DEMOGRAPHIC ANALYSIS OF BREAST TUMORS IN A SAMPLE OF IRAQI POPULATION

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Abstract. Breast cancer (BC) is the predominant type of cancer among the female population in Iraq, and one of the most common causes of death among females. Through the period from 2018 until 2020, A total of eighty- two Formalin Fixed-Paraffin embedded FFPE tissue blocks were collected from the archive of Histopathology Department in Teaching Laboratories of Medical City, Teaching Hospital of Al-Yarmouk, and a privately-owned laboratory in Baghdad, Iraq. The clinical information regarding age, gender, tumor size, tumor stage and grade, lymph nodes metastasis, in addition to the findings of estrogen receptor (ER), progesterone receptor (PR) and receptor of human epidermal growth factor (HER)-2 were acquired from carefully reviewing patients' medical records and pathology reports. Results showed that a high incidence of BC in patients at sixth and decades of age, most of tumors′ specimens were within group size of (2-5 cm) in both malignant and benign groups, comprising 57.14% and 80% respectively, the most prevalent histologic type was invasive ductal carcinoma (IDC) encompassing 73.8%. About 59.52% of cases had positive lymph node tumor metastasis, the majority of cases were in grade II 64%. Stage III of the disease had highest rate, most of the cases were ER positive (66%), PR positive (57%) and for the HER most of the cases were HER negative.

Keywords: breast cancer, epidemiology, incidence rate, Baghdad city.

List of Abbreviations

IDC – invasive ductal carcinoma
ILC – invasive lobular carcinoma
DCIS – ductal carcinoma in situ
ER – estrogen receptor
PR – progesterone receptor
HER – human epidermal growth factor receptor
FCC – fibrocystic change
EIBC – early-stage invasive breast cancer
DFS – disease free survival
BSE – breast self-examination

Introduction

Breast cancer, or BC, is among the worst tumors that may affect human life. it stands as the primary contributor to death associated with cancer among women on a global scale (Razmjooy *et al.*, 2023). There are many types of cancers such as bladder cancer (Ismael *et al.*,2023; Al-Humairi *et al.*, 2023), gastric cancer (Bresam *et al.*, 2023a; Sultan *et al.*, 2023), peptic ulcer (Bresam *et al.*, 2023b). In the year 2020, the global incidence of breast cancer in women amounted to 2.3 million new cases with a corresponding mortality rate of 685,000 deaths (Mohammed, 2022). Breast cancer is identified as the foremost among the top 10 malignant neoplasms that pose a significant threat to the population in Iraq (Mohsin & Mohamad, 2023). BC rates are steadily rising throughout the Middle East's emerging nations, such as Egypt, Lebanon, Syria, Jordan, Iran, Iraq, and Saudi Arabia (Karim *et al.*, 2015). Breast cancer is the prevailing form of cancer among females in Iraq. The Children's Cancer Research Institute (CCRI) argues that BC has highest position in terms of incidence among female malignancies, constituting almost one-third of all cancers recorded in the most recent Iraqi Cancer Register (Jalil *et al.*, 2019). Between 2006 and 2014, the Iraqi province Sulaymaniyah had the highest incidence rate of BC in females, and it was found to be the most frequent malignancy in Basra in 2017 (Abood *et al.*, 2020). The rate of new cancer cases in Iraq had an upward trend, with a rise seen from 52.00 per 100,000 individuals in the year 2000 to 91.66 per 100,000 individuals in the year 2019 (Alrawi, 2022). Non-modifiable risk factors for breast cancer include gender, age, genetic traits such as familial or personal breast cancer history,

ethnic background, and early initiation of menstruation or menopause. While modifiable risk factors that usually associated with exposure to carcinogens and lifestyle variables which encompass several elements, such as physical inactivity, being overweight or obesity, alcohol intake, parity, and the utilization of certain drugs, such as oral contraceptives (Youn & Han, 2020). The occurrence of breast cancer is notably elevated in industrialized countries, the prevalence of the disease in emerging nations is comparatively smaller when compared to its counterparts in western regions. The available statistical data suggests that breast cancer incidence rates are more prevalent and elevated in highly developed nations, but mortality rates associated with breast cancer are greater in less developed countries (Alrawi, 2022). The World Health Organization (WHO) has reported a rising prevalence of breast cancer in emerging nations, potentially attributed to factors such as urbanization, extended life expectancy, and the adoption of westernized lifestyles (Mutar *et al*., 2019). Unfortunately, the availability of exact statistical data on breast cancer in Iraq is limited. Consequently, the existing researches heavily rely on western knowledge due to the lack of globally published data (Karim *et al*., 2015).

Materials and Methods

Sample preparations and staining

A total of 82 tissue samples as formalin-fixed paraffin-embedded (FFPE) tissue blocks were retrieved from archive of Histopathology Department in Teaching Laboratories of Medical City, Teaching Hospital of Al-Yarmouk, and privately-owned laboratory in Baghdad, Iraq, for the years 2018, 2019, 2020 and 2021. The distribution of the cases was in the following manner: Forty-two cases identified as female malignant breast tumor, thirty cases were females' benign tumors, in addition to 10 samples of histologically normal breast tissues devoid of any significant pathology which were obtained from the Forensic Medicine Department in Baghdad after taking the required ethical consents and used for comparison purposes. These biopsies were fixed and preserved using 10% formalin and then subjected to tissue processing series.

Patients' medical pathologic reports were used to review and collect the clinical data regarding patients′ age, tumor size, tumor stage, and grade, lymph nodes metastasis, and lab results of ER, PR, and HER-2. Sections from paraffin blocks were cut at a thickness of 5 μm per each by a microtome cutter (Leica RM2125RTS). Then, sections were placed on a water bath (Electrothermal Cat No. MH 8501) heated at 40 °C and before carrying them on a standard slide and staining using Hematoxylin and Eosin (H&E).

Statistical analysis

The research used the Statistical Packages for Social Sciences (SPSS), specifically version 22, to assess the influence of various variables on the evaluated study parameters. The Pearson Chi-square test was utilized for this purpose, with the application of Yate's correction or the Fisher Exact test where appropriate. The data was presented using basic statistical measures such as frequency, percentage, mean, standard deviation, and range (represented by the lowest and maximum values).

