meat consumption with breast cancer (Delfino *et al.,* 2000). One study found a significant inverse association with poultry and white meat consumption only among Hispanic women (Kim et al, 2016) another found a significant inverse association with white meat among Uruguayan women (Ronco *et al.,* 2013).

The risk of radiation exposure was investigated to reveal whether this factor effected to grow BC. A recognized factor in the development of BC is early exposure to ionizing radiation, Data scored high percentage (33.75%) among patient women, while (66.25%) did not expose to radiation. (John *et al.,* 2007) showed that an increased risk of breast cancer was in women who had received radiation therapy in the past as part of cancer treatment and in women who underwent a control chest X-

ray during treatment for tuberculosis and pneumonia . (Moskowitz *et al*., 2014), showed that the risk of developing breast cancer was assessed depending on the dose and field of radiotherapy For women were exposed to the chest area due to cancer before the age of 21, (McPherson *et al*., 2000) indicated that the highest risk of developing breast cancer was in patients who were treated with radiation therapy at lower doses (14 Gy) but for a large chest area (whole lung field), consequently covering a larger area of breast tissue. The risk of developing breast cancer was lower if the radiation field included the ovaries (John *et al*., 2007). It was also shown that the cumulative risk of developing breast cancer at the age of 50 was 30%, with the highest (35%) in patients treated for Hodgkin lymphoma (Moskowitz *et al*., 2014) ,(Henderson *et al*., 2010). Also found that the highest risk of developing breast cancer occurred in patients treated in the past for Hodgkin lymphoma. (Travis *et al*., 2005) was assessing only the relationship between breast cancer and radiotherapy received in the chest area for Hodgkin lymphoma and showed that the cumulative absolute risk of developing breast cancer increased with the patient's age, sometimes after the diagnosis of cancer and the dose of irradiation . As for other cancers diagnostic methods, it is also believed that mammography performed in young women significantly increases the risk of BC (Nardin *et al*., 2020). Ionizing radiation (IR) increases the risk of breast cancer, especially in women and when exposed at a younger age, and the evidence generally supports the linear dose response relationship (Helm and Rudel, 2020). Ionizing radiation directly and indirectly causes DNA damage and increases the production of Reactive Oxygen and Nitrogen Species (RONS). The RONS lead to DNA damage and epigenetic changes leading to mutation and genomic instability that increases proliferation of breast cancer through pro-carcinogenic effects

on cells and tissues. This results scored approximately (34%) of patients were exposed to radiation , and consistent with the previous studies .

Smoking is a significant health problem and one of the few potentially modifiable risk factors for breast cancer development, Data regarding negative smoking was surveyed and revealed (57.5%) of patient women were exposed to negative smoking and (42.5%) were not exposed. There are accumulating data regarding the association between smoking and breast cancer. Mammary tissue is capable to uptake many tobacco carcinogens, including polycyclic aromatic hydrocarbons, aromatic amines and N-nitrosamines. In vitro studies and animal models found that several tobacco carcinogens may induce breast tumors (Terry and Goodman, 2006) and (Reynolds *et al*., 2013) and may cause a more aggressive breast cancer phenotype (Di *et al*., 2013). Moreover, these carcinogens might cause DNA damage and adduct formation in mammary epithelial cells (Catsburg *et al*., 2014). Evidence of higher prevalence of these tobacco-related DNA adducts, as well as p53 gene mutations in breast cancer tissue in smokers compared to non-smokers might implicate smoking as a factor in the pathogenesis of breast cancer (Conway *et al*., 2002) and (Li *et al*., 1999) .The existing literature links smoking with increased breast cancer incidence (IARC, 2012) reported that all-cause mortality rate is higher in smokers with breast cancer compared to non-smokers**. (**Holmes *et al*., 2007) however, the association of smoking with breast cancer specific mortality is inconsistent IARC 2012. Several studies found that smoking was associated with worse breast cancer specific survival (BCSS) (Braithwaite *et al*., 2012), while others did not (Sagiv *et al*., 2007). Some of the reports that found worse prognosis in patients with BC who smoked were restricted to specific subgroups, such as heavy smokers (Pierce *et al*., 2014) patients with slow N-acetyltransferase 2 activity or with tumor subtypes other than luminal B

