

**AN EVALUATION OF THE MANAGEMENT OF BREAST CANCER AT
AHMADU BELLO UNIVERSITY TEACHING HOSPITAL SHIKA, ZARIA**

BY

OLORUKOoba AMINA BUSOLA

**DEPARTMENT OF PHARMACOLOGY AND THERAPEUTICS
AHMADU BELLO UNIVERSITY, ZARIA
NIGERIA**

JUNE, 2011

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BY

OLORUKOOBA, AMINA BUSOLA B.pharm (ABU 2004)

MSc/ Pharm Sci/ 03282/2006-2007

**A THESIS SUBMITTED TO THE POSTGRADUTE SCHOOL, AHMADU BELLO
UNIVERSITY, ZARIA**

NIGERIA

**IN PARTIAL FULFILMENT FOR THE AWARD OF MASTER OF SCIENCE IN
PHARMACOLOGY**

DEPARTMENT OF PHARMACOLOGY AND THERAPEUTICS

AHMADU BELLO UNIVERSITY, ZARIA

NIGERIA

JUNE, 2011

DECLARATION

I declare that the work in the thesis entitled ‘An Evaluation of the Management of Breast Cancer at Ahamdu Bello University Teaching Hospital Shika, Zaria’ has been performed by me under the supervision of Prof. (Mrs) H.O. Kwanashie, Dr A. U. Zezi and Dr A. T. Olasinde.

The information derived from the literature has been duly acknowledged in the text and a list of references provided. No part this thesis was previously presented for the award of another degree or diploma at any university.

Olorukooba, Amina Busola

Signature

Date

CERTIFICATION

This thesis entitled “**AN EVALUATION OF THE MANAGEMENT OF BREAST CANCER AT AHMADU BELLO UNIVERSITY TEACHING HOSPITAL SHIKA, ZARIA**” by Olorukooba, Amina Busola meets the regulations governing the award of the degree of Master of Science in Pharmacology of Ahmadu Bello University, Zaria, and is approved for its contribution to knowledge and literary presentation.

_____ Date _____
Prof. (Mrs.) H. O. Kwanashie
Chairman, Supervisory Committee

_____ Date _____
Dr. A. U. Zezi
Member, Supervisory Committee

_____ Date _____
Dr. A. T. Olasinde
Member, Supervisory Committee

_____ Date _____
Dr. N. M. Danjuma
Head of Department

_____ Date _____
Prof. Joshua Adebayo
Dean, Post Graduate School

DEDICATION

Dedicated to Allah (SWT) for all the mercy and blessings He has showered upon me and my family.

To my parents; words cannot express how much I am indebted to you for all your love and support. May Allah reward you both with Al janatu firdaus. Amin.

To my darling husband Shax, my brother Taofik, my sisters Bukky, Bibi and Bob, to Saudat and Shola and to our kids Zainab, M.T, Mubarak, Maryam. Hidaya, Saelma, Amina and baby Abdallah, I pray to Allah to make us successful both in this world and in the hereafter. Amin.

ACKNOWLEDGEMENTS

All thanks and praises be to Allah, the Most Beneficent the Most Merciful who made it possible for me to conclude this work.

My sincere appreciation goes to my supervisors Prof. (Mrs) H. O Kwanashie, Dr. A. U Zezi and Dr. A. T Olasinde who, despite their tight schedules, always found time to guide, assist and encourage me. Prof. (Mrs) H. O Kwanashie thanks so much for being a mother to me, for your patience, wisdom and drive, you made this possible.

To my parents, husband, brother, sisters and children again, words cannot express how I feel. Your prayers, encouragement, assistance and sacrifice is what kept me going. May Allah reward you all. Amin.

To my colleagues that we started this journey together with, I say a big thank you and wish you the best.

ABSTRACT

The incidence and mortality from breast cancer in Nigeria is on the increase. The health care system in Nigeria is overburdened by the task of providing proper treatment and care to breast cancer patients. Preventative strategies in the fight against breast cancer have not been fully adopted. Anti-cancer drugs are not readily available and are expensive. This retrospective study was designed to evaluate the therapeutic protocol used in the management of breast cancer in a Nigerian Teaching Hospital, and also to investigate factors influencing the management of breast cancer, with a view of improving the care of patients with the disease. The clinical records of all cancer patients seen over a one year period (January to December, 2008) were reviewed. The study sample consisted of all breast cancer patients who had received therapy for a minimum of 6 months (total of 67 patients). Relative occurrence of breast cancer vis-à-vis other cancer types was 29%, closely followed by cervical cancer (27%). Mean age of diagnosis was 47.82 years. There were 66 females and 1 male. Fifty-three of the 67 patients (79%) were married; and almost unemployed. Prevalence by tribe, state of origin and geopolitical zone showed that breast cancer was ubiquitous. Previous family history of breast cancer was reported in 24% of the patients. About 68% of the patients had a previous lump and or cancer. Fifty-two per cent of the female patients were premenopausal and 56% were multiparous (para 4 and above). Thirty three percent used oral contraceptives. History of alcohol intake was recorded in 23% of the patients. Presence of a lump (93%) was the most common symptom and the cancer was mostly in the right breast (50.7%). Invasive ductal carcinoma was the most

frequently diagnosed type of breast cancer (76%). Individual pharmacy records were not available for all the patients. Majority of the patients were placed on Cyclophosphamide/Adriamycin/Fluorouracil regimen (43%). Few patients received a taxane-based regimen which is a more targeted therapy for breast cancer. Fifty per cent of the patients had radiotherapy. Hormonal therapy used in 75% of the patient was tamoxifen. Oncologists favored the use of newer hormonal drugs like anastrozole and exemestane. There were lots of discrepancies on which healthcare professional was responsible for providing services in a given information area. Surgeons and oncologists perceived themselves as being responsible for providing services in most of the information areas outlined. Roles of pharmacists in the management of breast cancer were not recognized by other health care professionals. In conclusion, there is the urgent need for the therapeutic protocol used in the management of breast cancer in the hospital be updated, standardized and harmonized, especially between the surgeons and the oncologists. Though the hospital protocol was in line with the Nigerian guidelines there is still need for the Nigerian guidelines be kept up to date with the recent advances in breast cancer chemotherapy, as outlined in the National Comprehensive Cancer Network clinical practice guidelines for breast cancer so as to improve the quality of care offered to patients, thus improving their relative survival rate.

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GLOSSARY AND SYMBOLS

3DRCT Three-dimensional conformal radiotherapy

5-FU 5-fluorouracil

ABUTH Ahmadu Bello University Teaching Hospital

ACS American Cancer Society

APBI Accelerated partial breast irradiation

BSE Breast Self-Exam

CAF Cyclophosphamide//adriamycin/fluorouracil

CBE Clinical breast exam

CC Craniocaudal

CEF Cyclophosphamide/epirubicin/fluorouracil

CMF Cyclophosphamide//methotrxate/fluorouracil

CNB Core needle biopsy

CP Capecitabine/paclitaxel

DCIS Ductal carcinoma in situ

EBRT External beam radiation

EPIC European Prospective Investigation of Cancer

ER Estrogen

FNAB Fine needle aspiration biopsy

GP Gemtricitabine/Paclitaxel

LCIS Lobular carcinoma in situ

MDT Multidisciplinary team

MRI Magnetic resonance imaging

NCCN National Cancer Comprehensive network

NR Not recorded

PET Position emission tomography.

PHT Post-hormonal therapy

POSTMENO Postmenopausal

PR Progesterone

PREMENO Premenopausal

SERD Selective estrogen receptor down regulators

SERM Selective estrogen receptor modulators

TNM Tumor Node Metastasis

WHO World Health Organization

CHAPTER 1

INTRODUCTION

1.1 STATEMENT OF THE PROBLEM

Cancer, according to the National Cancer Institute, is a term for diseases in which cells divide without control and can invade surrounding tissues. Stedman's Medical Dictionary defines cancer as a general term frequently used to indicate any of various types of neoplasm, most of which invade surrounding tissues, may metastasize to several sites and is likely to recur after attempted removal and to cause death of the patient except when adequately treated. Cancer is increasingly becoming of public health concern in recent years (Thomas, 1999). In 2002 alone, cancer was reported to have been responsible for 12.5% of all deaths, more than all deaths due to HIV/AIDS, tuberculosis, and malaria combined (WHO, 2005). More than 70% of all cancer deaths occur in low and middle income countries, and deaths are projected to continue rising with an estimated 12 million deaths in 2030 (WHO, 2009).

In Nigeria, the estimated number of cancer cases per year is predicted to be 100,000 and by 2010 it was estimated that about 500,000 new cases will be diagnosed annually (Thomas, 1999). In 2005, cancer killed approximately 89,000 people in Nigeria, 54,000 of which were under the age of 70 years (WHO, 2005). There are many types of cancers that affect the human body, and breast cancer is one of the most frequently occurring especially in women (ACS, 2005). Breast cancer occurs when there is an inappropriate and uncontrolled tumor growth arising from a single transformed cell in the breast tissue due to genetic mutation, which leads to loss of normal cell growth, regulation and differentiation. It is the

most common cancer in women and incidence has risen from 1 in 20 in 1960 to 1 in 8 in 2006 (ACS, 2006; NBCF, 2006). Male breast cancer also occurs but with a slightly higher incidence in the developing than in the developed world (Dogo *et al.* 2006, Kidmas *et al.*, 2000). Worldwide, breast cancer is the second most common cause of cancer death in women after lung cancer (ACS, 2008).

The picture of breast cancer in Nigeria is less optimistic with statistics indicating that the incidence of breast cancer had doubled within 20 years (Adebamowo and Ajayi, 2000; Okobia and Osime, 2001). There is paucity of sufficiently long time series of high quality cancer data in many developing countries now. Nonetheless, where available, statistics show increases in breast cancer incidence and mortality, an observation often more apparent within recent birth cohorts, and a probable consequence of the adoption of western lifestyle (Bray, *et al.*, 2004). Preventative strategies have not been fully adopted in the fight against breast cancer in Nigeria (Elmore *et al.*, 2005). Generally, proper treatment and care are seriously lacking in developing countries, Nigeria inclusive. Kanavos (2006) predicted that the majority of new cases of cancer morbidity and mortality will occur in developing countries due to their poor health infrastructure. The importance of cancer as a major health problem in Nigeria and probably many other poor sub-Saharan countries has always been underplayed by various governments in the country and international donor agencies, who tend to focus more on control of infant and maternal health, family planning, control of communicable diseases such as malaria, tuberculosis and more recently HIV/AIDS (Durosinmi, 2007). Widely cited reasons for global increase in breast cancer is the westernization of the developing world - a term that encompasses delayed child bearing,

low parity, reduced breast feeding, decreased exercise and less desirable dietary habits (Porter, 2008).

With a population of over 140 million in Nigeria, there was no national centre, structure or program dedicated to cancer care and research until very recently. An International Cancer Centre was set up in 2009 in Abuja, but this is yet to make a significant impact in the treatment of people affected with the disease. Anticancer drugs are not readily available and are expensive (Durosinmi, 2007). Radiotherapy facilities in Nigeria are not widespread and where present are finding it difficult to cope with the increasing demand for radiotherapy treatment. Access to radiologic services is limited by cost and the equipment is often faulty. Diagnostic methods to determine the hormone receptor status of the tumor are not widely available. Surgeons whose primary clinical field of practice is not oncology often perform breast cancer surgery and there is limited multidisciplinary cancer care (Adebamowo, 2007). Mammographic screening is available in few health care institutions but - there is no national or regional mammographic screening program (Adebamowo, 2007).

Ahmadu Bello University Teaching Hospital, Zaria is one of the Federally owned government hospitals that have a Radiology and Oncology department established since 2000. The department runs an oncology clinic that hosts referrals from within and outside Nigeria. It is therefore pertinent for the therapeutic protocol used in the management of breast cancer patients at the clinic to be reviewed and kept up to date with the national guidelines on cancer chemotherapy prepared by the Federal Ministry of Health and the standard guidelines of the National Comprehensive Cancer Network (NCCN), in order to optimize treatment modalities in patients which can result in increased quality of life and

relative survival rate. The NCCN clinical practice guidelines in oncology are a set of practice guidelines for oncology which have been developed specifically by oncologists and cover 97% of cancers. These guidelines are updated continually and are used in over 115 countries. The information gathered in the guidelines is based on a review of scientific evidence from oncology trials and studies. There is also the need to evaluate the roles of each member of the health care team in order to arrive at useful recommendations that will improve teamwork in patient care.

1.2 SIGNIFICANCE OF THE STUDY

The research is justified because the general impact of cancer in our lives cannot be overemphasized. Cancer was reported to cause more deaths than AIDS, tuberculosis and malaria combined, and by 2030 the numbers of deaths are expected to rise to 12 million (WHO, 2009). Breast cancer in particular is a major health burden worldwide including Nigeria. According to Adebamowo *et al.*, (2000), cancer of the breast is the most common cancer in Nigeria, and he projected that 27,840 new cases would have developed in 1999 with a prevalence of 11.6 per 100,000. In 2005, breast cancer was found to be the most common in Nigeria (WHO, 2009). While treatment and survival rate of breast cancer patients is very good in the developed affluent countries, the same cannot be said for developing countries, which include Nigeria and most of Africa. In the United States, several studies have affirmed the importance of prompt and accurate diagnosis in achieving favorable outcomes in breast cancer including continued development of cancer therapeutics and focus on awareness and screening initiatives (Elmore *et al.*, 2005). This has consequently led to a relative 5-year survival rate of 81% in the United States in

contrast to 32% in sub-Saharan Africa (Ries *et al.*, 2002). The declining rate of breast cancer mortality in the United States and other industrialized nations has been linked to increased utilization of mammographic screening, early detection of disease and availability of improved therapies and quality of available health care. It is therefore necessary to evaluate the therapeutic guidelines used in the management of breast cancer patients at Ahmadu Bello University Teaching Hospital, Shika which boasts of an Oncology Center and provides care for patients from all over the country, with a view to seeing whether the existing guidelines meets up with good control, management and treatment control as outlined by the National Cancer Comprehensive Network (NCCN). Studies in developed countries have shown that improving the quality of medical care improves the patients' quality of life and relative survival rate. It is hoped that the results and recommendations from this research will help improve the quality of available medical care for breast cancer patients in Nigeria and consequently improve the quality of life and survival rate of the patient.

To the best of our knowledge, pharmaceutical care standards and practices for the various professionals have not been documented for the Oncology center at Ahmadu Bello University Teaching Hospital, Zaria. Thus, the outcome of this research may have local, national and international impact.

1.3 THEORETICAL FRAMEWORK

Breast cancer is the most commonly occurring cancer in women (ACS, 2005). Its incidence has risen from 1 in 20 in 1960 to 1 in 8 in 2006 (ACS, 2006; NBCF, 2006). The Nigerian healthcare system is generally in decay. The government has placed more emphasis on

infant and maternal health, family planning, malaria, tuberculosis and HIV/AIDS leaving cancers out. Lack of proper treatment and care of breast cancers in Africa has led to a decrease in the 5-year relative survival rate compared to the developing world. Thus there is the need to evaluate the therapeutic protocol used in the treatment of breast cancer patients to improve patient care and quality of life, and also to give recommendations on how multidisciplinary team work can impact positively on patient care.

1.4 OBJECTIVES OF THE STUDY

The overall aim of the study is to evaluate the management of breast cancer patients who attended clinic at Ahmadu Bello University Teaching Hospital, Zaria between January and December 2008. The specific objectives of the study are as follows:

1. To ascertain the diagnostic procedure used for breast cancer, the relative occurrence of breast cancer vis-à-vis other types of cancer, the relative occurrence of its subtypes in the Ahmadu Bello University, Zaria including predisposing factors.
2. To evaluate the pharmacological and non-pharmacological management of breast cancer in the hospital comparing with national guidelines and WHO standard guidelines for breast cancer, including the roles of members of the health care team in the management of breast cancer patients.

1.5 RESEARCH QUESTION

Is there an effective treatment protocol used in the management of breast cancer patients attending the Oncology clinic at Ahmadu Bello University Teaching Hospital, Zaria (which

corresponds to the national guidelines on breast cancer chemotherapy) and thus improves survival rate and quality of life in breast cancer patients?

CHAPTER 2

LITERATURE REVIEW

The Greek physician Hippocrates was the first to use the word “cancer” from the Greek words “carcinos” and “carcinoma” to describe malignant tumors. These Greek terms actually described a crab, which Hippocrates thought a tumor resembled. Though he named cancer, the history of cancer can be traced back to ancient Egypt, in 1500 B.C where the world’s oldest case of cancer was documented. Details were recorded on a papyrus, documenting eight cases of tumors occurring in the breast. Cauterization using a fire drill was used to destroy the tissue. There was no recorded treatment for the disease; only palliative treatment was given (Fayed, 2009).

2.1 ANATOMY OF THE FEMALE BREAST

The breast is situated between the second and the sixth ribs, extending from the sternal edge to the edge of the axilla and lying against the pectoralis muscle on the chest wall. It covers a large part of the chest wall and projects into the axilla as the tail of Spence. The breast tissue may reach as far as the latissimus dorsi (muscle extending from the lower back) to the humerus bone of the upper arm. The breasts are not always the same size or shape. At birth, they are incompletely developed and in men remain small and undeveloped unless subjected to abnormal hormonal stimulation. (Ramsay *et al.*, 2005).

Clinically, the breast is divided into four quadrants, namely: the upper inner, upper outer, lower inner and lower outer quadrants. Most breast cancers occur often in the upper outer quadrant. The mature female breast is composed essentially of lobules (glands), milk ducts,

fat and connective tissue, nerves, blood vessels, lymph nodes and small amounts of muscle tissue. The glands secrete milk during pregnancy and breast-feeding. The canal that carries milk from the lobules to the nipple openings are the milk ducts. The mammary gland (breast) is composed of 15-20 lobes that radiate from the nipple. Surrounding the lobes that constitute the major duct system is fat and fibrous connective tissue. These lobes are further divided into lobules, which are the basic structural unit of the breast. Each lobule is composed of grape-like clusters of acini called alveoli – the hollow sacs that make and hold breast milk. The lobules are arranged around ducts that funnel milk to the nipples. The dark circular area around the nipple is the areola. Montgomery's glands surround each areola and release a lubricant that protects the nipple during nursing. (Cruz-Korchin and Korchin, 2004).

2.2 TYPES OF BREAST CANCER

Cancers are a group of chronic debilitating diseases that arise from inappropriate and uncontrolled tumor growth from a single transformed cell due to genetic mutation, which leads to loss of normal cell growth regulation and function. Cancers that occur in the tissues of the breast, either the duct or lobules are known as breast cancers. Many breast cancers arise from a sequence that begins with an increase in the number of breast cells (hyperplasia), to the emergence of atypical breast cells (atypical hyperplasia), followed by carcinoma in situ (non-invasive cancer) and finally invasive breast cancer. Carcinomas are divided into two major classes viz:

1. Non-invasive or in situ carcinoma
2. Invasive carcinoma

2.2.1 Non-invasive Carcinoma

This describes tumors that are discovered at an early stage, when they are still small and confined. Cancer cells have not grown into surrounding tissues and remain within the borders of the duct or lobule. Such tumors are called non-invasive, in situ tumors as they remain in the site of origin. They are usually too tiny to have formed a lump and so are not felt or detected during a physical exam. Diagnosis is by mammography. The different types are:

Ductal carcinoma in situ (DCIS)

Also known as intraductal carcinoma or non-invasive carcinoma and contains breast duct cells that have malignant characteristics but are incapable of invading the basement membrane. They do not metastasize to surrounding tissues, however the abnormal cells within DCIS may precede invasive breast cancer as the cells can spread throughout the ductal system to produce extensive lesions affecting an entire sector of a breast. According to Ekanem and Aligbe (2006), DCIS accounts for about 6.6% of breast cancers in Nigerian women. Histological types of DCIS are comedocarcinoma, noncomedocarcinoma, cribriform, papillary and micropapillary. Paget's disease of the nipple is also a form of DCIS that extends from the nipple ducts into the contiguous skin of the nipple and areola. The disease does not involve the surrounding skin and is typically limited to one breast.

Lobular carcinoma in situ (LCIS)

This occurs in women who have not yet undergone menopause. It is characterized by abnormal changes in the cells that line the milk producing lobules of the breast. Lobular carcinoma in situ is multifocal and affects both breasts.

2.2.2 Invasive (infiltrating) Carcinoma

There are several types of invasive carcinoma, and they include:

Invasive (infiltrating) ductal carcinoma (IDC) – This is the most common type of breast cancer. About 80% of invasive breast cancers are classified as invasive ductal carcinoma (ACS, 2006). Ekanem and Aligbe (2006) in a study on Nigerian women also found out that invasive ductal carcinoma were more prevalent by 75.5%. In IDC, cancer cells have penetrated the ductal wall and invaded surrounding breast tissue. The cells may metastasize to other parts of the body through the blood stream and lymphatic system. It presents as a firm palpable mass or as a mammographic abnormality.

Invasive (infiltrating) lobular carcinoma (ILC) – Invasive lobular carcinoma makes about 5-10% of breast carcinomas (ACS, 2006). ILC begins in the milk producing lobules where it extends into the adipose tissue of the breast. Due to their diffuse invasive pattern, invasive lobular carcinomas are difficult to detect either by physical examination or by radiological investigations. Patients are more often prone to bilateral disease.