Ethical Approval

Written informed consent was obtained from all participants. All experiments followed were in accordance with Helsinki Declaration of 1975, as revised in 2000. The College of Science Ethics committee approves the research proposal to be conducted in the presented form. This Ethics committee is working in accordance with College of Science guidelines on biomedical research (including the document number CSEC/0122/0016 dated January 20, 2022).

Results

Age

The age of the patients included in the study varied from 17 to 82 years, with a mean age of 44.07 years. The mean age for malignant group (52.52 ± 11.32), while the mean age for benign group (35.16 ± 13.40). The peak age frequency in benign group was within age >40 years comprising 70% of the total benign cases, while highest age frequency in malignant cases was in the sixth decade which comprised 45.23% (Fig. 1).

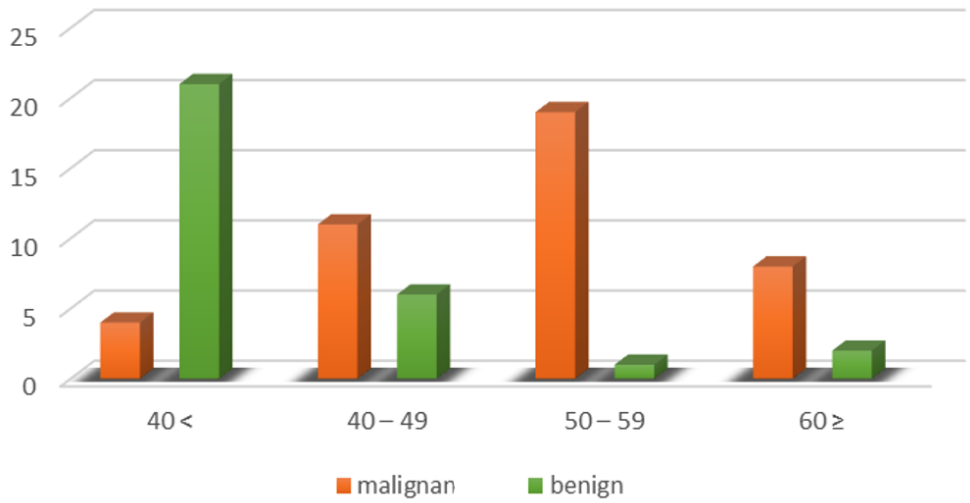


Fig. 1. Distribution of cases according to age groups

Tumor size

The mean size and standard deviation in benign cases was (3.4 ± 1.41 cm) and the mean size in malignant cases was (5.01 ± 4.97 cm). Breast tumors were categorized into three groups according to the size of the tumor: 2 cm <, 2-5 cm, and 5 cm > (Fig. 2).

Most of malignant tumors were within size group of 2-5 comprising 57.14%; 21.4% of these were in the fifth and the sixth decade of life. While in benign tumors 80% were in size group of 2-5; 60% of these were under the age of 40.

Histological type of tumor

The majority of malignant cases were invasive ductal carcinoma (IDC) encompassing 73.8% (31 of 42 of total malignant cases); 35.71% of these were within the sixth decade of life (Fig. 3). While in benign cases, the most frequent type was fibroadenoma comprising 56.6% (17 of 30 of total benign cases); 46.67% of these were with in age of less than 40 (Fig. 4).

Lymph node metastasis

The histological examination of the infected lymph nodes showed that 59.52% of cases had positive lymph node tumor metastasis, 33.33% of cases had no lymph nodes metastasis. It should be mentioned that there were 7.15% (3 cases) we did not have their lymph node status. (Fig. 5).

Grades of malignant cases

The process of tumor grading was done in accordance with the Nottingham modifications of the Bloom and Richardson system, and results showed that 4.76% of malignant cases were in grade I; 64.28% were grade II and 30.95% had grade III (Fig. 6).

Pathological stage

The staging of malignant cases was done according to AJCC staging system. Results revealed that stage III had the highest rate. The distribution of cases according to tumor stages was: 28.57% of cases within IIIC, 14.28% for IIIA, and 2.38% for IIIB, followed by stage II, 14.28% for IIA, and 14.28% for IIB. And cases in stage IA comprised 11.9%, stage IB – 7.14% of cases, while 7.27% of cases didn't have their stage information (Fig. 7).

ER expression

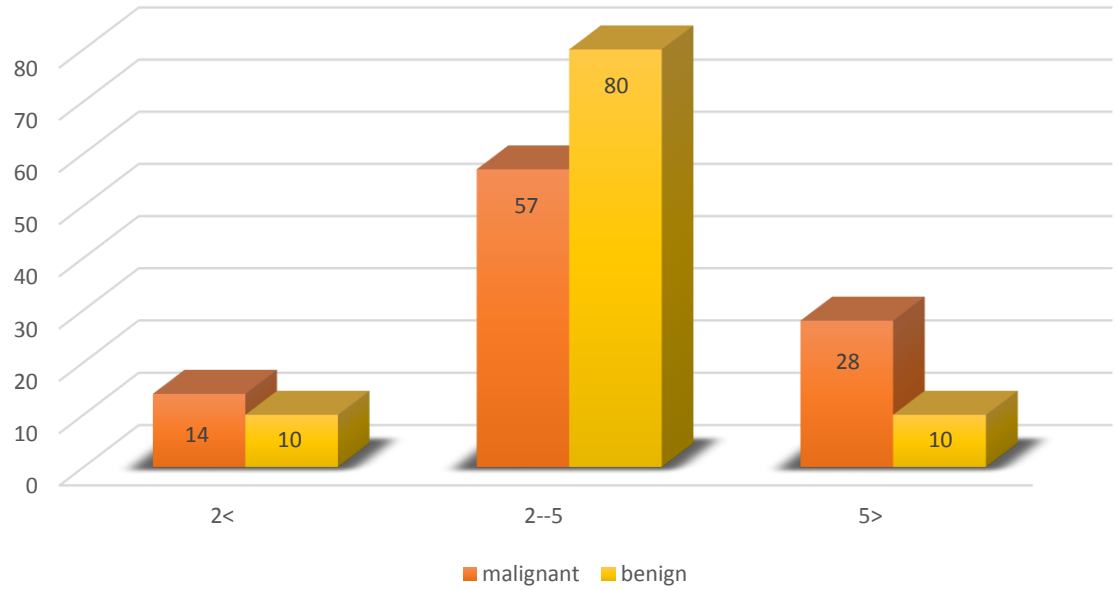
The data showed that malignant cases with positive ER results formed 66.66% (28 cases), while ER negative results were detected in 13 cases comprising 30.95% of total cases (Fig. 8).

