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Breast Cancer Therapy in the National Oncology Center – Yemen: Descriptive Study

A graduation research project submitted in partial fulfillment of requirements of the 5th year for obtaining bachelor degree in clinical pharmacy

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Dedication

This research is dedicated to our families who gave us support, not just financially but also physically and morally. They also supported us with their love, prayers, caring and sacrifices for educating and preparing us for our future.

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The researchers

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The researchers

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List of abbreviations

HER-2	Human epidermal growth factor receptor 2
ER	Estrogen receptor
PR	Progesterone receptor
DCIS	Ductal carcinoma in situ
BRCA1	Breast cancer gene 1
BRCA2	Breast cancer gene 2
CHEK	Checkpoint kinase 2
PALB2	Partner and localizer of BRCA2
BRIP1	BRCA1 interacting protein
IHC	Immunohistochemistry
TAC	Docetaxel, Doxorubicin, Cyclophosphamide
AC	Doxorubicin, Cyclophosphamide
FAC	5-FU, Doxorubicin, Cyclophosphamide
FEC	5-FU, Epirubicin, Cyclophosphamide
AC ⇒ T + H	Doxorubicin, Cyclophosphamide ⇒ Taxol+Herceptin
TC	Taxotere, Cyclophosphamide
TCH	Docetaxel, Carboplatin, Herceptin
CMF	Cyclophosphamide, Methotrexate, 5-FU
TCH-P	Docetaxel, Carboplatin, Herceptin, Pertuzumab

Abstract

Breast Cancer Therapy in the National Oncology Center – Yemen: Descriptive Study

Background: The present study was aimed to describe treatment patterns among breast cancer patients at the National Oncology Cancer, Sana'a.

Methods: A hospital-based cross-sectional study was conducted by collecting data from medical records of breast cancer patients who attended the breast cancer unit at the National Oncology Center in Sana'a during the period of November 1, 2019 to February 29, 2020.

Results: A total number 300 patients with breast cancer were mostly from Sana'a and Taiz governorates with a positive contraceptive history among 42.3% of patients. Out of all patients, 40.3% % were estrogen positive, 36% were progesterone positive and 51.7% were HER-2 positive. All patients have invasive form of breast cancer. Most of the patients (95%) have ductal invasive breast cancer as compared to 1.7% who have invasive lobular carcinoma. About 39% of the breast cancer patients were at stage 3, while 27.7% were at stage 4 and 25.4% were at stage 2. The most common treatment for breast cancer among the included breast cancer patients was combined surgery and chemotherapy (39%), then the standard method with surgery, radiotherapy, and chemotherapy in 32.7% of the patients. Chemotherapy alone represented 24.7% of the patients while chemotherapy along with radiotherapy represented 3.7% of the patients. Surgical procedures were undertaken for 71.4% of breast cancer patients. About 42.6% of patients with human epidermal growth factor receptor-2 (HER-2) positive breast cancer have not received biological therapy despite their positive receptor status.

Conclusions: All patients have invasive form of breast cancer which denotes that patients are usually diagnosed lately. Thus, screening of breast cancer is advised especially for patients with risk factors. Large proportion (42.6%) with human epidermal growth factor receptor-2 (HER-2) positive breast cancer patients have not received biological therapy despite their positive receptor status.

Chapter: 1

Introduction and Aim of the study

1.1 Introduction

Breast cancer is a leading cause of death worldwide, and ranks as the fifth cause of death from all cancers, and the most common cause of cancer death in women in both developing and developed countries. Prevalence of breast cancer alone accounts for 25% of all cancer cases and 15% of all cancer deaths among females **(Torre *et al*, 2015).**

Breast cancer is classified by whether the cancer started in the ducts or lobules, whether it grows or spread through the duct or lobule and how the cancer cells look under a microscope. It is broadly grouped in to those that are still in the breast lobules or ducts called noninvasive or carcinoma in situ and those that have started to grow and spread beyond the walls of the ducts or lobules called invasive carcinoma.Breast cancer stage is defined on the basis of the primary tumor extent and size (T1–4), presence and extent of lymph node involvement (N1–3), and presence or absence of distant metastases (M0–1) **(Dipiro *et al*, 2008)**. Treatment of breast cancer is dependent on disease stage, histologic and molecular subtypes and menopausal status **(Di Leo *et al*, 2015)**.Treatment of breast cancer includes surgery, radiation therapy, or both, and systemic treatment with chemotherapy, endocrine therapy, biologic therapy or combinations of these. The selection of various local or systemic therapies are based on several

prognostic and predictive factors including tumor histology, clinical and pathologic characteristics of the primary tumor, axillary lymph node status, tumor hormone receptor (estrogen receptor (ER)/ progesterone receptor (PR)) content, tumor human epidermal receptor (HER2) status, presence or absence of detectable metastatic disease, patient comorbid conditions, patient age, and menopausal status **(EMRO, 2015)**.

1.2. Aims of the study:

1.2.1. General objective

The present study was aimed to describe treatment patterns among breast cancer patients at the National Oncology Cancer.

1.2.2. Specific objectives

- To describe the clinical characteristics of breast cancer patients.
- To describe treatment modalities of breast cancer.

Chapter: 2

Review of Literature

2. Literature Review

2.1 Introduction:

Breast cancer is the most common cancer and also the leading cause of cancer mortality in women worldwide. Approximately 1.38 million new breast cancer cases were diagnosed in 2008 with almost half of all breast cancer cases and nearly 60% of deaths occurring in lower income countries **(Ferly *et al* , 2010) .**There is a large variation in breast cancer survival rates around the world, with an estimated 5-year survival of 80% in high income countries to below 40% for low income countries **(Coleman *et al*, 2008).**

Low and middle income countries face resource and infrastructure constraints that challenge the goal of improving breast cancer outcomes by early detection, diagnosis and treatment **(Anderson *et al*, 2008)** . In high income countries like the United States, approximately 232340 women will be diagnosed and 39620 will die of breast cancer in 2013 **(Seigel *et al*, 2013).**

For an American woman, the lifetime risk of developing breast cancer is 12.38% or 1 in 8 **(Seigel *et al*, 2013)**. The significant decrease in breast cancer-related mortality in the United States from 1975 to 2000 is attributed to continued improvement in both screening mammography and treatment **(Berry *et al*, 2005; Ries *et al*, 1975-2005)**. According to the World Health

Organization, improving breast cancer outcome and survival by early detection remains the cornerstone of breast cancer control.

2.2 Risk factor prediction:

Age, reproductive factors, personal or family history of breast disease, genetic pre-disposition and environmental factors have been associated with an increased risk for the development of female breast cancer.

2.2.1 Age

The risk of developing breast cancer increases with age. By using the Surveillance, Epidemiology, and End Results (SEER) database, the probability of a woman in the United states developing breast cancer is a lifetime risk of 1 in 8; 1 in 202 from birth to age 39 years of age, 1 in 26 from 40-59 years, and 1 in 28 from 60-69 years **(Siegel *et al*, 2013).**

2.2.2 Personal history

A personal history of breast cancer is also a significant risk factor for the development of a second ipsilateral or contralateral breast cancer. In fact, the most common cancer amongst breast cancer survivors is a metachronous contralateral breast cancer **(Curtis *et al*, 2006)**. Factors associated with an increased risk of a second breast cancer include an initial diagnosis of

DCIS, stage IIB, hormone receptor negative cancers, and young age **(Buist *et al*, 2010)**.

2.2.3 Breast pathology

Proliferative breast disease is associated with an increased risk of breast cancer. Proliferative breast lesions without atypia, including usual ductal hyperplasia, intraductal papillomas, sclerosing adenosis and fibroadenomas confer only a small increased risk of breast cancer development, approximately 1.5-2 times that of the general population **(Hartmann *et al*, 2005).** Atypical hyperplasia including both ductal and lobular, usually incidentally found on screening mammography, confers a substantial increased risk of breast cancer. Women with atypia have an approximately 4.3 times greater risk of developing cancer compared to the general population **(Hartmann *et al*, 2005; Doupont *et al*, 1993)**.

2.2.4 Family history

A woman's risk of breast cancer is increased if she has a family history of the disease. In the Nurses' Health Study follow-up, women with a mother diagnosed before age 50 had an adjusted relative risk of 1.69 and women with a mother diagnosed at 50 or older had a relative risk of 1.37 compared to women without a family history of breast cancer. A history of a

sister with breast cancer also demonstrated an increased relative risk of 1.66 if the diagnosis was made prior to age 50 and a relative risk of 1.52 if diagnosed after age 50 compared to patients without a family history **(Colditz *et al*, 2012).** The highest risk is associated with increasing number of first degree relatives diagnosed with breast cancer at a young age (under age 50). Compared with women who had no affected relative, women who had one, two or three or more affected first degree relatives had risk ratios of 1.80, 2.93 and 3.90, respectively **(Collaborative Group on Hormonal Factors in Breast , 2001).**

2.2.5 Genetic predisposition

Approximately 20%-25% of breast cancer patients have a positive family history but only 5%-10% of breast cancer cases demonstrate an autosomal dominant inheritance **(Lynch and Lynch, 1986; Margolin *et al*, 2006)**. Genetic predisposition alleles have been described in terms of clinical significance **(Lalloo and Evans, 2012).** High-risk predisposition alleles conferring a 40%-85% lifetime risk of developing breast cancer include BRCA1 and BRCA2 mutations, mutations in TP53 gene resulting in Li-Fraumeni syndrome, PTEN resulting in Cowden syndrome, STK11 causing Peutz-Jegher's syndrome, Neurofibromatosis (NF1) and (CDH-1) E-Cadherin **(Sharif *et al*, 2007).** Half of the breast cancer predisposition

syndromes are associated with mutations in BRCA1 and BRCA2. Women with BRCA1 or BRCA2 deleterious mutations have a significantly higher risk of developing breast cancer. Lifetime breast cancer risk ranges from 65% to 81% for BRCA1 mutation carriers and 45% to 85% for BRCA2 carriers **(Ford *et al*, 1998)**. Moderate risk genes including homozygous ataxia-telangiectasia (ATM) mutations **(Thompson *et al*, 2005)**, somatic mutations in tumor suppressor gene CHEK2, and BRCA1 and BRCA2 modifier genes BRIP1 **(Seal *et al*, 2006)** and PALB2 **(Wong *et al*, 2011)** confer a 20%-40% lifetime risk of breast cancer. Numerous low risk common alleles have been identified largely through genome-wide association studies **(Lalloo and Evans , 2012)** and the clinical application in the presence of these mutations is yet to be determined.

2.4 Endogenous hormone exposure and reproductive factors:

The cycles of endogenous estrogen levels throughout a woman's lifetime have implications for the development of or the protection against breast cancer.

2.4.1 Early menarche

Early age at menarche is a risk factor among both pre and postmenopausal women for developing breast cancer. Delay in menarche by two years is associated with corresponding risk reduction of 10% **(Hsieh *et al*,**

1990). Within the European Prospective Investigation into Cancer and Nutrition cohort, women who had early menarche (≤ 13 years) demonstrated a nearly twofold increase in risk of hormone receptor positive tumors **(Ritte *et al*, 2012)**.

2.4.2 Parity and age at first full term pregnancy

Nulliparous women are at an increased risk for the development of breast cancer compared to parous women. Young age at first birth has an overall protective effect, whereas relatively advanced age at first birth confers a relative risk of breast cancer greater than that of a nulliparous woman. Compared to nulliparous women the cumulative incidence of breast cancer in women experiencing their first birth at age 20, 25, and 35 years was 20% lower, 10% lower and 5% higher, respectively **(Rosner *et al*, 1994)**.

2.4.3 Breast feeding

Evidence suggests that breast feeding has a protective effect against the development of breast cancer. Breast feeding may delay return of regular ovulatory cycles and decrease endogenous sex hormone levels. It has been estimated that there is a 4.3% reduction for every one-year of breast feeding **(Collaborative Group on Hormonal Factors , 2002).**

2.4.4 Testosterone

High endogenous sex hormone levels increase the risk of breast cancer in both premenopausal and postmenopausal women. High levels of circulating testosterone in postmenopausal women have been linked to increased risk of developing breast cancer [relative risk (RR), 2.86-3.28] **(Sieri et al, 2009)**.

2.4.5 Age at menopause

Later onset of menopause has also been associated with increased breast cancer risk. Every year delay in the onset of menopause confers a 3% increase in risk and every five year delay in the onset of menopause confers a 17% increase in risk of breast cancer **(Hsieh et al, 1990; Kelsey *et al*, 1993)**.

2.5 Exogenous hormone exposure:

Evidence suggests a relationship between the use of hormone replacement therapy (HRT) and breast cancer risk. Breast cancers related to HRT use are usually hormone receptor positive. When compared with patients who do not use HRT, breast cancer risk is higher in HRT users **(Lahmann *et al*, 2004).** An international meta-analysis examining the risk of breast cancer with HRT found that in women who did not use HRT, RR

increased by a factor of 1.028 for each year older at menopause, comparable to the relative risk of 1.023 per year in women who use HRT or for those who ceased to use HRT up to four years previously **(Lancet, 1997)**.

In the Woman's Health Initiative randomized control trial, combined estrogen plus progestin in postmenopausal women with an intact uterus significantly increased the risk of breast cancer, delayed breast cancer detection and diagnosis, and significantly increased breast cancer mortality. The study was terminated early because of increased mortality in the combined estrogen plus progestin group. By contrast, the use of estrogen alone by postmenopausal women without a uterus did not interfere with breast cancer detection and statistically significantly decreased the risk of breast cancer **(Anderson *et al*, 2003).** Data from the Nurses' Health Study, however, suggest that women who use unopposed postmenopausal estrogen increase their risk of breast cancer by 23% at age 70 **(Colditz and Rosner , 2000)**.Timing and duration of HRT seem to be important factors associated with breast cancer risk as well. Breast cancer risk from exogenous hormone exposure is inversely associated with time from menopause. Women initiating hormone therapy closer to menopause have a higher breast cancer risk **(Chlebowski *et al*, 2013)**. Long term (> 5 years) combined HRT use has been associated with the highest risk whereas short-term use of combined

estrogen-progestin therapy does not appear to confer a significantly increased risk (RR = 1.023 per year) **(lancet, 1997).**

2.6 Lifestyle factors

Modifiable risk factors including the excessive use of alcohol, obesity and physical inactivity account for 21% of all breast cancer deaths worldwide **(Danaei *et al*, 2005).**

2.6.1 Alcohol consumption

Alcohol consumption has been associated with increased breast cancer risk that is statistically significant at levels as low as 5.0 to 9.9 g per day, equivalent to 3 to 6 drinks per week. Binge drinking, but not frequency of drinking, was associated with breast cancer risk after controlling for cumulative alcohol intake. Alcohol intake both earlier and later in adult life was independently associated with risk **(Chen *et al*, 2011).**

2.6.2 Physical activity

Consistent physical activity has been shown to reduce the risk of breast cancer in a dose dependent manner, with modest activity conferring a 2% decrease in risk and vigorous activity a 5% decrease in risk **(Wu *et al*, 2013)**.