Medullary carcinoma – This type of breast cancer starts in the milk ducts with large cancer cells that look very different from healthy cells and has a 1-year survival rate of 92% (Oliver *et al.*, 2003). It is found more frequently in young women and it is associated with family history (Weigelt, 2008). Histologically, the tumor is characterized by larger than

average cancer cells, with the immune system cells present on the edge of the tumor. In a study carried out by Ikpatt *et al.*, 2002 the occurrence of medullary carcinoma was reported to be disproportionately high.

Mucinous (colloid) carcinoma – Colloid carcinomas usually occur in postmenopausal women and the tumors may or may not be palpable. It is characterized by large amounts of extracellular mucin production.

Tubular carcinoma – Highly differentiated invasive carcinoma whose cells are regular and arranged in well-defined tubules. Pure tubular carcinoma has limited metastatic potential and better than average prognosis.

Metaplastic carcinoma – This type of carcinoma represents about 5% of all cancers (ACS, 2006; Weiglet, 2008). Lesions contain several different types of cells that are not typically seen in other forms of breast cancer. Clinical presentation is frequently a single palpable lesion often associated with rapid growth.

Invasive cribriform carcinoma – This is a well-differentiated cancer comprised of small uniform cells.

Invasive papillary carcinoma – Rare cancers that represent 1% or fewer of all invasive cancers. It is common in postmenopausal women and presents with nodular densities that may be multiple and are frequently lobulated (Weigelt, 2008).

Invasive micropapillary carcinoma – Invasive micropapillary carcinoma usually presents as a firm, immobile mass. It is not common and has an incidence of less than 3% (Weigelt, 2008).

Other types of breast cancer include:

Inflammatory breast cancer - Diagnosed on clinical presentations of breast inflammation, warmth, thickening/dimpling, peau de' orange and a palpable ridge at the margin of induration. Symptoms arise when cancer cells block the lymphatic vessels near the surface of the skin.

Phylloides tumor – Can be classified as benign, borderline or malignant. They are biphasic in nature and consist of benign epithelial elements and cellular connective tissue.

Correct classification of breast cancers into different histological types allows a more accurate prognostication of breast cancer patients and facilitates the identification of optimal therapeutic strategies (Weiglet, 2008).

2.3 ETIOLOGY OF BREAST CANCER

No etiology is known in 95% of breast cancer cases, while approximately 5% of new breast cancers are attributable to hereditary syndromes (Madigan *et al.*, 1995). There are many factors both known and unknown that contribute to human breast cancer. Though the exact cause of breast cancer is unknown, there are many factors that contribute to human breast cancer. Hereditary (family history), hormonal and reproductive, environmental including lifestyle are factors associated with risk for breast cancer (Debruin and Josephy, 2002). A risk factor can be defined as any characteristic or behavior that increases the chances of developing a disease. Modifiable risk factors like pollutants, occupational exposures, tobacco smoke, alcohol which are environmental agents are attributed to over 70% of breast cancers (Debruin and Josephy, 2002).

The American Cancer Society, 2008, has identified the following risk factors:

Gender – The most important risk factor for breast cancer is the female gender. The risk for females is 100 times that of males.

Age – Breast cancer risk increases with age. The older the woman the greater her chances for developing the disease. Most breast cancers (about 80%) develop in women over the age of 50. The age specific incidence rates have been found to be higher in women above 50 years compared to women less than 50 years (Gukas *et al.*, 2006).

Genetic Mutations – About 5-10% of breast cancers are hereditary. Certain genes have been identified to increase the risk of breast cancer. Women with an inherited BRCA1 and BRCA2 mutation have a greatly increased risk of developing breast cancer (Ford *et al.*, 1998), and a 45 to 65% chance of developing the disease by the age of 70 (Metcalf *et al.*, 2009). According to the National Cancer Institute of the United States, estimates range from 3 to 7 times that of women without these gene mutations. Other genes associated with breast cancer include p53, AT, RB suppressor gene, GADD repair group and the HER-2/neu oncogene.

Family history – The risk for breast cancer is increased (doubled) for women having a first-degree biological relative (mother, sister, and daughter) or a second-degree relative (grandmother, aunt, and niece) with the disease (Pharoah *et al.*, 1998). Cancers also occur in women without such a history.

Personal history of breast cancer - A patient who has had breast cancer previously has an increased risk of second primary breast cancer either in the opposite breast or in the same breast if there is remaining tissue (Levi *et al.*, 2006). The amount of risk depends on the presence of other factors like BRCA mutations, menopausal status, family history, time

since biopsy and treatment. For women with proliferative breast disease without atypia the risk is 2-fold, while those with atypical hyperplasia have a 4-fold increased risk (Hartmann *et al.*, 2005).

Breast density – Breast density is strongly and independently related to the risk of breast cancer (Oza and Boyd, 1993 and Tamimi *et al.*, 2007). Studies using quantitative methods for defining breast density, report 4- to 6-fold increase in relative risk for women with dense breast tissue (Mc Cormak and dos Santos, 2006). A number of factors, some of which include menopausal status, weight and number of children affect density but there is evidence that the most important determinant is inherited (Boyd *et al.*, 2003).

Radiation exposure – Ionizing radiation is an established risk factor for breast cancer (Hankinson and Hunter, 2002). Breast cancer risk is significantly increased in women who have been exposed to radiation either therapeutically or accidentally (through atomic bomb exposure). Studies have shown a 12- to 25-fold increase in risk for secondary breast cancer in women treated with mantle radiation therapy to the chest for Hodgkin's lymphoma before the age of 30 (Gold *et al.*, 2003; Kenney *et al.*, 2004 and Taylor *et al.*, 2008) Risk increases with younger age and higher radiation doses. The risk may however be lowered for patients who were treated with chemotherapy and the chemotherapy stopped ovarian hormone production (ACS, 2005).

Hormonal factors – Longer exposure to sex hormones particularly estrogen, increases the risk of breast cancer in women. Therefore women who have history of early menarche (early onset of menstrual period before the age of 12) have an increased risk for breast cancer. Good nutrition in early life has been reported to decrease the age of menarche

(Koprowski *et al.*, 1999). Women who have attained menopause later in life (after age 55 years) are more at risk of having breast cancer. Studies show that postmenopausal women with higher levels of testosterone and estrogen have 2-3 times the risk of women with lower levels (Key *et al.*, 2002). Link between these hormones and premenopausal breast cancer risk is not clear (Eliassen *et al.*, 2006). A higher level of prolactin has been associated with increased risk of breast cancer, particularly estrogen receptor positive tumors (Tworoger *et al.*, 2007). Higher levels of insulin have been linked to an increased risk of postmenopausal breast cancer in women not taking hormone replacement therapy (Yu *et al.*, 2002).

The following breast cancer risks are associated with lifestyle choices.

Not having children at all or having children later in life. – Women who have had their first child after the age of 30 years or have not had children at all, have a slightly higher risk of breast cancer. Being multiparous at an early age reduces breast cancer risk as pregnancy reduces the total number of lifetime menstrual cycles (Ewertz *et al.*, 1990). A 15% risk reduction has been shown for women with a twin birth compared to women giving birth to a singleton (Ji *et al.*, 2007).

Recent use of birth control pills – The use of birth control pills has been associated with an increased risk of breast cancer. Women that have stopped the use of oral pills for more than 10 years do not seem to have an increased risk (Collaborative group on hormonal factors in breast cancer and hormonal contraceptives, 1996).

Using post-hormonal therapy (PHT) – Post hormonal therapy used to help relieve the symptoms of menopause and to prevent osteoporosis, has been associated with an increased risk of breast cancer. There are two main types:

Combined PHT – This is used in women who still have uterus and are using a combination of estrogen and progesterone. This combination increases the risk of breast cancer and the chances of dying from the disease.

Estrogen replacement therapy – The use of estrogen for greater than 10 years in women who have had a hysterectomy has been found to increase the risk of ovarian and breast cancer.

The risk is higher with for use of estrogen-progesterone therapy compared to estrogen only (Schairer *et al.*, 2000 and Reeves *et al.*, 2006).

Not breastfeeding – Breastfeeding for 1 to 2 years has been found to slightly lower breast cancer risk. The longer a women breastfeeds, the greater the protection and risk is reduced for every 12 months of breast feeding (Collaborative group, 1996).

Alcohol intake – Women who have 2 to 5 drinks daily have about one and a half times the risk than women who do not take alcohol. Though there is no universally accepted standard drink definition (Kloner and Rezkalla, 2007), in the United States, one drink is usually considered to be 12 ounces of beer, 5 ounces of wine or 1.5 ounces of spirits delivering about 12 to 14g of alcohol (USDA, 2005). There is a recognized relationship between the consumption of more than 2 drinks a day and an increased level of estrogen in the blood. According to the American Cancer Society, 2005 one alcoholic drink a day confers only a slight risk, while 2-5 drinks daily increases the risk of breast cancer by 1.5 times. Estimates of the relative risk associated with every additional drink consumed on a regular basis ranges from about 7-12% (Key *et al.*, 2006; Rinaldi *et al.*, 2006). Some sex hormones have

been found to have higher levels in the blood stream of alcohol consumers than non-consumers (Boyd *et al.*, 2003).

Weight – Excess fat increases the risk of breast cancer. This is possible because the enzyme aromatase manufactured from body fat can make estrogen from androstenedione, a steroid released from the adrenal glands. Postmenopausal women with more body fat have more aromatase hence more estrogen and this increases their risk of developing breast cancer. Based on the results of the “Million Women Study” an estimated 7% of breast cancer in postmenopausal women in the United Kingdom is due to overweight and obesity (Reeves *et al.*, 2007).

Lack of exercise – The American Cancer Society has suggested that exercise for 45 to 60 minutes for five or more days a week reduces breast cancer risk. Studies have shown a 20-40% risk reduction for women with the highest category of physical activity (Marati, 2008). A recent European Prospective Investigation of Cancer (EPIC) study showed lower levels of estrogen and testosterone in postmenopausal women who reported higher levels of physical activity (Chan, 2007).

Race – Caucasian women in general have the highest rates of breast cancer. Incidences are lower in women of African-American ancestry, but this group of women has an increased mortality rate compared with white women. Many breast carcinomas in black women are diagnosed at younger than 40 years. These cancers are usually of high nuclear grade, more frequently lack hormone receptors and have different types of p53 mutations.

Uncertain risk factors associated with breast cancer include:

High fat diet – A meta-analysis of 45 studies (Boyd *et al.*, 2003) reported that higher total fat intake increased breast cancer risk by 13%, while a recent cohort study showed a small

but significant increase in risk for higher intakes of saturated, monounsaturated and polyunsaturated fat (Thiebaut *et al.*, 2007).

Antiperspirant - Darbre (2005), found out that aluminum salts used in antiperspirants can interfere with the function of estrogen receptors of MCF7 human breast cancer cells both in terms of ligand binding and in terms of estrogen-regulated reporter gene expression, though further studies are needed to identify the molecular basis of action. In 2006, Fakri *et al* examined antiperspirant use and other factors among 54 women with breast cancer and 50 women without breast cancer and found no association between antiperspirant use and the risk of breast cancer. Studies by Namer *et al.*, 2008 and the American Cancer Society, 2009 have found no association or good scientific evidence to support the claim that antiperspirants cause breast cancer.

Brassiere – According to the American Cancer Society, 2010 there is no scientifically valid study that shows that wearing bras of any type causes cancer.

Abortions- Pregnancies that end as a spontaneous or induced abortion do not increase a woman's risk of developing breast cancer (Melbye *et al*, 1997; Beral *et al.*, 2004).

Breast implants - The incidence of breast cancer in a study carried out by Bryant and Brasher, 1995 among women who had breast augmentation, could not be said to be either significantly higher or lower than that among the general population over the period during which the study was carried out.

Pollution – Several studies have linked the incidence of breast cancer and occupational exposure to benzene and poly aromatic hydrocarbons (Gammon *et al.*, 2002; Labreche 2003). Exposure to nitrogen dioxide a marker for traffic-related pollution has also been associated with increased incidence of post-menopausal breast cancer in Montreal, Quebec.

Though further studies are needed to confirm whether nitrogen dioxide or other components of traffic-related pollution are indeed associated with increased risk (Crouse et al, 2010).

Tobacco smoke – In Japanese women, tobacco smoking has been found to possibly increase the risk of breast cancer (Nagata *et al.*, 2006). Smoking of long duration, smoking before a first full-term pregnancy, and passive smoking have been found to possibly increase the risk of breast cancer (Terry and Rohan, 2002).

Night work – Evidence has shown that women who do night shift work have an increased risk for breast cancer (Megadal *et al.*, 2005). Other studies have shown that sleeping for longer periods reduces the risk of breast cancer (Kazikazi, 2008). The major melatonin metabolite 6- sulfatoxymelatonin when present in high levels has been shown to cause 38% reduction in breast cancer risk (Schernhammer *et al.*, 2009).

Height – Tallness is associated with an increased risk of breast cancer in postmenopausal women with an approximate 7% increase in relative risk for each additional 5 cm in height (Van den Brandt *et al.*, 2008).

Medications – Regular use of aspirin or other non-steroidal anti-inflammatory drugs by some women has been associated with up to 25% reduction in risk for breast cancer (Takkouche *et al.*, 2008). In a study carried out by Khuder and Mutgi, 2001 postmenopausal NSAID's users had lower levels of estrogen than non- users.

2.4 CLINICAL PRESENTATION

Breast cancer can present with symptoms of local or systemic disease. Many breast carcinomas may be asymptomatic. Changes in the breast include: axillary lump, change in

breast size/shape, nipple inversion, single duct discharge particularly if blood stained, breast skin change and itchy nipple.

Symptoms of metastatic spread include: breathing difficulties, bone pain, hypercalcemia, abdominal distension, jaundice, localizing neurological signs and altered cognitive function.

Skin metastasis can lead to: subcutaneous skin nodules, intracutaneous nodules and patchy hyper pigmented skin.

Spinal metastasis can present as: back pain, paraesthesia and paralysis.

When the brain is involved, the following symptoms are common: recurrent/persistent headache, blurring of vision, stroke and death due to increased intracranial pressure.

Metastasis to the brain and liver have poor prognosis with survival less than six months in many cases. Lung, pleural and bone metastasis have good prognosis with good response for chemotherapy and hormonal manipulation (Disibio and French, 2008).

2.5 DETECTION AND SCREENING

Breast cancer screening is an important tool in detecting cancer at its earliest possible stage before it causes symptoms. Cancers caught at an early stage are more likely to be treated successfully with less aggressive treatment strategies. Methods used for screening for breast cancer are, clinical breast examination (CBE), self-breast examination (SBE), mammography and magnetic resonance imaging (MRI). These methods are used to identify patients that need further evaluation.

Early detection and treatment is the key to surviving breast cancer. According to the American Cancer Society 2007, the 5-year relative survival rate for breast cancer when detected at a localized stage is as high as 98%. For regional disease, the survival rate is 86%. Spread of cancer to distant organs drops the 5-year survival to 26%. Large tumor size at diagnosis is associated with decreased survival.

Breast Self-Exam (BSE) – Breast self-exam is performed monthly about a week after the start of a woman's period, at the same time each month. Breast self-examination is better taught by a healthcare professional that performs clinical examinations (ACS, 2007). The procedure promotes a woman's familiarity with her breasts, which help her to readily detect changes and promptly report them to her healthcare provider. Women who choose to do breast self-exam should receive instruction and have technique reviewed by a health professional.

Clinical breast exam (CBE) – This is a visual and manual examination of the breasts by a trained healthcare professional. Women in their 20's and 30's with average risk should have CBE as part of a periodic health examination, preferably every 3 years (ACS, 2007). The American Cancer Society also recommends that asymptomatic women aged 40 and above should continue to receive CBE as part of their periodic health examination annually. A comprehensive clinical breast examination involves the examiner taking a clinical history, then using the pads of the fingers, the examiner gently feels the breast giving special attention to the shape, texture, location of any lumps, whether such lumps are attached to the skin or the deeper tissue. Visual inspection of the breasts for any skin changes or asymmetry is then done. The patient is further educated on symptoms of breast cancer and a follow up visit scheduled. The quality of CBE varies with the healthcare

professional's skill, experience and the time spent in performing the exam. The duration of a properly conducted CBE is influenced by breast size and composition. Generally, the procedure can take between 6 to 12 minutes.

Mammography – Mammography is the single most effective method of early detection of breast cancer since it can identify cancer several years before physical symptoms develop (ACS, 2007). It is a low dose X-ray procedure which allows visualization of the internal structure of the breast. Mammography can be used to detect breast changes in women who have no signs or symptoms of breast cancer. Testing is more accurate in postmenopausal women (Kerlikowske, 1997). Cancers that are not identified by mammography are few and may be missed due to breast density, faster tumor growth rate, inadequate positioning of the breast or due to failure in recognizing small early signs of abnormality.

A standard screening mammogram consists of 2 views of each breast: the craniocaudal (CC) and the mediolateral oblique (MLO) projections. Calcifications that cannot be felt can be detected by mammography. The accuracy of mammography depends upon the skill of the technologist who takes the mammogram and the radiologist who interprets the mammogram. Efforts to improve breast cancer screening using mammography have resulted in the development of digital mammography and computer aided detection. Digital mammography records x-ray images in computer code like a digital camera. Subtle differences between the tissues are more easily noted. Computer aided detection (CAD) on the other hand involves the use of computers to bring suspicious areas of a mammogram to the radiologist attention to see whether further evaluation is needed (Vyborny and Giger, 1994).

Magnetic resonance imaging (MRI) – Magnetic resonance imaging uses magnetic fields and radio waves to produce very detailed cross sectional images of the body. It is more sensitive than ultrasound for detecting breast cancer with an overall sensitivity of 96% (Davis *et al.*, 1997) and has been shown to detect more cancers than mammography alone. It is recommended for screening women at high risk for breast cancer. Problems associated with MRI include: inability to detect microcalcifications, equipment variability and a lack of standardized exam techniques and interpretation criteria, as well as its significant cost (Smith, 2003).

Breast ultrasound – Can be used to detect cancer among women with dense breast tissue when used in combination with mammography. Ultrasound is an imaging technique that uses high frequency sound waves for examining tissues and internal organs. Breast ultrasound distinguishes not only between cysts and solid masses but also differentiates benign from malignant disease (Stavros *et al.*, 1995). Scan is limited to the focal area of concern (Gordon and Goldenburg, 1995). Like mammography, it has a lower specificity in younger women (O’Driscoll *et al.*, 2001) and is associated with higher rate of false positives than mammography (Smith, 2003).

Other methods currently being evaluated for their screening potential include: breast fluid sampling, nuclear medicine imaging, electrical impedance imaging, thermography and optimal imaging.

2.6 DIAGNOSIS

The first step in the evaluation of a patient with suspected breast cancer starts with a complete medical history and physical examination followed by specific imaging tests. The following steps are necessary:

Clinical examination – Involves taking a detailed medical history which includes: presenting complaints, past medical history of breast disease in detail, family history of breast and other cancers and reproductive history (age at menarche, age at first delivery, number of pregnancies, children, miscarriages, age at onset of menopause, history of hormonal use including contraceptive pills types and duration of use, hormonal replacement therapy-type and duration of use).

Physical examination which should cover: performance status, weight, height and body surface area, general examination of other systems, local examination of breast (size, location, shape, consistency, fixation to the skin, pectoral muscle and chest wall, multiplicity).

Skin changes may occur and include: erythema (location and extent), edema (location and extent), dimpling, infiltration, ulceration and satellite nodules.

Nipple changes can present as: retraction, erythema, erosion, ulceration and discharge.

Nodal status: axillary nodules on both sides or supraclavicular nodes.

Other steps are: Local examination of possible metastatic sites, laboratory investigations (Complete blood count and differential, renal and hepatic profile, bilateral mammography/ultrasound, chest x-ray +/- computed tomography of chest if needed, abdominal ultrasound, bone scan if indicated, electrocardiogram and echocardiogram or multiple gated acquisition scan if age greater than 60 years, positron emission tomography (PET) scan.

Imaging tests – Commonly used imaging tests for evaluating abnormal breast findings are diagnostic mammogram and breast ultrasound. Others are magnetic resonance imaging, ductogram, scintimammography and positron emission tomography.

Diagnostic mammogram – Similar to screening mammogram but in addition to the standard craniocaudal and mediolateral oblique views, it may also include lateromedial, mediolateral, exaggerated craniocaudal views, spot compression and magnification.

Breast ultrasound – Is used in conjunction with diagnostic mammography and is helpful in distinguishing between a solid mass and a fluid filled cyst. Evaluating women with breast dense tissue is possible using breast ultrasound.

Magnetic resonance imaging (MRI) – More sensitive than mammography and breast ultrasound in viewing palpable abnormalities. It can define the size and extent of cancer in breast tissue and locate multifocal disease. MRI is useful in scanning other regions of the body for signs of metastasis.

Ductogram – This is a valuable method for diagnosing benign tumors and cancers. It is a type of contrast-enhanced mammography used for determining the cause of abnormal nipple discharge.

Scintimammography – Employs the use of radioactive tracer Tc99m sestamibi, to help detect breast cancer. It is specific for palpable lesions and useful for detecting axillary involvement. Women with dense breast tissue or implants can be diagnosed within this procedure.

Positron electron tomography (PET) – Highly sensitive and specific for imaging different types of breast disease. The method uses a wide range of labeled metabolites e.g. fluorinated glucose (18FDG) to detect metabolic activity, vascularization, oxygen consumption and tumor receptor status.

Electric impedance imaging (Transcan, Tscan) -- Evaluates tumors detected by mammography using a hand held probe that scans the breast for electrical conductivity sending two-dimensional images of breast tissue to a computer screen.