PR expression

Data displayed that the number of cases with positive PR results made up 57.14% (24 cases), 35.71% (15 cases) with negative PR, and 7.15% (3 cases) didn't know their PR status (Fig. 9).

HER2 Expression

Results revealed that HER2 positive results were detected in 33.33% of cases, while HER2 negative outcome found in 64.28% of total (Fig. 10).



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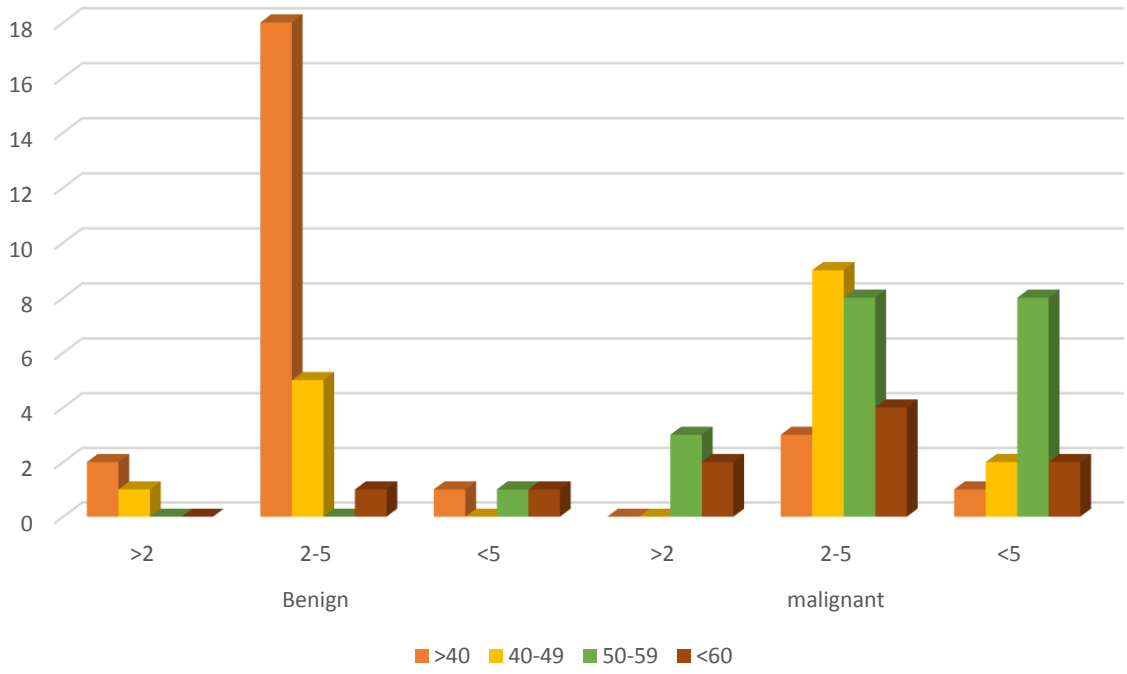
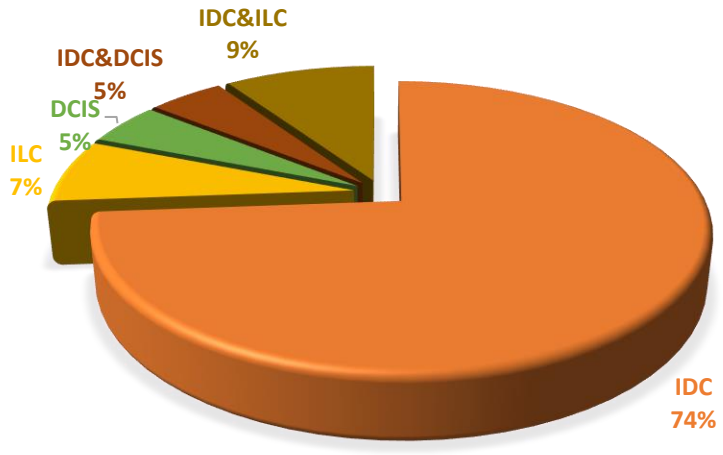


B

Fig. 2. A) Distribution of breast tumor cases according to tumor size.
B) Distribution of breast tumor size according to age group



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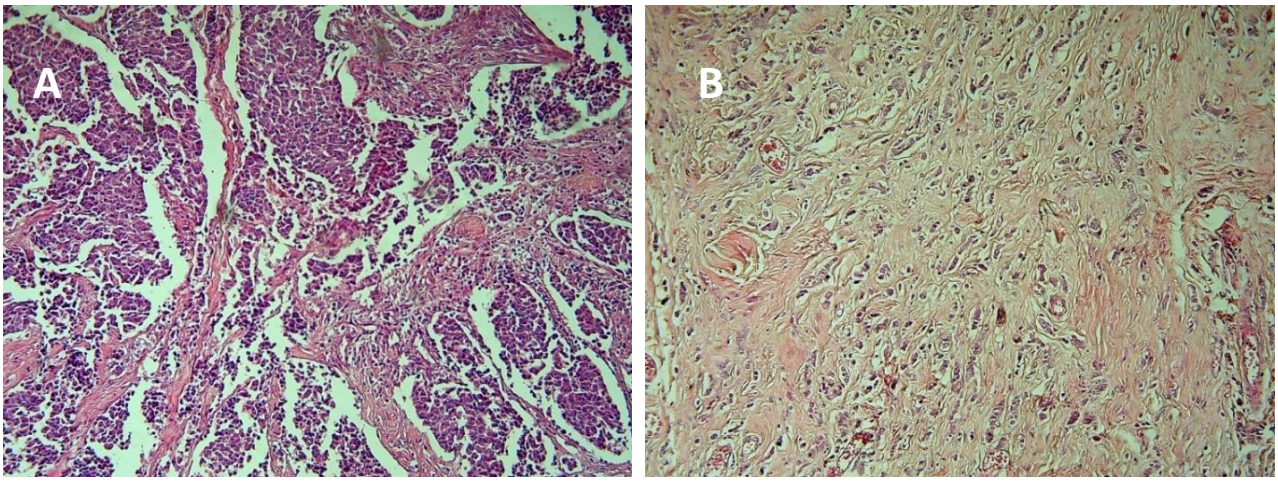