2.6.3 Obesity

Obesity, specifically in postmenopausal women, has also been shown to increase a woman's risk of breast cancer. In the EPIC multicenter prospective cohort study, postmenopausal women who did not use HRT had elevated breast cancer risk with increasing weight, body mass index (BMI) and hip circumference **(Lahmann *et al*, 2004).** In this cohort, multivariate relative risk was 1.28 for overweight women (BMI 25.0-29.9) and obese women (BMI > 30.0) compared to women in the normal weight range. Lean women on HRT are incongruously at an increased risk of breast cancer (RR = 2.04) compared to their overweight (1.93) and obese (1.39) counterparts **(Lahmann *et al*, 2004)**. Insulin resistance and hyperinsulinemia have been studied as a risk factor for the comorbidities associated with obesity including cardiovascular disease and diabetes. Insulin has anabolic effects on cellular metabolism and insulin receptor overexpression has been demonstrated in human cancer cells **(Milazzo *et al*, 1992)**. Hyperinsulinemia has been shown to be an independent risk factor for breast cancer in nondiabetic postmenopausal women and may help to explain the relationship between obesity and breast cancer **(Gunter *et al*, 2009)**.

2.6.4 Radiation

Radiation exposure from various sources including medical treatment and nuclear explosion increases the risk of breast cancer. Radiation to the chest wall for treatment of childhood cancer increases the risk of breast cancer linearly with chest radiation dose **(Henderson *et al*, 2010)**. Survivors of childhood cancers who received therapeutic radiation are at a dose dependent risk for the development of breast cancer, and those treated for Hodgkin's disease are at highest risk (RR = 7) **(Guibout *et al*, 2005)**. Radiation effects on the development of female breast cancer have also been demonstrated in Japan post nuclear attack on Hiroshima and Nagaskai **(Preston *et al*, 2007)** and positively correlate with age younger than 35 years at time of exposure. The incidence of breast cancer has also increased in areas of Belarus and Ukraine. A significant two fold increase was seen in the most contaminated areas around Chernobyl following the nuclear accident and manifest in women who were younger at the time of the exposure **(Pukkala *et al*, 2006).**

2.7 Screening

2.7.1 Breast self- and clinical breast examination

Utility of the breast self-examination (BSE) is controversial as the benefit in terms of decreased mortality has not been demonstrated **(Kösters and Gøtzsche, 2003).** Most clinicians encourage women to perform monthly BSE to become familiar with their normal anatomy and empower them with regards to their own healthcare **(McCready *et al*, 2005).** The 2013 NCCN guidelines recommend annual clinical breast examination (CBE) for women of average risk > 40 years of age as well as BSE to develop and exhibit breast self-awareness **(National Comprehensive Cancer Network, 2013).**

2.7.2 Mammography

One of the most important advances in the treatment of breast cancer is early detection of non-palpable masses. In the 1960's, the first randomized control trials comparing periodic mammography screening *vs* clinical examination demonstrated a decreased mortality by approximately one third in the experimental group. However there is still controversy regarding mortality from breast cancer in the subset of women aged 40-49 years **(Shapiro *et al*, 1971; Shapiro *et al*, 1985).** Contemporary randomized control trials have demonstrated the benefits from screening mammography

in women aged 40 to 70 years **(Freedman *et al*, 2004; Nyström *et al*, 2002).** A 2013 Cochrane Review suggests that mortality is an outcome biased toward screening, routine mammography leads to undue stress and uncertainty in the face of false-positive results with increase in total numbers of lumpectomies and mastectomies but no decrease in mortality **(Gøtzsche and Jørgensen , 2013).** Controversy surrounding mammography is related to the inherent lead time and length time biases in screening for disease. Lead time bias is an overestimation of survival among screen detected cases compared to clinically detected cases when true survival time actually remains unchanged. Length bias is an overestimation of survival time among screening-detected cases, which is caused by those slowly progressing cases that may never be clinically relevant. The 2013 NCCN guidelines recommends annual screening mammography in women ≥ 40 years of average risk and annual mammography at age 25 or individualized based on onset of cancer in proband in patients who are high risk by prediction models, known history or genetic predisposition syndrome as well as the counseling and education of risks and benefits related to participating in cancer screening **(National Comprehensive Cancer Network, 2013).**

Mammography remains the mainstay in breast cancer detection **(Smetherman , 2013)**. Diagnostic mammograms are performed in women

who have a palpable mass or other symptom of breast disease, a history of breast cancer within the preceding 5 years, or have been recalled for additional imaging from an abnormal screening mammogram. Diagnostic mammograms include special views such as focal compression of one area of the breast tissue or magnification images. The breast imaging reporting and database system (BI-RADS) is the standardized method for reporting of mammographic findings **(American College of Radiology, 2003)**. Carcinomas present as masses, asymmetries, and calcifications (Table 1).

Table 1: breast imaging and reporting system

Category	Assessment	Follow-up
0	Need additional imaging evaluation	Additional imaging needed before a category can be assigned
1	Negative	Continue annual screening mammograms (women older than 40 yr)
2	Benign	Continue annual screening mammograms (women older than 40 yr)
3	Probably benign	Initial short term follow-up (usually six month) mammogram (< 2% chance of malignancy)
4	Suspicious abnormality	Biopsy should be considered (2%-95% chance of malignancy)
5	Highly suggestive of malignancy	Requires biopsy (> 95% chance of malignancy)
6	Known cancer	Biopsy-proven malignancy

2.7.3 Magnetic resonance imaging

Mammography remains the gold standard for breast imaging but magnetic resonance imaging (MRI) has become an important modality in the detection, assessment, staging, and management of breast cancer in selected patients. Screening MRI is more sensitive but less specific for the detection of cancer in high risk women. The sensitivity of MRI is 0.77-0.79 compared to mammographic sensitivity of 0.33-0.39. Specificity of MRI is 0.86-0.89 compared to mammographic specificity of 0.95 **(Warner *et al*, 2008; Kriege *et al*, 2004).** In a systematic review, MRI and mammography demonstrated a combined sensitivity and specificity of 0.94 and 0.77, respectively **(Warner *et al*, 2008).** The 2013 NCCN guidelines recommend patients who have increased (> 20%) lifetime risk of developing breast cancer undergo annual mammography and MRI starting at age 25 or an age tailored to the risk of the patient on an individual basis. MRI is valuable in the screening of select high risk patients, patients in whom breast augmentation prevents effective screening mammography, or in patients with equivocal findings on other imaging modalities.

2.7.4 Ultrasound

There are several studies supporting the use of adjunctive screening ultrasound in high risk patients with dense breast tissue, which imparts a substantial but accepted number of false positives **(Berg *et al*, 2008).** No randomized controlled trials have been conducted to evaluate the impact of screening ultrasonography on breast cancer mortality rates. Whole breast ultrasound may allow the clinician to screen for breast cancers not detected by traditional mammography, especially in dense breasts where mammographic sensitivity is lower **(Kelly *et al*, 2010)**. Single center studies have shown that the incremental detection of breast cancer by ultrasound following screening mammogram offers only marginal added benefit in women of average risk **(Gartlehner *et al*, 2013).**

2.10 Prognostic indicators

2.10.1 Estrogen receptor and progesterone receptor status

Estrogen receptor (ER) and progesterone receptor (PR) represent weak prognostic factors for patients with breast cancer, but these receptors are the strongest predictive factors for response to endocrine therapy. ER and PR assays should be performed on all invasive breast cancers **(Fitzgibbons *et al*, 2000)**. Both ER and PR are assessed by

immunohistochemistry (IHC) on paraffin sections. IHC allows assessment of the expression specifically in either invasive or *in situ* cancer. Positive interpretation requires at least 1% of tumor cells showing positive nuclear staining of any intensity. Receptor negative is reported if less than 1% of tumor cells show staining of any intensity **(Hammond *et al,* 2010).** The cutoff to define positivity is 1% because patients with even 1% ER/PRpositive tumors may benefit from hormonal therapy. About 70% of all breast cancers are ER-positive and 60% to 65% of all breast cancers are PR-positive. For the patients with a "weak positive' result an Allred score helps differentiate positive from negative receptor status. The Allred score categorizes the percentage of cells (scored from 0 to 5) with the intensity (scored from 0 to 3) and adds these two scores to give a numerical score from 0 to 8 **(Allred *et al,* 1998)**. A score of 0-2 was regarded as negative and 3-8 as positive.

2.10.2 HER2 protein expression and gene amplification

HER-2/neu is a proto-oncogene that encodes for a transmembrane tyrosine kinase growth receptor, and it is involved in several regulatory pathways in breast, involving proliferation, survival, cell motility, and invasion. HER2 is usually assessed by IHC. Fluorescence *in situ* hybridization (FISH) assay of HER2 expression is usually performed when

the evaluation by IHC is equivocal. HER2 is a prognostic factor for outcome in both nodenegative and node-positive patients and is a predictive factor for response to certain therapies that target the HER-2/neu receptor such as trastuzumab (Herceptin), a monoclonal antibody targeted to the HER2 protein, and other newer anti-HER2 agents. Overexpression/amplification is reported in 10% to 34% of invasive breast cancers. Gene over expression and amplification and surface membrane protein expression are concordant in more than 90% of cases **(Wolff et al, 2007; Hicks & Kulkarni , 2008).**

2.10.3 Commercially available gene assays

OncotypeDX (Genomic Health, Inc, Redwood City, California) is a reverse transcription polymerase chain reaction-based assay that can be performed on paraffin sections. It is based on analysis of the expression of 21 genes and provides a "recurrence score" that correlates with outcome. Although it was initially used to assess prognosis in ER-positive, node-negative patients **(Paik *et al*, 2004),** data have indicated that it is an equally valuable prognostic indicator in ER-positive, node-positive patients. Another molecular profiling product is the Amsterdam 70-gene profile, Mammaprint (Agendia, Amsterdam, Netherlands), in which a microarray analysis of gene expression is used on breast cancer tissue. It is used to determine the prognosis of patients with breast cancer and can be used for all tumors,

including node-positive, *HER- 2 neu*-positive, and ER/PR-negative disease **(van de Vijver *et al*, 2002).**

2.11 Staging:

After a breast cancer has been diagnosed, the patient is clinically staged using the American Joint Commission on Cancer (AJCC) guidelines (Tables 2 and 3).

Table 2: American Joint Commission on Cancer guidelines–tumor node metastasis classification:

Primary tumor (T)	
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma in situ
Tis (DCIS)	Ductal carcinoma in situ
Tis (LCIS)	Requires biopsy (> 95% chance of malignancy)
Tis (Paget's)	Paget's disease of the nipple
T1	Tumor ≤ 20 mm in greatest dimension
T1mi	Tumor ≤ 1 mm in greatest dimension
T1a	Tumor > 1 mm but ≤ 5 mm in greatest dimension
T1b	Tumor > 5 mm but ≤ 10 mm in greatest dimension
T1c	Tumor > 10 mm but ≤ 20 mm in greatest dimension
T2	Tumor > 20 mm but ≤ 50 mm in greatest dimension
T3	Tumor > 50 mm in greatest dimension
T4	Tumor of any size with direct extension to the chest wall and/or to the skin (ulceration or skin nodules)
T4a	Extension to the chest wall, not including only pectoralis muscle adherence/invasion

T4b	Ulceration and/or ipsilateral satellite nodules and/or edema (including peau d'orange) of the skin, which do not meet the criteria for inflammatory carcinoma
T4c	Both T4a and T4b
T4d	Inflammatory carcinoma
	Regional lymph nodes (N)
NX	Regional lymph nodes cannot be assessed (for example, previously removed)
N0	No regional lymph node metastases
N1	Metastases to movable ipsilateral level Ⅰ, Ⅱ axillary lymph node(s)
N2	Metastases in ipsilateral level Ⅰ, Ⅱ axillary lymph nodes that are clinically fixed or matted; or in clinically detected ipsilateral internal mammary nodes in the absence of clinically evident axillary lymph node metastases Metastases in ipsilateral level Ⅰ, Ⅱ axillary lymph nodes fixed to one another (matted) or to other structures
N2a	Metastases only in clinically detected ipsilateral internal mammary nodes and in the absence of clinically evident level I, II axillary lymph node metastases
N2b	
N3	Metastases in ipsilateralinfraclavicular (level Ⅲ axillary) lymph node(s) with or without level Ⅰ, Ⅱ axillary lymph node involvement; or in clinically detected ipsilateral internal mammary lymph node(s) with clinically evident level Ⅰ, Ⅱ axillary lymph node metastases; or metastases in ipsilateral supraclavicular lymph node(s) with or without axillary or internal mammary lymph node involvement
N3a	Metastases in ipsilateralinfraclavicular lymph node(s)
N3b	Metastases in ipsilateral internal mammary lymph node(s) and axillary lymph node(s)

N3c	Metastases in ipsilateral supraclavicular lymph node(s)
	Distant metastasis (M)
M0	No clinical or radiographic evidence of distant metastases
cM0(i+)	No clinical or radiographic evidence of distant metastases, but deposits of molecularly or microscopically detected tumor cells in circulating blood, bone marrow, or other nonregional nodal tissue that are no larger than 0.2 mm in a patient without symptoms or signs of metastases
M1	Distant detectable metastases as determined by classic clinical and radiographic means and/or histologically proven larger than 0.2 mm

Table 3: Clinical Staging-American Joint Commission on Cancer Guidelines

Stage 0	Tis	N0	M0
Stage I A	T1	N0	M0
Stage I B	T0	N1mi	M0
	T1	N1mi	M0
Stage II A	T0	N1	M0
	T1	N1	M0
	T2	N0	Mo
Stage II B	T2	N1	M0
	T3	N0	M0
Stage III A	T0	N2	M0
	T1	N2	M0
	T2	N2	M0
	T3	N1	M0
	T3	N2	M0
Stage III B	T4	N0	M0
	T4	N1	M0
	T4	N2	M0
Stage III C	Any T	N3	M0
Stage IV	Any T	Any N	M1

2.12 Management:

Table 3: Common Combination Regimens for Treatment of Breast Cancer

Regimen	Dose and Schedule	Frequency	Cycles
TAC			
T - Docetaxel	75 mg/m² IV day 1	Every 21 days	6
A – Doxorubicin	50 mg/m² IV day 1		
C - Cyclophosphamide	500 mg/m² IV day 1		
AC ⇒Taxol (T) (conventional regimen)			
Doxorubicin	60 mg/m² IV day 1	Every 21 days	4
Cyclophosphamide	600 mg/m² IV day 1		
Followed by			
Paclitaxel	175 mg/m² IV day 1	Every 21 days	4
Dose-dense			
Doxorubicin	60 mg/m² IV day 1	Every 14 days	4
Cyclophosphamide	600 mg/m² IV day 1		
Followed by			
Paclitaxel	175 mg/m² IV day 1	Every 14 days	4
Metronomic regimen			
Doxorubicin	20 mg/m² IV day 1	Every week	12
Cyclophosphamide	50 mg/m² PO	Every day	
Followed by			
Paclitaxel	80 mg/m² IV day 1	Every week	12
AC ⇒T + H (trastuzumab [Herceptin])			
Trastuzumab dosage: 4 mg/kg IV load, then 2 mg/kg weekly with paclitaxel, then give 6 mg/kg IV every 3 weeks for 40 weeks NOTE: Trastuzumab to be added to a weekly paclitaxel regimen in HER2-positive breast cancer patients			
FEC100			
5-Fluorouracil (5-FU)	500 mg/m² IV day 1	Every 21 days	6
Epirubicin	100 mg/m² IV day 1		
Cyclophosphamide	500 mg/m² IV day 1		
FAC			
5-FU	600 mg/m² IV day 1	Every 21 days	4
Doxorubicin	60 mg/m² IV day 1		

