THE RELATIONSHIP BETWEEN AGE AT FIRST DIAGNOSIS AND TREATMENT OUTCOME OF BREAST CANCER IN NAMIBIA

THESIS

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ABSTRACT

The purpose of this study was to evaluate the relationship between age at first diagnosis and outcomes of women treated of breast cancer at Windhoek central hospital between 2009 and 2011 and to describe and compare the outcomes of young and older patients in relation to socio-demographic and clinical factors. The study was a retrospective cohort study involving a document review of 334 women diagnosed and treated of breast cancer at Windhoek central hospital between 2009 and 2011. Patients were followed up from date of diagnosis to a period of 5 years after treatment. Patients were grouped into two groups defined as young (age≤40years) and older (age>40years) for analysis. Survival rates, metastases and recurrences were compared between the younger patients and the older patients. 19% were younger patients and 81% were older patients. Good outcome was defined as 5-year survival with no metastasis or recurrence and poor outcome as either death within 5 years or development of metastasis or recurrence within 5 years after treatment. 47.6 % of the older patients and 43.1% of the young patients had good outcomes. Statistical analyses indicated that young patients had an 8% increased risk (Crude RR=1.08, 95% CI of 0.85 to 1.38) of having poor outcomes than older patients and after adjusting for potential confounders the risk was found to be just 3% (adjusted RR=1.03, 95%CI 0.9 to 1.1). There was no statistical difference (p>0.05) between the outcomes of younger patients and older patients in the study. Predictively, older patients had higher overall 5- year survival rate of 56.5% compared to 52.3% of younger patients. The disease free survival rates for the older patients and the young patients were more or less similar (43% 5-year disease free survival for the young patients and 47% for the older patients).With regards to metastasis, 39.4% of the older patients and 49.2% of the young patients had metastases within 5 years after treatment. The study did not find any differences in risks of recurrence after treatment between the young patients and the older patients (4.6% for the young and 4.5% for the older group, RR =1.03, 95CI 0.3 to 3.5). Factors such as rural residence, nulliparity, unemployment and being single were linked to poor outcomes among younger patients. Clinical factors such as non-familial breast cancer, Stage II breast cancer, hormone receptor negative tumours and chronic /other illnesses were linked to poor outcomes in younger patients as well. Treatment commencement delays were more than 70days amongst all patients in Namibia, which could have resulted in very low overall survival rates of all patients.

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LIST OF ABBREVIATIONS AND ACRONYMS

BRCA - Breast Cancer Susceptibility Gene 1 OR 2

BSE - Breast Self-examination

CI - Confidence Interval

CT - Computed Tomography

DCIS - Ductal carcinoma in situ

DDT - Dichlorodiphenyltrichloroethane

DDT - Dichlorodiphenyltrichloroethane

DFS - Disease Free Survival

ER+/ER- - Oestrogen receptor positive/ negative

FNA - Fine Needle Aspiration

HER2 - Human epidermal growth factor receptor 2

HIV - Human Immunodeficiency Virus

HR - Hazard Ratio

HRT - Hormone Replacement Therapy

LCIS - Lobular carcinoma in situ

MRI - Magnetic Resonance Imaging

NOS - Breast cancer not otherwise specified

NST - Breast cancer of no special type

PCB - Polychlorinated biphenyl

PCB - Polychlorinated biphenyls

PET - Positron Emission Tomography

PR+/PR- - Progesterone positive/ negative

RR - Risk Ratio/ Relative Risk

SES - Socioeconomic Status

TNM - Tumour-Node-Metastasis

UICC - International Union against Cancer

UK - **U**nited Kingdom

WHO - World Health Organisation

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DEDICATION

This research paper is dedicated to my first-born daughter Hailey Chiridza. Let this achievement be a source of inspiration, which will take you through as you grow and as you pursue your goals in life.

It is also dedicated to my loving wife, Emildah, for her support, love and caring.

DECLARATION

I, Simbarashe Chiridza, hereby declare that this study is my own work and is a true reflection of my research, and that this work, or any part thereof has not been submitted for a degree at any other institution.

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CHAPTER 1

ORIENTATION AND BACKGROUND OF THE STUDY

1.1 INTRODUCTION

This chapter introduces the study and explains in detail the background of the study, the problem statement, the purpose, objectives and the significance of the study.