Selection of the imaging test to be used may be based on age, sensitivity, specificity, local availability and cost.

Pathological diagnosis – A pathological diagnosis using breast biopsy is the most definitive method for diagnosing breast cancer. Biopsy involves the removal of tissue or cells for examination microscopically. Specimens can be obtained from the symptomatic area or from an area identified by breast imaging. The different types of breast biopsies are:

Needle biopsy – There are two types of needle biopsies used to diagnose breast cancer. They include:

Core needle biopsy (CNB) –Uses a large needle to remove a small cylinder of tissue (core) about the size of a rice grain to be analyzed. Two to five cores are usually removed although more can be taken. The core tissue samples are then analyzed by a pathologist for malignant cells.

Fine needle aspiration biopsy (FNAB) – Least invasive method of breast biopsy. A thin hollow needle is inserted into the breast to withdraw cells from a suspicious lesion. Cells are then analyzed in the laboratory.

Image guided biopsy – When abnormalities can be seen from one or more imaging tests, image guided biopsy is used to facilitate sampling of cells or tissues from the abnormalities. Image guided biopsy can be carried out with mammography, magnetic resonance imaging or ultrasound.

Surgical biopsy – Used for lesions that cannot be assessed by needle biopsy. Also called open biopsy and are of two types: incisional and excisional biopsy. In incisional biopsy a small portion of the lesion is removed while excisional biopsy involves the removal of the entire lesion, as well as any surrounding margin of normal breast tissue. Tissues removed are sent to a pathology laboratory for microscopic evaluation.

Triple Assessment/Test

Diagnostic accuracy can be increased and false negative results eliminated as much as possible using the triple assessment principle or test. This test refers to a correlation of findings from - Clinical breast exam (Clinical diagnosis), breast imaging (usually mammography and or ultrasonography) and biopsy (cytopathological diagnosis).

The triple test seeks concordance of findings using different screening and diagnostic techniques. It also ensures follow up of abnormal findings.

2.7 STAGING

Staging is a process that has been developed to determine the growth and extent of cancer in the body. The staging of breast cancer is done based on information from pathological results, findings from imaging studies and surgery. Staging is important as it helps the physician to plan treatment and offers insights into patient's prognosis. Staging also provides a standardized means by which medical providers communicate with one another about an individual case and a method by which cancer researchers may compare notes (ACS, 2005). Generally, the lower the stage number, the less the severity of the cancer. The stage of breast cancer is determined by information gathered from tests on tumor tissue, lymph nodes and distant organs. Clinical staging occurs prior to surgery and is based on information obtained from physical examination and imaging tests. Pathological staging

occurs after biopsy and includes both clinical information and findings from microscopically examined tissue. The later is more definitive for planning treatment and estimating prognosis (ACS, 2005).

2.7.1 Tumor Node Metastasis (TNM) System of Staging

The system most commonly and widely used for breast cancer staging is the “tumor node metastasis” (TNM) system. The American Joint Committee on Cancer (AJCC) and the National Cancer Institute (NCI) devised the TNM system. In the system, each letter is followed by a number or additional letters that describes what is known about the growth and extent of the disease at diagnosis.

The “T” component designates the size and invasiveness of the primary tumor with the numeric value increasing with tumor size and extent of invasiveness.

The “N” component designates the presence or absence of regional node involvement, with the numeric value based on the number or location of involved lymph nodes.

“M” component identifies the presence or absence of distant metastasis, including lymph nodes that are not regional.

2.7.2 Stage Groupings and TNM Categories

According to the American Cancer Society, 2005 breast cancer can be staged as shown below in table 2.1:

Table 2.1 Stage Groupings and TNM Categories

Stage	TNM	Description
0	Tis,N0,M0	Carcinoma in situ (Tis) with no positive lymph nodes (N0) and no known distant metastasis (M0).
I	T1,N0,M0	Tumor is 2cm or less in diameter (T1) with no positive lymph nodes (N0) and no known distant metastasis (M0).
IIA	T0,N1,M0	No tumor is found in the breast (T0) but in 1-3 axillary lymph nodes with no known distant metastasis (M0) or
	T1,N1,M0	Tumor is 2cm or less (T1) and has spread to 1-3 axillary lymph nodes or found by sentinel node biopsy as microscopic in internal mammary nodes but not on imaging studies or by clinical exam (N1) with no known distant metastasis (M0) or
	T2,N0,M0	Tumor is larger than 2cm but less than 5 cm in diameter (T2) with no positive lymph node (N0) and no distant metastasis (M0).
IIB	T2,N1,M0	Tumor is larger than 2cm but less than 5 cm in diameter (T2) and has spread to 1-3 axillary lymph nodes or found by sentinel node biopsy as microscopic in internal mammary nodes but not on imaging studies or by clinical exam (N1) with no known distant metastasis (M0) or
	T3,N0,M0	Tumor is larger than 5 cm and does not grow into the chest wall or skin (T3) with no positive lymph nodes (N0) and no known distant metastasis.
IIIA	T0-2,N2,M0	Tumor is smaller than 5 cm in diameter (T0-2) and has spread to 4-9 lymph nodes on the same side as the breast cancer or internal

		mammary nodes found by imaging studies or clinical exam (N2) but with no known distant metastasis (M0), or
	T3,N1-2,M0	Tumor is larger than 5 cm (T3) and has spread to 1-9 axillary lymph nodes on the same side as the breast cancer or to internal mammary nodes found by imaging studies or clinical exam (N1-2) but with no known distant metastasis (M0).
IIIB	T4,N0-2,M0	Tumor has grown into chest wall or skin (T4) and may or may not have spread to lymph nodes up to 9 or may not have spread to internal mammary nodes (N0-2). There is no known distant metastasis (M0).
IIIC	T0-4,N3,M0	Tumor is any size (T0-4) and has spread to 10 or more nodes in the axilla or to 1 or more intraclavicular or supraclavicular lymph nodes or to internal mammary lymph nodes, which are enlarged because of the cancer- all on the same side as the breast cancer (N3). No known distant metastasis (M0).
IV	T0-4,N0-3,M1	Tumor is any size (T0-4) with known metastasis to organs (most often the bones, lungs, liver or brain) or to lymph nodes distant from the breast (M1).

2.8 5-YEAR SURVIVAL RATE

This refers to the percentage of patients that live at least 5 years from diagnosis. Survival rates can be relative in which case the observed survival of people with breast cancer is compared with that expected for people without breast cancer. According to the American Cancer Society, 2005 the relative 5-year survival rate for each stage of breast cancer, based on patients data diagnosed from 1995-1998 is as shown below in table 2.2:

Table 2.2 5-year relative survival

Stage	5-year relative survival (%)
0	100
1	100
IIA	92
IIB	81
IIIA	67
IIIB	54
IIIC	Not available
IV	20

2.9 PROGNOSTIC FACTORS

Prognostic factors for breast cancer can be classified into two namely –

1. Minor prognostic factors
2. Major prognostic factor

Minor prognostic factors

Minor prognostic factors are used to predict the response of tumors to specific therapeutic agents. These factors can be used to determine which chemotherapy regimen and or hormonal therapies a breast cancer patient is likely to benefit from maximally. They are:

- i) Tumor grade – This classifies breast cancer cells on the basis of three features; rate of cell division (mitotic rate), percentage of cancer cells composed of tubular structures (tubule formation) and change in cell size and uniformity (nuclear grade). Each feature is assigned a score ranging from 1 to 3 based on microscopic examination of the cells. A total

of the three scores are taken. A lower total number is generally associated with a more favorable prognosis.

ii) Hormone receptor status – Refers to the estrogen and progesterone receptors on the surface of cells that bind to circulating hormones. Response to therapy can be predicted using hormone receptors. Tumors that contain estrogen and progesterone receptors are referred to as estrogen receptor positive or progesterone receptor positive respectively. Hormone receptor positive breast cancers respond to hormone therapy (tamoxifen, aromatase inhibitors) and their prognosis is generally more favorable than cancers without this feature.

iii) HER-2/neu expression – Human epidermal growth factor 2 (a transmembrane glycoprotein) is a type of cell surface receptor that functions to regulate cell growth. Testing for HER-2/neu is of clinical value in assessing prognosis and choice of treatment. While HER-2/neu over expression is generally associated with adverse prognosis, it also predicts response to the monoclonal antibody trastuzumab (herceptin). HER-2/neu over-expression affects approximately 20 -30% of breast cancer patients.

iv) DNA content (ploidy) – DNA content is measured by flow cytometry which is a technique that separates, classifies and quantifies cell types. Tumors with DNA index of 1 have the same total amount of DNA as normal diploid cells. Aneuploid tumors are those with abnormal DNA indices and have a slightly worse prognosis.

v) Cell proliferation rate (S- phase fraction) – Also measured by flow cytometry and refers to the rate of at which cells divide and grow. High values indicate faster rates of growth and less favorable disease outcomes (Domagala, *et al*, 1996).

Major prognostic factors

The American Joint Committee on Cancer (AJCC, 2002) staging system has outlined a number of prognostic factors that have been shown to be strong predictors of death from breast cancer. These factors include:

i) Type of cancer – May be invasive carcinoma or *in situ* disease which have different implications for prognosis. Breast cancer deaths linked with ductal carcinoma *in situ* (DCIS) are usually due to subsequent development of invasive carcinoma in areas of invasion not detected during diagnosis. When DCIS is properly treated it is cured, while half of invasive carcinomas will have metastasized locally or distantly at the time of diagnosis.

ii) Tumor size – Increased size of carcinoma increases the risk of axillary lymph node metastasis. Small tumors are capable of distant metastasis but this is rare. Women with carcinomas under 1 cm in diameter and are node negative have a prognosis approaching that of women without breast cancer.

iii) Distant metastasis – Cure is unlikely once distant metastasis sets in. For women with hormonally responsive tumors, long term remissions and palliation can be achieved. Common sites for metastasis include the lungs, bones, liver, adrenals, brain and meninges.

Lymph node metastasis – Biopsy is necessary for accurate assessment of lymph node metastasis, as clinical assessment of nodal involvement can be inaccurate.

Locally advanced disease – Any tumor invading into the skin or skeletal muscle is associated with concurrent or subsequent distant disease.

Inflammatory carcinoma – The prognosis for women with inflammatory carcinoma is very poor. The 3-year survival rate is 3-10% (Giordano and Hortobagyi, 2003).

2.10 TREATMENT

There are five main treatment modalities employed in the treatment of breast cancer and they are: surgery, radiation treatment, chemotherapy, hormone therapy and biological therapy.

For optimal cancer management, surgery is usually combined with one or more additional therapies. Treatment plan for each patient varies and may be based on age, menopausal status, overall health, medical history, type, size, and location of cancer, tolerance for specific medications and procedures, characteristics of the cancer cells as determined by laboratory and pathology tests, expectations of the course of the disease and the patients opinion or preference.

2.10.1 Surgery

The first line of attack (primary treatment) against breast cancer is usually surgery, to remove the cancer. There are different kinds of surgical procedures that can be used depending upon a number of factors which include: the size and location of the tumor, type and stage of breast cancer, size of the breast and a woman's personal preference. Women with breast cancer can choose between total removal of the breast (mastectomy) and breast conserving surgery (lumpectomy, wide local excision, tylectomy and quadrantectomy).

Lumpectomy – Lumpectomy is a less invasive surgery that removes the cancer and a surrounding margin of normal breast tissue while preserving much of the appearance and sensation of the breast. For women with invasive breast cancer, lumpectomy (also known as breast conserving surgery BCS) is always followed by radiation therapy. Eligibility for BCS depends on whether the patient has a single area of cancer, a breast tumor less than 5

cm in diameter and a lesion that can be completely removed by lumpectomy and is willing to undergo follow up radiation therapy.

The disadvantages of lumpectomy are that there is a risk of developing local recurrence of the cancer than after mastectomy. Also the breast cannot tolerate additional radiation if there is recurrence in the same breast after a previous lumpectomy. Lumpectomy can be carried out under general or local anesthesia (Fisher *et al*, 2002). Risks associated with the procedure are that there might be loss of sensation and numbness in parts of the breast, and the breast in which tissue was removed may not appear the same size and shape compared with the unaffected breast.

Mastectomy – Surgical procedure that involves the removal of the entire breast. Radiotherapy may be included based on the pathology results. For women who do not meet the criteria for breast conserving surgery or have more advanced breast cancers, mastectomy is the preferred choice of treatment.

Types of mastectomy

Radical/ Halstead mastectomy – Involves the surgical removal of the breast, all surrounding lymph nodes and the underlying chest muscle. This procedure deforms the chest contour and impairs arm movement.

Simple mastectomy - Here the entire breast is removed without the axillary lymph nodes or muscular tissue beneath the breast. This procedure is also called total mastectomy.

Subcutaneous mastectomy – Removes most but not all the breast tissue via a small surgical incision that leaves the breast skin and nipple unchanged.

Modified radical mastectomy – This is a surgical procedure that removes the entire breast and some axillary lymph nodes. It is a combination of axillary lymph node dissection and total mastectomy. In some cases the pectoralis minor may be removed if cancerous.

Skin sparing mastectomy – This is a new procedure where breast tissue is removed through a tiny circular incision that is made around the nipple. The technique minimizes disfigurement, leaves the skin undamaged and enables immediate breast reconstruction (Cunnick and Mokbel, 2006).

2.10.2 Radiation therapy

Radiation therapy is also known as radiotherapy makes use of high energy x-rays or gamma rays to destroy cancer cells. These high-energy rays are delivered by linear accelerator machines that direct the rays as an external beam. A cobalt machine that gives off gamma rays from a radioactive source of cobalt can also be used. Cancer cells are unable to repair radiation induced damage unlike normal cells, hence the use of radiation in breast cancer chemotherapy. Radiation therapy is usually given after lumpectomy as an adjuvant therapy to destroy any remaining undetected cancer cells in the breast, chest wall or axilla. It is used to prevent regrowth of breast cancer at the original site and to avoid the need for mastectomy. In Nigeria, radiotherapy has become an important modality alone or in conjunction with surgery or chemotherapy in the treatment of cancers (Olasinde and Dawotola, 2004). Recent clinical trials indicate that post mastectomy radiation therapy may significantly reduce both 5-year recurrence and 15-year mortality rates in women with early stage cancer. (Ragaz *et al*, 1997).

Radiotherapy can be used before surgery (neo-adjuvant therapy) to shrink the size of a tumor before operating. In cases of advanced breast cancer, radiation therapy is also used to

relieve pain and other symptoms without altering the course of the disease. A new technique called hyperthermia may be used in combination with radiation therapy. Hyperthermia (thermal heating) involves heating cancer cells to a high temperature using ultrasound or microwave as energy source, to make cancer cells more sensitive to radiation.

Types of radiation therapy

i) External beam radiation (EBRT) – High energy x-rays are delivered from an external source (for example a linear accelerator) to target the area affected by the cancer with minimal impact on adjacent tissues. The whole breast is irradiated with or without the chest wall and axilla. Radiation therapy is usually administered 5 times a week for 5 to 7 weeks. The treatments are free from pain and may last about 30 minutes or less.

A newer technique called three-dimensional conformal radiotherapy (3DRCT) has been developed. The technique reduces the amount of radiation to surrounding healthy tissues using three dimensional computer images to develop complex plans for the delivery of highly focused beams. The technique has the advantage of allowing for the treatment of breast tumor considered too close to vital organs and structures for conventional radiotherapy.

Accelerated partial breast irradiation (APBI) is another new technique that limits the exposure of healthy tissues to radiation and reduces the total time required to receive radiation therapy.

ii) Internal radiation – Internal radiation involves the placement of a radioactive source in form of pellets or seeds inside the body to kill cancer cells. Radioisotopes are implanted directly into the breast tissue close to the site of the surgical removal or into the tumor

mass. This procedure is also called brachytherapy. Treatment using radiotherapy is individualized, depending on the physicians' decision and can be administered in different treatment sequences. Examples of treatment sequences include:

Surgery ----- Radiation ----- Hormonal therapy

Surgery -----Chemotherapy ----- Hormonal therapy

Chemotherapy/ targeted therapy/ hormonal therapy -----Surgery -----

Radiotherapy

The size of the cancer, type of surgery carried out, involvement of lymph nodes are factors that influence the amount of radiation to be given to a breast area.

Radiotherapy is associated with many side effects. Possible long-term side effects, which can occur after 6 months, are telangiectasia (appearance of little red thread like blood vessels on the site of irradiation), change in size and texture of the treated breast and sun burn like changes in the skin. Short-term side effects are tiredness, loss of appetite, moistness and breast soreness. Radiation therapy should not be used in pregnant women, in women who have already had radiation to the same part of the body or have connective tissue disease.

2.10.3 Chemotherapy

Chemotherapy is a systemic mode of treatment that uses cytotoxic drugs (cancer killing drugs) to kill and prevent the growth of cancer cells. The drugs may be administered orally, intramuscularly, subcutaneously, intravenously or through a port or catheter. Chemotherapy can be used as adjuvant, neo-adjuvant or palliative therapy. Therapy is administered in

cycles with each period of treatment followed by a recovery period and treatment may last several months (ACS, 2009).

Adjuvant Chemotherapy – Adjuvant chemotherapy is given after surgery to reduce the risk of recurrence of cancer. Surgery is used to remove all of the cancer cells that can be seen, while adjuvant chemotherapy is used to kill any cancer cells that may have been left behind after surgery and was not detected (ACS, 2009). Randomized trials have shown improved survival with the use of adjuvant chemotherapy after surgery. Young age at presentation, pathological tumor size of more than 2cm, high grade of tumor, presence of peri-tumoral vascular invasion, positive axillary lymph nodes, hormone negative tumors and over expression or amplification of the HER2/neu gene are indicators for adjuvant chemotherapy (Tsang, 2008). Both chemotherapy and hormonal therapy can be used as adjuvant chemotherapy.

Neo- adjuvant chemotherapy – Chemotherapy given before surgery to shrink the size of the tumor so that they are small enough to be removed by lumpectomy is called neo-adjuvant chemotherapy. Here physicians are able to observe how cancer responds to chemotherapy and assess the need for drug change if necessary.

Palliative chemotherapy – In this case, chemotherapy is used to control but not cure cancer in situations where cancer has spread beyond the breast and localized lymph nodes.

Dense dose chemotherapy – Involves giving cycles of chemotherapy close together, including a growth factor to help boost the white blood cell count to ensure that the white blood cell count returns to normal in time for the next cycle. This approach has more side effects but tumors shrink more and it is associated with less risk of recurrence.

Factors to consider when choosing chemotherapy regimen:

- i. Characteristics of the cancer – i.e. cancer stage, hormone receptor status, HER2/neu status and lymph node status.
- ii. Menopausal status
- iii. General health (presence of any co morbid illness)

According to the American Cancer Society, 2009, chemotherapy is given in cycles with each period of treatment followed by a rest period. Time interval between administering each cycle of therapy is generally 2-3 weeks, but varies according to the specific drugs used (Epinosa *et al*, 2003).

2.10.3.1 *Classification of Anticancer Drugs*

Anticancer drugs can be classified using different criteria which include:

Classification according to biochemistry mechanism of anticancer action:

Block nucleic acid (RNA, DNA) biosynthesis (antimetabolites)

Folic acid antagonists – Inhibit dihydrofolate reductase e.g. methotrexate

Pyrimidine antagonists – i) Inhibit thymidylate synthetase e.g. 5 – fluorouracil

ii) Inhibit DNA polymerase e.g. cytarabine

Purine antagonists – Inhibit interconversion of purine nucleotide e.g. mercaptopurine

Ribonucleotide diphosphate reductase antagonists – e.g. hydroxyurea

Interfere with protein synthesis

Antitubulin – vinca alkaloids, taxanes

Interfere with function of ribosome – harringtonines

Influence amino acid supply – l-aspariginase

Interfere with transcription and block RNA synthesis

Bind with DNA to block RNA production – doxorubicin

Interfere with structure and function of DNA

Alkylating agents– cyclophosphamide, thiotepa

Platinum complexes – cisplatin

Antibiotics – bleomycin, mitomycin

Topoisomerase inhibitors – camptothecine, podophyllotoxin

Influence hormone homeostasis

Drugs influence hormone homeostasis by binding to the receptors to block the actions of the sex hormones thereby inhibiting tumor growth. They are:

Estrogen and estrogen antagonists

Androgen and androgen antagonists

Progestogens

Glucocorticoid drugs

Gonadotropin releasing hormone inhibitor – leuprolide, goserelin

Aromatase inhibitor - aminoglutemide (Epinosa et al, 2003).

According to the cycle or phase specificity of the drug:

Cycle of cell replication involves 4 phases, the M phase (mitosis phase), the G1 phase (Gap 1 period before S phase that precedes DNA synthesis), the S phase (DNA synthesis phase) and G2 phase (Gap 2 period after S phase, interval following termination of DNA synthesis).

Cell cycle non-specific drugs are drugs that are active throughout the cell cycle and they are alkylating agents, platinum compounds and antibiotics. While the cell cycle specific drugs are those drugs that act during specific phase of the cell cycle. Examples include S phase specific drugs (antimetabolites, topoisomerase inhibitors), M phase specific drugs (vinca alkaloids, taxanes) and G2 phase specific drugs (bleomycin).

Alkylating agents – These agents bind irreversibly with the nucleic acids and thus interfere with DNA synthesis and cell division. After alkylation, DNA is unable to replicate and therefore can no longer synthesize proteins and other essential cell metabolites. This ultimately leads to cell death. They may be bifunctional, in which case cytotoxic effects predominate or monofunctional, with greater capacity for mutagenesis and carcinogenesis.