Cyclophosphamide	600 mg/m² IV day 1		
5-FU	500 mg/m² IV days 1 and 8	Every 28 days	6
Doxorubicin	30 mg/m² IV days 1 and 8		
Cyclophosphamide	100 mg/m² PO days 1-14		
CMF (Bonadonna regimen)			
Cyclophosphamide	100 mg/m² PO days 1-14	Every 28 days	6
Methotrexate	40 mg/m² IV days 1 and 8		
5-FU	600 mg/m² IV days 1 and 8		
Metronomic regimen			
Cyclophosphamide	50 mg/m² PO days 1-7	Weekly	24
Methotrexate	15 mg/m² IV		
5-FU	300 mg/m² IV		
TC			
Taxotere (Docetaxel)	75 mg/m² IV day 1	Every 21 days	4
Cyclophosphamide	600 mg/m² IV day 1		
TCH			
Docetaxel	75 mg/m² IV day 1	Every 21 days	6
Carboplatin	AUC* 6 IV day 1		
Trastuzumab	8 mg/kg loading dose IV followed by 6 mg/kg/wk q3wk		17
TCH-P			
Docetaxel	75 mg/m2 IV day 1	Every 21 days	6
Carboplatin	AUC*6 IV day 1		
Trastuzumab	8 mg/kg loading dose IV followed by 6 mg/kg		17
Pertuzumab	840 mg loading dose IV followed by 420 mg on subsequent doses		6

*AUC = systemic exposure.

https://emedicine.medscape.com/article/1946040-overview#a3

Chapter: 3

Subjects and Methods

3. Subjects and Methods:

3.1 Study protocol:

The study was a hospital-based cross-sectional study by collecting data who were female older than 18 years who visited the National Oncology Center from between November 1, 2019 and February 29, 2020.

3.2 Study population:

The source population constitutes all medical records of breast cancer patients who attended the breast cancer unit at the National Oncology Center, Sana'a. The study population constitutes all medical records of breast cancer patients who attended the center that fulfill the inclusion criteria of the study.

3.3. Inclusion and exclusion criteria

Inclusion

- Medical charts of female breast cancer patients
- Age ≥ 18 years.
- Patient attended to the National Oncology Center between November 1, 2019 and February 29, 2020.

Exclusion

- Patients who were diagnosed with other cancer.

3.4. Sample size

All breast cancer patients who attended the breast cancer unit of the National Oncology Center from November 1, 2019 to February 29, 2020 and fulfilled the inclusion criteria of the study were included in the study. As a result, there were 300 breast cancer patients who newly visited the oncology center and fulfilled the inclusion criteria and hence were included in the study.

3.5 Statistical analysis:

Statistical analysis was performed using Statistical Package for Social Science software (SPSS, version 15) and Microsoft office Excel 2010 was used for data processing and statistical analysis. The chi-squared test was used for the assessment of association between the variables studied. The p-value of less than 0.05 was significant statistically.

Chapter: 4

Results

4. Results

4.1. Demographic data:

4.1.1 Age distribution of the patients:

Total number of sample enrolled in the present study was 300 patients with breast cancer. All patients were females. Patients' age ranged between 21 and 80 years. The present study observed that most cases of breast cancer patients aged between 30-59 years (78.4%). The age distribution of the sample is represented in **table (1)** and graphically illustrated in **Figure (1)**.

Table (1): Age distribution for a sample of breast cancer patients:

	Frequency	Percent
20-29 years	22	7.3
30-39 years	89	29.7
40-49 years	86	28.7
50-59 years	60	20.0
60-69 years	31	10.3
70-80 years	12	4.0
Total	300	100.0

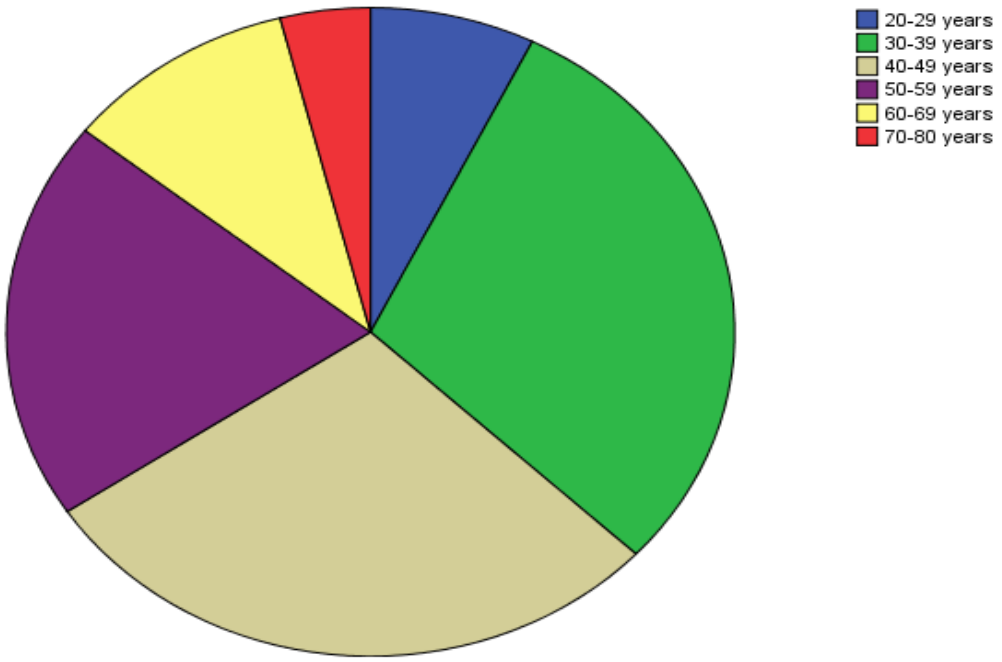

Figure (1): Age distribution for a sample of breast cancer patients

4.1.2 Marital status of the patients:

The majority of enrolled patients (73.3%) were married. Widowed patients were about 13.3% while divorced patients were 4.7%. In the other hand, single patients were about 8.7%. The distribution of the sample is represented in **table (2)** and graphically illustrated in **Figure (2)**.

Table (2): Marital status distribution among a sample of breast cancer patients:

	Frequency	Percent
married	220	73.3
single	26	8.7
divorced / separated	14	4.7
widowed	40	13.3
Total	300	100.0

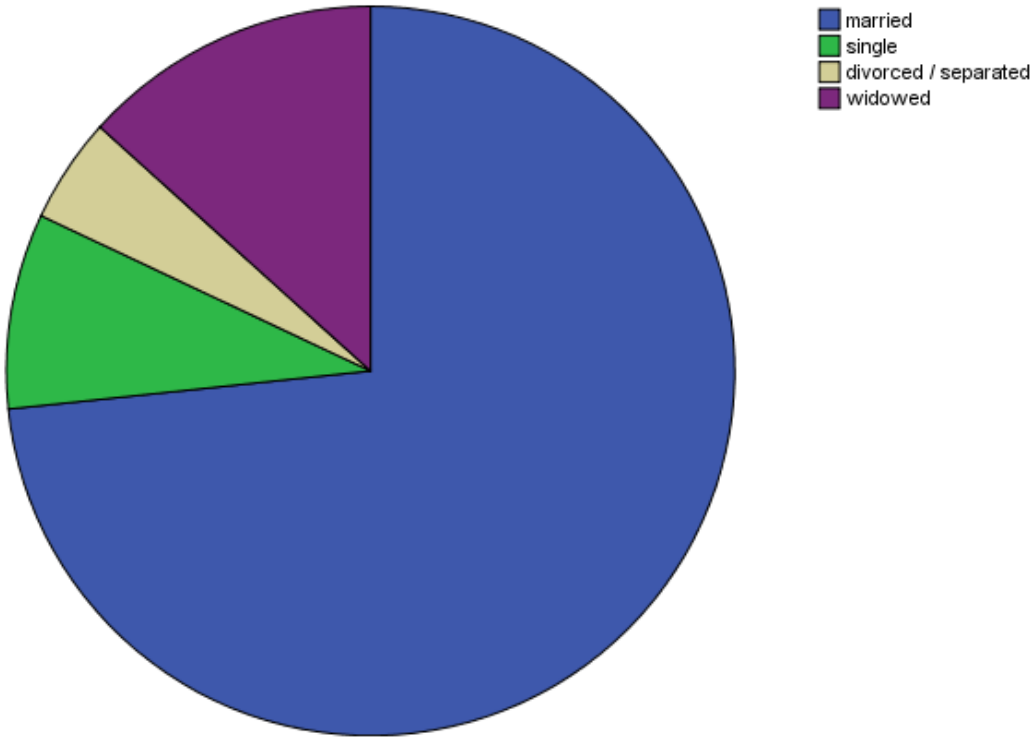

Figure (2): Marital status distribution among a sample of breast cancer patients

4.1.3 Ethnicity of the patients:

Almost all breast cancer patients (98%) were of Caucasian ethnicity while 2% were African race. The distribution of the sample is represented in **table (3)** and graphically illustrated in **Figure (3)**.

Table (3): Ethnicity distribution among a sample of breast cancer patients:

	Frequency	Percent
Caucasian	294	98.0
African	6	2.0
Total	300	100.0

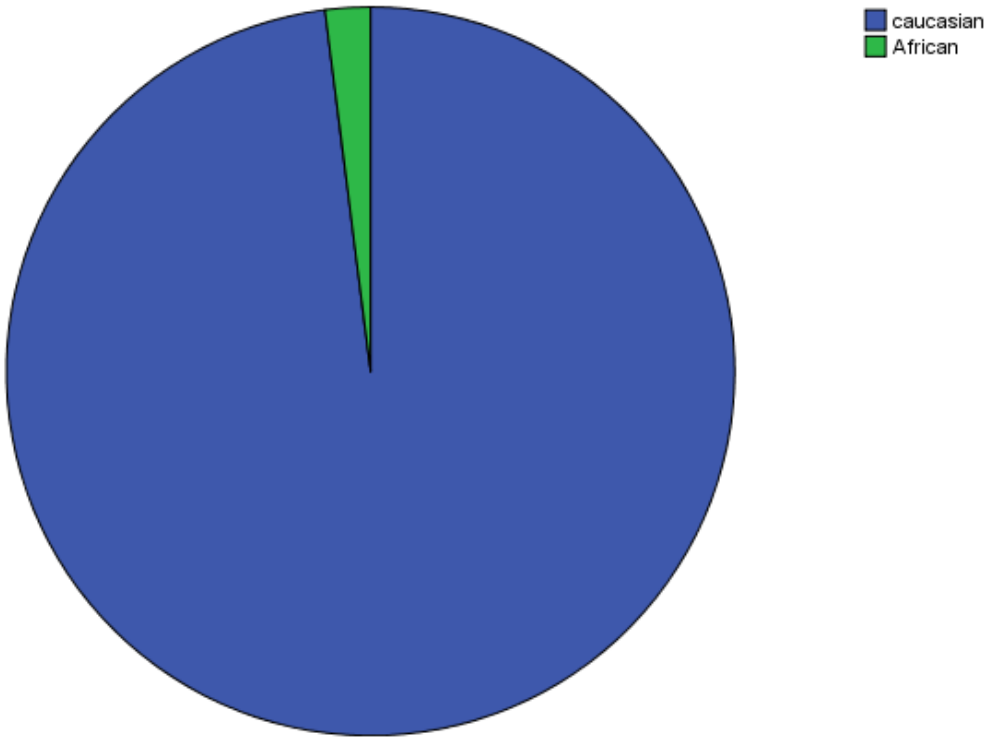

Figure (3): Ethnicity distribution among a sample of breast cancer patients

4.1.4 Residence of the patients:

Most patients of breast cancer (31.3%) were from Sana'a and from Taiz (15.7%) governorates. The second common places of breast cancer patients were Ibb (10.3%), Thamar (8.7%), and Hodeidah (6.7%) governorates. Other governorates ranked lower. The distribution of the sample is represented in **table (4)** and graphically illustrated in **Figure (4)**.

Table (4): Region distribution among a sample of breast cancer patients:

	Frequency	Percent
Sana'a	94	31.3
Taiz	47	15.7
Thamar	31	10.3
Ibb	26	8.7
Hodeidah	20	6.7
Saada	12	4.0
Amran	11	3.7
Albaidha	10	3.3
Hajah	9	3.0
Almahweet	9	3.0
Rimah	7	2.3
Aldhalae	7	2.3
Aden	7	2.3
Lahj	3	1.0
Aljouf	2	.7
Socotra	2	.7
Hadhrmoot	1	.3
Mareb	1	.3
Mahrah	1	.3
Total	300	100.0

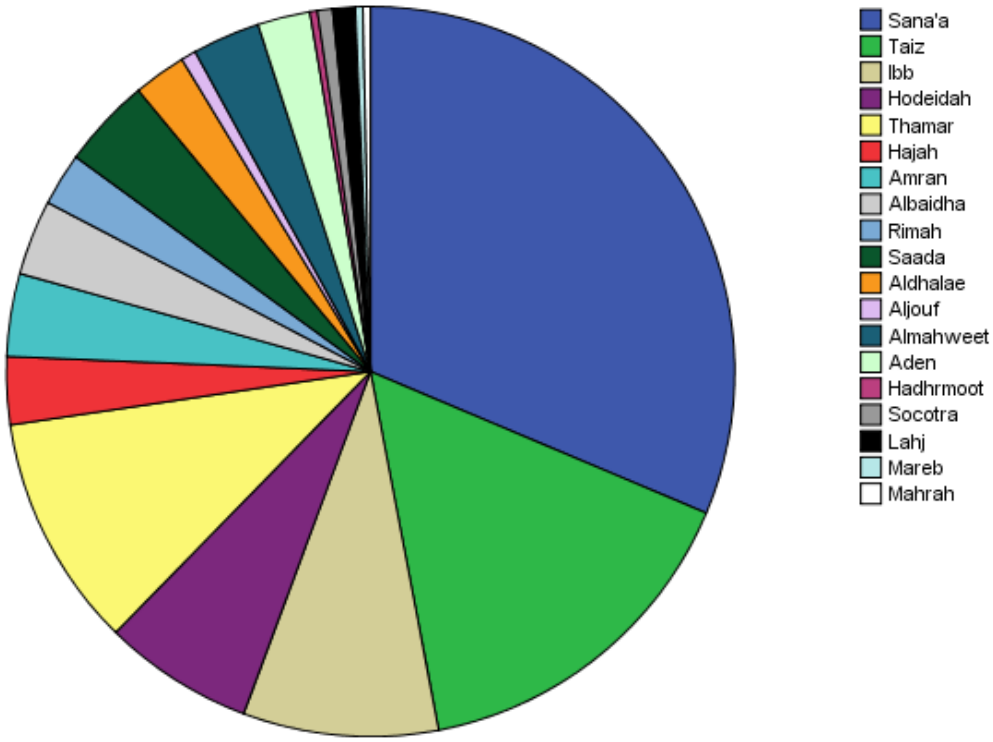

Figure (4): Region distribution among a sample of breast cancer patients

4.1.5 Occupation of the patients:

Most breast cancer patients (82.3%) were housewives. Peasant women were about 10.7% while employed patients represented 4.7%. The distribution of the sample is represented in **table (5)** and graphically illustrated in **Figure (5)**.