(Seibold *et al*., 2014). Recent meta-analysis comprising almost 40,000 patients found smoking increases risks of all-cause and breast cancer specific mortality in patients with breast cancer. (Wang *et al*., 2016) . Information regarding the impact of smoking on breast cancer characteristics is scarce. The aim of this study was to evaluate the influence of smoking on breast cancer characteristics and outcome.Several studies focus on women with early stage, estrogen receptor (ER) positive, human epidermal growth factor receptor 2 (HER2) breast cancer as this group represent the majority of breast cancer patients (Harvey *et al*., 1999**)** and there is stronger association between smoking and this subgroup of patients (Kawai et al., 2014). With the addition of molecular tools, such as the Oncotype-DX (ODX) test to our daily practice (Paik *et al*., 2006) patients benefit from an objective prognostic and predictive tool to evaluate risk for disease recurrence.

Patients that had symptoms were revealed 5 years ago or less were (45 %) , while ones who had the disease symptoms appearance for 16-20 years were (3.75 %) .The class of 6-10 symptoms years was (32.5%) and the class of 11-15 years was (18.75%) , five-year survival rates refer to the percentage of patients who lives for at least 5 years from diagnosis. An approximate 5-year relative survival rate for various stages of breast cancer includes (100%), (100%), (93%), (72%) and (22%) for stages 0, I, II, III, and IV, respectively (Chen *et al*., 2014). The low survival rates in less developed countries can be explained mainly by the lack of early detection programs, as well as by the lack of adequate diagnosis and treatment facilities, resulting in a high proportion of women presenting with late-stage disease (WHO, 2015).

Breast Self-Examination (BSE) was the highest Detection method that reached (80%) for the patients. Mammogram and Mammography methods were (15%) and 5% respectively. Early detection is the

cornerstone of breast cancer prevention. Mammography is an effective screening method other imaging device such as magnetic resonance imaging, ductography, scintimammography and molecular breast imaging may be applied along with the above tests to improve diagnostic accuracy (Salem *et al*., 2013).

The normal average was observed for the most sample (7/12) patient women before chemotherapy**,** meanwhile decrease in mean value of Hb concentration was observed from (14-17) Hb g/dl to 10 g/dl. Above average was observed for WBC count, LYM % and PLT count at values 18.7, 49.45 and 428 respectively.

Response of various hematological parameters has been correlated and studied. Hemoglobin (Hb) and packed cell volume (PCV) are indirectly associated with increased risk of cardiac failure in cancer patients (Mozaffarian *et al*., 2003). Total leucocyte count (TLC), if elevated, predicts poorer prognosis (Grimm *et al*., 1985). The prognostic significance of neutrophils, lymphocytes, plasma cells, mean platelet volume (MPV), platelet/lymphocyte ratio, and neutrophil/lymphocyte ratio studied in gastric cancer patients showed influence on overall survival (Aliustaoglu *et al*., 2010).

After chemotherapy as revealed in normal range was observed for the most cases. Above average was found for 2 cases with LYM value of 48.65% and one case for PLT that its count was (656 10ˆ3/ul). Primary chemotherapy is very beneficial as it enables the surgeons to use breast-conserving procedures. (Bonadonna *et al*., 1996). In women with large tumors (>5.0 cm), primary chemotherapy can be safely administered. Moreover, it allows breast sparing surgery in a high fraction of patients (Bonadonna *et al*, 1998). Different drugs were used as chemotherapy and some of them resulted in improved quality of life. The efficacy of doxorubicin and methotrexate was compared in combination with IV

cyclophosphamide and 5- flourouracil (FAC versus CMF) as adjuvant therapy for operable breast cancer. It was concluded that doxorubicin is more efficient than methotrexate when given in combination with day 1 IV cyclophosphamide and 5- flourouracil as adjuvant therapy in breast cancer patients (Martin *et al*., 2003). Long term follow up study confirmed that FAC regimen reduces the risk of recurrence effectively. Moreover, it's also prolongs the survival of high risk patients.