1.2 ORIENTATION OF THE STUDY

Breast cancer is the most frequently diagnosed cancer and the leading cause of cancer death among females, accounting for 23% of the total cancer cases and 14% of all the cancer deaths (Jemal, Bray, Center, Ferlay and Forman, 2011). Although breast cancer is thought to be a disease of the developed world, almost 50% of breast cancer cases and 58% of deaths occur in less developed countries (Ferlay , Shin ,Bray ,Forman ,Marthers and Rebelo , 2010). According to the latest World Health Organisation data published in May 2014, breast cancer deaths in Namibia reached 76 or 0.59% of total deaths in 2013. The age-adjusted death rate is estimated at 10.47 per 100,000 people and Namibia ranks number 139 in the world (WHO, 2014).

Prior research by Brandt, Garne, Tengrup, & Manjer (2015) clearly indicates that younger patients tend to have lower survival rates than older patients and this has been proven to be true for African-American women and White women from developed countries. Another study conducted in the United Kingdom on breast cancer outcomes of Asian women living in the UK did not show any significant difference on survivals between younger women and older women (Velikova, Booth, Johnston, Forman, & Selby, 2004).

According to Newman (2005) ,other developing countries such as India and Latin American countries presented an even greater proportion of breast cancer cases and deaths among young women as compared to older women.

Research done by Anders, Johnson, Litton, Phillips, & Bleyer, (2009) indicated that across all histologic subtypes and stages, breast cancer survival rates are comparatively lower for women less than 40 years of age than for older women. Young women with breast cancer tend to have a higher prevalence of adverse prognostic indicators, suggesting a more virulent form of disease compared with disease that is seen among older women (Shavers, Harlan, & Stevens, 2003). Young women have larger tumours, poorer grade tumours, more lymph node involvement, higher S-phase fractions, more aneuploid tumours, fewer hormone receptor positive tumours, earlier and more frequent local recurrences, and poorer overall survival and disease-specific survival (Shavers, Harlan, & Stevens, 2003). Chung, Chang, Bland, and Wanebo (1996) have found that women who were diagnosed with invasive breast cancer at 40 years of age and younger had a poor 5-year disease free survival of 60.8% second only to women older than 80 years of age. Surprisingly, a population-based study conducted in Switzerland showed that young women presented with larger tumours and more aggressive tumours, and it found no effect of age on survival (Rapiti et al., 2001). Results of a study in Saudi Arabia by Al-Idrissi , Ibrahim, Kurashi and Sowayan (1992) and another study in Singapore by Chia, Sankaranarayanan, Sankila, and Lee (2004) did not report an adverse effect of age on survival.

As indicated by Anders et al.(2009), that breast cancer is the most common malignancy in women under 40 years of age and approximately one third of breast cancer is diagnosed in women aged 70 years and older, it is therefore important to evaluate the relationship between age at diagnosis and breast cancer survival in

Namibian women. This is mainly because previous research done in other countries has proposed that young and old age may be adverse prognostic factors, although data is conflicting between regions.

1.3 STATEMENT OF THE PROBLEM

According to DeVita, Lawrence and Rosenberg (2011), in the past 50 years, there has been a rise in the incidence of breast cancers in many less developed countries, with the most notable increases in traditionally low-incidence African countries, such as Namibia. The reasons for these trends are not completely understood, but likely reflect changes in reproductive patterns, nutrition, and physical activity (DeVita et al., 2011). In line with this notable increase in breast cancer in Africa, the researcher has noticed a higher mortality and prevalence of post treatment metastasis of younger breast cancer patients in Namibia but this had not been proven through a systematic research. In 2009 there were 32 patients below 40yrs of age treated for breast cancer at Windhoek central hospital, 10 of them have died up to date and 4 had recurrences and 6 had brain and spinal metastases within a period of 3 years after treatment (Radiation Oncology statistics Windhoek central hospital, 2015). This is a cause for concern among younger female breast cancer patients.

Varying research results on the effect of age on outcomes between continents, coupled by differences in diagnostic and treatment methods between Africa and developed countries led the researcher to question if age at first diagnosis is related to breast cancer outcome in Namibia as it is in the western countries.

Therefore, it was significant to assess the relationship between age at first diagnosis of breast cancer and outcome of treatment in the Namibian context since treatment methods, diagnosis and socioeconomic lifestyles differ between women from developed countries and African women. In addition , a study of this nature has never been conducted in Namibia so little is known regarding the effect of age on outcomes of breast cancer in Namibian women.