Table (4): Occupation distribution among a sample of breast cancer patients:

	Frequency	Percent
peasant	32	10.7
private	7	2.3
employed	14	4.7
house wife	247	82.3
Total	300	100.0

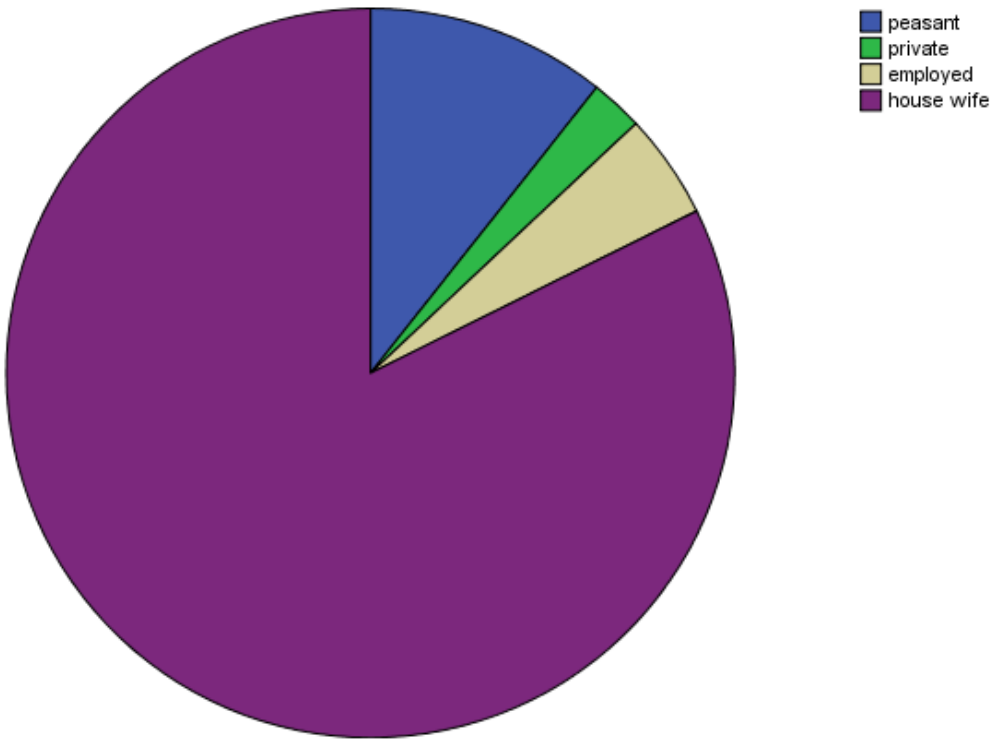

Figure (5): Occupation distribution among a sample of breast cancer patients

4.1.6 Education of the patients:

Most breast cancer patients (61.7%) were illiterate. Patients who have primary school education were 18.7%, and patients with secondary school certificate were 10.7%, while patients who had a university degree were 8%. The distribution of the sample is represented in **table (6)** and graphically illustrated in **Figure (6)**.

Table (6): Education among a sample of breast cancer patients:

	Frequency	Percent
no	185	61.7
primary school	56	18.7
secondary school	32	10.7
university	24	8.0
other	3	1.0
Total	300	100.0

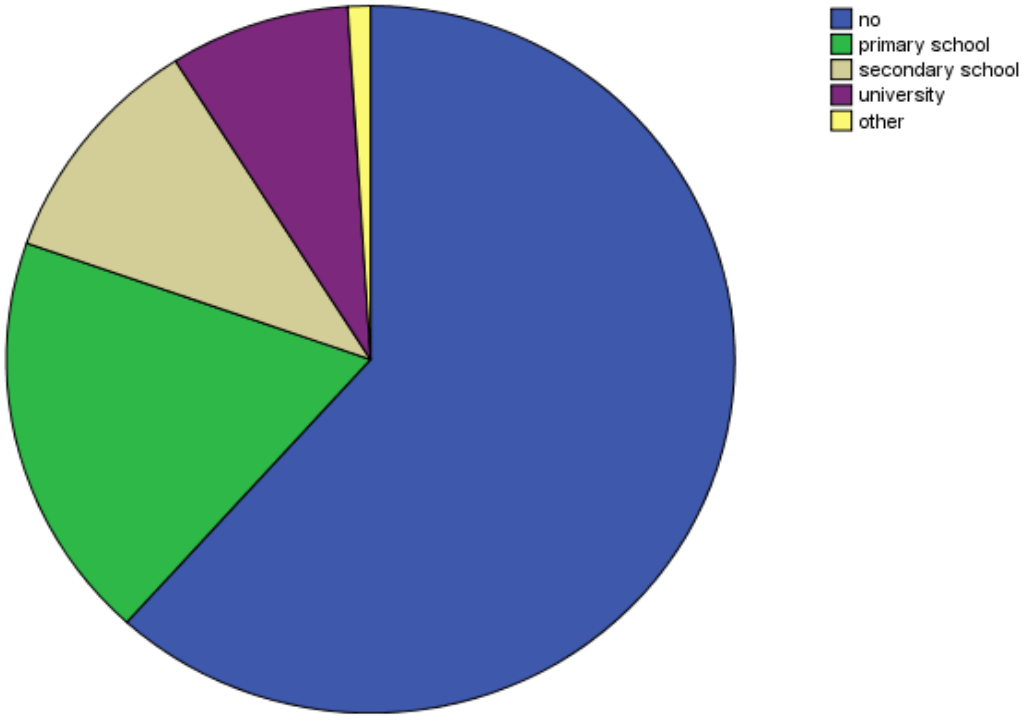

Figure (6): Education among a sample of breast cancer patients

4.1.7 Smoking habit distribution among patients:

Smoking habit was found less popular among breast cancer patients in about 18.7% while non-smokers were 81.3%. The distribution of the sample is represented in **table (7)** and graphically illustrated in **Figure (7)**.

Table (7): Smoking habit among a sample of breast cancer patients:

	Frequency	Percent
No smoking	244	81.3
Yes smoking	56	18.7
Total	300	100.0

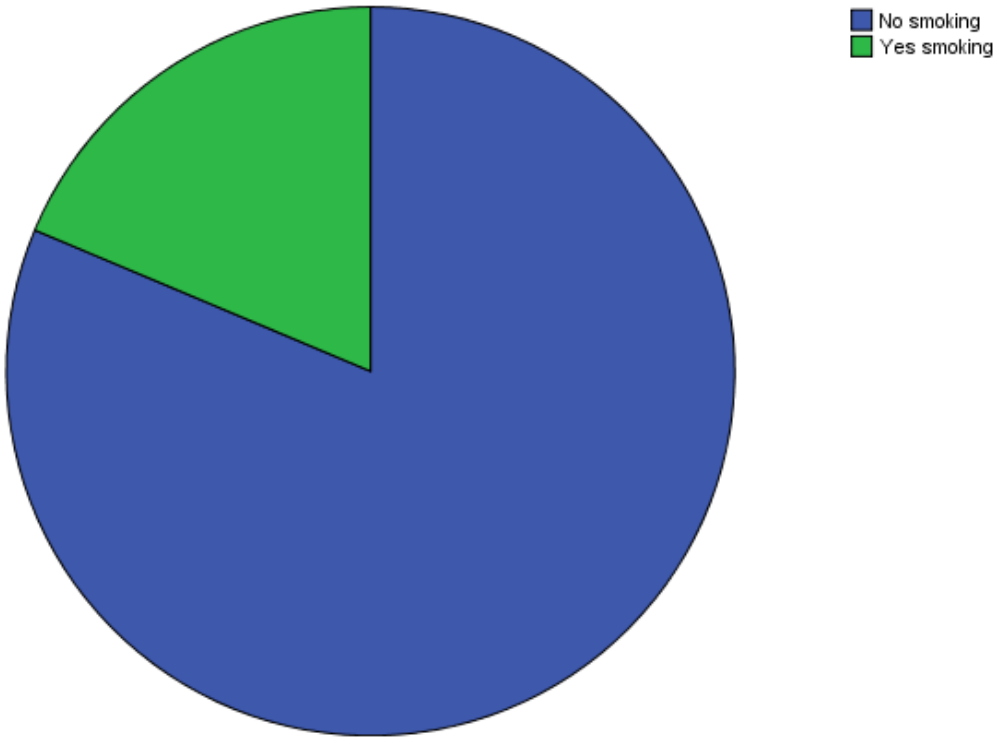

Figure (7): Smoking habit among a sample of breast cancer patients

4.1.8 Khat habituation among patients:

Khat habituation was found among 53.7% breast cancer patients while non-khat chewers were 46.3%. The distribution of the sample is represented in **table (8)** and graphically illustrated in **Figure (8)**.

Table (8): Khat habituation among a sample of breast cancer patients:

	Frequency	Percent
No khat chewing	139	46.3
Yes khat chewing	161	53.7
Total	300	100.0

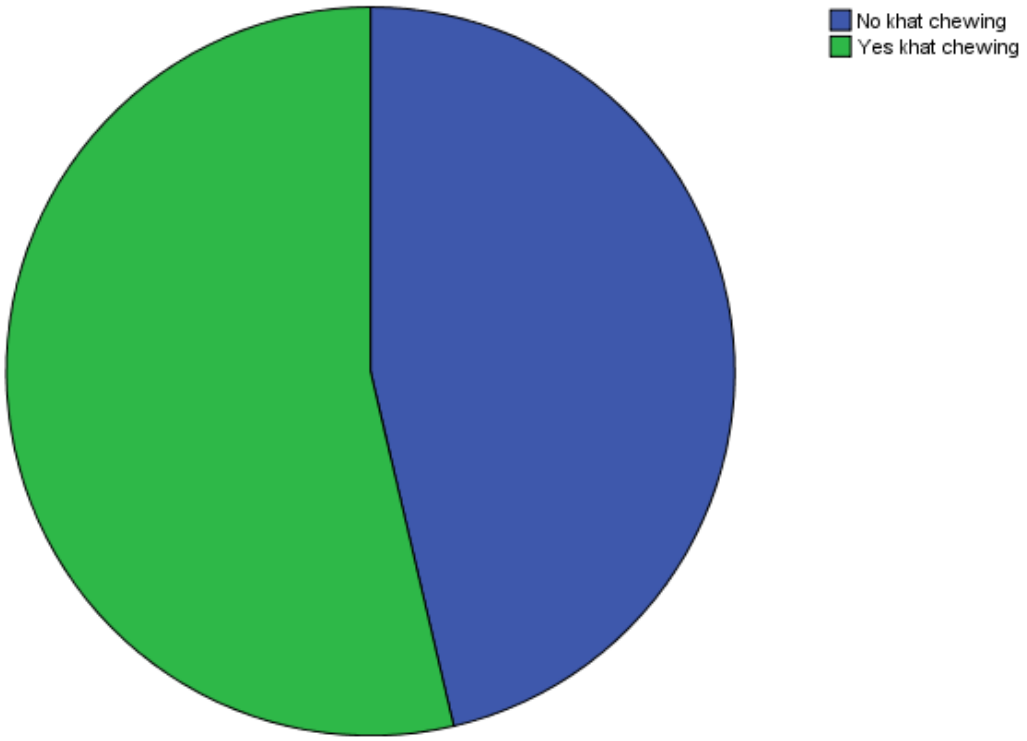

Figure (8): Khat habituation among a sample of breast cancer patients

4.2 Reproductive risk factors:

4.2.1 Hormonal contraceptive history among patients:

History of contraceptive use was found among 42.3% of breast cancer patients while 57.7% of the patients stated there had not used any contraceptives during their life. The distribution of the sample is represented in **table (9)** and graphically illustrated in **Figure (9)**.

Table (9): History of hormonal contraceptive use among a sample of breast cancer patients:

	Frequency	Percent
no contraceptive history	173	57.7
yes contraceptive history	127	42.3
Total	300	100.0

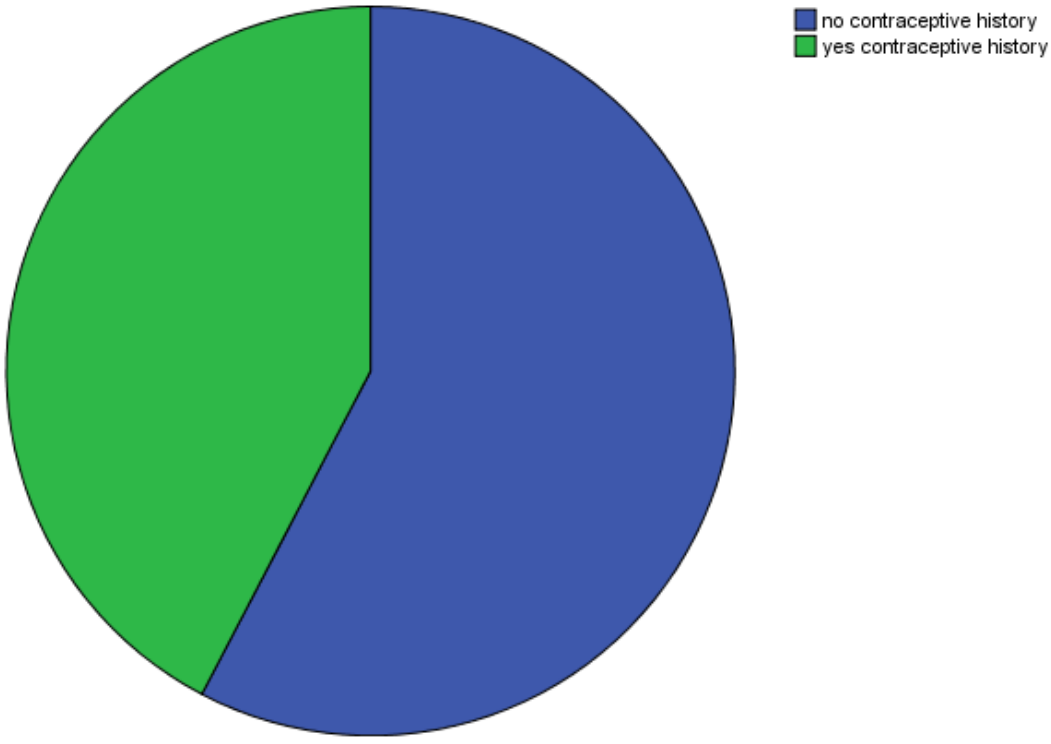

Figure (9): History of hormonal contraceptive use among a sample of breast cancer patients

4.2.2 Age at first menarche:

Age at first menarche was less than 11 years in about 10.3% of breast of breast cancer patients while 89.7% of the patients aged at first menarche between 12 and 18 years. The distribution of the sample is represented in **table (10)** and graphically illustrated in **Figure (10)**.