Alkylating agents include:

Nitrogen mustards – Cyclophosphamide, Ifosfamide, Chlorambucil, Melphalan

Ethyleneimine and methylamine – Altretamine, Thiotepa

Alkyl sulfonates – Busulfan

Nitrosoureas – Streptozocin, Carmustine, Lomustine

Triazines – Darcabazine, Temozolamide

Toxicities of alkylating agents

Bone marrow toxicity – acute myelosuppression, bone marrow depression,

Mucosal toxicity – mucosal ulceration, intestinal denudation

Neurotoxicity – nausea, vomiting, altered mental status, coma, generalized seizures, cerebellar ataxia.

Others are veno-occlusive disease, renal failure, alopecia, nephrotoxicity, irreversible azoospermia in men, pulmonary fibrosis. (Volpea and Warrenb, 2003).

Antimetabolites –

Antimetabolites have structures similar to that of some vitamins and amino acids, which are precursors of DNA, or RNA found naturally in the human body. They interfere with DNA and RNA synthesis by substituting for these precursors (building blocks) of DNA and RNA causing damage to the cells in the S phase. Examples include:

i. Folic acid analogues –

These act by inhibiting the enzyme dihydrofolate reductase (DHFR), responsible for the synthesis of thymidylate and purines (precursors of DNA). Folate antagonists kill cells during the S phase of the cell cycle and are most effective when the cells are rapidly proliferating. Examples are methotrexate, raltitrexed, and pemetrexed.

Toxicities of folic acid analogues include thrombocytopenia, hepatic fibrosis, seizures, coma, alopecia, dermatitis, nephrotoxicity, nausea, diarrhoea and myelosuppression.

ii. Pyrimidine analogs –

This class of drugs inhibits the synthesis of essential precursors of DNA. Examples include 5-fluorouracil, cytarabine, gemcitabine and capecitabine.

5- FU inhibits thymidylate synthetase preventing the synthesis of thymidine triphosphate, a major building block of DNA. It may also be incorporated into RNA by RNA polymerase

to interfere with RNA function. Adverse effects of 5-FU include nausea, vomiting, myelosuppression, oral and gastrointestinal ulceration.

Gemcitabine is a deoxycytidine antimetabolite that is incorporated into DNA strands to inhibit both DNA replication and repair.

Cytarabine is a potent inducer of tumor cell differentiation. Fragmentation of DNA and evidence of apoptosis is seen in treated cells. Toxicities of cytarabine are nausea, acute myelosuppression, stomatitis and alopecia (Epinosa et al, 2003).

iii. Purine antagonists -

Purine analogues inhibit the first step in the synthesis of purine bases. The 6 thiopurine analogs: 6-mercaptopurine and 6-thioguanine inhibit the first step in the de novo synthesis of purine bases. Principal toxicity of 6-mercaptopurine is bone marrow depression; others are thrombocytopenia, granulocytopenia, anorexia, nausea or vomiting.

Fludarabine phosphate inhibits DNA polymerase, DNA primase, DNA ligase and ribonucleotide reductase. The drug also inhibits RNA function, RNA processing and mRNA translation.

Cladribine on the other hand produces DNA strand breaks, depletion of essential enzymes as well as apoptosis. It is also a potent inhibitor of ribonucleotide reductase.

Antimitotic agents-

Mitotic inhibitors include naturally occurring compounds like plant alkaloids. These drugs are not only active during the M phase of the cell cycle, they also damage cells in all phases. They also inhibit enzymes from producing proteins needed for cell reproduction.

i. Vinca alkaloids –

Vinblastine, vincristine, vindesine and vinorelbine are cell cycle specific agents that bind to microtubular protein in a dimeric form to block its ability to polymerize with alpha tubulin into microtubules. Cell division is arrested in the late G2 phase and the cells undergo changes characteristic of apoptosis. Toxicities include nausea, vomiting, myelosuppression, alopecia, muscle weakness, peripheral neuritis, granulocytopenia, and leukopenia (Takimoto and Calvo, 2008).

ii. Taxanes –

Paclitaxel and docetaxel are mitotic spindle poisons. They bind specifically to the beta tubulin subunit of microtubules preventing their disassembly and stopping mitosis. Toxic effects are neutropaenia, mucositis, peripheral neuropathy, asthenia and hypersensitivity reactions (Ferguson *et al*, 2007).

iii. Epothilones - Ixabepilone

iv. Erasmustine

Camptothecin analogs –

These are inhibitors of the nuclear enzyme topoisomerase I and II, therefore preventing DNA strand breakage and resealing. In other words they interfere with DNA transcription,

replication and function to prevent DNA supercoiling. This results in the accumulation of single-stranded breaks in DNA. Examples of topoisomerase I include topotecan and irinotecan. Topoisomerase II inhibitors include etoposide and teniposide. Toxicities are dose-limiting and include neutropaenia, mucositis, diarrhea, myelosuppression, fever, fatigue, rash, hypersalivation, abdominal cramps and rhinorrhea (Kehrer *et al*, 2001).

Antibiotics – Antibiotics used in cancer chemotherapy include:

i. Anthracyclines (Doxorubicin and Daunorubicin) – Have high affinity for binding to DNA through intercalation, resulting in blockade of DNA and RNA synthesis. Agents are primarily toxic during the S phase of the cell cycle. Toxic manifestations include anorexia, nausea, vomiting, alopecia, desquamation, bone marrow depression and cardiac toxicity.

ii. Dactinomycin – Binds to double stranded RNA through intercalation between adjacent guanine-cytosine base pairs, thus inhibiting all forms of DNA-dependent RNA synthesis. Side effects of dactinomycin are bone marrow depression, oral ulcers, skin eruptions and immunosuppression.

iii. Mitomycin – Bio reductive alkylating agent that undergoes metabolic reductive activation through an enzyme-mediated reduction to generate an alkylating agent that cross links DNA. Once DNA is cross linked strand breakage occurs and DNA synthesis is inhibited. Mitomycin is associated with severe myelosuppression, renal toxicity and intestinal pneumonitis.

iv. Bleomycin – Binds to DNA resulting in single and double strand breaks following free radical formation and inhibition of DNA synthesis. It is a cell cycle specific drug that

causes accumulation of cells in G2 phase. It is associated with pulmonary fibrosis and blistering.

Other antibiotics include: pirarubicin, idarubicin, and epirubicin. (Lord *et al*, 2004).

Etoposide and teniposide derivatives of podophyllotoxin are similar in action; they form tertiary complexes with topoisomerase II and DNA, preventing resealing, leading to an accumulation of DNA breaks and cell death. They are effective in the G1 and S phase of the cell cycle. Clinical toxicities are leukopenia, thrombocytopenia, alopecia, phlebitis and anaphylaxis (Smith *et al*, 1999).

Enzymes – L-asparaginase used with other agents like methotrexate, vincristine and doxorubicin deprives malignant cells of asparagine necessary for protein synthesis leading to cell death (Schwartz, 1973). It has minimal toxic effects on bone marrow and gastrointestinal mucosa. Hypersensitivity reactions may occur including hyperglycemia, hypoalbuminemia and thrombosis.

Miscellaneous agents –

Hydroxyurea

Differentiating agents – retinoids, arsenic trioxide which act on cancer cells to make them mature into normal cells.

Protein kinase inhibitors – imatinib, gefitinib, erlotinib

Corticosteroids – Though not considered chemotherapy are used commonly to help prevent nausea and vomiting caused by chemotherapy. They can also be used before chemotherapy

to help prevent hypersensitivity reactions. Examples include dexamethasone and prednisone (Wooldridge *et al*, 2001).

2.10.4 Hormone Therapy

Also called endocrine therapy; uses drugs to remove hormones or block the action of hormones that promote the growth of cancer cells. These drugs act by interfering with the actions of estrogen and progesterone, which stimulate the growth of certain types of breast cancer cells. Therefore, hormone therapy is only effective in treating women whose cancers are estrogen and progesterone receptor positive. These drugs can either lower the amount of estrogen in the body or block the action of the hormones on breast cancer cells.

Hormone therapy can be used alone, in combination or sequentially with surgery, radiotherapy and even chemotherapy. The various types of hormone therapy are:

Selective estrogen receptor modulators (SERM's) – These anti-estrogens selectively bind to estrogen receptors and thereby block the effects of estrogen in the tissues. When these drugs bind to the estrogen receptors there is no room for estrogen to bind therefore cancer cells which rely on these hormones for their growth and multiplication cannot perform these functions. Examples are tamoxifen (Nolvadex), raloxifen (Evista) and toremifene (Farestin). SERM's are beneficial in treating both pre and post menopausal women. They also decrease the likelihood of breast cancer in women at high risk. Side effects of these anti-estrogens are: hot flushes, fatigue, night sweats, vaginal discharge, mood swings, blood clots, stroke and endometrial cancer. Raloxifene has been found to be an effective alternative to tamoxifen for post menopausal women with increased risk for breast cancer (Fryar, 2006).

Selective estrogen receptor down regulators (SERD's) – These are drugs that act by binding to the estrogen receptors of the cells to interfere with the process of cell proliferation. They also reduce the number of estrogen receptors and change their shape so that the receptors are not recognized by the hormones. An example is fulvestrant (Faslodex) which is frequently used to treat post menopausal women with advanced breast cancer unresponsive to tamoxifen.

Aromatase inhibitors – Aromatase inhibitors stop the production of estrogen in postmenopausal women by blocking the enzyme aromatase which converts androgens into estrogen. Less estrogen is therefore available to stimulate the growth of hormone receptor-positive breast cancer cells. These classes of drugs are not effective in premenopausal women as they cannot prevent their ovaries from producing estrogen. In postmenopausal women aromatase inhibitors can be used either as initial treatment or after tamoxifen. It has superior efficacy and tolerability to tamoxifen and megestrol in the treatment of advanced breast cancer (Tobias, 2004). Side effects associated with SERD's are joint and muscle pain. Long term use may cause osteoporosis. Examples include anastrozole (Arimidex), exemestane (Aromasin) and Letrozole (Femara).

Ovarian ablation – The hormone estrogen is usually produced by the ovaries in premenopausal women. Hence, hormone receptor positive breast cancers tend to grow more in such situations. Reducing the amount of estrogen in the body or blocking its action can thus help shrink hormone receptor positive breast cancer and reduce the risk of recurrence. The ovaries can also be surgically removed (prophylactic oophorectomy) to stop them from producing estrogen. Drugs such as luteinizing hormone releasing hormone (LHRH) agonists can also be used to suppress ovarian production of estrogen e.g. goserelin

(Zoladex) and leuprolide (Lupron). Hot flushes, decreased sexual desire, amenorrhea and vaginal discharge are part of the side effects associated with these drugs. Prophylactic ovary removal before menopause can reduce the number of new breast cancer cases among high risk women by 50% (NCI, 2005 and Clarke *et al*, 2006).

Progestin – megestrol (Megace) very useful in treating women with metastatic advanced breast cancer when treatment with tamoxifen or anastrozole has failed. Side effects include fluid retention and weight gain.

Glucocorticoids – dexamethasone and prednisone for example play a valuable role in fighting cancers. They produce remissions more rapidly than the antimetabolites.

2.10.5 Biological therapy

Also known as targeted or biological response modifier therapy. It is directed at specific targets in the body (cellular receptors, proteins and enzyme systems) to help fight cancer.

Examples include interferon-alpha, interleukin-2, imatinib, gefitinib, erlotinib and sunitinib.

2.10.6 Immunotherapy

This is a relatively new method of treatment where drugs are administered to people with cancer to stimulate their immune system to effectively recognize and attack cancer cells.

Active immunotherapy stimulates the immune system of the body to fight the disease, while passive immunotherapies use immune system components outside the body. Types of immunotherapies include:

Monoclonal antibody: example trastuzumab, rituximab

Non-specific immunotherapies and adjuvant: interleukin-2, interferon-alpha

Immunomodulating drugs: thalidomide, lenalidomide

Cancer vaccines represent an emerging type of biological therapy that is still mostly experimental (ACS, 2011).

2.11 PROBLEMS WITH CANCER CHEMOTHERAPY

Drug resistance – This can be further divided into:

De novo resistance – which arises because drugs are unable to reach the target cells due to permeability barriers like the blood-brain barrier or de novo genetics where the cells are initially inherently resistant.

Acquired resistance – may result from genomic mutations such as the induction or deletion of enzymes involved in drug inactivation or drug activation respectively.

Multidrug resistance – may be as a result of the induction of P-glycoprotein which transports many naturally occurring drugs out of neoplastic cells.

Drug toxicity – Common toxicities of antineoplastic drugs result from inhibition of cell replication in the bone marrow, gastrointestinal epithelium, and hair follicles. Many antineoplastic drugs also stimulate the chemoreceptor trigger zone in the medulla and thereby elicit nausea and vomiting.

2.12 MULTIDISCIPLINARY TEAM ROLES IN BREAST CANCER

MANAGEMENT

The multidisciplinary team (MDT) evolved in response to the increasing complexities of patient care, with each discipline contributing particular skills and knowledge for the benefit of the patient (Hall and Weaver, 2001). This has led to numerous centers adopting

the MDT approach with the aim of providing the patient with the best care (Calman and Hine, 1995). Major professions involved in providing multidisciplinary care to patients with cancer are surgery, oncology, pathology, radiology and nursing. It may also include palliative care, psychiatry/psychology, genetics and plastic surgery (NHS Executive, 1999, 2002, 2004). For health care professionals to work effectively with one another there is the need for good team spirit, communication, mutual respect for all members of the health care team and equal value placed on contribution to current team practices (Freeman *et al.*, 2000). According to Miller *et al.*, 2001 the above functions can only be achieved when each member of the team understands the other's contribution to care, and why they practice in the way they do. Multidisciplinary teamwork is expected to benefit both the patients and the members of the health care team.

Landheer *et al.*, (2001) examined the relationship between cancer teams and the quality of care delivered showed that a working multidisciplinary team benefited patients through improved access to, and use of, standardized and up to date therapy. Accomplishment of complex tasks is easier when professionals within the health care teams have clear goals, are cooperative and mutually supportive of one another, and are aware of each others' role (Jenkins *et al.*, 2001). Other studies have also shown the necessity of a multidisciplinary approach for optimizing outcomes in patients with cancer (Van Laetham *et al.*, 2001; Blumberg and Ramanathan, 2002). The composition of the team, working methods and workloads has been shown to be related to the quality of clinical care and the effectiveness of team (Haward *et al.*, 2003). Lack of adequate information between members of a multidisciplinary team can adversely affect the patient. The patient may become confused

about diagnosis, prognosis and future management plans, a situation that can be frustrating and professionally unrewarding to team members (Jenkins *et al*, 2001).

Recognition of patients needs, clarifying responsibility, respect, maintaining good communication and updates are important in setting up a multidisciplinary team (Kataoka *et al.*, 2005). According to Zorbas *et al*, (2003) a multidisciplinary team should comprise of representatives from all the core disciplines, which can include surgery, oncology (radiation and medical oncology), pathology, genetics, psychiatry and supportive care. There should be an effective communication network between team members as well as regular interactive sessions to discuss cases. The size and location of an institution should not affect the delivery of multidisciplinary care services to breast cancer patients. All members of the multidisciplinary team involved in patient care should practice according to specific guidelines, taking into consideration patients' circumstance and wishes. Diagnosed women should be fully informed of her treatment options as well as the benefits, risks and possible complications of treatment offered. Information should be made available to the woman in a form that is appropriate to her educational level, language and culture. A reduction in breast cancer incidence and mortality has also been associated with a multidisciplinary focus that involves prevention, diagnosis and treatment (Pruthi *et al.*, 2007).

2.13 CO-MORBID DISEASES AND BREAST CANCER

Coexisting illness is a significant concern of patients with cancer (Ogle *et al.*, 2000). Co-morbidity can be defined as an illness other than the principal diagnosis that influences the outcome of treatment (Klabunde *et al.*, 2002) or as chronic illnesses which exist simultaneously with and usually independent of another condition. It can also be defined as a disease, disorder or condition that exists with a primary disease but can stand on its own

as a specific disease unrelated to it. Previous studies have shown that cancer will increase the severity and outcome of co-morbid chronic illnesses, which are usually present 5-15 years before a cancer diagnosis (Ogle *et al.*, 2000).

Co-morbidity has been found to predict the survival of women with breast cancer independently of other factors such as stage of cancer at diagnosis (West *et al.*, 1996). Diabetes, stroke and a previous cancer have been found to be among the conditions that predicted early mortality in women with breast cancer (Stariano and Ragland, 1994; Yancik *et al.*, 2001). Fleming *et al.* (2003), reported that women with cardiovascular disease, musculoskeletal disorders, mild to moderate gastrointestinal disease and non malignant benign breast disease, had a 14%, 8%, 16% and 25% lower odd respectively of being diagnosed with advanced breast cancer. Other co-morbidities including diabetes, endocrine disorders, psychiatric disorders and hematological disorders, increased the odds of late stage diagnosis by 18%, 11%, 23% and 20% respectively. Studies previously carried out on breast cancer cases concluded that deaths from non-breast cancer-related co-morbid diseases were approximately as common as breast-cancer-related deaths (Chapman *et al.*, 2008).

2.14 PALLIATIVE CARE

The word palliative is derived from the Latin word “pallium”, to cloak or cover and connotes an action that ameliorates. It also refers to any form of medical care or treatments that concentrate on reducing the severity of disease symptoms rather than striving to halt, delay or reverse progression of the disease itself or provide care. According to World Health Organization, palliative care is an approach that improves the quality of life of patients and their families facing problems associated with life-threatening illness, through

the prevention and relief of suffering, early identification and impeccable assessment and treatment of pain and other problems, psychosocial and spiritual. Palliative care:

Provides relief from pain and other distressing symptoms; affirms life and regards dying as a normal process; intends neither to hasten nor postpone death; integrates both the psychosocial and spiritual aspects of patient care; offers a support system to help patients live as actively as possible until death; offers a support system to help the family cope during the patients illness and in their bereavement; uses a team approach to address the needs of patients and their families, including counseling where indicated; will enhance quality of life, and may also positively influence the course of illness; is applicable early in the course of illness in conjunction with other therapies that can prolong life, such as chemotherapy and radiation therapy.

The palliative care team might include: a palliative care specialist, local general practitioner with skills in palliative care, palliative care nurse, palliative care volunteers and allied health professionals, such as a health professional who specializes in providing advice about what to eat (NBOCC, 2009).

The palliative care team can provide: expert treatment of pain and other symptoms; close, clear communication, help navigating the healthcare system; guide with difficult and complex treatment choices, detailed practical information and assistance, emotional and spiritual support for the patient and family.

Palliative care differs from hospice care in that palliative care may be provided at any time during the person's illness and may be given as curative treatment; hospice care on the other hand focuses on terminally ill individuals who are expected to live for 6 months or

less. Hospice care is aimed at meeting the physical, emotional and spiritual needs of the dying individual while fostering the highest quality of life possible. In the United States, 55% of hospitals with more than 100 bed capacity offer palliative care programs and nearly one-fifth of community hospitals also have such programs (Lynn, 2004). Both hospice and palliative care provide symptom relief and pain management (Hill, 2007). For palliative care to be effective, a multidisciplinary approach that involves the family is necessary. Common palliative care problems include pain, cachexia, asthenia, dyspnoea, malignant bowel obstruction and wound issues, which may necessitate an interdisciplinary approach (Krouse, 2008).

2.15 NATIONAL COMPREHENSIVE CANCER NETWORK (NCCN) CLINICAL PRACTICE GUIDELINES IN ONCOLOGY

The NCCN is a non-profit alliance of 21 of the world's leading cancer centers that is dedicated to improving the quality and effectiveness of care provided to cancer patients. The NCCN clinical practice guidelines in oncology are a set of practice guidelines for oncology which have been developed specifically by oncologists and cover 97% of cancers. These guidelines are updated continually and are used in over 115 countries. The information gathered in the guidelines is based on a review of scientific evidence from oncology trials and studies. The published NCCN Guidelines is composed of three parts, and they include: an algorithm that follows the step-by-step clinical decision-making process; a discussion which reviews the data the recommendations are based on and the issues that were considered by the panel; and a bibliography. Each recommendation is categorized according to both the level of evidence supporting the recommendation and the

degree of consensus among the NCCN Member Institutions that the recommendation is appropriate (NCCN, 2010).

CHAPTER 3

METHODOLOGY

The study was retrospective, involving analysis of data from patients' folders who attended clinic at the Radiotherapy and Oncology Center of Ahmadu Bello University Teaching Hospital (ABUTH) Zaria for the period spanning from 1 January, 2008 to 31 December, 2008. Data was collected between January to February, 2009.

The first stage of data collection involved the use of attendance registers from the records department of the oncology clinic to get the total number of different types of cancers recorded for the specified period. Folder selection criteria included all breast cancer patients who attended the clinic and were at that time receiving chemotherapy, radiotherapy, and/or hormone therapy.

Socio-demographic data which included sex, marital status, age at first visit, ethnicity, state of origin, occupation, place of residence and specific diagnosis were then collected from the folders. A researcher designed data form was used to guide the collection of data on medical history, drug and non-drug management, side effects and their management, laboratory investigations carried out, etc. (Appendix I).