1.4 PURPOSE OF THE STUDY

In line with the problem stated above, the purpose of this study was to determine the relationship between age at first diagnosis and treatment outcome of breast cancer in Namibian women and to verify whether breast cancer patients diagnosed at 40 years and below have poorer treatment outcome than those above 40. In addition, the study seeks to describe and compare socio-demographic factors and clinical characteristics that influence treatment outcomes of young and older patients.

1.5 OBJECTIVES OF THE STUDY

- To describe the frequency of treatment outcomes of breast cancer by socio-demographic and clinical characteristics of young and older patients.
- To determine the association between age at diagnosis and outcome of breast cancer treatment in Namibian women.

1.6 HYPOTHESES OF THE STUDY

Hypothesis 1

H0 =There is no relationship between diagnosis of breast cancer at 40 years and below and poor outcome

H1 = there is a relationship between diagnosis of breast cancer at 40 years and below and poor outcome

Hypothesis 2

Young patients

H0 = There is no relationship between the socio-demographic characteristic/clinical factos in this study and the outcome of breast cancer treatment in the young patients (age≤40)

H1 = There is a relationship between the socio-demographic characteristic/clinical factor in this study and the outcome of breast cancer treatment in the young patients (age≤40).

Older patients

H0 = There is no relationship between the socio-demographic characteristic/clinical factor in this study and the outcome of breast cancer treatment in the older patients (age>40)

H1 = There is a relationship between the socio-demographic characteristic/clinical factor in this study and the outcome of breast cancer treatment in the older patients (age>40).

1.7 SIGNIFICANCE OF THE STUDY

The results of the study will bring useful knowledge on the relationship between age at diagnosis and treatment outcome of breast cancer patients in Namibia. This will in turn be used by policy makers and health workers to formulate strategies aimed at reducing the impact of age on breast cancer treatment and survival, thus improving the survival rates of breast cancer patients in Namibia.

Currently treatment methods are the same for older and younger patients and young women are at particular risk of emotional and psychosocial problems, and require appropriate support from age and disease specific psychosocial and medical challenges such as loss of body image due to total mastectomy, and sexual dysfunction due to therapy or disease.

This study results will expose socio-demographic and clinical factors that might contribute to poor treatment outcomes of breast cancer patients and this will help in developing strategies and treatment/diagnostic methods that can be used to improve breast cancer treatment outcomes among Namibian women.

1.8 DEFINITION OF TERMS

Breast Cancer: Refers to abnormal growth of cells in the breast tissue. These tumours are invasive and can spread to other organs in the body such as the lung, brain and bone. In Namibia, breast cancer diagnosis is initiated at clinics where the health worker or the patient identifies lumps or any abnormalities on the breast. The patient is usually referred for a mammogram on the breast to identify the tumour.

Definitive diagnosis is usually performed through a biopsy, which will result in a histological report containing stage of cancer and the histological type and grading. If diagnosis of cancer has been done, the patient is referred to an Oncologist for further management at Dr A B May cancer centre.

Radiotherapy: Is the use of high-energy rays, usually x-rays and similar rays (such as electrons) to treat disease. It works by destroying cancer cells in the area that is treated. Although normal cells can also be damaged by radiotherapy, they can usually repair themselves, but cancer cells cannot.

Radiotherapy treatment in Namibia is done at Dr A B May Cancer centre with the use of a Cobalt 60 machine that produces high energy gamma rays. Radiation therapists are responsible for the administration of radiotherapy treatment to the patient at the centre.

Chemotherapy: Is a category of cancer treatment that uses one or more anti-cancer drugs that are destructive to malignant cells and tissues. Chemotherapy may be given by mouth, injection, or infusion, or on the skin, depending on the type and stage of the cancer being treated. Oncology nurses and oncologists are responsible for the administration of chemotherapy drugs at DR A. B May Cancer centre. Chemotherapy and radiotherapy can be done concurrently or one after the other as adjuvant treatment.

Mastectomy: Refers to the surgical removal of one or both breasts, partially or completely. A mastectomy is usually carried out to treat breast cancer. The initial stage of treatment of breast cancer in Namibia is usually surgery, followed by radiotherapy and chemotherapy. The oncologist refers the patient to a surgeon for mastectomy, specifying the type of mastectomy to be done to the patient.

Prognosis: In cancer, it generally refers to the probable course or outcome of treatment especially in chances of recovery. Poor prognosis would mean very low chances of survival or high chances of metastases and recurrences.