Table (10): Age at first menarche among a sample of breast cancer patients:

	Frequency	Percent
9-11 years	31	10.3
12-18 years	269	89.7
Total	300	100.0

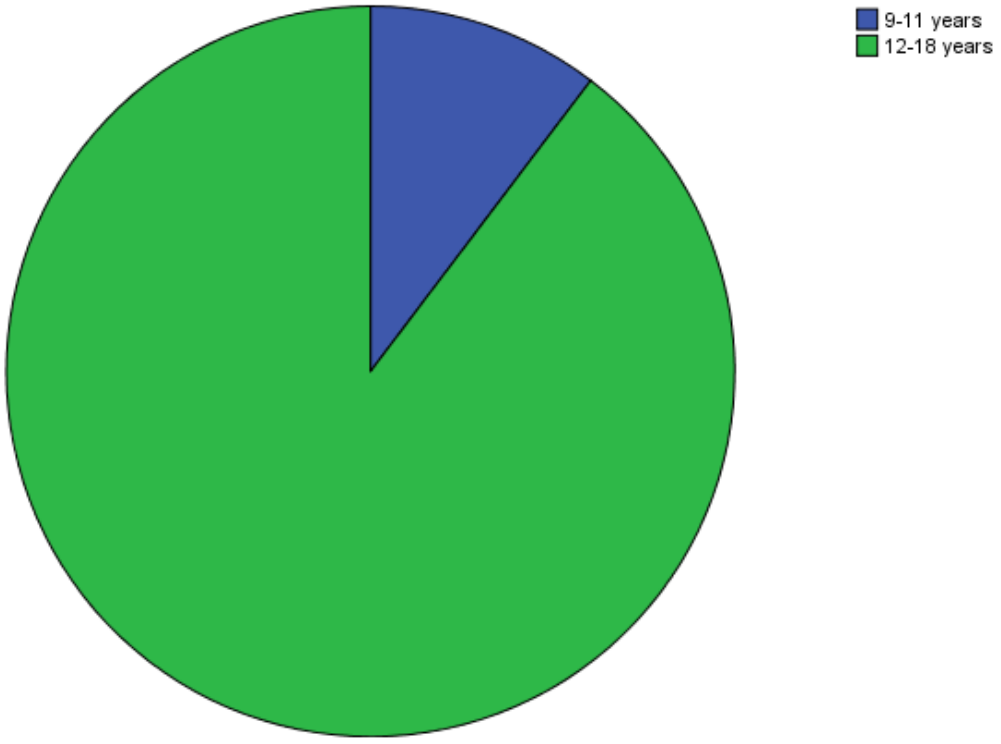

Figure (10): Age at first menarche among a sample of breast cancer patients

4.2.3 Age at first delivery:

About 18% of breast cancer patients were nulliparous as the either had not children despite marriage or because they are single. Age at first delivery ranged between 12 and 42 years. Most patients 71.3% had got their children while they aged 12-29 years old. About 6% of the patients had their children between 30-34 years while 4.7% of the patients had their children after age 35 years old. The distribution of the sample is represented in **table (11)** and graphically illustrated in **Figure (11)**.

Table (11): Age at first delivery among a sample of breast cancer patients:

	Frequency	Percent
no children	54	18.0
12-19 years	90	30.0
20-29 years	124	41.3
30-34 years	18	6.0
35-42 years	14	4.7
Total	300	100.0

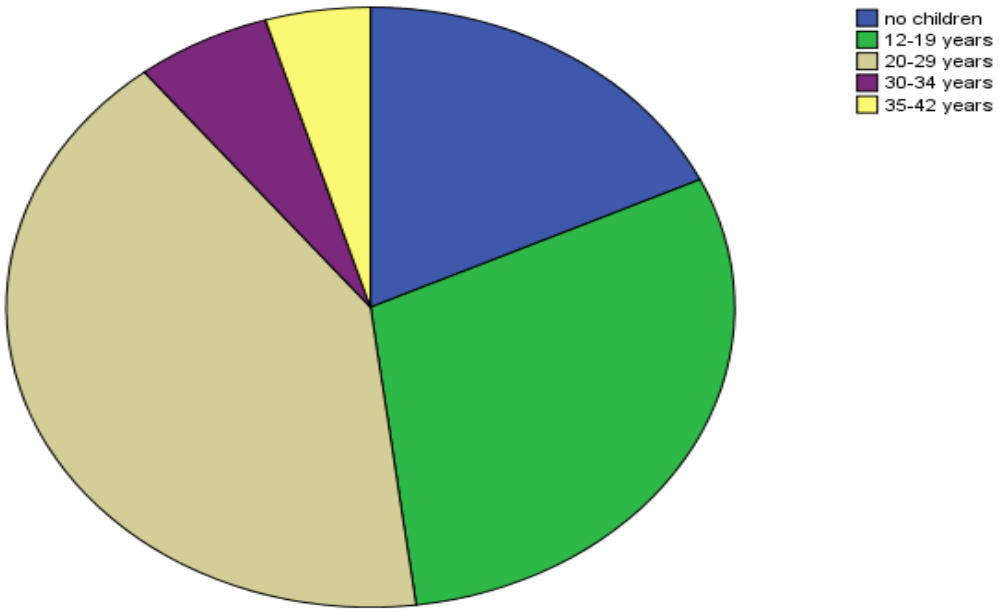

Figure (11): Age at first delivery among a sample of breast cancer patients

4.2.4 Number of children:

The number of children ranged between 1 and 14 for breast cancer women. Relatively large percentage (38.7%) of mothers had 3-6 children followed by mothers having 7-10 children (18.3%) or 1-2 children (16%). In the other hand, 9% of enrolled mothers had 11-14 children. The distribution of the sample is represented in **table (12)** and graphically illustrated in **Figure (12)**.

Table (12): Average number of children among a sample of breast cancer patients:

	Frequency	Percent
no children	54	18.0
1-2 children	48	16.0
3-6 children	116	38.7
7-10 children	55	18.3
11-14 children	27	9.0
Total	300	100.0

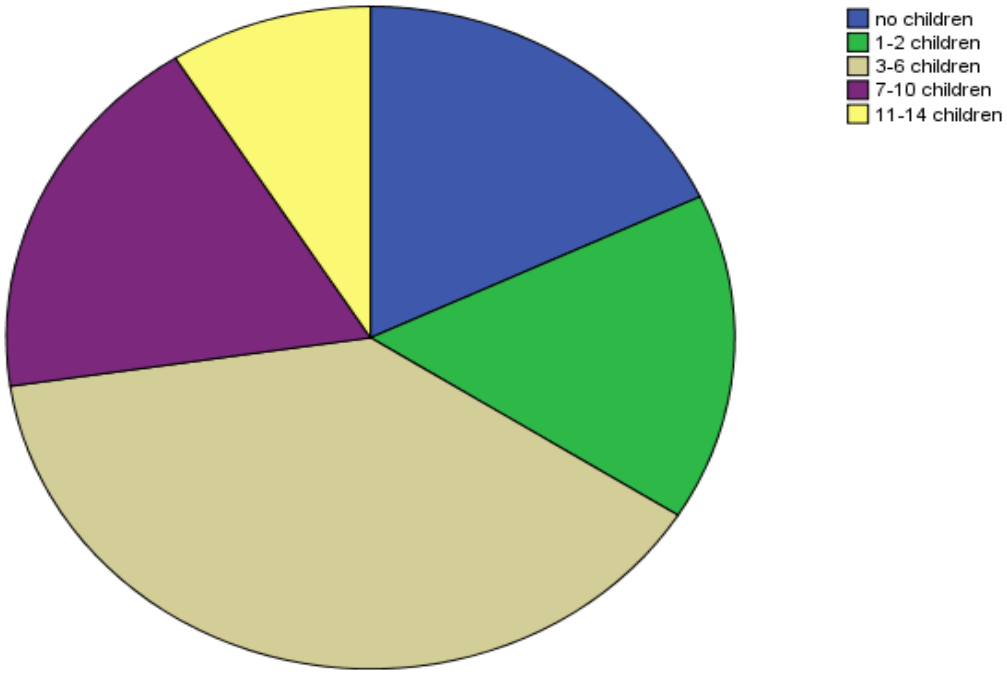

Figure (12): Average number of children among a sample of breast cancer patients

4.3 Clinical characteristics of the study patients:

4.3.1 Estrogen receptor status:

Out of a total 300 breast cancer patients, 40.3% were estrogen positive, and 59.7% were estrogen negative. The distribution of the sample is represented in **table (13)** and graphically illustrated in **Figure (13)**.

Table (13): Estrogen status among a sample of breast cancer patients:

	Frequency	Percent
negative	179	59.7
positive	121	40.3
Total	300	100.0

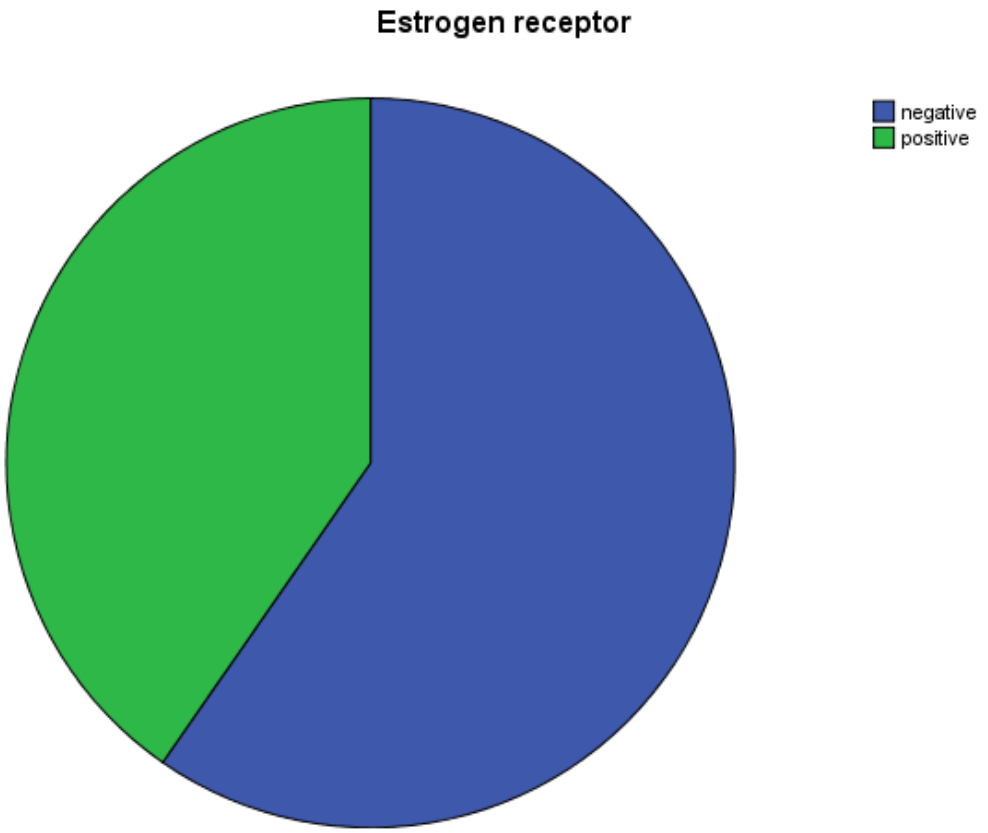

Figure (13): Estrogen status among a sample of breast cancer patients

4.3.2 Progesterone receptor status:

Out of a total 300 breast cancer patients, 36% were progesterone positive, and 64% were progesterone negative. The distribution of the sample is represented in **table (14)** and graphically illustrated in **Figure (14)**.

Table (14): Progesterone status among a sample of breast cancer patients:

	Frequency	Percent
negative	192	64.0
positive	108	36.0
Total	300	100.0

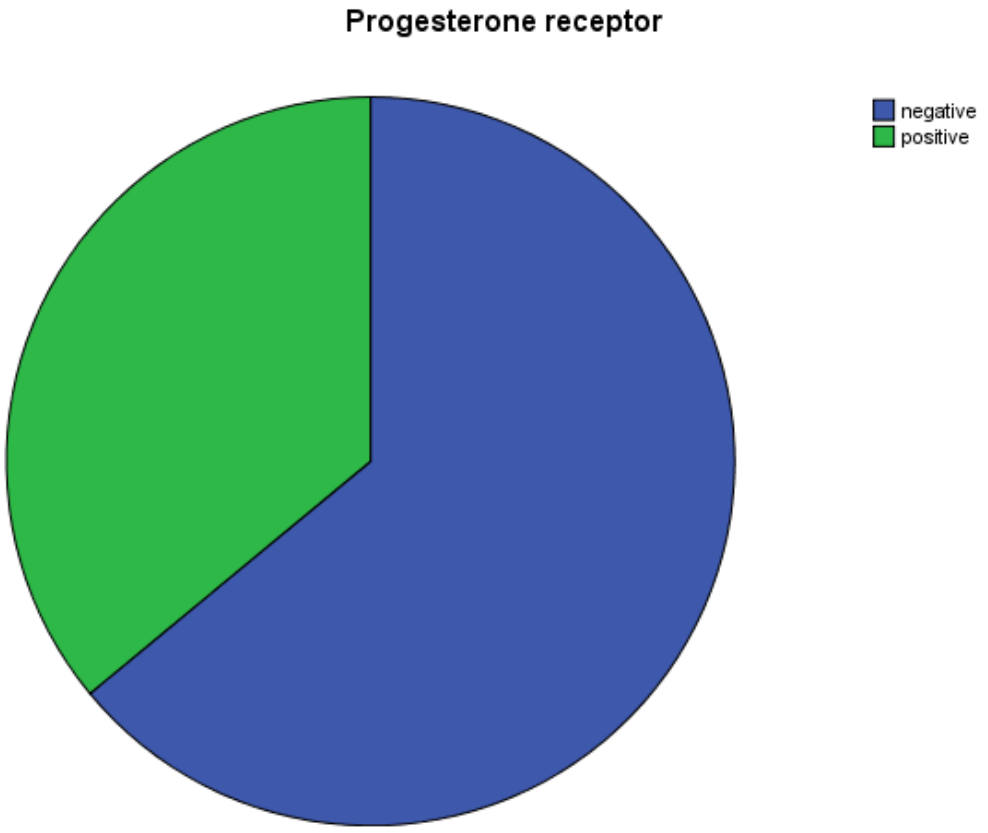

Figure (14): Progesterone status among a sample of breast cancer patients

4.3.3 Human epidermal growth factor receptor-2 (HER 2) status:

Out of a total 300 breast cancer patients, 51.7% were HER-2 positive, and 48.3% were HER-2 negative. The distribution of the sample is represented in **table (15)** and graphically illustrated in **Figure (15)**.