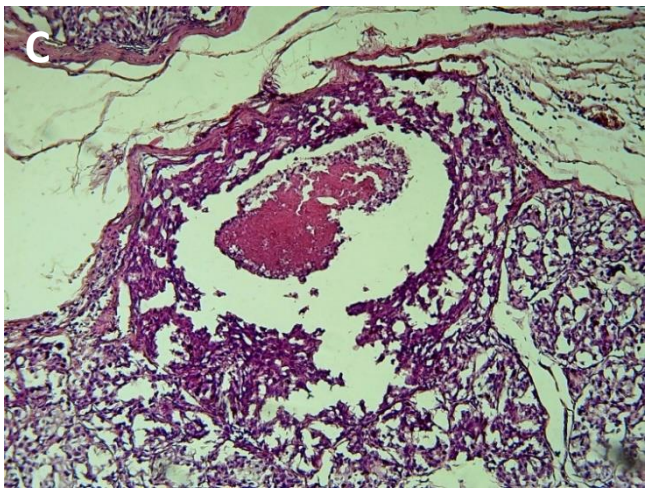

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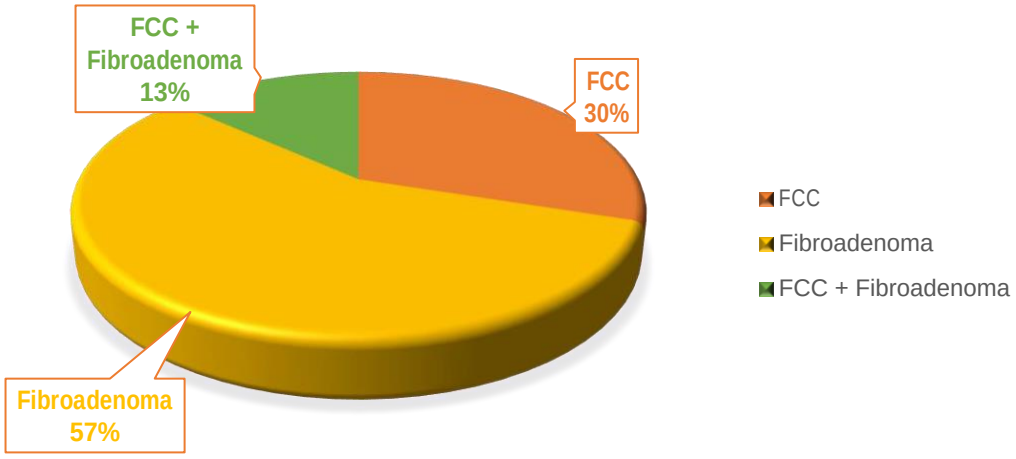
Fig. 3. A) Distribution of malignant cases according to histological type. B) Tissue sections stained with hematoxylin and eosin (H&E) for malignant cases, A&B: ILC (10X) & IDC (10X). C: DCIS (10X)



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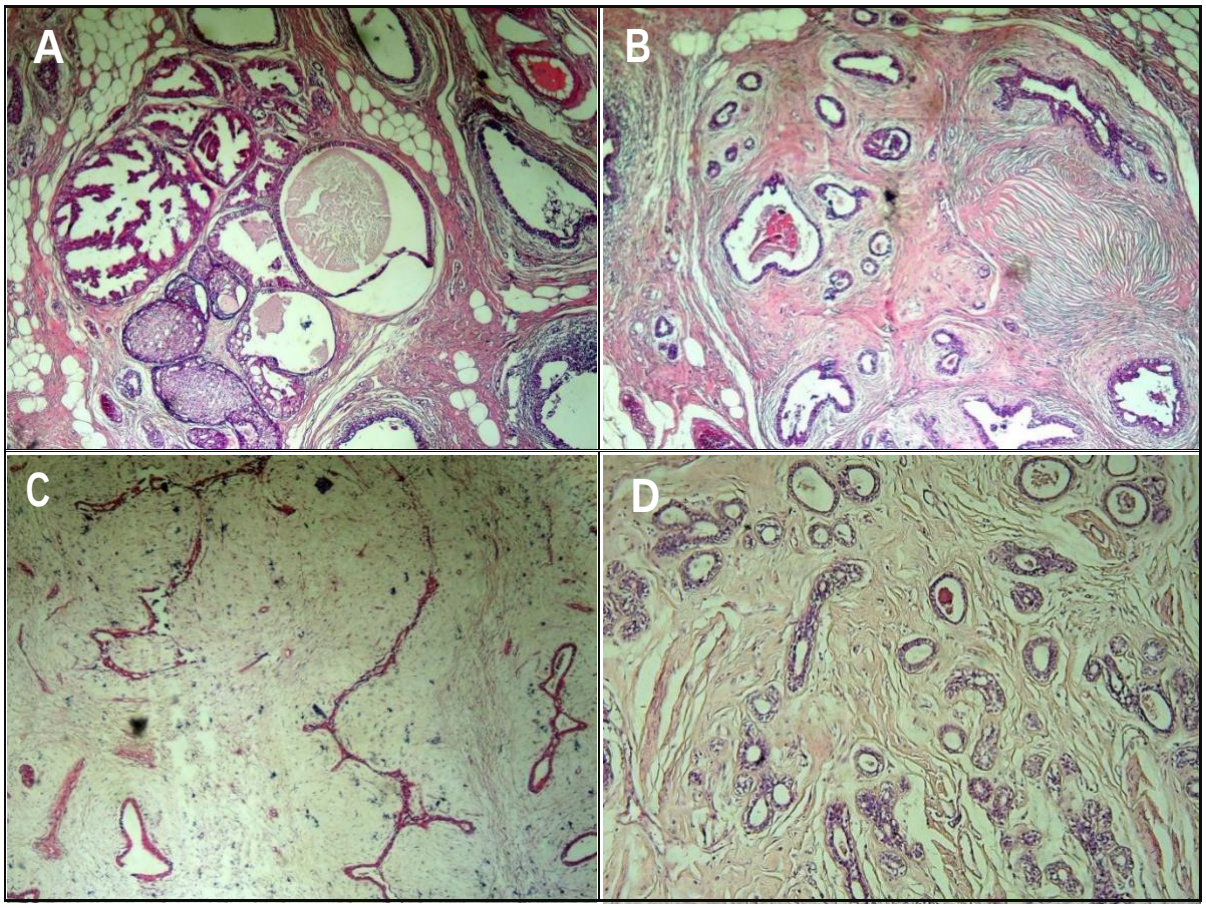
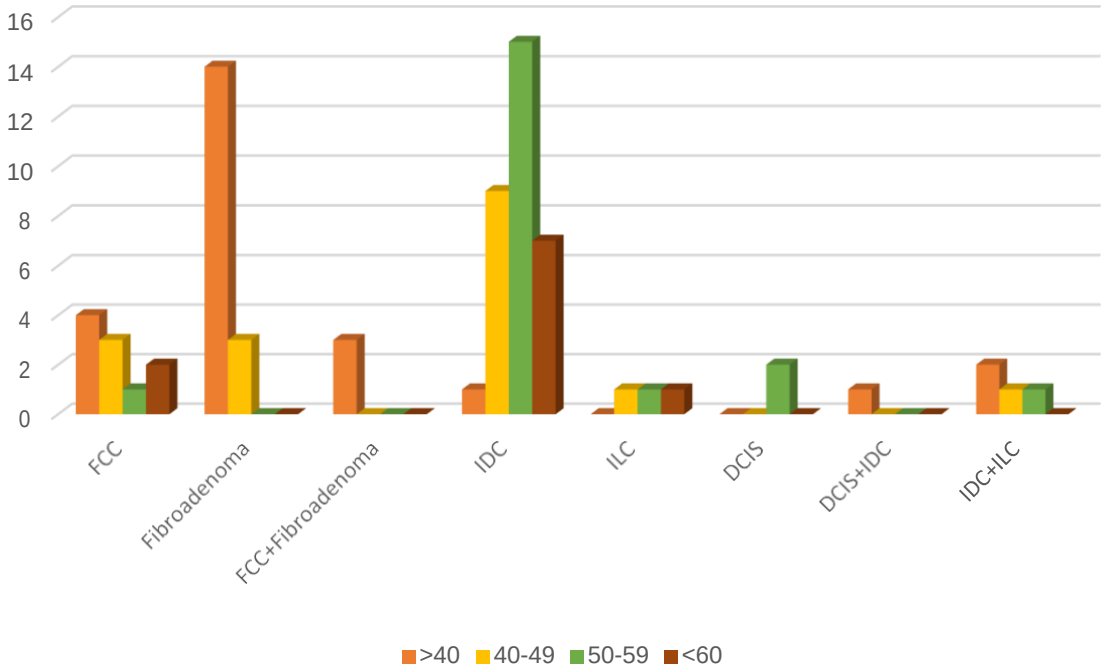