Outcome of cancer treatment: This refers to the end result after treatment of cancer. Measures such as mortality and morbidity assess the unintended consequences of treatment in a very concrete, measurable way, while survival and recurrence rates similarly depict whether the treatment has achieved its intended goal.

For the purposes of this study, the researcher defined good outcome as 5-year survival with no metastasis or recurrence and poor outcome as either death within 5 years or development of metastasis or recurrence within 5 years after treatment.

1.9 SUMMARY

There has been a marked rise in breast cancer incidence rates amongst African women especially in the Sub-Saharan Africa, which is characterised by high mortality rates especially in the younger women below 40 years of age. This study focused on determining if younger women diagnosed of breast cancer in Namibia have a poorer outcome as compared to older women and to establish the link between age at diagnosis and outcomes with regards to socio-demographic factors and clinical characteristics of the women diagnosed of breast cancer in Namibia. This chapter explained the background, purpose of the research, problem statement and the setting of the research. It is anticipated that the research findings will increase our knowledge on the general trends and outcomes of breast cancer patients especially the younger women in the Namibian setting and this will in turn help in the improvement of the management of younger women diagnosed of breast cancer in Namibia. The next chapter presents the literature review

CHAPTER TWO

LITERATURE REVIEW

2.1 INTRODUCTION

This chapter covers the literature review in relation to this study in terms of types, source, theme and content. It also forms the basis of information that will be used in the conduction and interpretation of the research results. A literature review is a critical and in-depth evaluation of previous research. It is a summary and synopsis of a particular area of research, allowing anybody reading the paper to establish why a particular research is conducted (Fulton & Krainovich-Miller, 2010). In this study, the researcher obtained and compiled various breast cancer literature from published journals, textbooks, newspapers, web sources and reports. The literature review detailed different aspects of breast cancer, and the comparison between young and old age female breast cancer with regards to prevalence, outcomes and management globally and in Africa.

2.2 WHAT IS BREAST CANCER?

Cancer is an abnormal growth of cells caused by multiple changes in gene expression leading to a dysregulated balance of cell proliferation and cell death and ultimately evolving into a population of cells that can invade tissues and metastasise to distant sites, causing significant morbidity and, if untreated, death of the host (Ragunath, Reddy, Abhinand & Ahmed, 2012). Breast cancer is a malignant neoplasm originating from breast tissue, most commonly from the inner lining of milk ducts or the lobules that supply the ducts with milk (Ragunath, Reddy, Abhinand & Ahmed, 2012).

According to DeVita, Hellman & Rosenberg (2011), it is a heterogeneous disease fundamentally caused by progressive accumulation of genetic aberrations, including point mutations, chromosomal amplifications, deletions, rearrangements, translocations and duplications.

2.3 WORDWIDE BREAST CANCER STATISTICS

Breast cancer is the most frequently diagnosed cancer and the leading cause of cancer death worldwide among females, accounting for 23% of the total cancer cases and 14% of all the cancer deaths (Jemal et al, 2011). Although breast cancer is thought to be a disease of the developed world, almost 50% of breast cancer cases and 58% of deaths occur in less developed countries (Ferlay et al., 2010). Breast cancer is now also the leading cause of cancer death among females in economically developing countries, a shift from the previous decade during which the most common cause of cancer death was cervical cancer (Jemal et.al, 2011). According to Globocan (2013), in 2012, 1.7 million women were diagnosed with breast cancer and there were 6.3 million women alive who had been diagnosed with breast cancer in the previous five years.

Since the 2008 estimates, breast cancer incidence has increased by more than 20%, while its mortality has increased by 14%. Breast cancer is also the most common cause of cancer death among women (522 000 deaths in 2012) and the most frequently diagnosed cancer among women in 140 of 184 countries worldwide. It now represents one in four of all cancers in women (Globocan, 2013).

According to Ferlay et al. (2013), incidence of breast cancer has been increasing in most regions of the world, but there are huge inequalities between rich and poor countries. Incidence rates remain highest in more developed regions, but mortality is relatively much higher in less developed countries due to a lack of early detection and access to treatment facilities. For example, in Western Europe, breast cancer incidence has reached more than 90 new cases per 100 000 women annually, compared with 30 per 100 000 in eastern Africa. In contrast, breast cancer mortality rates in these two regions are almost identical, at about 15 per 100 000, which clearly points to a later diagnosis and much poorer survival in eastern Africa (Ferlay et al., 2013).