Table (15): HER-2 status among a sample of breast cancer patients:

	Frequency	Percent
negative	145	48.3
positive	155	51.7
Total	300	100.0

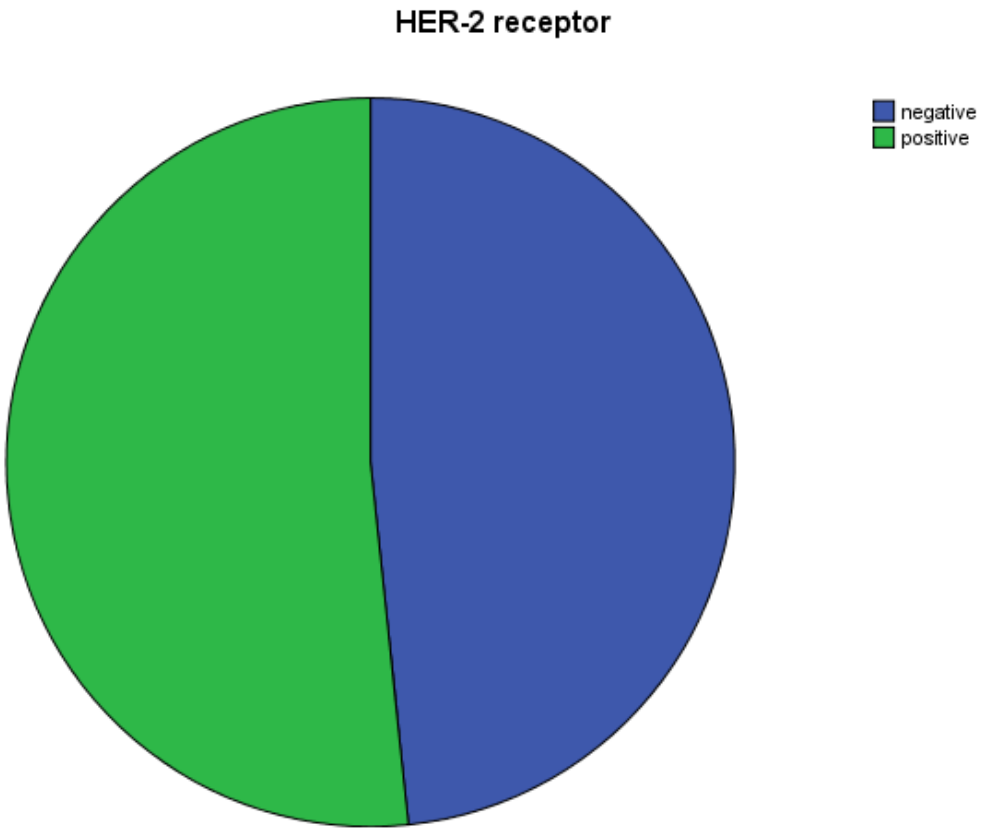

Figure (15): HER-2 status among a sample of breast cancer patients

4.3.4 Invasive history:

About 95% of the patients have invasive ductal form of breast cancer as compared to 1.7% who have invasive lobular carcinoma in situ. Some patients (2%) have both ductal and lobular invasive breast cancer. The distribution of the sample is represented in **table (16)** and graphically illustrated in **Figure (16)**.

Table (16): Invasive history among a sample of breast cancer patients:

	Frequency	Percent
ductal invasive	285	95.0
lobular invasive	5	1.7
ductal and lobular invasive	6	2.0
ductal and medullar invasive	2	.7
ductal and tubular invasive	2	.7
Total	300	100.0

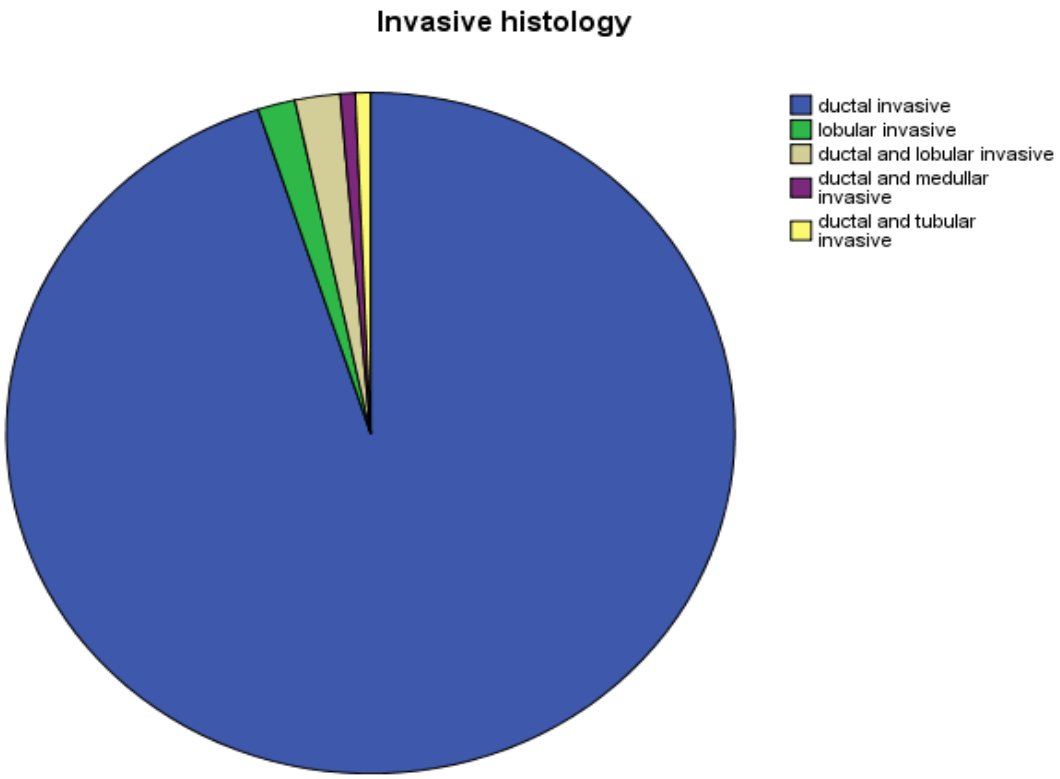

Figure (16): Invasive history among a sample of breast cancer patients

4.3.5 TNM clinical staging of breast cancer:

About 39% of the breast cancer patients were at stage 3, while 27.7% were at stage 4 and 25.4% were at stage 2. In the other hand, 6.7% of breast cancer patients have not been stated their clinical stage. Only, 1.3% of the patients were at stage 1. The distribution of the sample is represented in **table (17)** and graphically illustrated in **Figure (17)**.

Table (17): TNM clinical staging among a sample of breast cancer patients:

	Frequency	Percent
stage 1	4	1.3
stage 2a	20	6.7
stage 2b	56	18.7
stage 3a	54	18.0
stage 3b	34	11.3
stage 3c	29	9.7
stage 4	83	27.7
not-stated	20	6.7
Total	300	100.0

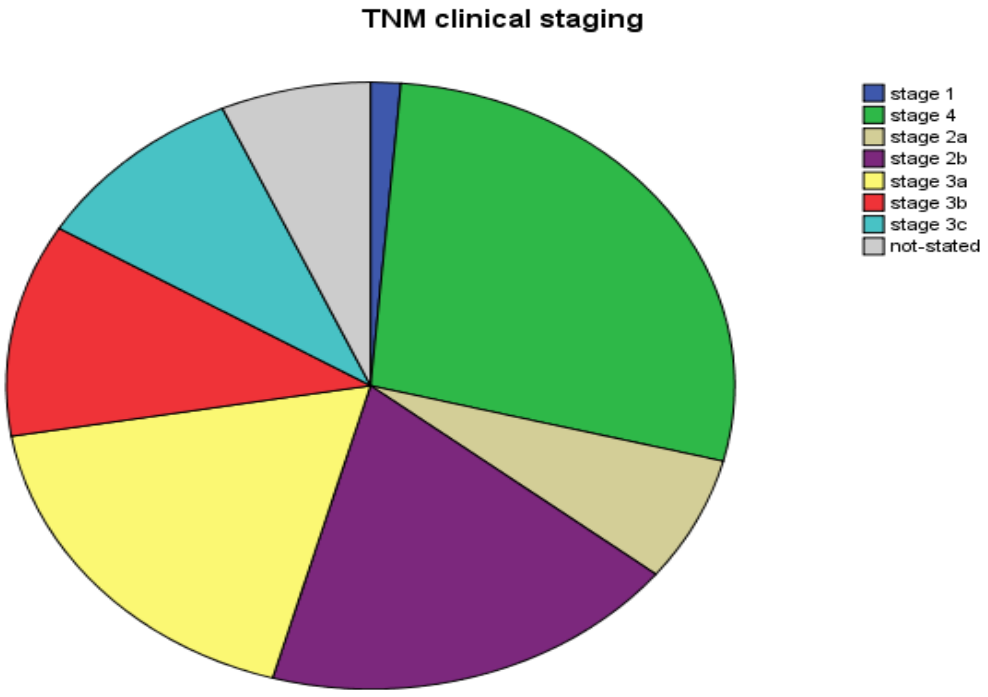

Figure (17): TNM clinical staging among a sample of breast cancer patients

4.5 Treatment of breast cancer:

4.5.1 Mode of treatment:

The most common treatment for breast cancer among the included breast cancer patients was combined surgery and chemotherapy (39%), then the standard method with surgery, radiotherapy, and chemotherapy in 32.7% of the patients. Chemotherapy alone represented 24.7% of the patients while chemotherapy along with radiotherapy represented 3.7% of the patients. The distribution of the sample is represented in **table (18)** and graphically illustrated in **Figure (18)**.

Table (18): Mode of treatment among a sample of breast cancer patients:

	Frequency	Percent
chemotherapy	74	24.7
radiotherapy and chemotherapy	11	3.7
chemotherapy, radiotherapy, surgery	98	32.7
surgery and chemotherapy	117	39.0
Total	300	100.0

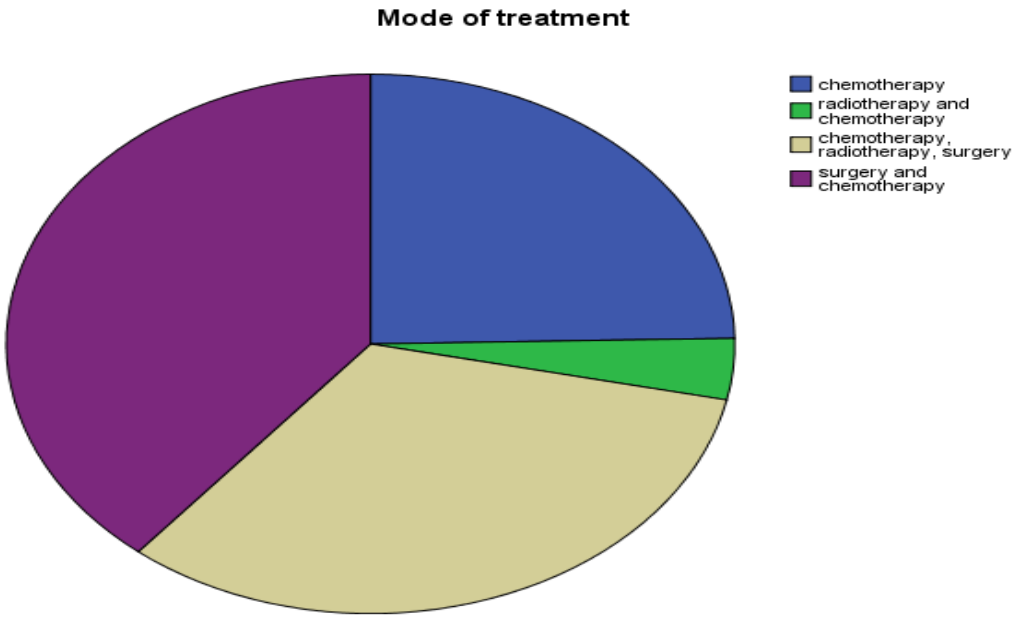

Figure (18): Mode of treatment among a sample of breast cancer patients

4.4.2 Type of chemotherapy:

The most common combined regimens used for treatment of breast cancer were AC→T "doxorubicin + cyclophosphamide → taxol" (34.3%) followed by AC "doxorubicin + cyclophosphamide" (16.3%). FAC regimen "5-flurouracil + doxorubicin + cyclophosphamide" was prescribed for 14%, and FAC→T regiment "5-flurouracil + doxorubicin + cyclophosphamide → taxol" was prescribed for 13% of the patients. Other patients were treated with various or sequential chemotherapy combinations. The distribution of the sample is represented in **table (19)** and graphically illustrated in **Figure (19)**.

Table (19): Type of chemotherapy among a sample of breast cancer patients:

	Frequency	Percent
ACT	103	34.3
AC	49	16.3
FAC	42	14.0
FACT	39	13.0
ACTP or ACTGP	19	6.3
FACTP or FACTGP	19	6.3
other	29	9.7
Total	300	100.0

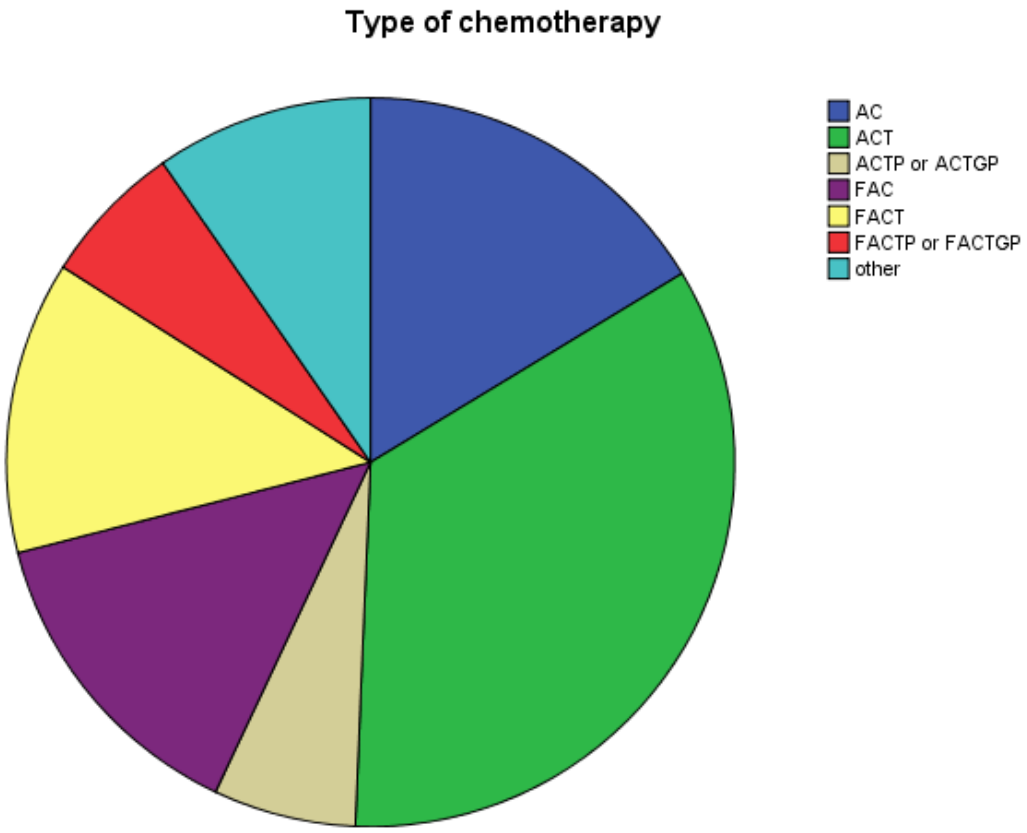

Figure (19): Type of chemotherapy among a sample of breast cancer patients

4.4.3 Number of chemotherapy cycles:

Chemotherapy cycles ranged from 4-18 cycles. Most patients (32%) have received 8 cycles of chemotherapy regimens. Large percent of patients received either 6 (17.7%) or 4 cycles (15.7%). The distribution of the sample is represented in **table (20)** and graphically illustrated in **Figure (20)**.