Analysis of previous vitamin D (VD) was surveyed among patient women. Data was (47.5%) and (52.5%) for yes and no answers . Findings in this regard are in line with the results of (Lopes *et al*., 2010) where they reported that in human BC tissue, VD has inversely correlated with BC aggressiveness. In benign breast lesions, the VD was significantly more expressed than in breast carcinoma lesions (in situ and invasive) .

Vitamin D analysis before and after incidence were scored and revealed (39.5%) before and (60.5%**)** after BC incidence. Different groups demonstrated that VD in BC tissue diminished during tumor progression, this mean less sensitive to vitamin D3 (Lopes *et al*. 2010) and (Welsh *et al*., 2017). Indeed, BC cells with low or no VD were least sensitive to 1,25(OH)2D3 or its analogues (Murray *et al*., 2017).

Updated VD analysis was performed by (43.8%) of patients were performed, while (56.2%) were not it. Analysis of VD expression in human BC tissue showed that during de-differentiation and BC progression, vitamin D metabolism and signalling were deregulated (Welsh *et al*., 2017).

The mean level of vitamin D in blood is 20 ng/ml. Surveyed patients and control group revealed different levels of this vitamin. Control group rate was (30%) at level 4-10,(20%) for 11-17ng/dl ,(20%) for 18-24ng/dl showed (20%) and (10%) was scored for the three rate groups 25-31,32-

38 and 39-44ng/dl patients revealed high percentage (45%) for the 4-10 rate group, the three rate groups 3< ,11-7 and 18-24 scored 15,20,20 respectively, while the last three rate groups scored 0% .Analysis conducted by (Ordonez-Mena *et al* 2016), showed increased breast cancer risk with higher VD concentrations. The different finding of this study from the previous other analysis studies may be explained by different settings, different enrolled populations, and differences in the adjusted levels. research is required to prove the effectiveness of vitamin D3 analogues in combination therapies to treat different BC subtypes. Although, in vitro and in vivo studies describe promising results for the use of VD3 or its analogues to decrease BC growth and progression. In recent years, there has been much interest in the role of vitamin D in breast cancer incidence as well as survival and mortality. Although current evidence is lacking on the possible protective effects of vitamin D in early development (Shui *et al*., 2014), there is no evidence of any protective effect of vitamin D supplementation on breast cancer etiology. In the Women's Health Initiative trial in 36,282 women, 25 (OH)D (400 IU D3 per day) given with supplemental calcium showed no effect on lowering breast cancer incidence (Chlebowski *et al*., 2013).

CHAPTER 5

CONCLUSION & RECOMMENDATION

5.1 Conclusion

Knowing the risk factors for breast cancer may help take preventive measures to reduce the likelihood of developing the disease. This study shows that patient women with biological risk factors have great association to initiate breast cancer. In addition to unmodified factors (age, Family history, Pregnancy, lactation, Menstrual period menopause, and Non-cancerous breast diseases) some modified factors (body mass index, smoking, red meat intake, dark dyes and radiation) were surveyed and revealed as causes that activate the incidence of the breast cancer. So far, mammography and mammogram are the most common screening tests enabling quite an early detection of. The present study also focused on evaluation of ABO/Rh relation with grow breast cancer, the results showed strong relationship with A^+ and O^+ of blood group. As well as complete blood count of breast cancer patients undergoing chemotherapy treatment. Chemotherapy treatment may results in increasing or decreasing level of different components of blood hence affecting the diseases mortality. Complete blood cell count (CBC) being low cost, standardized, routinely used test and offer useful information regarding the behavior of diseases progression. The study shows low level of vitamin D among patient women.