The health care professionals' involved in the management of breast cancer patients were identified and a modified Informational Roles Questionnaire (IRQ) (Jenkins *et al*, 2001) (Appendix II), administered to them. The questionnaire had two parts. The first part measured healthcare professional's perceptions of their own roles and their awareness of their colleagues' roles in providing information to the patient during their treatment and

care. The information areas covered included patient history, examination, ordering for laboratory investigations, discussing diagnosis, choosing management to adopt, surgery, chemotherapy, hormone therapy, radiotherapy, dispensing medication, counseling on side effects, providing palliative care, patient follow up, passing information leaflets and determining of estrogen-progesterone status of the patient.

Healthcare professionals were also asked to indicate whether they and which of their colleagues had a regular role in discussing patient problems in each of the five areas of psychosocial concern: 1) physical well being (pain, side effects, lethargy) 2) functional well being (work, sleeping) 3) sexual well being (attractiveness, personal relationships) 4) psychological well being (depression, anxiety, hope) and 5) social well being (social activities, relationship with family and friends). Professionals who played key roles in their specialty were identified and interviewed for 10 minutes each to get a summary of the roles they felt they played as members of the health care team managing breast cancer patients.

Data obtained were subjected to analysis using statistical package for social scientists SPSS Version 11.5. Analysis included calculation of frequency tables. P-values < 0.05 was taken to be statistically significant. Results were presented in diverse formats such as: mean \pm SEM, percentages, tables and figures.

CHAPTER 4

RESULTS

4.1 RELATIVE OCCURENCE OF BREAST CANCER AND BIO DATA OF STUDY PATIENTS

Table 4.1 shows that breast cancer was the most frequently occurring cancer type (29%) in this study, closely followed by cervical cancer (27%); amongst a list of 17 cancer types. Of the 80 breast cancer patients, only 67 which had commenced treatment were included in the study; one of which was male.

From the study, the age range of breast cancer patients was between 25-80 years with a modal age group of 30-39 years although 40-49 years and 50-59 years also approximated this group – see Figure 4.1.

Fifty-three of the 67 patients (79%) were married; and almost unemployed – see Figure 4.2.

Prevalence by tribe (Table 4.2), state of origin (Table 4.3) and geopolitical zone (Table 4.4) showed that breast cancer was ubiquitous.

Table 4.1 Relative occurrence of breast cancer among cancer patients attending ABUTH Oncology Clinic in 2008

Type of cancer	Frequency	Percent (%)
Breast	80	29
Cervix	76	27
Connective and soft tissues	18	6
Skin melanoma	14	5
Nasopharynx	12	4
Prostate	12	4
Kaposi sarcoma	11	4
Rectum	10	4
Bladder	9	3
Eye and adenexa	8	3
Bone	5	2
Lip	5	2
Brain	4	1
Non Hodgkin's Lymphoma	4	1
Oropharynx	4	1
Palate	4	1
Hodgkin's	3	1
Total	279	100

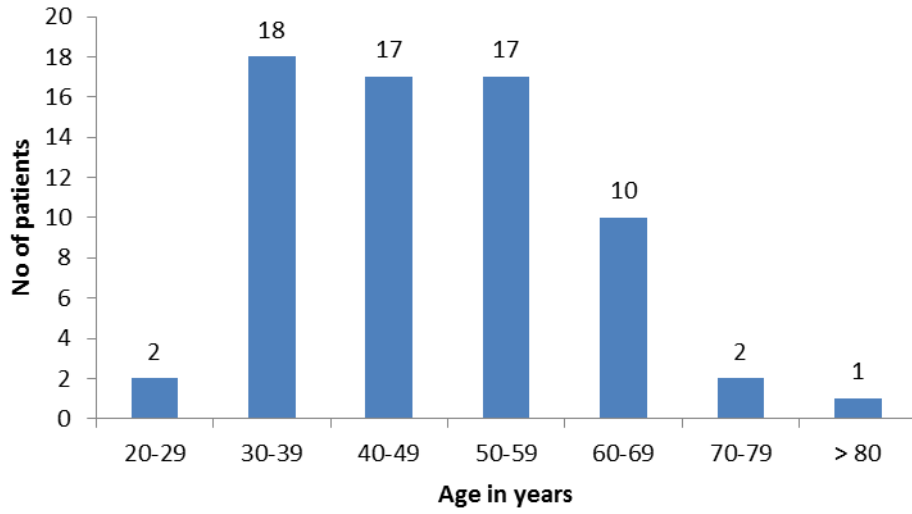


Figure 4.1: Age distribution of breast cancer patients attending the Oncology Clinic in 2008

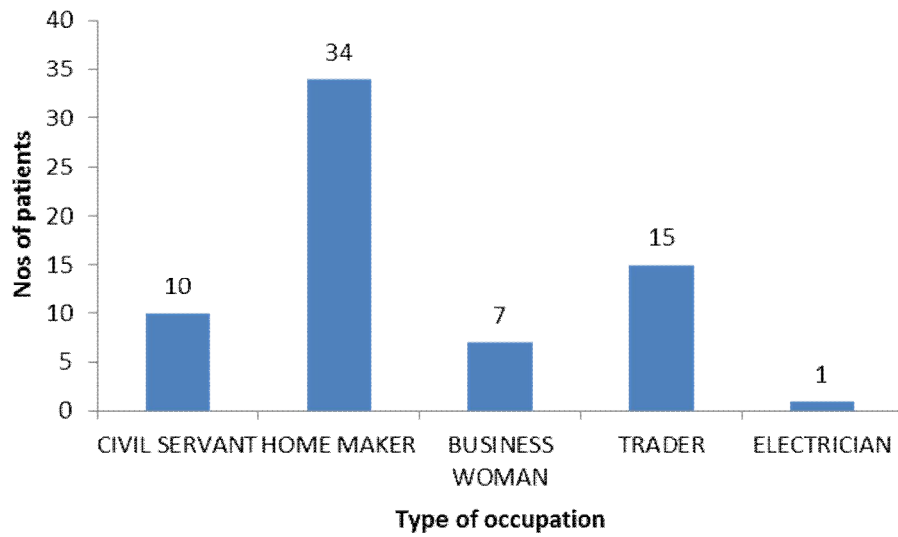


Figure 4.2: Occupation of breast cancer patients who attended the clinic

Table 4.2 Prevalence by tribe

Tribe	Frequency	Percent (%)	Cumulative percent (%)
Others	34	51	51
Ibo	18	27	78
Hausa	11	16	94
Yoruba	4	6	100
Total	67	100	

Table 4.3 Prevalence by state of origin

State of origin	Frequency	Percent (%)	Cumulative percent (%)
Kogi	9	13.4	13
Kano	6	9	22.4
Imo	5	7.5	29.9
Kaduna	5	7.5	37.4
Niger	5	7.5	44.9
Abia	4	6	50.9
Anambra	4	6	56.9
Edo	4	6	62.9
Not recorded	4	6	68.9
Benue	3	4	72.9
Enugu	3	4	76.9
Delta	2	3	79.9
Nassarawa	2	3	82.9
Taraba	2	3	85.9
Bauchi	1	1.5	87.4
Cross River	1	1.5	88.9
Gombe	1	1.5	90.4
Katsina	1	1.5	91.9
Kwara	1	1.5	93.4
Plateau	1	1.5	94.9
Rivers	1	1.5	96.4
Sokoto	1	1.5	97.9
Zamfara	1	1.5	99.9
Total	67		

Table 4.4 Prevalence by geopolitical zone

Geopolitical zone	Frequency	Percent (%)	Cumulative percent (100%)	Remarks
North central	26	39	39	North=39 (58%)
North east	4	6	45	
North west	9	13	58	
South east	16	24	82	South=28 (42%)
South south	8	12	94	
Not recorded	4	6	100	
Total	67			

4.2 PREDISPOSING FACTORS

Only 24% of the patients had records indicating family history of cancer, of which a relatively large number (62.5%) occurred in a first degree biological relative (sister and mother) or a second degree relative (grandmother, niece and cousin) – 37.5%.

About 68% of the patients had had a previous lump and or cancer – Figure 4.3.

Figure 4.4 shows that 51.5% of the patients were premenopausal while 43.9% were postmenopausal. Of the postmenopausal group, the majority (66.7%) attained menopause before the age of 50 years (Table 4.5).

Table 4.6 shows the ages at which menarche commenced and corresponding frequencies obtained from the study.

Mean age at first full term pregnancy was found to be 22.05 ± 0.69 years for the 37 patients for which this data was available (Figure 4.5). Nearly half of the patients (45.9%) had their first full term pregnancy between 20-24 years; while an additional (27%) had theirs between 25-29 years. Figure 4.6 shows the number of full term pregnancies and their corresponding frequency of occurrence.

Of the 39 women whose breastfeeding of their children was recorded, 36 (92%) had breastfed their children – Figure 4.7.

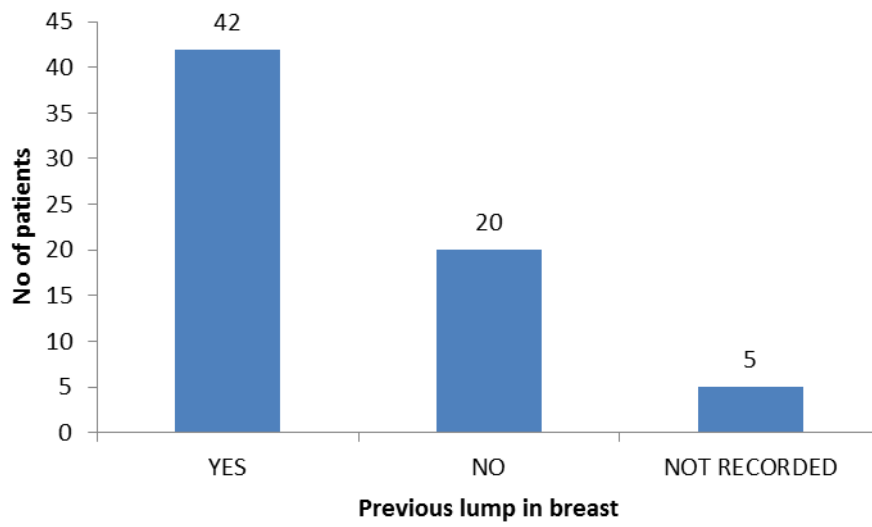
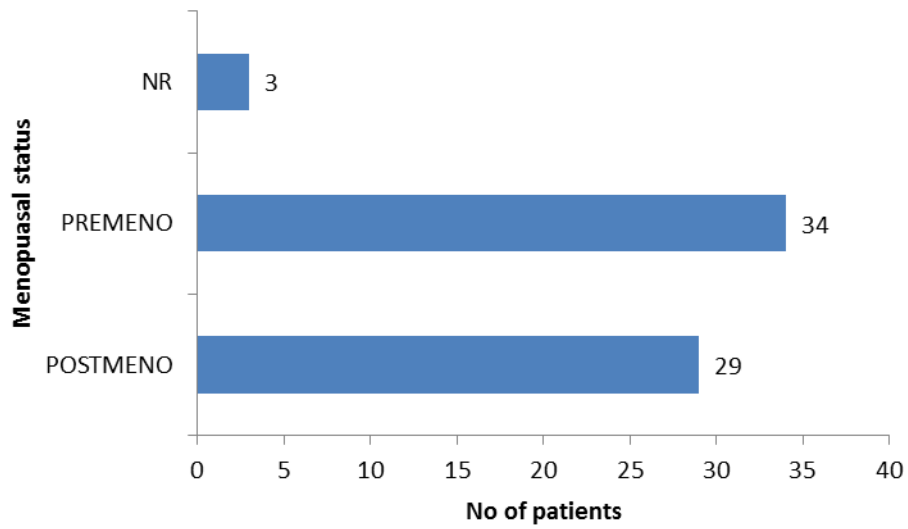


Figure 4.3: Presence of previous lump in the breast



NR – Not recorded PREMENO – premenopausal POSTMENO – postmenopausal

Figure 4.4: Number of patients' pre and postmenopausal

Table 4.5 Age distribution at which menopause commenced

Age (Years)	Frequency	Percent (%)	Cumulative percent (%)
< 40	2	3	3
40-49	18	27	30
> 50	10	15	45
Not recorded	36	55	100
Total	66		100

Table 4.6 Age at first menarche

Age (Years)	Frequency	Percent (%)	Cumulative percent (%)
8	1	1.5	1.5
12	2	3.03	4.53
13	5	7.57	12.1
14	5	7.57	19.67
15	6	9.09	28.76
17	1	1.5	30.26
18	2	3.03	33.29
19	1	1.5	34.79
20	1	1.5	36.29
Not recorded	42	63.6	99.89
Total	66		

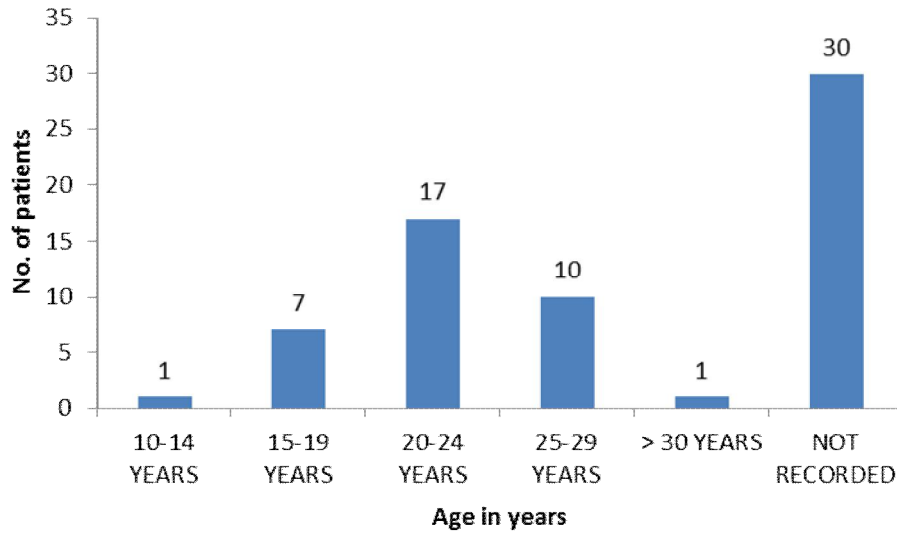


Figure 4.5: Age distribution at first full term pregnancy

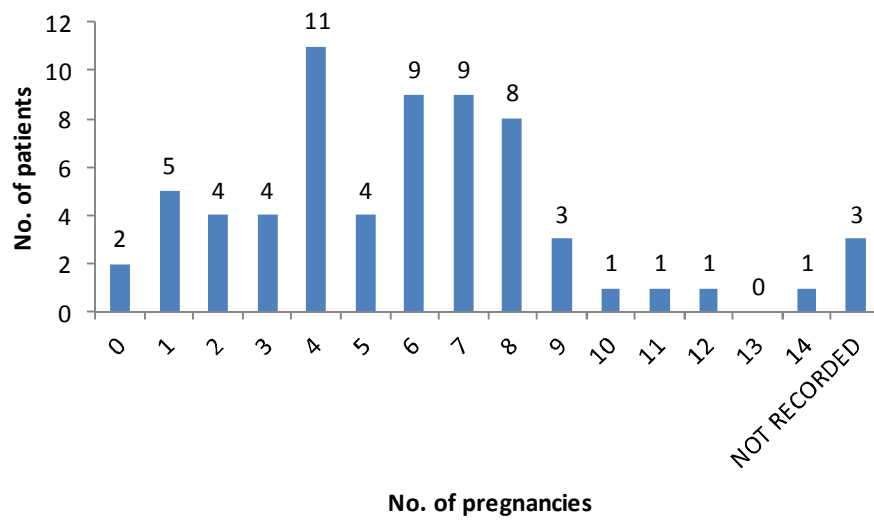


Figure 4.6: Number of full term pregnancies

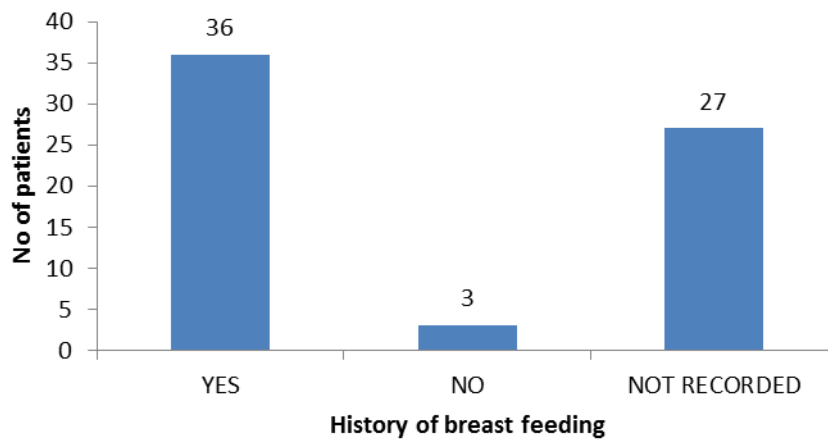


Figure 4.7: History of breast feeding

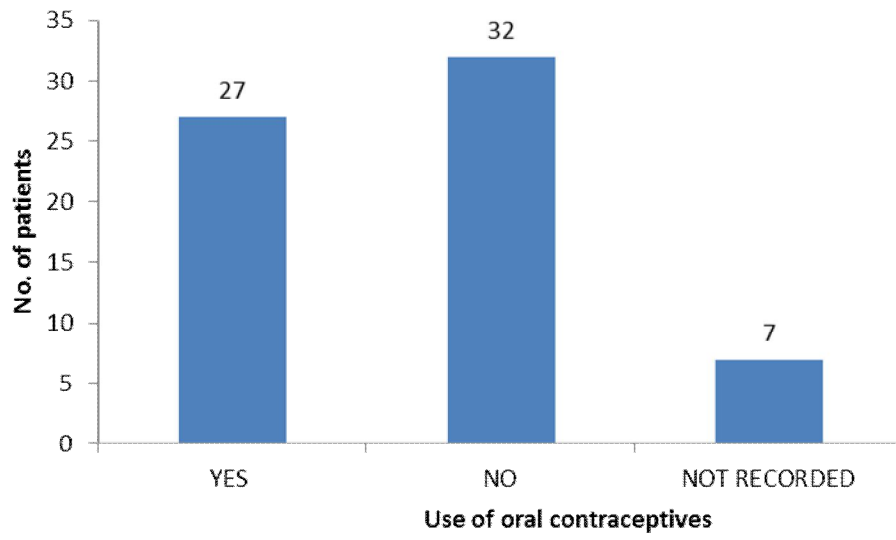


Figure 4.8: History of using oral contraceptives

Table 4.7 Types of contraceptives used

Type	Frequency	Percent	
		(%)	Cumulative percent
Norestirat	8	12	22.5
Pills	7	10	36.5
Copper T Intrauterine Device (IUD)	5	7.5	7.5
Diaphragm	3	4	26.5
Depoprovera	2	3	10.5
Not recorded	41	61	100

4.3 CO-MORBIDITY, DIAGNOSIS AND LABORATORY INVESTIGATIONS

Co-morbid illnesses were present in 49% of the patients (Figure 4.9), the most common of which was hypertension. Other co-morbid illnesses were hypertension plus diabetes, hypertensive cholelithiasis, diabetes, arthritis, cholelithiasis, asthma, goiter, fibroids, HIV/AIDS and depression.

Data regarding side of the breast affected revealed that more of the cancers occurred in the right breast (50.7%), while 41.8% occurred in the left breast and 7.4% of the patients had bilateral breast cancer.

Biopsy was the most common diagnostic procedure used (Figure 4.10). A fine needle aspiration biopsy was carried out in 98% of the patients; mammography was done in 18% of the patients, while 7.5% had a breast ultrasound.

Signs and symptoms frequently reported included lump in the breast 62 (93%) patients, breast pain 25 (37%), change in breast size 18(27%), breast discharge 11 (16%), and ulceration 10 (15%). Other symptoms included inverted nipples, peau de'orange, bleeding, back pain, puckered breast, chest pain, weight loss, fever, loss of appetite, hot sensation in the breast, pain in the armpit and neck (Table 4.8).

Invasive ductal carcinoma was the most frequently diagnosed type of breast cancer (76%), while infiltrating ductal carcinoma (10%), metastatic ductal carcinoma (6%), and invasive lobular carcinoma (4%), advanced metastatic and medullary carcinoma 1.5% each were also reported – Figure 4.11.

Analysis of the data on laboratory investigations revealed that WBC and differentials, liver function tests, chest x- ray and serum, creatinine and electrolyte were frequently requested for in all the patients. Other laboratory investigations that were frequently requested for included; ultrasound, widal test, urinalysis, retroviral screening, electrocardiogram, calcium phosphate and fasting blood sugar (Table 4.9).

4.4 DRUG MANAGEMENT

Analysis of the data on anticancer regimen showed that majority of the patients 29 (43%) were placed on Cyclophosphamide/Adriamycin/Fluorouracil (CAF) regimen, 13 (19%) were placed on gemtricitabine and paclitaxel, 7 (10%) received Cyclophosphamide/Epirubicin/Fluorouracil (CEF) regimen, 5 (7%) of the patients received Cyclophosphamide/Methotrexate/Fluorouracil (CMF) regimen and 3 (4.4%) were administered a combination of capecitabine and paclitaxel (Figure 4.12).

Majority 50 (83%) of the patients were given tamoxifen, while the others were given newer hormonal drugs; anastrozole and exemestane (17%) (Table 4.10).

Haematinics (mainly ferrous sulphate) were the most frequently prescribed non anti-cancer drug (91%). Metoclopramide and hydrocortisone were administered to 39 (58%) patients each. Thirty-two patients (48%) received dexamethasone. See table 4.11.