Table (20): Number of chemotherapy cycles among a sample of breast cancer patients:

	Frequency	Percent
4.00	47	15.7
6.00	53	17.7
8.00	96	32.0
10.00	45	15.0
12.00	21	7.0
14.00	18	6.0
16.00	18	6.0
18.00	2	.7
Total	300	100.0

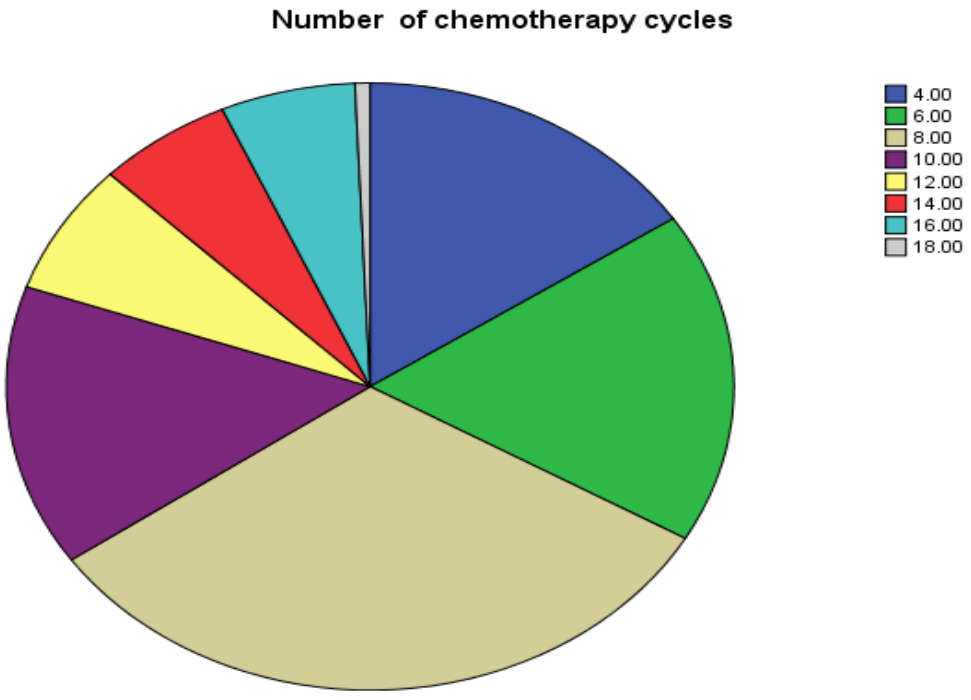

Figure (20): Number of chemotherapy cycles among a sample of breast cancer patients

4.4.4 Types of surgery:

Surgical procedures were undertaken for 71.4% of breast cancer patients. Total masotoidectomy was the most common surgery (63.7%) while lobectomy was carried out for 7.7% patients. The distribution of the sample is represented in **table (21)** and graphically illustrated in **Figure (21)**.

Table (21): Types of surgery undertaken for a sample of breast cancer patients:

	Frequency	Percent
no surgery	86	28.7
lopectomy	23	7.7
mastoidectomy	191	63.7
Total	300	100.0

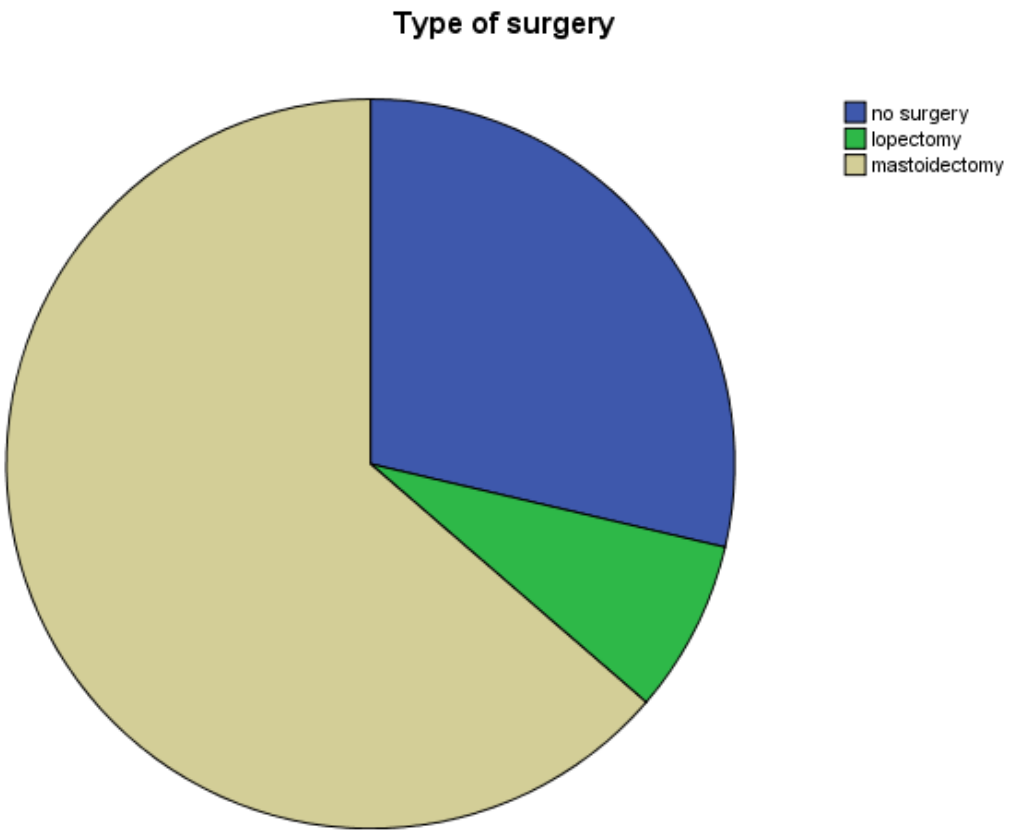

Figure (21): Types of surgery undertaken for a sample of breast cancer patients

4.4.5 Hormonal therapy:

Almost all patients (44%) with estrogen and progestin receptors positive breast cancer had received any hormonal therapy according to their receptor status. The distribution of the sample is represented in **table (22)** and graphically illustrated in **Figure (22)**.

Table (22): Hormonal therapy among a sample of breast cancer patients:

			Estrogen and progesterone receptor		
			negative	positive	Total
Hormonal therapy	no	Count	168	0	168
		% within Estrogen and progesterone receptor	100.0%	.0%	56.0%
	yes	Count	0	132	132
		% within Estrogen and progesterone receptor	.0%	100.0%	44.0%
Total		Count	168	132	300
		% within Estrogen and progesterone receptor	100.0%	100.0%	100.0%

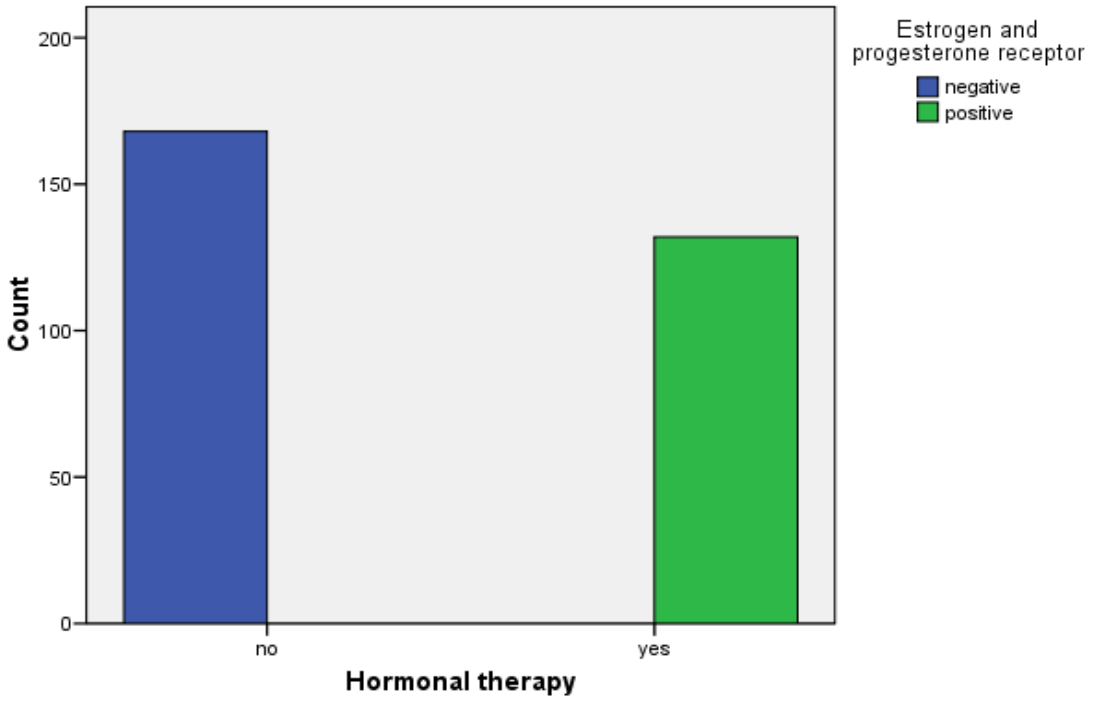

Figure (22): Hormonal therapy among a sample of breast cancer patients

4.4.6 Biological therapy:

About 42.6% of patients with human epidermal growth factor receptor-2 (HER-2) positive breast cancer have not received biological therapy despite their positive receptor status. The distribution of the sample is represented in **table (23)** and graphically illustrated in **Figure (23)**.

Table (23): Biological therapy among a sample of breast cancer patients:

			HER-2 receptor		
			negative	positive	Total
Trastuzumab therapy	no	Count	145	66	211
		% within HER-2 receptor	100.0%	42.6%	70.3%
	yes	Count	0	89	89
		% within HER-2 receptor	.0%	57.4%	29.7%
Total		Count	145	155	300
		% within HER-2 receptor	100.0%	100.0%	100.0%

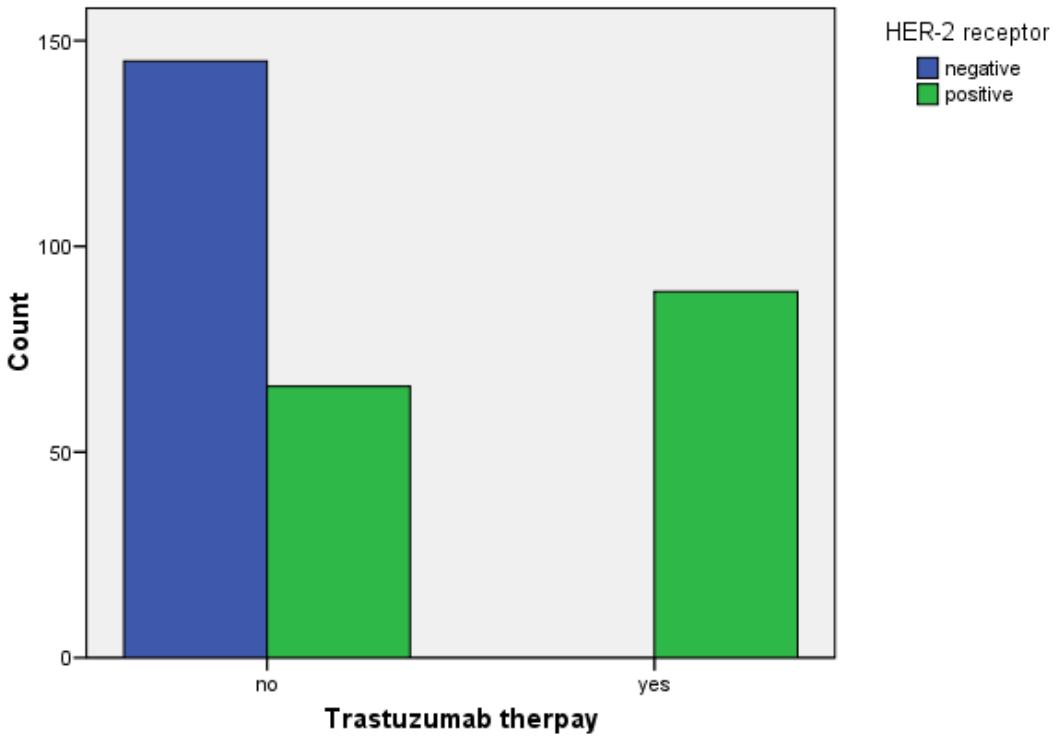

Figure (23): Biological therapy among a sample of breast cancer patients

4.5 Treatment outcomes of breast cancer:

4.5.1 Post-radiation therapy complications:

The most common post-radiation therapy complications were cutaneous symptoms among 12.3% of the patients while neurological symptoms represented 4% of cases. The distribution of the sample is represented in **table (24)** and graphically illustrated in **Figure (24)**.