5.2 Recommendations

The current study recommended the following:

- Specific strategies should be developed to target the high-risk groups with preventive screening programmers and early diagnosis.
- avoid as much as possible from resorting to diagnostic radiation exposure, especially for those with blood groups that are more likely to develop breast cancer (A^+ & O^+).
- Education strategies should be done to raise awareness regarding the risk factors of breast cancer to reduce the incidence of this disease.
- Further follow-up studies are required to clarify the role of predictive markers of risk in development of different types of gynaecological cancer.

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University of Zawia

Faculty of Sciences -Zoology Department

……

A questionnaire form for visitors to the breast oncology clinic

- **Gender:** Female ☐
- **Tall:** 1.10m – 1.20m☐ 1.21m – 1.30☐ 1.31m – 1.40☐ 1.41m – 1.50☐ 1.51m – 1.60 ☐ 1.61m – 1.70☐ 1.71 > ☐
- **Weight:** 50 – 60 Kg☐ 61- 70Kg☐ 71 – 80 Kg☐ 81- 90 Kg☐ 91 – 100Kg☐
- **Blood Group:** A^+☐ A^- ☐ B^+☐ B^-☐ AB^+☐ AB^-☐ O^+☐ O^- ☐
- **Age: 29 – 39 40 – 50 51 – 60 61 – 70**
- **Age at first menstrual period:** ☐ ☐ ☐ ☐
- **Age at menopause:** ☐ ☐
- **Residence: Urban** ☐ **Rural** ☐
- **How long have you been living in this zone?** ☐ **Year** ☐ **Month**
- **Have you lived in the same zone since birth? Yes** ☐ **N0** ☐
- **If the answer is no: mention the name of the previous region: Rural**☐ **Urban** ☐
- **Marital status: Single** ☐ **Married** ☐ **Widow** ☐
- **D o you have children: Yes** ☐ **No** ☐
- **Age at birth of first Baby:** ☐
- **How many kids do you have?** ☐
- **Type of breastfeeding: natura**☐**, Artificial** ☐**, Mixed** ☐
- **Have you used contraceptives? Yes**☐ **No** ☐
- **If the answer is yes, what type of contraceptive was used? ……..**
- **Age when symptoms of the disease appear:** ☐
- **Method of detecting the disease:** Mammogram☐ Mammography ☐ **Breast self-**examination (BSE) ☐
- **The presence of breast cancer in first-degree relatives: Yes** ☐ **No** ☐ **Mum** ☐**Sister** ☐
- **The presence of breast cancer in second-degree relatives: Yes** ☐ **No** ☐ **Aunt dad side**☐**aunt mum side**☐ **niece brother side** ☐ **niece sister side**☐
- **The presence of other types of tumors: Yes** ☐ **No** ☐
- **If the answer is yes: - What is a tumor type? ……**
- **Have you had a vitamin D test previously? Yes** ☐ **No** ☐

- **If the answer is yes: -** Before infection ☐ during the discovery of the disease ☐
- **Have you had a recent vitamin D test? Yes** ☐ **No** ☐
- **Have you ever had other diseases before: Yes** ☐ **No** ☐
- **Previous exposure to radiation: Yes** ☐ **No** ☐
- **You have previously taken specialized medications: Yes** ☐ **No** ☐
- **Do you redness or swelling on the breast: Yes** ☐ **No** ☐
- **Period of redness:** ☐
- **What is the degree of redness? Severe** ☐ **moderate** ☐ **mild** ☐
- **Having an orange peel texture appearance: Yes** ☐ **No** ☐
- **Are there clear mass: Yes** ☐ **No** ☐
- **Do you use black dye? Yes** ☐ **No** ☐
- **Duration of use of the dye:** ☐
- **Do you eat meat: Yes** ☐ **No** ☐
- **Which types of meat are the most eaten?** Red meat ☐ white meat ☐ fish ☐
- **Frequency of eating red meat:** Daily ☐ more than three times a week ☐ Once a week ☐ Rarely ☐
- **Does anyone in the family smoke?** Yes ☐ No ☐