The most frequently prescribed analgesic was tramadol 25 (37%), followed by diclofenac sodium 20 (30%) and morphine 14 (21%). Other analgesics prescribed included; pethidine, dihydrocodeine, pentazocine, ibuprofen and paracetamol. Table 4.12

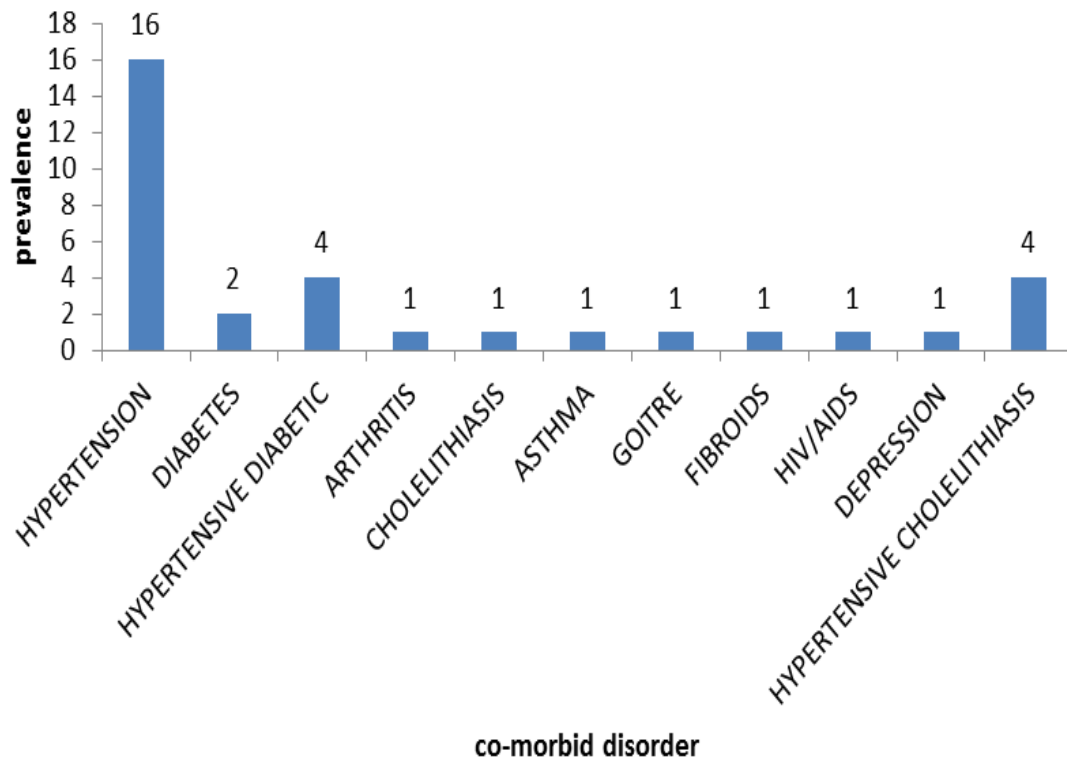


Figure 4.9: Prevalence of co morbid disorder

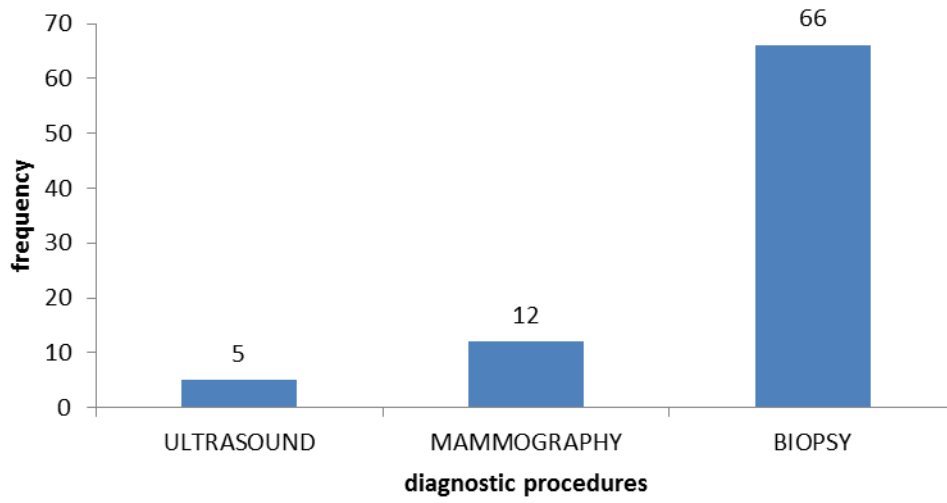


Figure 4.10: Frequency of diagnostic procedure used

**Table 4.8 Signs and symptoms
in breast cancer patients**

Signs/Symptoms	Frequency	Percent (%)
Lump	62	93
Headache	2	3
Breast pain	25	37
Inverted nipples	7	10
Breast discharge	11	16
Bleeding	6	9
Puckered breast	3	4
Breast tenderness	7	10
Change in breast size	18	27
Ulceration	10	15
Peau de'orange	6	9
Back pain	5	7
Chest pain	4	6
Weight loss	4	6
Difficulty in walking	3	4
Fever	2	3
Lymphadenopathy	9	13
Loss of appetite, dyspnoea, hot sensation in the breast, pain in armpit and neck	1	1.5

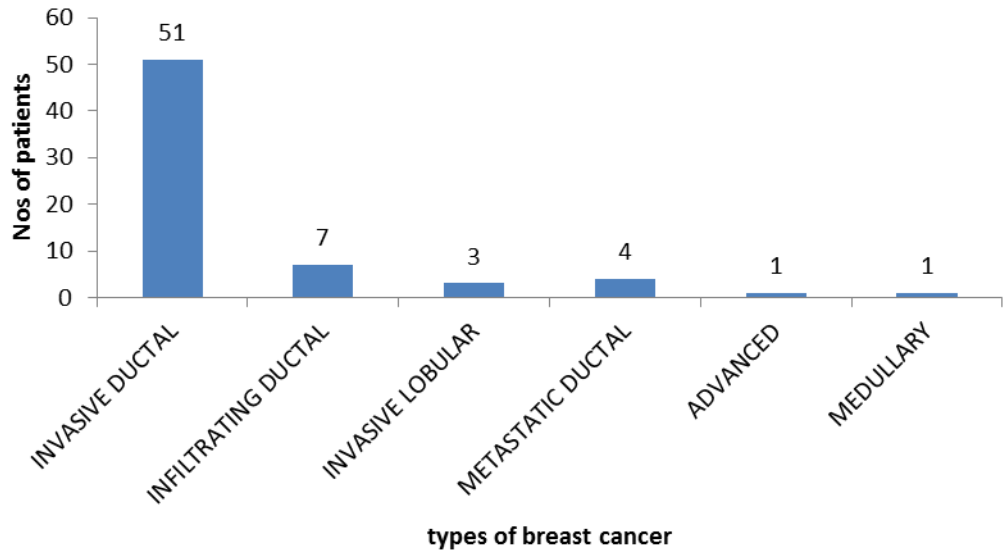
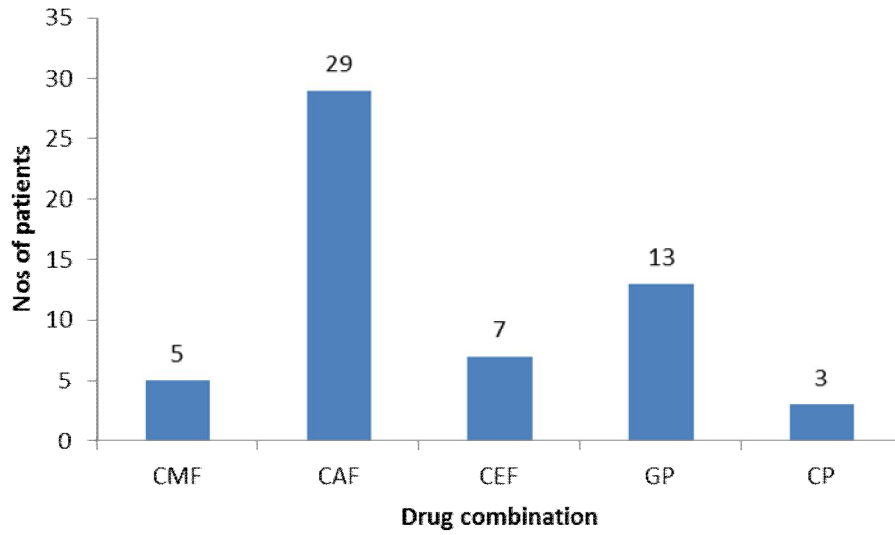


Figure 4.11: Types of breast cancer diagnosed and frequency

Table 4.9 Laboratory investigations carried out

Investigation	Frequency	Percent (%)
WBC and differentials	67	100
Liver function test	67	100
Chest x-ray	67	100
Serum, creatinine and electrolyte	67	100
Abdominal- pelvic ultrasound	46	69
Calcium phosphate	40	60
Retroviral screening	35	52
Electrocardiogram	26	39
Fasting blood sugar	21	31
Urinalysis	19	28
Widal test	4	6



CMF - Cyclophosphamide/Methotrexate/Fluoro-uracil

CAF - Cyclophosphamide/Adriamycin/Fluoro-uracil

CEF - Cyclophosphamide/Epirubicin/Fluoro-uracil

GP - Gemtricitabine/Paclitaxel

CP - Capecitabine/Paclitaxel

Figure 4.12: Frequency of chemotherapy regimen used

Table 4.10 Hormonal drugs used

Drug	Frequency	Percent (%)
Exemestane	7	10
Anastrozole	3	4
Tamoxifen	50	75

Table 4.11 : Non anti-cancer drugs used

Non anti-cancer drugs	Frequency	Percent (%)
Haematinics	61	91.0
Hydrocortisone	39	58.0
Metoclopramide	39	58.0
Dexamethasone	32	48.0
Augmentin	10	15.0
Ampiclox	9	13.4
Coartem	7	10.0
Gestid suspension	6	9.0
Ciprofloxacin	5	7.5
Nifedipine	5	7.5
Metformin	4	6.0
Aldomet	3	4.5
Daonil	3	4.0
Cimetidine	3	4.0
Promethazine	3	4.0
Bendrofluazide	3	4.0
Moduretic	3	4.0
Loratidine	2	3.0
Cough syrup	2	3.0
Ranitidine	2	3.0
Amitryptiline	1	1.5
Diazepam	1	1.5
Prednisolone	1	1.5
Ofloxacin	1	1.5

Table 4.12 Types of analgesics used for pain

Analgesic	Frequency	Percent (%)
Tramadol	25	37
Cataflam	20	30
Morphine	14	21
Pethidine	9	13
Dihydrocodeine	7	10
Pentazocine	7	10
Ibuprofen	5	7
Paracetamol	2	3

4.5 SIDE EFFECTS OF CHEMOTHERAPY AND RADIOTHERAPY

Vomiting was the commonest side effect (56.7%), observed in the study, followed by rib/ chest pain (30%), cough (28.3 %), and anemia (26.9%). See table 4.13.

Table 4.13 Prevalence of side effects observed with Chemotherapy and Radiotherapy

Side effects	Frequency	Percent (%)
Vomiting	38	56.7
Rib/ chest pain	20	30.0
Cough	19	28.3
Anemia	18	26.9
Thrombocytopenia	9	13.4
Headache	7	10.4
Thrombophlebitis	7	10.4
Skin desquamation	5	7.5
Drug induced menopause	5	7.5
Pin prick sensation	3	4.5
Leucopenia	3	4.8
Alopecia	3	4.8
Skin darkening	2	3.0
Pericarditis	1	1.5
Fever	1	1.5
Sore throat	1	1.5

4.5 INTERRUPTION OF DRUG USE

Treatment at one point or the other was interrupted or discontinued in majority of the patients (82%). Reasons for this included; financial (22%), no space on cobalt machine (16%), faulty machine (10%), absence of physicist (7%) and no known reason (25%) – Table 4.14. Drug regimen was changed in 11 (16.4%) of the patients. The reasons for change in chemotherapy regimen included; financial constraints 6 (54.5%) followed by no control of tumor 3 (27.2%) and side effects 2 (18.2%).

4.6 PHARMACEUTICAL CARE

Individual pharmacy records were not available for all the patients.

4.7 PALLIATIVE CARE

Only one patient (1.5%) was recorded to be aware of the presence of a palliative care team in the hospital.

4.8 USE OF UNORTHDOX MEDICINE

Four patients (5.9%) admitted to have used traditional medicine for treatment before coming to the hospital.

4.9 SPECIALTY VIEW

Findings from analysis of the data showed that the professionals who consistently played a major role in providing information were the surgeons and the oncologists (Table 4.15).

Tables 4.16 to 4.22 show particular professionals specialty view against their colleagues view.

Table 4.14 : Reasons for interruptions during therapy

Reason	Frequency	Percent (%)
Absconded no known reason	17	25
Financial	15	22
No space on the machine	11	16
Faulty machine	7	10
Physicist not around	5	7

Table 4.15 Number of professionals covering each informational area

Information area	Professional groups regularly providing information	n
Patient history	Surgeons, Oncologists, Oncology nurse, Record Officer	4
Patient examination	Surgeons, Oncologists, Oncology nurse	3
Ordering for lab investigations	Surgeons, Oncologists, Oncology nurse	3
Discussing diagnosis results	Surgeons, Oncologists,	2
Choosing management plan to adopt	Surgeons, Oncologists, Physicist	3
Surgery	Surgeons, Physicist	2
Radiotherapy	Oncologists, Physicist	2
Chemotherapy	Surgeons, Oncologists	2
Hormone therapy	Surgeons, Oncologists	2
Dispensing medication	Pharmacists	1
Counseling on side effects of medication	Surgeons, Oncologists, Oncology nurse, Pharmacists	4
Providing palliative care	Surgeons, Oncologists, Record Officer	3
Follow up of patient	Surgeons, Oncologists, Record Officer	3
Passing information leaflets	Oncologists, Oncology nurse, Record Officer	3
Determining ER/PR status	Surgeons, Oncologists	2
Physical well being	Surgeons, Oncologists	2
Functional well being	Surgeons, Oncologists, Oncology nurse	3
Sexual well being	Surgeons, Oncologists, Oncology nurse	3
Psychological well being	Surgeons, Oncologists	2
Social well being	Surgeons	1

(Regularly is defined as greater than 75% of a professional group agreeing they provide information on an area, n represents the number of professionals).

Table 4.16 Surgeon's specialty view against colleagues view.

	Surgeons role			
	Specialty view		Colleagues view	
	6	%	51	%
Patient history	6	100.0	34	66.7
Patient examination	6	100.0	35	68.6
Ordering for lab investigation	6	100.0	34	66.7
Discussing result of diagnosis	6	100.0	38	74.5
Choosing management plan to adopt	6	100.0	28	54.9
Surgery	6	100.0	50	98.0
Radiotherapy	2	33.3	6	11.8
Chemotherapy	6	100.0	11	21.6
Hormone therapy	6	100.0	12	23.5
Dispensing medication	0	0.0	3	5.9
Counseling patients of side effects of medication	6	100.0	15	29.4
Providing palliative care	5	83.3	14	27.5
Follow up of patient	6	100.0	26	51.0
Passing information leaflets	1	16.7	18	35.3
Determine ER/PR status	6	100.0	14	27.5
Physical wellbeing	6	100.0	25	49.0
Functional wellbeing	5	83.3	19	37.3
Sexual wellbeing	5	83.3	15	29.4
Psychological wellbeing	5	83.3	13	25.5
Social wellbeing	5	83.3	13	25.5

Table 4.17 Oncologists specialty view against colleagues view.

	Oncologists role			
	Specialty view		Colleagues view	
	4	%	53	%
Patient history	4	100	42	79.2
Patient examination	4	100	47	88.7
Ordering for lab investigation	4	100	48	90.6
Discussing result of diagnosis	4	100	48	90.6
Choosing management plan to adopt	4	100	46	86.8
Surgery	1	25	16	30.2
Radiotherapy	4	100	21	39.6
Chemotherapy	4	100	39	73.6
Hormone therapy	4	100	36	67.9
Dispensing medication	0	0	1	1.9
Counseling patients of side effects of medication	4	100	30	56.6
Providing palliative care	4	100	35	66.0
Follow up of patient	4	100	47	88.7
Passing information leaflets	4	100	24	45.3
Determine ER/PR status	3	75	38	71.7
Physical wellbeing	3	75	40	75.5
Functional wellbeing	4	100	38	71.7
Sexual wellbeing	3	75	29	54.7
Psychological wellbeing	4	100	30	56.6
Social wellbeing	2	50	21	39.6

Table 4.18 Radiographers specialty view against colleagues view.

	Radiographers role			
	Specialty view		Colleagues view	
	3	%	54	%
Patient history	0	0.0	12	22.2
Patient examination	2	66.7	8	14.8
Ordering for lab investigation	0	0.0	1	1.9
Discussing result of diagnosis	0	0.0	10	18.5
Choosing management plan to adopt	1	33.3	3	5.6
Surgery	1	33.3	0	0.0
Radiotherapy	2	66.7	28	51.9
Chemotherapy	0	0.0	1	1.9
Hormone therapy	0	0.0	2	3.7
Dispensing medication	1	33.3	1	1.9
Counseling patients of side effects of medication	1	33.3	1	1.9
Providing palliative care	2	66.7	6	11.1
Follow up of patient	0	0.0	5	9.3
Passing information leaflets	1	33.3	10	18.5
Determine ER/PR status	0	0.0	1	1.9
Physical wellbeing	1	33.3	5	9.3
Functional wellbeing	0	0.0	5	9.3
Sexual wellbeing	0	0.0	2	3.7
Psychological wellbeing	0	0.0	3	5.6
Social wellbeing	0	0.0	2	3.7

Table 4.19 Oncology nurses specialty view against colleagues view.

	Oncology nurses role			
	Specialty view		Colleagues view	
	6	%	51	%
Patient history	6	100.0	40	78.4
Patient examination	6	100.0	45	88.2
Ordering for lab investigation	6	100.0	46	90.2
Discussing result of diagnosis	4	66.7	13	25.5
Choosing management plan to adopt	1	16.7	1	2.0
Surgery	0	0.0	3	5.9
Radiotherapy	1	16.7	6	11.8
Chemotherapy	4	66.7	37	72.5
Hormone therapy	1	16.7	17	33.3
Dispensing medication	1	16.7	6	11.8
Counseling patients of side effects of medication	6	100.0	23	45.1
Providing palliative care	3	50.0	36	70.6
Follow up of patient	3	50.0	16	31.4
Passing information leaflets	5	83.3	20	39.2
Determine ER/PR status	2	33.3	4	7.8
Physical wellbeing	4	66.7	22	43.1
Functional wellbeing	6	100.0	26	51.0
Sexual wellbeing	5	83.3	21	41.2
Psychological wellbeing	4	66.7	21	41.2
Social wellbeing	2	33.3	16	31.4

Table 4.20 Pharmacists specialty view against colleagues view.

	Pharmacists role			
	Specialty view		Colleagues view	
	34	%	23	%
Patient history	18	52.9	22	95.7
Patient examination	1	2.9	0	0.0
Ordering for lab investigation	3	8.8	0	0.0
Discussing result of diagnosis	12	35.3	0	0.0
Choosing management plan to adopt	12	35.3	0	0.0
Surgery	2	5.9	2	8.7
Radiotherapy	1	2.9	1	4.3
Chemotherapy	18	52.9	2	8.7
Hormone therapy	13	38.2	5	21.7
Dispensing medication	34	100.0	18	78.3
Counseling patients of side effects of medication	32	94.1	16	69.6
Providing palliative care	16	47.1	6	26.1
Follow up of patient	22	64.7	0	0.0
Passing information leaflets	23	67.6	7	30.4
Determine ER/PR status	2	5.9	2	8.7
Physical wellbeing	23	67.6	14	60.9
Functional wellbeing	11	32.4	6	26.1
Sexual wellbeing	9	26.5	3	13.0
Psychological wellbeing	11	32.4	6	26.1
Social wellbeing	8	23.5	3	13.0

Table 4.21 Record officers' specialty view against colleagues view.

	Specialty view		Record officers role Colleagues view	
	3	%	54	%
Patient history	3	100	19	35.2
Patient examination	0	0	0	0.0
Ordering for lab investigation	0	0	1	1.9
Discussing result of diagnosis	0	0	1	1.9
Choosing management plan to adopt	0	0	1	1.9
Surgery	0	0	0	0.0
Radiotherapy	0	0	1	1.9
Chemotherapy	0	0	0	0.0
Hormone therapy	0	0	0	0.0
Dispensing medication	0	0	0	0.0
Counseling patients of side effects of medication	0	0	0	0.0
Providing palliative care	3	100	3	5.6
Follow up of patient	3	100	2	3.7
Passing information leaflets	3	100	12	22.2
Determine ER/PR status	0	0	0	0.0
Physical wellbeing	0	0	0	0.0
Functional wellbeing	0	0	0	0.0
Sexual wellbeing	0	0	0	0.0
Psychological wellbeing	0	0	0	0.0
Social wellbeing	0	0	1	1.9

Table 4.22 Physicist specialists view against colleagues view.