Fig. 4. A) Distribution of benign cases according to histological types. B) Tissue sections stained with hematoxylin and eosin (H&E) for benign cases, A&B: Fibrocystic change (10X). C&D: Fibroade- noma and control (10X). C) The distribution of malignant & benign histologic type according to age group (continuation of the drawing on p. 75)



C

Fig. 4. A) Distribution of benign cases according to histological types. B) Tissue sections stained with hematoxylin and eosin (H&E) for benign cases, A&B: Fibrocystic change (10X). C&D: Fibroade- noma and control (10X). C) The distribution of malignant & benign histologic type according to age group (beginning of the drawing on p. 74)

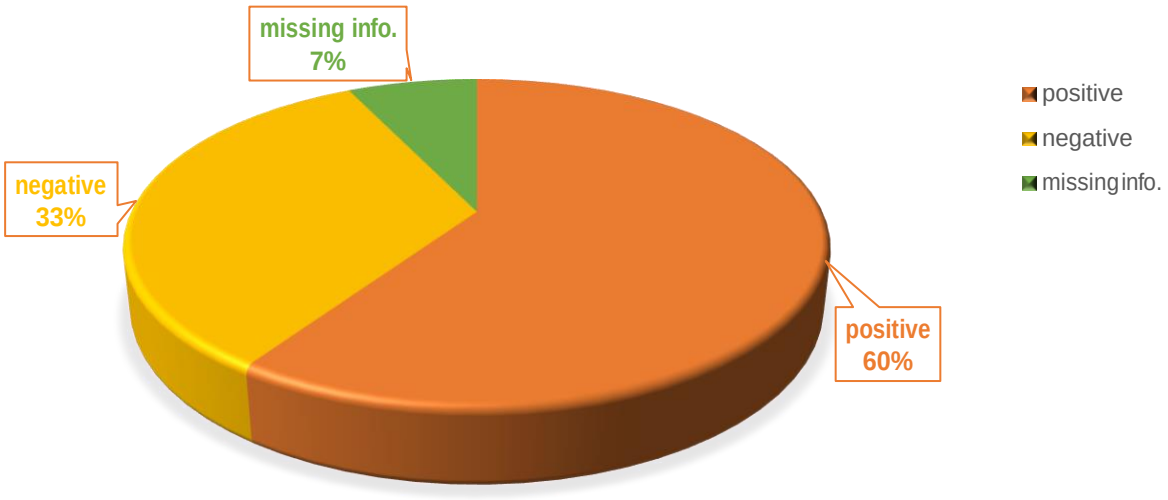
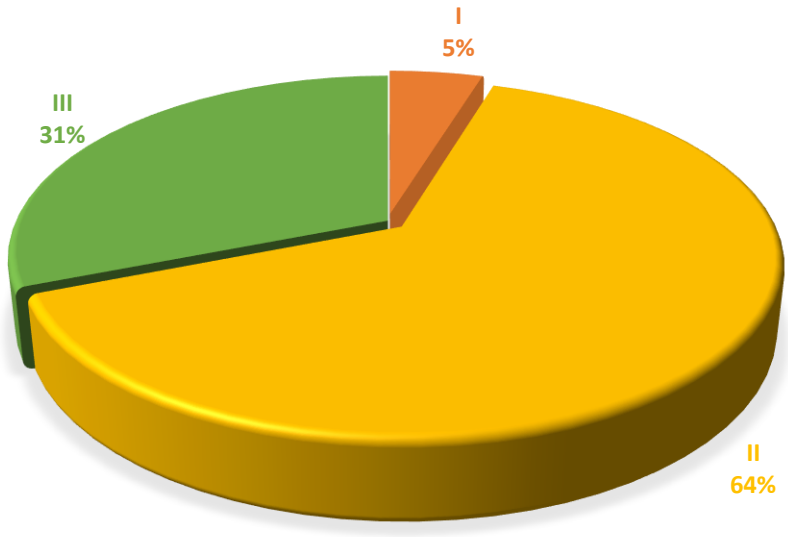