إستمارة إستبيان للمترددين على عيادة أورام الثدي

- **الجنس: أنثى** ☐ - **الطول** ☐ - **الوزن** ☐ - **نوع فصيلة الدم** ☐
- **العمر**: 29-39 ☐ 40-50 ☐ 51-61 ☐ 62 فأكبر ☐
- **العمر عند أول دورة شهرية** ☐
- **العمر عند إنقطاع الطمث** ☐
- **مكان الإقامة** : حضر ☐ ريف ☐
- **هل إقامتك منذ الولادة بنفس المنطقة** : نعم ☐ لا ☐
- **إذا كانت الإجابة لا :** يذكر اسم المنطقة السابقة ريف ☐ حضر ☐
- **مدة الإقامة بالسكن الحالي** ☐

- **الحالة الاجتماعية :-** عزباء ☐ متزوجة ☐ أرملة
- **هل لديك اطفال :-** نعم ☐ لا ☐
- **العمر عند إنجاب أول طفل** :- ☐
- **كم عدد الاطفال** ☐
- **نوع الرضاعة :** طبيعية ☐ صناعية ☐ مختلطة ☐
- **هل تناولتي موانع الحمل** :- نعم ☐ لا ☐

- **إدا كانت الإجابة نعم :-** ما نوع المانع المستخدم .....
- **العمر عند ظهور أعراض المرض** ☐
- **طريقة كشف المرض :** Mammogram ☐ Mammography ☐

☐ Breast self –examination (BSE)

- **وجود سرطان الثدي في الأقارب من الدرجة الأولى** نعم ☐ لا ☐

أم ☐ أخت ☐

- **وجود سرطان الثدي في الأقارب من الدرجة الثانية :-** نعم ☐ لا ☐

العمة ☐ الخالة ☐ بنت الأخت ☐ بنت الأخ ☐

- **وجود أنواع أخرى من الأورام :** نعم ☐ لا ☐

<u>إذا كانت الإجابة نعم</u> :- ما هو الورم :-.....

- **هل أجريتي تحليل فيتامين D في السابق :-** نعم ☐ لا ☐

<u>إذا كانت الإجابة نعم</u> :- قبل الإصابة ☐ أثناء إكتشاف المرض ☐

- **هل أجريتي تحليل حديث ل فيتامين D :-** نعم ☐ لا ☐
- **هل سبق إن أصبتي بأمراض أخرى من قبل : -** نعم ☐ لا ☐
- **التعرض للأشعة مسبقا :-** نعم ☐ لا ☐
- **سبق ان تناولت أدوية :-** نعم ☐ ☐
- **هل يوجد إحمرار وتورم بالثدي:** نعم ☐ لا ☐
- **فترة ظهور الاحمرار :-** ☐
- **ماهي درجة الاحمرار** شديدة ☐ متوسط ☐ بسيط ☐
- **وجود مظهر ملمس قشرة البرتقال:** نعم ☐ لا ☐
- **هل توجد كتل واضحه:** نعم ☐ لا ☐
- **هل تستعملين الصبغة السوداء:** نعم ☐ لا ☐
- **مدة إستعمال الصبغة :-** ☐
- **هل تتناولين اللحوم:-** نعم ☐ لا ☐

أي أنواع اللحوم أكثر تناولا لحوم حمراء ☐ لحوم بيضاء ☐ أسماك ☐

- **معدل أكل اللحوم الحمراء**: يومياً ☐ أكثر من ثلاثة مرات في الأسبوع ☐

  مرة في الاسبوع ☐ نادرا ☐

- هل يدخن أحد في الأسرة نعم ☐ لا ☐

وزارة التعليم العالي والبحث العلمي

إدارة الدراسات العليا والتدريب

كلية العلوم

قسم علم الحيوان

بيولوجية عوامل الخطر في نشوء سرطان الثدي ودورها في الكشف المبكر له

رسالة مقدمة إلى قسم الدراسات العليا بكلية العلوم بالزاوية إستكمالاً لمتطلبات درجة الماجستير في العلوم في علم الحيوان

إعداد الطالبة:

إينـــاس مصطفى عبد السلام شليـق

تحت إشراف :

الدكتور. فكـري علـي أبوشوفـــه

ربيع 2024