Table (24): Post-radiation therapy complications among a sample of breast cancer patients:

	Frequency	Percent
no	248	82.7
cutaneous	37	12.3
neurological	12	4.0
other	1	.3
hematological and neurological	1	.3
cutaneous and neurological	1	.3
Total	300	100.0

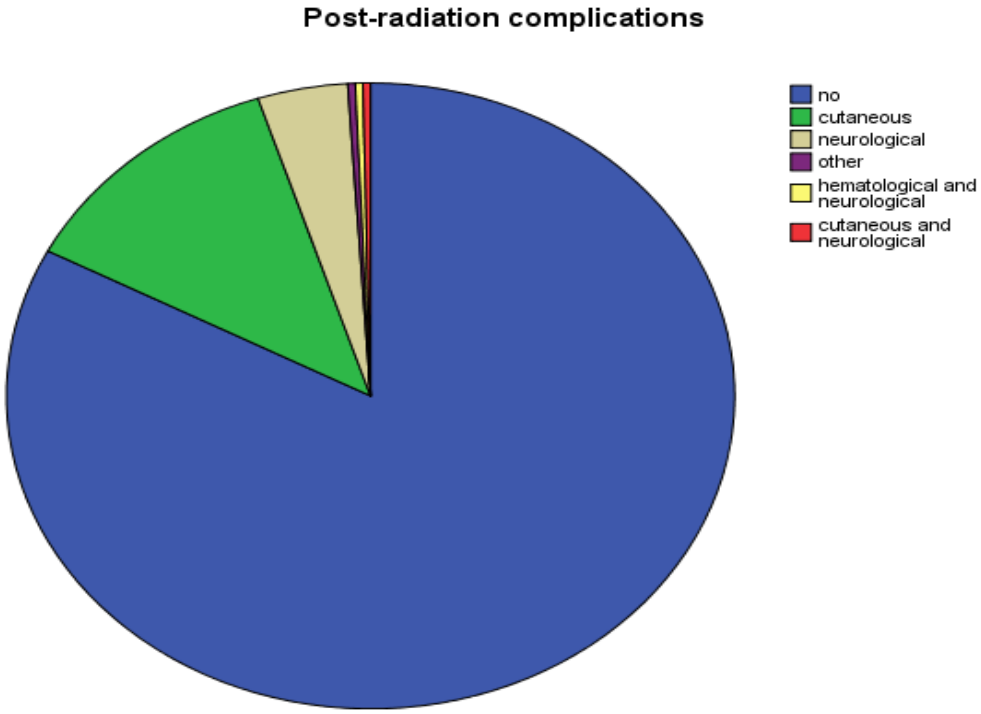

Figure (24): Post-radiation therapy complications among a sample of breast cancer patients

4.5.2 Post-surgical complications:

The most common post-surgical complications were neurological symptoms (4%) and lymphedema (2.7%) or both (1.7%). The distribution of the sample is represented in **table (25)** and graphically illustrated in **Figure (25)**.

Table (25): Post-surgical complications among a sample of breast cancer patients:

	Frequency	Percent
no	275	91.7
lymphedema	8	2.7
neurolgical	12	4.0
lymphedema + neurological	5	1.7
Total	300	100.0

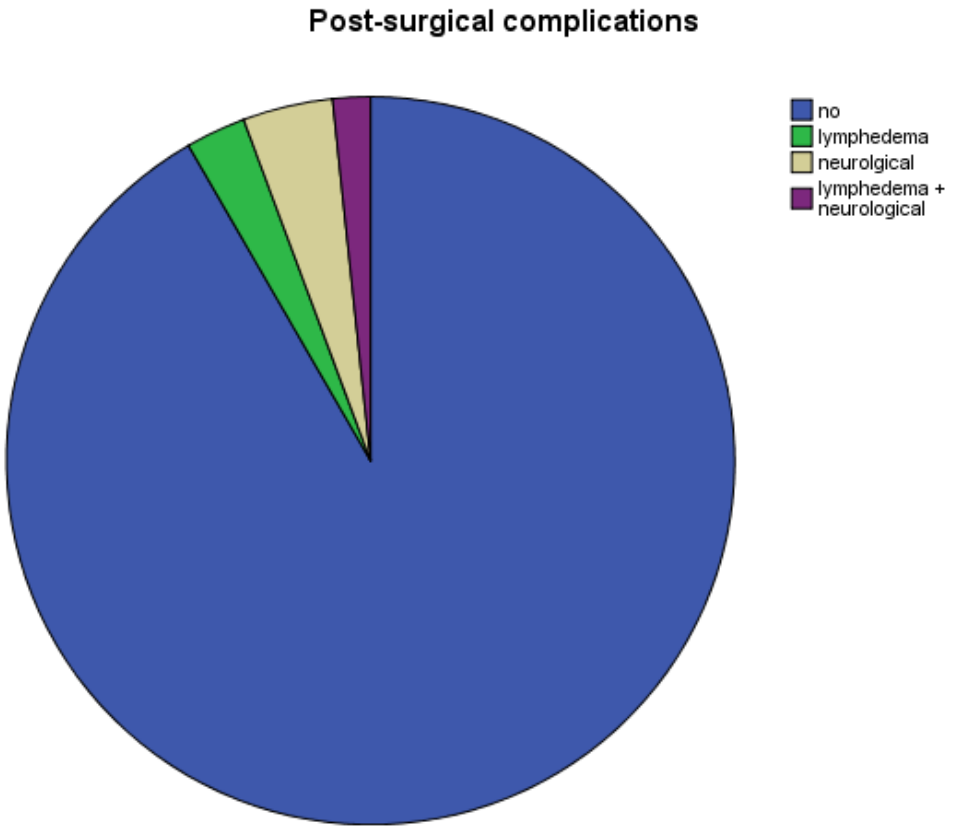

Figure (25): Post-surgical complications among a sample of breast cancer patients

Chapter: 5

Discussion

5. Discussion

The study assessed treatment outcome among breast cancer patients at National Oncology Center, Sana'a. Most of the patients were in the age range of 30-59 years. This might be a result of increased hormonal activity and tissue responsiveness or use of hormonal contraceptives in this age group. The study also showed that many patients were from Sana'a region. This can be explained by the fact that people in Sana'a and nearby regions have easy access to National Oncology Center to seek diagnosis and treatment.

In this study, 300 histologically proven treated breast cancer patients were included. Based on histologic classification, all cases were found to have invasive carcinoma. This is in line with other studies that showed majority of breast cancer cases to be of invasive type **(Breast cancer treatment guideline 2006; Kakarala *et al*, 2010; Syed *et al*, 2011; Tovar *et al*,2014; Rahal *et al*, 2015)**, This could probably be due to a result of spread to the axillary lymph nodes.

The result of the study showed that majority of the patients came to National Oncology Center when they were on the third stage of the disease. This might be due to low knowledge of the basic symptoms of breast malignancy and absence of a nearby diagnostic center. Majority of cancers

in developing countries are diagnosed at an advanced stage of disease because of lack of screening and early detection services, as well as limited awareness of early signs and symptoms of cancer among the public and health care providers. Stigma associated with diagnosis of cancer also plays a role in late-stage presentation in most parts of Africa **(Tigeneh *et al*, 2015)**. Thus, one can take note of that women who are diagnosed early and put on treatment is one way of improving breast cancer treatment outcomes. However, a different result was reported from a study done in Brazil , where majority of the cases 56 (93%) had an early stage tumor **(Tovar *et al*, 2014)**.This might be is a result of difference in education, economic, social status as well as health seeking behavior between the study population of the studies.

In the present study, chemotherapy and surgical treatment appear to be a pillar component in the National Oncology Center adult oncology protocol. The most common combined regimens used for treatment of breast cancer were AC→T "doxorubicin + cyclophosphamide → taxol" (34.3%) followed by AC "doxorubicin + cyclophosphamide" (16.3%). FAC regimen "5-flurouracil + doxorubicin + cyclophosphamide" was prescribed for 14%, and FAC→T regiment "5-flurouracil + doxorubicin + cyclophosphamide → taxol" was prescribed for 13% of the patients. Studies done in Spain

(Martin *et al*, 2003), Kenya **(Wata *et al*, 2013)** and USA **(Anampa *et al*, 2015)** found that grater proportional use of FAC regimen for treatment of breast cancer.

Surgery for breast cancer usually involves breast-conserving surgery (BCS) or mastectomy **(Cancer Treatment Facts, 2014-2015)**. Modified radical mastectomy has traditionally been the standard of care for early-stage invasive breast cancers.Therefore, this general mastectomy practice for majority of them in the National Oncology Center may contribute for patient survival. Similar findings were also found in Lebanon that showed mastectomy rates in Arab countries are high amounting to 79.9%–82% in Egypt, 65% in Oman, 70% among Palestinians, 88% in Syria, and 82.4% in Tunisia **(Tfayli *et al*, 2010)**. This might be because of mastectomies were performed due to the more advanced nature of their breast cancer, more nodal involvement, or even larger tumor size. However, different results were reported in studies from France, where most of the patients had breast-conserving surgery **(Rahal *et al*, 2015)**. This might be because of histologic subtypes other than invasive ductal carcinoma or acceptable cosmetic outcome can be achieved in almost all patients undergoing breast-conserving surgery without compromising the of local tumor control.

Chapter: 6

Summary and Conclusions

6. Summary and Conclusions

The present study was aimed to assess treatment outcome among breast cancer patients at the National Oncology Cancer. A hospital-based cross-sectional study was conducted by collecting data from medical records of breast cancer patients who attended the breast cancer unit at the National Oncology Center in Sana'a during the period of November 1, 2019 to February 29, 2020.

Total number of sample enrolled in the present study was 300 patients with breast cancer. Patients' age ranged between 21 and 80 years. The present study observed that most cases of breast cancer patients aged between 30-59 years (78.4%). Most patients of breast cancer (31.3%) were from Sana'a and from Taiz (15.7%) governorates. History of contraceptive use was found among 42.3% of breast cancer patients. Age at first menarche was less than 11 years in about 10.3% of breast of breast cancer patients while 89.7% of the patients aged at first menarche between 12 and 18 years. About 18% of breast cancer patients were nulliparous as the either had not children despite marriage or because they are single. Age at first delivery ranged between 12 and 42 years. Most patients 71.3% had got their children while they aged 12-29 years old. The number of children ranged between 1 and 14 for breast cancer women.

Out of all patients, 40.3% % were estrogen positive, 36% were progesterone positive and 51.7% were HER-2 positive. All patients have invasive form of breast cancer. Most of the patients (95%) have ductal invasive breast cancer as compared to 1.7% who have invasive lobular carcinoma. Some patients (2%) have both ductal and lobular invasive breast cancer. About 39% of the breast cancer patients were at stage 3, while 27.7% were at stage 4 and 25.4% were at stage 2.

The most common treatment for breast cancer among the included breast cancer patients was combined surgery and chemotherapy (39%), then the standard method with surgery, radiotherapy, and chemotherapy in 32.7% of the patients. Chemotherapy alone represented 24.7% of the patients while chemotherapy along with radiotherapy represented 3.7% of the patients. The most common combined regimens used for treatment of breast cancer were AC→T "doxorubicin + cyclophosphamide → taxol" (34.3%) followed by AC "doxorubicin + cyclophosphamide" (16.3%). FAC regimen "5-flurouracil + doxorubicin + cyclophosphamide" was prescribed for 14%, and FAC→T regiment "5-flurouracil + doxorubicin + cyclophosphamide → taxol" was prescribed for 13% of the patients. Chemotherapy cycles ranged from 4-18 cycles. Most patients (32%) have received 8 cycles of chemotherapy regimens while other patients received either 6 (17.7%) or 4

cycles (15.7%). Surgical procedures were undertaken for 71.4% of breast cancer patients. Total masotoidectomy was the most common surgery (63.7%) while lobectomy was carried out for 7.7% patients. Almost all patients with estrogen and progestin receptors positive breast cancer had received hormonal therapy while 42.6% of patients with human epidermal growth factor receptor-2 (HER-2) positive breast cancer have not received biological therapy despite their positive receptor status.

From the results of the present study, it could be concluded that:

- Most breast cancer patients had estrogen positive (40.3%), progesterone positive (36%), and HER-2 positive (51.7%) disease.
- All patients have invasive form of breast cancer which denotes that patients are usually diagnosed lately.
- Large proportion (42.6%) with human epidermal growth factor receptor-2 (HER-2) positive breast cancer patients have not received biological therapy despite their positive receptor status.

Thus, from these results and conclusions, it could be concluded that:

- National screening of breast cancer is advised especially for patients with risk factors.
- Government is advised to provide the biological therapy for patients with HER-2 positive breast cancer.

Chapter: 7

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Chapter: 8

Arabic Abstract

ملخص عربي

معالجة سرطان الثدي في المركز الوطني للأورام – صنعاء : دراسة وصفية

مقدمة: هدفت الدراسة الحالية إلى وصف أنماط العلاج لدى مرضى سرطان الثدي في المركز الوطني للأورام في صنعاء.

الطريقة: أجريت دراسة مستعرضة من خلال جمع البيانات من السجلات الطبية لمرضى سرطان الثدي الذين حضروا وحدة سرطان الثدي في المركز الوطني للأورام في صنعاء خلال الفترة من 1 نوفمبر 2019 إلى 29 فبراير ، 2020.

النتائج: كان إجمالي عدد المرضى المصابين بسرطان الثدي 300 شخصاً معظمهم من محافظتي محافظتي صنعاء وتعز لدى بعضهم (42.3٪) تاريخ سابق لاستخدام وسائل منع الحمل. وقد كان بين جميع مرضى سرطان الثدي الذين شملتهم الدراسة 40.3٪ من الحالات الموجبة لمستقبلات الاستروجين، و 36٪ موجبة لمستقبلات البروجسترون، بينما 51.7٪ من الحالات الموجبة لمستقبلات عامل نمو البشرة **HER-2**. وقد تم تشخيص جميع المرضى بأن لديهم شكل من أشكال سرطان الثدي الغازية. وكان معظم المرضى (95٪) يعانون من سرطان الثدي الغازي القنوات. وتم تشخيص 39 ٪ من مرضى سرطان الثدي في المرحلة الثالثة ، بينما كان 27.7 ٪ في المرحلة الرابعة و 25.4 ٪ في المرحلة الثانية. وكان العلاج الأكثر شيوعًا لسرطان الثدي بين المرضى هي الجراحة مع العلاج الكيميائي (39 ٪) ثم طريقة العلاج بالجراحة مع العلاج الإشعاعي والعلاج الكيميائي في 32.7٪ من المرضى. وكان العلاج الكيماوي وحده يمثل 24.7٪ من المرضى بينما العلاج الكيماوي مع العلاج الإشعاعي يمثل 3.7٪ من المرضى. وتم إجراء العمليات الجراحية لـ

71.4٪ من مرضى سرطان الثدي. واظهرت النتائج أن 42.6٪ من المرضى الذين يعانون من سرطان الثدي الإيجابي لمستقبلات عامل نمو البشرة **HER-2** لم يتلقوا علاجًا بيولوجيًا على الرغم من حالة مستقبلاتهم الإيجابية.

الاستنتاجات: جميع المرضى يعانون من شكل سرطان الثدي الغازية مما يدل على أن المرضى عادة ما يتم تشخيصهم مؤخرًا. وبالتالي ، ينصح بالكشف عن سرطان الثدي خاصة للمرضى الذين يعانون من عوامل الخطر. ونسبة كبيرة (42.6٪) من المرضى الذين لديهم سرطان ثدي ايجابي لمستقبلات عامل نمو البشرة **HER-2** لم يتلقوا العلاج البيولوجي على الرغم من حالة مستقبلاتهم الإيجابية.

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معالجة سرطان الثدي في المركز الوطني للأورام – صنعاء: دراسة وصفية

بحث تخرج مقدم كمتمم جزئي للحصول على درجة البكالوريوس في الصيدلة السريرية

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