Fig. 5. The distribution of malignant cases according to the lymph node metastasis status



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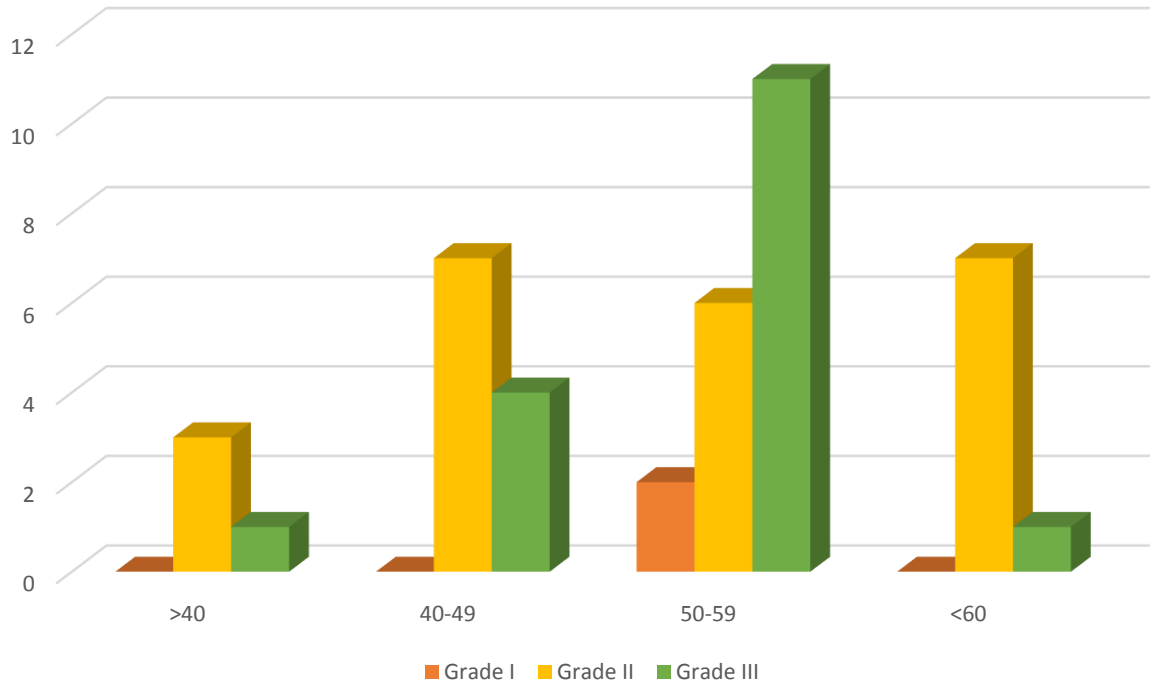

B

Fig. 6. A) The distribution of 42 breast cancer cases according to the Bloom Richardson grading system. B) The distribution of histologic grade according to age groups

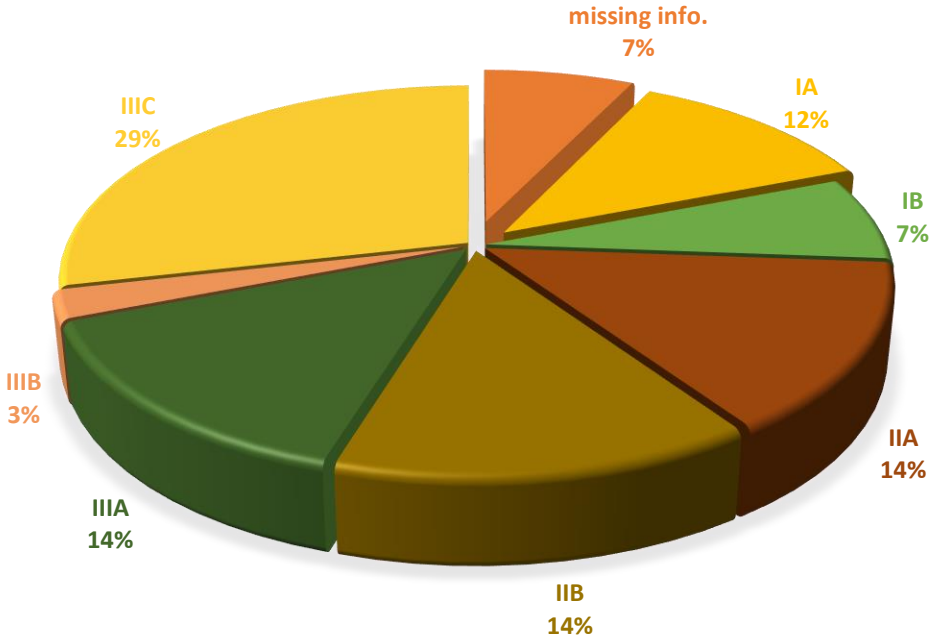

Fig. 7. The distribution of malignant cases according to the pathological stage

Fig. 8. The distribution of malignant cases according to the ER status

Fig. 9. Distribution of malignant cases according PR status

Fig. 10. The distribution of malignant cases according HER2 status

Discussion

Our collected data indicate that significant incidence rate of breast cancer accurse during the sixth decade of life which comprised 45.23% of all malignant cases, this agrees with (Alrawi, 2022) who found an increase in incident rates of BC among women over 50 (Jalil *et al*., 2019) research revealed that individuals within the age ranges of 40-49 years and 50-59 years exhibited the greatest incidence rates of cases. In the same way, a study in Mosul by (Al-Hashimi, 2021) who found that high incident rates of breast cancer are significantly high in age groups 50–59 and 60–69 yrs. On the other hand, study by Alwan *et al*. (2019) found that the peak frequency occurred among the age groups 35–49 years and 60–64 years. Moreover, according to the incidence report of the Saudi Cancer Registry in 2017, breast cancer (BC) was identified as the most prevalent cancer among women, the median age at the time of diagnosis for women with BC was 51 years, with a range spanning from 17 to 82 years (AlSaleh, 2022). Other study in Lebanon by Fares *et al*. (2019) found high incident rate in age groups 45-49, 50-59 as well as 60 and above. In Europe, a study by Dafni *et al*. (2019) revealed that BC in women is directly linked to a later onset of menopause, they found that incidence rates are progressively increasing the risk around age of 50 years (i.e., around menopause).