	Physicist role			
	Specialty view		Colleagues view	
	1	%	56	%
Patient history	0	0	16	28.6
Patient examination	0	0	12	21.4
Ordering for lab investigation	0	0	11	19.6
Discussing result of diagnosis	0	0	14	25.0
Choosing management plan to adopt	1	100	10	17.9
Surgery	1	100	5	8.9
Radiotherapy	1	100	15	26.8
Chemotherapy	0	0	3	5.4
Hormone therapy	0	0	4	7.1
Dispensing medication	0	0	1	1.8
Counseling patients of side effects of medication	0	0	4	7.1
Providing palliative care	0	0	7	12.5
Follow up of patient	0	0	8	14.3
Passing information leaflets	0	0	11	19.6
Determine ER/PR status	0	0	7	12.5
Physical wellbeing	0	0	8	14.3
Functional wellbeing	0	0	7	12.5
Sexual wellbeing	0	0	5	8.9
Psychological wellbeing	0	0	8	14.3
Social wellbeing	0	0	6	10.7

CHAPTER 5

DISCUSSION

5.1 RELATIVE OCCURENCE OF BREAST CANCER AND BIO DATA OF STUDY PATIENTS

The present data which showed that breast cancer was the most frequently occurring cancer type at ABUTH is in line with reports in the literature, where breast cancer had been shown to be the leading female malignancy in the world and the most common cancer in Nigeria (Ngadda *et al.*, 2008; Omonoyi *et al.*, 2009 and Adeyanju *et al.*, 2010). The female preponderance of breast cancer observed in the current study supported previous reports that male breast cancer is rare worldwide (Adeniyi *et al.*, 1997; Giordiano *et al.*, 2002; Dogo *et al.*, 2006; Fentiman *et al.*, 2006 and Umoh *et al.*, 2009). It is informative that the second most commonly occurring cancer type seen at the clinic was found to be cervical cancer, an exclusive female malignancy. Together breast and cervical cancers accounted for more than half (56%) of the cancers seen.

Most of the breast cancer cases occurred between the ages of 30 and 60 years and this corresponds with findings by Ashindoitiang and Anunobi, (2009) who reported in Nigeria, a modal age bracket of 30-50 years. Mean age at diagnosis was 47.82 ± 1.49 years and this was similar to the results of other studies; 48 years (Yip and Ng. 1996), 46.1 years (Okobia *et al.*, 2006) and 46.85 years (Anyanwu, 2008). Others had reported that peak incidence in Nigeria is at least a decade earlier than in Caucasians with mean age of presentation in Caucasians between 60-64 years (Yip and Ng. 1996; Adebamowo and Ajayi, 2000; Gukas,

et al., 2006). The one male in the study group was aged 58 years. Peak incidence for male breast cancer has been reported to be at the third and sixth decades of life (Umoh *et al.*, 2009). Thus the present bio data agrees with earlier reports in the literature.

Prevalence of breast cancer at ABUTH by tribe, state of origin and geo-political zone showed breast cancer diseases were ubiquitous. Although prevalence reported an Ibo majority (27%), more of the patients were from the North (58%), which was not unexpected as ABUTH is located in the north western zone of the country.

5.2 PREDISPOSING FACTORS

Several factors predispose an individual to breast cancer including: family history, history of previous lump and or cancer, menopausal status, age at first menarche and number of first full term pregnancies. Other factors are; number of full term pregnancies, history of breastfeeding, use of oral contraceptives, ingestion of fat, alcohol consumption and tobacco smoking.

Although family history tops the list of predisposing factors, the larger majority (76%) of patients reported that there was no history of such occurrences in their families. It is generally accepted that the risk of developing breast cancer is increased for women having a first degree biological relative (mother, sister, daughter) or second degree relative (grandmother, aunt, niece), with the disease (ACS, 2008). In this study, the sister was often reported to have had the disease before, and this corresponds with the study by Anyanwu, (2008). In another study in Iran, 10% of patients were reported to have a positive family history of breast cancer with 36% reported to have occurred in first degree relatives (compared to 62.5% in this study), while 64% (compared to 37.5% in this study) reported

the existence of breast cancer in other family members (Montazeri *et al.*, 2008). The greater the number of biological relatives with breast cancer, especially relatives diagnosed before the age 50, the higher a woman's breast cancer risk (ACS, 2008).

Having had breast cancer previously is a known risk factor (3 to 4 fold risk) for recurrence of cancer either in the opposite breast, or in the same breast (ACS, 2005 and Levi *et al.*, 2006). Stariano and Ragland (1994) and Yancik *et al.*, (1996) found that having a previous cancer predicted early mortality in women with breast cancer. Results from this study which shows that a history of previous cancer was associated with an increased risk for breast cancer was in support of these data from elsewhere.

That more (52%) of the patients were premenopausal rather than postmenopausal (44%) is consistent with the results of others studies who had reported that breast cancer occurs more in premenopausal women in Nigeria (Adebamowo and Ajayi, 2000; Ikpatt *et al.*, 2002; Adesunkanmi *et al.* 2006, Okobia *et al.*, 2006; Oluwatosin and Olopade 2006). Sixty-two percent of the patients attained menopause between the ages of 40-49 years, while 34% attained menopause at age greater than 50 years. Late onset of menopause has been associated with a higher risk of breast cancer in Nigerian women (Adebamowo and Ajayi, 2000). The risk of breast cancer is said to increase by almost 3% for each year older at menopause; so that a woman who has not had menopause at 55 (rather than 45 years), has approximately 30% higher risk (CGHF, 2002).

Regarding menarche, the 14.54 ± 0.52 years observed was similar to 13.67 years reported by Anyanwu (2008) and 14 years (by 67.5% of patients) reported by Ashindoitiang and Anunobi (2009). Early onset of menarche and late menopause are associated with increased

lifetime exposure to estrogen and increases breast cancer risk (Adebamowo and Ajayi, (2000) and Okobia and Bunker, (2005). Nearly 80% of patients in this study had first menarche at 15 years or younger.

Age at first full term pregnancy greater than 20 years as observed in the present study (72.9%) has been associated with an increased risk for breast cancer (Adebamowo and Adekunle, 1999 and Okobia *et al.*, 2006). In another study, 64% of the breast cancer patients were reported to have had their first full term pregnancy at age 25 years and above (Ashindoitiang and Anunobi, 2009).

Child bearing and the high number of full term pregnancies have been found to reduce the risk of breast cancer with risk reducing by 30% for each full term pregnancy compared to nulliparous women (Ewertz *et al.*, 1990). Studies in Nigeria have also associated high parity or multiparity with decreased risk for breast cancer (Adebamowo and Ajayi, 2000; Adesunkanmi *et al.*, 2006). The present study showed that 56% of the women had between 5 to 14 children. Mean parity in the study was 5.46 ± 0.37 which was higher than that in another study (mean parity of 4.28 ± 0.28) Anyanwu (2008). Okobia *et al.*, 2006 in another study reported that women who were para 4 and above had a decreased risk for breast cancer. Findings from this study however represented a deviation from these previous studies. More than 50% of the women had 5 children and above and this did not seem to decrease their risk for breast cancer. Adebamowo and Adekunle (1999), also reported that the women with breast cancer in their study had a higher mean number of pregnancies compared with controls.

Findings from analysis of history of breast feeding showed that 54.5% of the women were reported to have breast fed their children. The mean duration of feeding could not be determined. Breast feeding for 1 to 2 years has been found to slightly lower breast cancer risk as it lowers a woman's total number of menstrual cycles and hence exposure to estrogen (ACS, 2008).

Forty-one percent of the patients admitted to have used one form of birth control measure. 33% were reported to have used oral contraceptives and this is high compared to another study which reported that 5% used oral contraceptives (Ashindoitiang and Anunobi, 2009). Using birth control pills has been associated with an increased risk for breast cancer (CGHF, 1996 and ACS, 2008). Oral contraceptives contain estrogen and estrogen is the primary stimulant for breast epithelial proliferation (Pike *et al.*, 1983).

Findings on the analysis of data on alcohol intake revealed that only 14 (23%) of the patients admitted to have taken alcohol out of which 8 were reported to have taken 1 bottle per week while the 6 claimed they drank occasionally. In another study by Anyanwu (2008), less than 15% of the patients were reported to have taken alcohol, alcohol intake was described as social to less than a drink monthly. Alcohol abuse was however reported in a case-control study of the epidemiological risk factors for breast cancer in Nigeria (Adebamowo and Adekunle, 1999). There is a recognized relationship between the consumption of more than 2 drinks of alcohol and increase in the level of estrogen in the blood (ACS, 2005). Some sex hormones have also been found to have higher levels in the blood stream of alcohol consumers than in non-consumers (Rinaldi *et al.*, 2006). Results from this study showed no strong relationship between alcohol and breast cancer, although

it is possible that majority of the patient did not give a true account whether they used to take alcohol or not considering the environment in which the study was carried out.

Only one woman admitted to have smoked tobacco, though it is possible that the number may have been higher and the women did not want to admit to smoking. In a study carried out by Anyanwu (2008) none of the patients admitted to have smoked tobacco. In Japanese women, tobacco smoke has been found to possibly increase the risk of breast cancer (Nagata *et al.*, 2006). Evidence between second hand smoke (passive smoking) and breast cancer risk is not clear (ACS, 2008).

5.3 CO-MORBIDITY, DIAGNOSIS AND LABORATORY INVESTIGATIONS

The survival of women with breast cancer is dependent on the presence or absence of other co morbid diseases (West *et al.*, 1996). Amongst conditions that predict early mortality in women with breast cancer are diabetes, stroke and a previous cancer which had earlier on been reported (Stariano and Ragland, 1994; Yancik, 2001). The duo of hypertension and diabetes as seen in the present study as co morbid diseases may increase mortality in the study population.

More of the cancers occurred in the right breast (50.7%) while 41.8% occurred in the left breast, 7.4% of the patients had bilateral breast cancer. This finding is not similar to results of the works of Ekanem and Aligbe (2006) and Adesunkanmi *et al.*, (2006) who found that breast cancers occurred more on the left breast than on the right. Anyanwu (2008) on the other hand reported that 49% each of breast cancer cases occurred in both right and left breasts, while 2% were bilateral.

Biopsy is the most definitive method for diagnosing breast cancer; this probably accounted for the reason why majority of the patients had one done. Mammography which can be used to identify cancer several years before physical symptoms develop (ACS, 2007), was used in diagnosing 18% of the patients. This low percentage (18%) could be attributed to the fact that carrying out a mammogram is very costly, and as majority of the patients were housewives and unemployed they probably could not afford the high cost.

Signs and symptoms frequently reported included lump in the breast, breast pain, change in breast size, breast discharge and ulceration. Other symptoms included inverted nipples, peau d'orange, bleeding, back pain, puckered breast, chest pain, weight loss, fever, loss of appetite, hot sensation in the breast, pain in the armpit and neck. Adesunkanmi *et al.*, 2006 on the other hand reported breast pain as the most common symptom of breast cancer in their study.

That invasive ductal carcinoma is the most common sub-type of breast cancer as observed in this study is consistent with several published literature (Ries *et al.*, 2002; Ekanem and Aligbe, 2006 and Ngadda *et al.*, 2006). Other literature had reported infiltrating ductal carcinoma to be the most common (Anyanwu, 2008 and Bowtra, 2010). Infiltrating ductal carcinoma was the second most common sub-type in the present study. Thus, the prevalence of breast cancer sub-types seen is consistent with what is in the literature.

The laboratory investigations carried out were usually required for following the prognosis of the patients. The frequent requests for hematological investigations were probably due to the fact that most anti-cancer drugs cause bone marrow depression leading to anemia, thrombocytopenia, and leucopenia, hence the need to monitor all hematological parameters

to give the interventions where needed. Chest x-rays were to monitor the size of the heart and also to check for evidence of metastasis to other sites. Electrocardiograms were necessary as some of the patients are hypertensive and some anti-cancer drugs are cardiotoxic.

5.4 DRUG MANAGEMENT

From the study, five different chemotherapy combinations were used in the treatment of breast cancer patients. The most frequently used regimen, CAF is a second line therapy in the Nigerian guidelines for breast cancer chemotherapy. The CAF regimen was the most frequently used regimen as majority of the breast cancer patients presented at advanced stages of the disease (late presentation). CMF was also used though in few patients and this drug combination is the first line of choice in the guidelines and is used when breast cancer is in its early stage. It is surprising to note that newer regimens containing the taxane group of anticancer agents were employed in 16 patients, though these agents are the third line of choice in the Nigerian guidelines. Adesunkanmi *et al.*, (2006) in their study reported that the most common drug regimens used for breast cancer therapy were CMF + prednisolone and CAF. Comparison of the regimens used in the hospital with that of NCCN guideline showed that the NCCN guidelines favored using more targeted therapies like the taxanes and monoclonal nuclear antibodies. Other regimens like CAF, CMF, and CEF which were mainly used in the hospital were classified under other adjuvant regimen in the NCCN guidelines. There seemed to be wide gap in the prescription patterns between the oncologists and surgeons. Generally oncologists at the hospital were observed to have started prescribing newer drugs like the taxanes, this was not so with the surgeons. The Nigerian guidelines have adopted the use of taxanes as third line therapy. Adjuvant

chemotherapy with taxanes has been found to lower the risk of death and reduce the number of breast cancer recurrences (Clavarezza *et al.*, 2006 and Ferguson *et al.*, 2007).

Hormonal therapy in the national guidelines was with tamoxifen only and this is consistent with findings from this study which revealed that majority of the patients were given tamoxifen. Few patients were given newer hormonal drugs (anastrozole and exemestane) and about half (50%) of the patients had radiotherapy. In another study by Adesunkanmi *et al.*, (2006), tamoxifen was used in all the patients and 33.2% received radiotherapy.

Other drugs were used in the treatment of the breast cancer patients, as many anticancer drugs have deleterious side effects like bone marrow depression, nausea and vomiting. Cytotoxic drugs and radiotherapy adversely affects hematological parameters, thus majority of the patients were placed on ferrous sulphate. Metoclopramide was administered to counteract the nausea and vomiting. 5HT₃ histamine antagonists like granisetron and ondansetron was also used to alleviate nausea and vomiting.

From the study it was observed that hydrocortisone, dexamethasone and prednisolone were frequently used. Steroids are natural hormones and hormone like drugs that are useful in treating some types of cancers as well as other illnesses and they are an important class of drugs used in cancer chemotherapy (ACS, 2009).

Tramadol a synthetic analogue of codeine has been shown to be more effective in treating cancer pain (Bono and Cuffari, 1997). It is a centrally acting analgesic and together with its metabolite are agonists at the mu receptors (Keskinbora and Aydinli, 2006). Tramadol is available in drops, capsules and sustained-release formulations for oral use, suppositories

for rectal use and solution for intramuscular, intravenous and subcutaneous injection (Grond and Sablotzki, 2004). Diclofenac sodium, a non-steroidal anti-inflammatory drug (NSAID) was also prescribed. A number of patients from the study were administered morphine either as tablet or injection. Morphine is the drug of choice for moderate or severe cancer pain (Hoskins and Hanks, 1991). It is a prototype of receptor agonists and exerts its effects by mimicking naturally occurring endogenous opioid peptides. Other analgesic drugs used included; Dihydrocodeine a synthetic derivative of morphine, pethidine an opioid analgesic and pentazocine a potent analgesic with mixed agonist and antagonist. Analgesia is attributed to interactions at the kappa receptor and to a lesser extent the mu receptor. According to Yerima *et al.* (2006) pentazocine has no role in the modern management of cancer pain given the high rate and severity of associated side effects.

Analgesic medication use was generally low and this finding was consistent with available literature (Yerima *et al.*, 2006; Omoti and Omoti, 2007). Omoti and Omoti, (2007) in their study, reported that associated cancer pain is often undertreated in developing countries where there are problems of poor economy, poor purchasing power, poor manpower, fake adulterated and expired drugs, poor drug storage conditions, and adverse temperature conditions combined with poor power supply which may affect drug efficacy. They also reported that health care providers had a poor understanding of physio-pharmacology of cancer pain management.

5.5 SIDE EFFECTS OF CHEMOTHERAPY AND RADIOTHERAPY

The most common side effect observed from the study was vomiting which was mostly due to chemotherapy with anticancer drugs. Classes of anticancer drugs that can induce

vomiting include alkylating agents, antimetabolites, antibiotics, mitotic inhibitors and anti-hormones. Some of the patients reported a cessation in menstruation. This was probably due to the use of alkylating agents as part of their chemotherapy regimen. Long term use of alkylating drugs (cyclophosphamide, procarbazine, melphalan) can bring about amenorrhea in women and infertility in men. Anemia, leucopenia and thrombocytopenia are all due to bone marrow depression which is a common side effect of anti-cancer drugs. Cough was experienced in some of the patients. The cough may have been due to methotrexate which occasionally produces an acute lethal lung toxicity that is thought to be allergic or hypersensitivity pneumonitis. Some patients experienced alopecia which is a common side effect of methotrexate, cyclophosphamide, bleomycin, daunorubicin and 5- fluorouracil. Few patients complained of swollen veins and this could either have been due to the intravenous lines used to administer the cytotoxics or drugs such as doxorubicin. Pericarditis was reported in one patient, drugs which affect the heart function cyclophosphamide (can cause arrhythmias and congestive heart failure) and doxorubicin associated with transient cardiac arrhythmias and depression of myocardial function. Skin desquamation, pin prick sensation and skin darkening were observed in some of the patients who received radiotherapy.

5.6 INTERRUPTION OF DRUG USE

The study observed that many patients had their treatment interrupted or discontinued at one point or another. Many reasons were proffered for this, the most common being financial constraints. This was expected as a large proportion of the patients were housewives with no steady source of income, and anticancer drugs are very expensive and sometimes not readily available. In a country where most people live on less than one

dollar a day, it is not surprising that the patients' could not afford to buy these drugs which cost thousands of naira. A number of patients could not start radiotherapy on time as there was no space on the machine. Similarly, some of the patients who had actually commenced radiotherapy had their course interrupted due to the fact that the radiotherapy machine developed faults. This is very unfortunate as there are only 5 radiotherapy centers in Nigeria, and with a population of over 140 million there is no way that these 5 centers can cope with the increasing demand for radiotherapy services. The physicist's absence for a period of time also delayed treatment for some patients. Some patients on the other hand absconded with no known reason.

Chemotherapy regimen for some patients had to be changed. This change was due to several reasons the most significant of which was financial constraints, followed by no control of tumor and side effects; particularly cardiotoxicity due to doxorubicin which was observed in two patients. Financial constraints prevented physicians from placing the affected patients on more targeted therapies which are more expensive but more efficacious.

5.7 PHARMACEUTICAL CARE

The non-availability of individual pharmacy records for all the patients was observed in this study. The pharmacy department does not keep individual pharmacy records for patients as a rule and this is not a good trend as it makes it difficult for one to follow the prescription pattern for a particular patient. Also pharmacovigilance would not be possible where individual pharmacy records are not kept.

5.8 PALLIATIVE CARE

Awareness of the presence of a palliative care team in the hospital by patients seemed to be very low. Presently at the hospital there is only one trained palliative care specialist who is a nurse. Her primary duty is training volunteers who want to be members of the palliative care team. Usually physicians refer patients to the palliative team who then assess the patient so as to know how to apply palliative care. There are 5 major aspects the palliative team tries to address and these are emotional, social, physical, psychological and spiritual well-being of the patient. The palliative care team of the hospital is composed of different professionals from within and outside the hospital who volunteer to help patients. They meet monthly on Wednesdays where the specialist lectures them for about an hour after which they move into the wards to see patients. After their ward round they meet again to discuss patient problems and make recommendations on how best to solve the problems. For example where pain control is not adequately achieved they communicate with the physicians to come and review the patients' pain prescription. They help patients to get financial assistance for their therapy and train family members to care for their loved ones. In the United States today, many hospitals offer palliative care programs (Lynn, 2004), but this is not the case in Nigeria.

5.9 USE OF UNORTHODOX MEDICINE

The use of traditional medicine was not common amongst the patients. Only few patients were reported to have used traditional medicines. This might have contributed to their coming to the hospital late thus affecting prognosis. Late presentation of patients to the hospital is a hallmark for breast cancer in Nigeria as reported by numerous publications (Chiedozi, 1985; Shavers *et al.*, 2005; Smith *et al.*, 2006 and Anyanwu, 2008). Reasons for

late presentation are believed to be due to ignorance, superstition, self-denial, fear of mastectomy and unavailability of treatment facilities (Anyanwu, 2008). Non-pharmacological management employed was counseling (10 patients), exercise for 3 patients, surgery and radiotherapy in 50% of the patients.

5.10 SPECIALTY VIEW

The surgeons and the oncologists were the two main professional groups who perceived themselves as being responsible for providing information on 17 out of the 20 information areas identified. Together with the oncology nurses, they perceived themselves as having a major role in taking patient history, patient examination, ordering for laboratory investigations, discussing results of diagnosis and counseling patients on side effects of medication. Their colleagues shared the same view with them except that they did not agree that the oncology nurse had a major role in discussing results of diagnosis.

All the surgeons in consensus agreed they were the only professional group involved in surgery, majority of their colleagues were of the same view. The only variant was the physicist who perceived themselves as having a role in surgery a view that was not shared by other colleagues.

Oncologists saw themselves as having an important role to play in radiotherapy; unfortunately their other colleagues did not think so. Radiographers were of the opinion that they were in charge of radiotherapy and this was agreed as a major role by their colleagues. Surgeons, oncology nurses, pharmacists and record officers did not perceive themselves as having a major role in radiotherapy confirmed by their colleagues. The physicist's role in radiotherapy was however not recognized by the others.