2.4 EPIDEMIOLOGY OF BREAST CANCER IN AFRICA

Breast cancer is the second most common cancer among women in Sub-Saharan Africa, accounting for 16.8 percent of all female cancers. Central, West, and East Africa appear to have lower incidence rates than Southern Africa, the latter estimated at 33.4 per 100,000. An estimated 48,600 cases occurred in Sub-Saharan Africa in 2002 (Sitas, Parkin, Chirenje, Stein, Mqoqi and Wabinga, 2006). In Sub-Saharan Africa, higher incidence rates and relative frequencies of breast cancer have been reported in association with urban residence than with rural residence (Oettlé and Higginson, 1966; Schonland and Bradshaw, 1968), but data are sparse. The incidence of breast cancer is much higher among white women in Africa than among black African women; for example, in Harare between 1993 and 1995, the incidence was 127.7 per 100,000 in whites and 20.4 in blacks (Chokunonga, Levy, Basset, Mauchaza, Thomas and Parkin, 2000). These differences may be a reflection of the distribution of lifestyle factors thought to be important in the development of breast cancer, for example, low parity and high body mass.

According to the Cancer Association of Namibia (2014), breast cancer is the leading cancer affecting women in Namibia and many women still neglect to go for screening, which is very important in detecting cancer early and giving one a better chance to receive treatment. In 2005 there were 179 cases of breast cancer reported in Namibia, but by 2012 the number had increased to 407 (Cancer Association of Namibia, 2014).

The government of Namibia does not have a cancer registry that would indicate the prevalence and survival rate of breast cancer so it is not very clear how high the numbers are especially in rural areas where people have little access to health facilities (Marketing, 2015). In 2005 there were 179 cases of breast cancer reported in Namibia, but by 2012 the number had increased to 407 and it has been noted that more younger women are being diagnosed of breast cancer than previous decades although this information is not well documented (Cancer Association of Namibia, 2014). According to the latest WHO data published in 2014, Breast Cancer Deaths in Namibia reached 76 or 0.59% of total deaths. The age adjusted Death Rate is 10.47 per 100,000 of population and these statistics ranks Namibia number 139 in the world (WHO, 2014).

2.5 RISK FACTORS OF BREAST CANCER

According to DeVita, Hellman and Rosenberg, (2011), multiple factors are associated with an increased risk of developing breast cancer, including increasing age, family history, exposure to female reproductive hormones (both endogenous and exogenous), dietary factors, benign breast disease, reproductive history, and environmental factors. It has been estimated that approximately 50% of women who develop breast cancer have no identifiable risk factor beyond increasing age and female gender. Hence, just being a female is the major risk factor in having breast cancer (DeVita et al., 2011).

A family history of breast cancer has long been recognized as a risk factor for the disease. According to "Breast Cancer Risk and Prevention", (2015), it's important to note that most women (about 8 out of 10) who get breast cancer do not have a family history of the disease, but women who have close blood relatives with breast cancer have a higher risk of the disease. Having a first-degree relative (mother, sister, or daughter) with breast cancer almost doubles a woman's risk and having two first-degree relatives increases her risk about 3-fold ("Breast Cancer Risk and Prevention", 2017).

DeVita et al. (2011), explained that mutations in the breast cancer susceptibility genes BRCA1 and BRCA2 are associated with a significant increase in the risk of breast and ovarian cancer and account for 5% to 10% of all breast cancers.

According to Pike, Gerkins, Casagrande, Gray, Brown and Henderson (1979), a prolonged or increased exposure to oestrogen is associated with an increased risk for developing breast cancer whereas reducing exposure is thought to be protective. Therefore, according to Trichopoulos, MacMahon and Cole (1972), factors that increase the number of menstrual cycles are associated with an increased likelihood for developing breast cancer, such as early age at menarche, nulliparity, and late onset of menopause. When compared with nulliparous women, uniparous women have an elevated risk of breast cancer soon after delivery, which only declines some years later (Robertson and Boyle, 1998).

Breastfeeding particularly for long periods lowers the risk of breast cancer diagnosis (DeVita et al., 2011). The combined effects of reproductive history and breastfeeding may account for the substantial differences of breast cancer prevalence between developed countries and developing countries.

(Hill, Giacosa & Caygill, 1994) reviewed about 20431 women in a study conducted and the results showed a significant increase in the risk of breast cancer associated with obesity. According to "Breast Cancer Risk Factors", (2016) being overweight is associated with increased risk of breast cancer, especially for women after menopause.