In the United States, there has been a noticeable increase in breast cancer cases among women aged 50-84 years, particularly affecting those aged 60 years and older. Interestingly, studies conducted in East Asian countries, as reported by Lin *et al*. (2019) have shown a rise in incidence of breast cancer among women aged 40 years and older. The variations in age might potentially be attributed to environmental influences, lifestyle choices, and dietary factors, and how these factors may interact with genetic predisposition to alter the likelihood of cancer development. (Abdulrazzaq & Ahmed, 2020b). Other aspect of the study is tumor size; breast tumors were categorized into 3 groups: size of less than 2 cm, 2-5cm and greater than 5 cm distributed according to age groups. In the current study mean size for benign cases was 3.4 cm ± 1.4 as for malignant cases mean size was 5.01 cm ± 4.88. Most of malignant tumors were within size group of 2-5 comprising 57.14%; 21.4% of these were in the fifth and the sixth decade of life. While in benign tumors 80% were in size group of 2-5; of these 60% were under the age of 40.

A study in Diwanyiah by Abdulabbas and Hussein (2023) found that mean size of tumor mass was 3.24 cm. A very recent study by Khoshnaw *et al*. (2023) in Erbil also found high population of 46% within size of 3-5 cm and 47% were > 3. Similarly, a study in India reported that 60% of premenopausal cases and 63% of postmenopausal cases were in tumor size of 2-5cm (Nimbalkar *et al*., 2023). A study by Abdulrazzaq and Ahmed (2020b) found that tumors > 5cm represent largest population group. Other study by (Liu *et al*., 2021) demonstrated that the mean tumor size was 3.08 cm and largest population appeared in sizes of 2-5cm. Other task by Elesawy *et al*. (2014) also reported that the largest population appear with tumors of 2-5cm. Disagreeing with our finding, Abdul-Kareem and Mahdi (2021) in their study found that 72% of the patients had tumor size of 2 cm or less and 27% had tumor size between 2-5. Also, adequate health education insufficiency and the limited awareness among women in Iraq on the need of breast self-examination (BSE) and early medical consultation might be identified as contributing factors to this issue. Late diagnosis of the disease means more progressed tumor with large size which actually due to lack of proper screening tests to make early detection of suspicious lesions (Abdulabbas & Hussein, 2023). However, study date back to 2009 from Switzerland by Spitale *et al*. (2009) found that 62% of the cases represented by tumors of less than 2 cm, and 35% had tumor size ranged 2-5 cm. This could result from the early detection strategies that are common among Western nations, the diagnosis of the disease is becoming easier and faster because of the availability of clinicians with subspecialty of oncology and laboratory facilities to examine tissue biopsies with minimal invasive techniques and most importantly screening programs especially to those with risk factors.

According to our data, the majority of malignant cases were invasive ductal carcinoma (IDC), encompassing 73.8% (31 of 42 of total malignant cases); 35.71% of these that is 15 of 42 cases were in their sixth decade. This agrees with Abdul-Kareem and Mahdi (2021) who found 90% of the cases in their study in Baghdad were IDC. Also, a study in Iraq by Mutar *et al*. (2019) found that 83% were IDC and 7% of the patients were lobular carcinoma. Another study by Pandit *et al*. (2020) conducted on 2062 patients also found that 96% of the cases were IDC. Similarly, Ooko *et al*. (2023) found that highest frequencies were in IDC comprising 81.8%. A cohort included 818,000 female patients by Li *et al*. (2020) in China found that 73% of the patients were IDC. In addition, a study in India by Gogia *et al*. (2018) also found that 96% of the cases were IDC followed by invasive lobular carcinoma (ILC) comprising 2.5% and only 1.5% for other types. A study included 547 patients in Korea by Song *et al*. (2023) found 82.1% of the patients were IDC and 9.5% of the patients were ILC and other types make up 8.4%. The observed result may be attributed to a delay in the individual's decision-making process to seek medical attention subsequent to the identification of indicative symptoms. Women may experience fear or have the belief that the symptoms they are experiencing are not of a serious nature when faced with the possibility of a cancer diagnosis. The delay may have been attributed to reasons of religious or spiritual nature (Mutar *et al*., 2019). Another important prognostic factor in this study is the involvement of axillary lymph node. The histological examination of the lymph nodes showed that 59.52% of population study came with positive lymph node and this outcome is in harmony with that of Abdulrazzaq and Ahmed (2020a), their study included 50 cases in Erbil, of them; 72% had positive lymph node metastasis. While Khushk *et al*. (2021) reported that 46% of cases were negative to lymph node metastasis and 54% were positive with lymph node metastasis in varying degrees (N1, N2 and N3). A study in Saudi Arabia by Elsamany *et al*. (2022) found that 31.52% were negative and 68.4% were positive to lymph node metastasis. In Jordan, a study included 776 patients by Abdel-Razeq *et al*. (2021) they reported 35.1% cases negative and 64.8% cases positive for lymph node metastasis. While Yuan *et al*. (2019) found that 44.23% of study cases were negative and 55.76% were positive for lymph node metastasis. Abdul-Kareem and Mahdi (2021) reported that 55% of cases were negative and 45% were positive. The assessment of lymph node status has significant importance in predicting prognosis and determining appropriate treatment strategies. Axillary lymph node (ALN) is a crucial diagnostic and prognostic indicator for disease-free survival (DFS) in cases of early-stage invasive breast cancer (EIBC) where there is no clinical evidence of axillary illness (Yu *et al*., 2019). Tumor size and estrogen receptor status are frequent variables affecting axillary lymph node involvement in breast cancer patients. Since the number of affected lymph nodes is closely connected to tumor size. The use of routine screening programs for all women has the potential to identify cancer at earlier stages and smaller sizes, hence enhancing prognosis and increasing survival rates (Mohammed, 2019). Other aspect investigated in this study is the tumor grade, the histological grade of the tumor was evaluated using the Nottingham modification of the Bloom and Richardson system. Patients were graded in to 3 major grades: I, II and III distributed in in four age groups. Study revealed that most of cases in grade III in the sixth decade of life comprising 26.1% of total malignant cases. This is consistent with studies like Ren *et al*. (2018) found that the largest proportion was in grade III group (57.9 %) versus only 42.1% for both grade I and II. Likewise, a study by Cimino-Mathews *et al*. (2016) revealed that grade III group constituted the largest proportion by 71% and only 29% were in grade II. However, other studies like Song *et al*. (2023) who declared in their study that the largest population (74%) was within grade II. Another study by Li *et al*. (2020) in China also found the highest percentage was within grade II group (42%) followed by grade III (35%) then grade I (21.3%). Our results also agree with Khoshnaw *et al*. (2023) who reported the highest frequency