Radiographers, physicist and record officers perceived themselves as not having a major role in chemotherapy this view was corroborated by their colleagues. Surgeons, oncologists and pharmacists claimed to be important in chemotherapy. Their colleagues did not agree with them. The oncology nurse was the only professional that both the specialty view and colleague view agreed that they had a major role in chemotherapy of patients (they also administer cytotoxics).

Radiographers, nurses, pharmacists, physicist and record officers all agreed that they did not play a major informational role in hormone therapy, a view shared by their colleagues. Oncologists perceived themselves as having a major role which was confirmed by their colleagues.

When it came to dispensing medication the pharmacists were the only professionals who saw themselves as playing a major role. A large percentage of their colleagues agreed to this. All other professionals felt they had no business with dispensing medication.

Surgeons and oncology nurses felt they were the only professionals to be involved in counseling patients on side effects of medication, their colleagues did not agree with them. Radiographers, physicists and record officers perceived themselves as not being involved in counseling, while oncologists and pharmacists agreed they were important on counseling patients on side effects of medication.

Providing palliative care was seen to be one of the primary roles of the oncology nurse and oncologists. Radiographers, surgeon and record officers also felt they had a role to play, but this view was not shared by their colleagues. Pharmacists and physicists saw themselves as not being important in providing palliative care.

Only the oncologist and the oncology nurse felt they had a major role in passing information leaflets, other professionals felt they had no business passing information leaflets and their colleagues agreed with them.

Surgeons and oncologists claimed to be involved to a high degree in patient follow up, corroborated by their other colleagues view. Radiographers and physicists did not perceive themselves as having as having a role in following up patients. Nurses, pharmacists and record officers even when they felt they a role to play, their colleagues did not think so.

Determining of estrogen/progesterone (ER/PR) status was seen to primarily be the responsibility of the oncologist. Discussing functional, sexual, physical, psychological and social well being was seen to be the primary responsibility of the surgeon and the oncologist. Radiographers, physicist, pharmacists, record officers and the oncology nurses mostly felt they had no role in performing these functions.

There were lots of discrepancies on which health care professional was responsible for providing services in a given information area. For example the oncology nurse felt they should be able to order for laboratory investigations, the physicists feeling they have an important role to play in surgery. Pharmacists on the other hand perceived themselves as having only 2 major informational roles - dispensing of medication and counseling patients on side effects of therapy. Several studies have no report on the role of pharmacists as part of the multidisciplinary team in the care of cancer patients (Jenkins *et al.*, 2001; Amiruddin, 2002; Catt *et al.*, 2005 and Pruthi *et al.*, 2007).

Pharmacists are very important professionals on any multidisciplinary team. Pharmacists suggest possible effects on prescribing behavior, optimize drug regimens to reduce adverse

effects and thus increase efficacy (Wagner, 2000). According to Barbour (2008), pharmacists have many roles which include; patient education as the physicians do not always have time to talk to patients, development of institutional guidelines for the management of side effects, ensuring that the appropriate laboratory tests have been performed, reconciliation of medications for patients who have been hospitalized and helping to improve treatment adherence for patients who are using oral therapies,. Pharmacists can provide a wealth of information to patients to ensure that they receive proper pharmacological interventions and that appropriate monitoring occurs (Pfeilschifter, 2000), help provide supportive care and can also evaluate patients for non-pharmacologic interventions and supplement interventions to ensure the appropriateness of the pharmacological choices (Miller and Brinkman, 2010). Pharmacists are in a position to address some of the psychosocial issues of cancer patients or refer patients to psychosocial counselors (De Lemos, 2004).

Pharmacists at Ahmadu Bello University Hospital, Shika particularly felt they had many roles to play in the management of breast cancer patients. Roles they felt they should take part in included; awareness programs for breast cancer in the community and nationally, following up of patients' response to treatment, providing quality and efficacious drugs at affordable costs, providing drug information services and carrying out researches on drugs and side effects.

CHAPTER SIX

CONCLUSION AND RECOMMENDATION

6.1 CONCLUSION

Breast cancer is the most common cancer occurring in Nigerian women today. Studies have shown it has recently overtaken cervical cancer as the most common female malignancy in areas of Western and Eastern Nigeria. In developing countries breast cancer is characterized by late presentation, occurrence at relatively young ages and mortality.

The incidence of breast cancer was found to conform to expectations, the disease showed no geopolitical, ethnic or tribal barriers. The average age of occurrence corresponded with other studies and showed that breast cancer occurred at a younger age in Nigerian women and at least a decade earlier than in the Caucasians. Familial history of breast cancer was found in about a quarter of the patients.

Co-morbid diseases were the rule rather than the exception. Co-morbid diagnosis showed no association with sex or marital status. Factors which seemed to increase breast cancer risk included; age at first full term pregnancy greater than 20 years, early onset of menarche, attaining menopause at a later age, presence of family history of breast cancer, history of previous breast cancer in a patient, frequent use of oral contraceptive pill and not breast feeding. Majority of the women were premenopausal. Laboratory investigations that were frequently carried out included; white blood cell count and differentials, liver function test, chest x-ray and serum creatinine and electrolytes.

Breast cancer occurred more in the right breast than in the left, few patients had bilateral breast cancers. Invasive ductal carcinoma was the most common type of breast cancer diagnosed and the diagnostic procedure that was routinely used was biopsy. Signs and symptoms presented by patients varied, the most common symptom being the presence of a lump, followed by breast pain, change in breast size and discharge. Patients were managed with surgery, chemotherapy, radiotherapy, and or hormone therapy either singly or in combination. Differences were observed between the chemotherapy regimens. While physicians at the oncology department had started to introduce taxanes as part of their drug regimen in accordance with newer therapy guidelines, the Nigerian guideline placed use of taxanes under third line. As adjuvant chemotherapy with taxanes has been found to lower the risk of death and reduce the number of breast cancer recurrences, it is important that the use of taxanes be promoted in Nigeria, so as to offer patients better quality of care. Chemotherapy regimens used were CMF, CAF, CEF, gemtricitabine + paclitaxel and capecitabine and paclitaxel. Hormone therapy was mainly with tamoxifen, other hormonal drugs used were exemestane and anastrozole. Non-pharmacological management employed was counseling (10 patients) and exercise in 3 patients. Drug use was associated with side effects in significant number of patients and these side effects were managed by discontinuing the suspected drug or using other drugs to cancel out effects. Other drug classes encountered include analgesics, antibiotics, antihypertensive, antidiabetic and antiulcer drugs.

Results from the informational role questionnaire showed many discrepancies revealing the lack of interdisciplinary awareness amongst the health care professionals about their roles in the management of breast cancer patients. There were distinct difference in the

prescription pattern between the oncologists and surgeons as they did not have a consensus guideline which they used to manage breast cancer patients. Many studies do not recognize the roles of pharmacists in the management of breast cancers. From this study pharmacists were only expected to dispense drugs and counsel patients on side effects of medication.

6.2 RECOMMENDATIONS

There is an urgent need for a consensus guideline between oncologists and surgeons to be used in the management of breast cancer patients in the hospital to be developed. The process of development of this guideline should involve all the members of the healthcare team managing the patients. Also in the course of this research, many areas were identified where data was either scanty or unavailable. Comprehensive pharmacy records should also be kept as this was not available. There was the issue of incomplete documentation of patient history. This is very important especially when analyzing factors that contribute to the risk factors for breast cancer. Physicians should be encouraged to clerk patients in detail so as to collect all necessary information pertaining to breast cancer. For pharmacoeconomic management complete patient records (records on patient income, occupation and basic lifestyle behaviors), are essential to ensure that therapy is tailored to suit patient and ensure compliance with therapy.

More radiotherapy centers should be set up across the country and obsolete equipment and machines in previously set up centers replaced. Increased funding by the government, donor agencies can lead to a decrease in the incidence of the disease. National mammographic centers should be set up and screening if not made free be carried out at affordable prices. More nuclear medicine departments should be set up to help with

research. Treatment of cancer can be included into the National Healthcare scheme so that patients can access drugs at affordable prices. There should be clear definition of roles of members of the health care team to avoid monopolization of roles by a particular professional group or overcompensation. This can be by carrying out training activities to educate the health care professionals. Molecular diagnostic methods should be made available. Breast self examination (BSE) should be taught to women and clinical breast exam (CBE) to health workers. The national guidelines for breast cancer chemotherapy should be updated to inculcate newer advances in treatment.

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APPENDICES

APPENDIX I – Patients’ Data Form

(To be completed from patients’ folder)

To whom it may concern:

This research data form relates primarily to the pharmacological and non- pharmacological management of breast cancer, including the roles of members of the healthcare team in patient care at Ahmadu Bello University Teaching Hospital Shika. The purpose of this study is to generate baseline data that would, in addition to contributing to literary scholarship, impact on improved care of patients with breast cancer, not only in this hospital, but nationally. All information obtained, either retrospectively or prospectively, will be treated with outmost level of confidence and will not be used for any other purpose than that stated. The data will be reported as a thesis for an MSc degree in Pharmacology.

Mrs. Amina B. Olorukooba (MSc. Candidate)

Prof. (Mrs.) H. O Kwanashie, Dr. A.U Zezi, Dr. T. Olasinde (Supervisors)

PERSONAL DATA

1. Unit Number: _____

2. Sex: _____

3. Age at diagnosis (years): _____

4. Weight (Kg): _____

5. Marital status: Single () Married () Divorced () Widowed ()

6. Occupation: Civil servant () Unemployed () Home maker ()

Retired () Business () Others (specify): _____

7. Highest Educational level: No formal education () Primary school ()

Secondary level () Tertiary education ()

DIAGNOSIS AND FEATURES

8. Presenting signs and symptoms: Lump () Headache ()

Breast pain () Bleeding () Inverted nipples () Breast discharge ()

Breast tenderness () Puckered breast (with dimples) () Change in breast shape/size () Others specify): _____

9. Diagnostic procedures used: Ultrasound () Mammography () Clinical breast examination () Breast MRI () Biopsy ()

10. Types of cancer diagnosed at the Oncology clinic:

Colorectal () Cervical () Leukemia () Connective tissue ()

Prostate () Skin () Bone () Hodgkin's lymphoma ()

Burkitt's lymphoma () Liver () Non-Hodgkin's lymphoma ()

Breast () Stomach () Brain and spinal () Kaposi sarcoma ()

Neuroblastoma () Retinoblastoma ()

11. Side of breast affected: Right () Left () Bilateral involvement ()

12. Type of breast cancer diagnosed: _____

13. Stage of cancer at diagnosis:

I () II () III () IV ()

14. Report of pain associated with the cancer? Yes () No ()

FAMILY, CLINICAL AND SOCIAL HISTORY

15. a. Recorded family history of breast lump/cancer: Yes () No () don't know ()

b. If yes, relationship _____

16. Presence of previous breast lump/cancer: Yes () No ()

17. Age at first menarche (years): _____

18. Age at first pregnancy (years): _____

19. Number of pregnancies: _____

20. a. Menopausal status: premenopausal () postmenopausal ()

b. If post menopausal, at what age did it start? _____

21. a. History of taking oral contraceptives: Yes () No () Not recorded ()

b. If yes, what type was taken? _____

22. History of breastfeeding: _____

23. a. History of alcohol intake: Yes () No () Not recorded ()

b. If yes, specify type and quantity: _____

24. History of smoking cigarettes? Yes () No () Not recorded ()

25. a. Co-morbid illness apart from breast cancer Yes () No ()

b. If yes, specify: _____

26. Laboratory investigations carried out:

WBC and differential () Liver function test () Widal test ()

Urinalysis () Serum electrolyte and creatinine ()

Others (specify): _____, _____

MANAGEMENT PLAN

27. Therapeutic plan adopted:

Chemotherapy ()

Hormone therapy ()

Surgery (mastectomy or lumpectomy) ()

Radiotherapy ()

28. Chemotherapy:

Data on drugs used, dosage and frequency of administration.

29. Hormone therapy:

Data on drugs used, dosage and frequency of administration.

30. a. Onset of pain in relation to surgery: Before () After ()

b. Any pain medication administered to control pain? Yes () No ()

c. Data on type of analgesic prescribed, dosages and frequency of administration.

31. Radiotherapy, total dose of treatment prescribed by physician:

32. Side effects observed and recorded when using drugs and radiotherapy:

Vomiting () Rib/Chest pain () Skin desquamation ()

Cough () Leucopenia () Alopecia ()

Headache () Anemia () Thrombophlebitis ()

33. a. Any drug changes? Yes () No () b. If yes, number of times: _____

c. Reasons for drug change(s)?

No control of tumor () Poor compliance ()

Side effects () Cost ()

Availability () Not stated ()

34. Reasons for discontinuation of therapy

Side effects () Therapeutic failure () Prohibitive costs ()

None () Others (specify): _____, _____

35. Assessment of drug adherence: Poor () Good ()

36. Other management approaches:

Psychotherapy () Group counseling () Counseling with family ()

Others (specify): _____, _____

Referral for palliative care? Yes () No ()

37. Individualized pharmacy records for the patient: Available () Not available ()

Anticancer drugs –

S\No	Drug name	Dose (mg)	Frequency/day

Non anti- cancer drugs used

S\No	Drug name	Dose (mg)	Frequency/day

APPENDIX II – MULTIDISCIPLINARY TEAM QUESTIONNAIRE

Age (years) –

Department -

Specialty -

A) Please tick which of the under listed health care professionals including you has a major role in providing the following services in the management of breast cancer patients.

ROLES	Surgeon	Oncologist	Chemotherapy nurse	Radiologist	Radiographer	Pharmacist	Counselor	Physicist	Records	Others specify
Patient history										
Patient examination										
Ordering for laboratory investigations										
Discussing results of diagnosis										
Choosing management plan to										

adopt										
Surgery										
Radiotherapy										
Chemotherapy										
Hormone therapy										
Dispensing medication										
Counseling patients on side effects of medication										
Providing palliative care										
Follow up of patient										
Passing information leaflets										

B) Please tick which of the members of the health care team has a major role in discussing patient problems in the following areas.

ROLES	Surgeon	Oncologist	Chemothe rapy nurse	Radiolo gist	Radiogr apher	Pharm acist	Coun selor	Physici st	Recor ds	Others specify
Physical well being (pain, side effects, lethargy)										
Functional well being (work, sleeping)										
Sexual well being (attractiveness, personal relationships)										
Psychological well being (depression, anxiety, hope)										
Social well being (social activities, relationship with family and friends)										

APPENDIX III -NATIONAL GUIDELINES FOR BREAST CANCER CHEMOTHERAPY (2007) FOR NIGERIA

Treatment guidelines depend on the disease stage at diagnosis and are as shown below:

1. Stage I breast cancer

Surgery plus adjuvant radiotherapy and or chemotherapy

a. Breast conserving surgery

Lumpectomy, Quadrantectomy plus Radiotherapy

i) Unifocal breast cancer.

ii) Well differentiated breast cancer.

iii) Availability of radiotherapy.

iv) Not used for subareolar tumor.

b. Modified radical mastectomy, chemotherapy, radiotherapy if:

i) Family history of breast cancer.

ii) Early stage of onset < 40 years.

iii) Poorly differentiated.

iv) Poor histological variants.

2. Stage II Breast cancer

- i) Modified radical mastectomy plus adjuvant chemotherapy/radiotherapy
- ii) Neoadjuvant chemotherapy followed by surgery and then chemotherapy may be used in some cases
- iii) If tumor is estrogen receptor positive , progesterone positive: hormonal therapy (tamoxifen) plus chemotherapy (6 cycles) administered together.

3. Stage III Breast cancer

- i) Neoadjuvant chemotherapy followed by surgery.
- ii) Radiotherapy for unresectable tumor.
- iii) Herceptin/Trastuzumab for HER/2 neu positive cancers.
- iv) Hormonal therapy for ER+/PR+ tumor.

4. Stage 4 Breast cancer

- i) Radical surgery is not usually indicated.
- ii) Palliative care including
 - Tube insertion or pleural effusion.
 - Radiotherapy to the spine for spinal metastasis.
 - Internal fixatore for pathological failure.
 - Compression elastic sleeve or bandage or Jobst pump for lymphoedema of the arm.

- Biphosphonates in malignant hypercalcemia and metastatic tumors.

Neoadjuvant/Adjuvant chemotherapy regimens for breast cancer.

First line

CMF (28 day cycle for 4-6 weeks)

Cyclophosphamide 100mg/m² PO days 1-14

Methotrexate 40mg/m² IV days 1-8

5- fluorouracil 600mg/m² IV days 1-8

Second line

VAC P (21 day cycle for 4-6 weeks)

Vincristine 1.4mg/m² IV day 1

Adriamycin 50mg/m² IV day 1

Cyclophosphamide 200mg/m² PO days 3-6

Prednisolone 40mg/m² PO days 1-5

CAF (21-28 day cycle for 4-6 weeks)

Cyclophosphamide 600mg/m² IV day 1

Adriamycin 60mg/m² IV day 1

5-FU 600mg/m² IV day 1

AC (21 day cycle for 4-6 weeks)

Cyclophosphamide 600mg/m² IV day 1

Adriamycin 60mg/m² IV day 1

Third line

PA (28 day cycle for 4-6 weeks)

Paclitaxel 175mg/m² IV day 1

Adriamycin 50mg/m² IV day 1

Capecitabine 1000mg/m²

Hormonal Therapy

Tamoxifen 20mg po daily for 5 years

**APPENDIX IV - NATIONAL COMPREHENSIVE CANCER NETWORK
PRACTICE GUIDELINES IN ONCOLOGY FOR BREAST CANCER**

1. Preferred Adjuvant Regimens

TAC Chemotherapy (every 21 days for 6 cycles)

Docetaxel 75mg/m² IV day 1

Doxorubicin 50mg/m² IV day 1

Cyclophosphamide 500mg/m² IV day 1

Dose dense AC followed by paclitaxel chemotherapy

Doxorubicin 60mg/m² IV day 1

Cyclophosphamide 500mg/m² IV day 1

Every 14 days for 4 cycles

Followed by

Paclitaxel 175mg/m² by 3hr IV infusion day 1

Every 14 days for 4 cycles

AC followed by paclitaxel chemotherapy

Doxorubicin 60mg/m² IV day 1

Cyclophosphamide 600mg/m² IV day 1

Every 21 days for 4 cycles

Followed by

Paclitaxel 80mg/m² by 1hr IV infusion weekly for 12 weeks

TC Chemotherapy

Docetaxel 75mg/m² IV day 1

Cyclophosphamide 600mg/m² IV day 1

Every 21 days for 4 cycles

AC Chemotherapy

Doxorubicin 60mg/m² IV day 1

Cyclophosphamide 600mg/m² IV day 1

Every 21 days for 4 cycles

2. Other Adjuvant Regimens

FAC Chemotherapy

5-Fluorouracil 500mg/m² IV days 1 and 8 or days 1 and 4

Doxorubicin 50mg/m² IV day 1

Cyclophosphamide 500mg/m² IV day 1

Every 21 days for 6 cycles

CAF Chemotherapy

Cyclophosphamide 100mg/m² IV day 1

Doxorubicin 30mg/m² IV day 1 and 8

5-Fluorouracil 500mg/m² IV days 1 and 8

Every 28 days for 6 cycles

CEF Chemotherapy

Cyclophosphamide 75mg/m² IV day 1

Epirubicin 60mg/m² IV day 1 and 8

5-Fluorouracil 500mg/m² IV days 1 and 8

With cotrimoxazole support

Every 28 days for 6 cycles

CMF Chemotherapy

Cyclophosphamide 75mg/m² IV day 1

Methotrexate 40mg/m² IV day 1 and 8

5-Fluorouracil 600mg/m² IV days 1 and 8

Every 28 days for 6 cycles

AC followed by docetaxel chemotherapy

Doxorubicin 60mg/m² IV day 1

Cyclophosphamide 600mg/m² IV day 1

Every 21 days for 4 cycles

Followed by

Docetaxel 100mg/m² IV day 1

Every 21 days for 4 cycles

EC Chemotherapy

Epirubicin 100mg/m² IV day 1

Cyclophosphamide 830mg/m² IV day 1

Every 21 days for 8 cycles

APPENDIX V

POSTGRADUATE OFFICE



FACULTY OF MEDICINE
AHMADU BELLO UNIVERSITY TEACHING HOSPITAL
SHIKA - ZARIA, NIGERIA.



P. M. B. 06 Samaru Zaria
Phone: 069 - 551399
Fax: 069 - 555001
E - mail: abuthpg@yahoo.com

Your Ref: _____

Our Ref: ABUTH/PGO/COMM/9

20th March, 2009
Date: _____

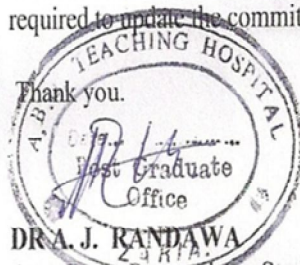
Olosukooba Amina Busola
Pharmacology and Clinical Pharmacy Dept
Ahmadu Bello University
Zaria

ETHICAL CERTIFICATE

Your application for ethical clearance on your proposal titled "AN EVALUATION OF THE THERAPEUTIC PROTOCOL USED IN THE MANAGEMENT OF BREAST CANCER AT AHMADU BELLO UNIVERSITY TEACHING HOSPITAL ZARIA". refers.

This is to convey ethical approval for you to commence the study. You would be required to update the committee of progress on your work.

Thank you.



DR A. J. RANDAWA
Asst. Dean, Postgraduate Studies/
Residency Training Co-ordinator.