in grade II comprising (73%) versus 3.2% 23.4% in grade I and III respectively. The grading of breast cancer is a highly influential prognostic indicator in the context of early-stage illness, the inclusion of tumor grade as a stage modifier in the American Joint Committee on Cancer tumor, node, metastases staging system is a significant development, since it is a key component in several management decision aids (Rakha *et al*., 2018). Tumor grade evaluation involves the examination of histologic differentiation at a microscopic level, which includes the assessment of tubule formation, nuclear pleomorphism, and proliferation, as indicated by the mitotic index (Tsang & Tse, 2020). The variance in the reported proportion of each grade in different studies can be attributed to the distinction between early and advanced breast cancer groups, as well as the specific methods employed for tissue fixation (Rakha *et al*., 2010). Moreover, the assessment of the staging methodology in this research was carried out in compliance to the seventh edition of the American Joint Committee on Cancer (AJCC) staging system. and according to our data the largest population was the patients with stage III 45.23% followed by stage II 28.56%, while the lowest population was within the group with stage I of disease. A study by Abdulrazzaq and Ahmed (2020b) from al Sulaymaniyah came in accordance with our results, they found that the largest population was within stage III and IV by 54% versus only 46% of patients were in stage I and II. Unlike Khoshnaw *et al*. (2023) in Erbil who found high frequency in stage II of the disease, Gogia *et al*. (2018) recorded that the highest frequency was in stage III (45%) and other stages comprised 4%, 33% and 18% for stage I, II and IV respectively.

Different outcomes were reported in a study from Egypt by Alwan *et al*. (2021) their largest population of patients were within stage II (IIA and IIB). Similarly, Cimino-Mathews *et al.* also found that highest proportions were recorded in stage II (60%), while stage I and III comprised 24% and 16% respectively (Cimino-Mathews *et al*., 2016). The late presentation of the disease can be related to a deficiency in infor-mation and awareness of the condition, as well as a failure to recognize the warning signs. To be more explicit, studies revealed that 29.5% of patients refrained from seeking medical help until they had discomfort or experienced abnormal discharge, ulceration, or a change in breast texture (Mutar *et al*., 2019). The primary factor contributing to elevated rates of morbidity and death, particularly in developing nations, is the diagnosis at an advanced stage of the disease. This observation may elucidate the reasons for the high mortality rate. Our findings regard ER, PR and HER showed that 68.29% were ER positive, 61.53% were PR positive, and 34.14% HER positive. This comes to agreement with Abdulrazzaq and Ahmed (2020b) who found that 68% of the cases were ER positive and 58% PR positive. Similarly, Khoshnaw *et al*. (2023) also found that 87% were ER positive, and 85.3% PR positive. Another study by Elesawy *et al*. (2014) had close outcome regarding ER positive expression which was 53.6%, while PR expression was positively expressed in only 36.8% of total cases. A study by Song *et al.* found that PR was positively expressed in 91% of the patients and only 9% showed a negative expression (Song *et al*., 2023). In his study, Wang *et al*. (2019) reported a percentage of 54.3% of the cases for ER positive and PR positive. Both ER and PR are valuable in classifying breast cancer patients for prognostic purposes (Parise & Caggiano, 2014), The evaluation of endocrine sensitivity, as determined by the presence of estrogen receptor (ER) and/or progesterone receptor (PR) expression, has been widely acknowledged as a prognostic indicator for the efficacy of tamoxifen or ovarian suppression. In the same way, the overexpression of HER2 has proven to be advantageous in the identification of targeted anti-HER2 treatment. (Parise *et al*., 2009). In the present study the great majority of cases were HER negative comprising 65.74%. Our finding is consistent with (Pournabee *et al*., 2023) who also found that 62.33% of the patients were HER negative. (Kim *et al*., 2018) also had similar values to ours regarding HER, the highest frequency seen in HER negative patients with percentage of 69% and only 30% for patients that positively express HER. Another task by Rosa *et al*. (2020) found 76% were HER-2 negative and 24% were

HER=2 positive. In the same way, Dihge *et al*. (2019) found 87% were HER-2 negative and 13% were HER-2 positive. However, Sun *et al*. (2014) disagreed with our data and found that 24.89% of the patients were HER negative while 75.12% were HER positive. Breast cancer exhibiting human epidermal growth factor receptor-2 (HER-2) positivity is characterised by a high degree of invasiveness, unfavourable clinical outcomes, and an elevated likelihood of recurrence, Therefore, the amplification and overexpression status of HER-2 in breast cancer holds significant implications for prognosis and therapy approaches (Xu *et al*., 2022). The primary function of this gene is to control excessive or uncontrolled cell growth, differentiation and repair (Padayachee *et al*., 2020). Breast cancers that are positive for HER2 exhibit morphological characteristics of poor differentiation, including significant pleomorphism and a high rate of cell proliferation, indicating high grade cancers. These cancers have a tendency to spread to the lymph nodes, display resistance to specific chemotherapeutic agents, and have a higher likelihood of recurrence and distant metastasis, ultimately leading to a higher mortality rate (Sareyeldin *et al*., 2019).

Conclusion

Based on the findings of this study, it was observed that the occurrence of breast cancer (BC) was more prevalent among individuals in their sixth decade of life. The most commonly observed histologic type was the invasive ductal carcinoma (IDC) accompanied by lymph node metastasis. Furthermore, a significant proportion of malignant cases were classified as histologic grade II presented at advanced stage of the disease, stage III. Last but not the least, it is worth noting that a large proportion of patients had positive expression of estrogen receptors (ER) and progesterone receptors (PR), although most cases tested negative for human epidermal growth factor receptor 2 (HER2). Therefore, it is imperative to emphasize the importance of breast cancer (BC) awareness and early identification by routine breast screening in order to minimize the mortality and morbidity associated with this malignant neoplasm.

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Conflict of interest: the authors declare that they have no conflicts of interest.

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