Observational studies by Alexander, Morimoto, Mink & Lowe (2010) have suggested that high fat diets were associated with higher rates of breast cancer than low fat diets and there may be a moderate protective effect from high vegetable consumption, but results for fruits, fibre and meat consumption are inconclusive. In contrast, there appears to be a positive association between alcohol and breast cancer risk, with risk increasing linearly with the amount of alcohol consumed (Singletary & Gapstur, 2001). Researchers at the American Cancer Society have found an increased breast cancer risk among women who smoke, especially those who start smoking before they have their first child (Simon, 2013).

Age is another important risk factor of breast cancer. Williams, Bulstrode & O'Connell (2013) observed that breast cancer is very uncommon before the age of 20 years, but the incidence gradually increases with age, and by the age of 90 years, one-fifth of women are affected.

In addition to that, Dumitrescu & Cotarla (2005) reported that less than 10 new cases were recorded per 100,000 women aged below 25 years, and increased up to 100 times by the age of 45 years. This indicates that the reproductive hormones produced by the ovaries and the adrenal glands are involved in the pathogenesis of breast cancer, since cancers that are not responsive to hormones will not show any appreciable change of incidence during the female reproductive period (Abdulkareem, 2013).

Furthermore, it is also believed that the age at menarche and menopause contribute to the duration of exposure to the carcinogenic effects of the gonadal (sex) hormones (Aguas, Martins, Gomes, Sousa and Silva, 2005). In support of this, the authors observed that the risk of breast cancer reduces by 15-20% for each year that menarche is delayed, and that late menopause at 55 years or older is a risk factor. This is because early menarche and delayed menopause will increase the duration of oestrogen exposure during a woman's reproductive years, but there has to be collaboration with genetic and environmental factors for breast cancer to develop (Abdulkareem, 2013).

According to Boyd, Guo, Martin, Sun and Stone (2007), mammographic breast density is an important risk factor of breast cancer, in addition to making breast cancer detection more difficult. Women with high breast density are four to five times more likely to get breast cancer than women with low breast density (Yaghiyan, Colditz, Collins, Schnitt, Rosner and Tamimi, 2011).

Ionizing radiation is a well-established mammary carcinogen (Ronchers, Erdman and Land, 2005). Increased breast cancer risk has been shown following acute radiation exposure from the atomic bombings in Japan and following high cumulative doses associated with the treatment of some diseases such as Hodgkin's lymphomas and multiple diagnostic radiographic examinations. It has been documented that the risk of breast cancer increases with the increasing radiation dose up to at least 40 Gy (Ronchers et al., 2005)).

Other environmental factors associated with breast cancer risk include organochlorine pesticides, dichlorodiphenyltrichloroethane (DDT) and polychlorinated biphenyls (PCBs), which were widely used for insect control in forestry, agriculture, and building protection (Vilnius, 2005). These have been long known to be highly carcinogenic and have been banned in many of the countries (Fattore, 2002).

Furthermore, breast cancer mortality and incidence rates have been found to be inversely associated with the increasing levels of total average sunlight energy (Boscoe & Schymura , 2002). Knight, Lesosky, Barnett, Raboud & Vieth, (2007) reported reduced breast cancer risks associated with increasing sun exposure from ages 10 to 19 years, weaker associations from ages 20 to 29 years, and no association for ages 45 to 54 years.

2.6 DIAGNOSIS OF BREAST CANCER

Diagnosis of breast cancer entails one of the most important components of successful breast cancer management. Breast cancer diagnosis involves a multidisciplinary approach with the use of imaging procedures such as mammography, MRI, CT, X-ray exam, and ultrasound. These imaging modalities aid in the definitive diagnosis of tumours together with tissue sampling. A biopsy remains the standard technique for diagnosing both palpable and non-palpable breast abnormalities (DeVita et al., 2013).

2.6.1 Medical history and physical exam

A thorough clinical assessment is required, including details of breast related symptoms, particularly breast pain, nipple discharge, changes noted in the skin (erythema, dimpling) or shape of the breast, indrawing or distortion of the nipple, axillary lumps and systemic symptoms of weight loss, anorexia, nausea, vomiting, bone pain, breathlessness, headache or motor or sensory disturbance (Kunkler, 2012). Symonds, Deehan, Mills & Meredith, (2012) also stated the importance of taking a full menstrual history including the onset of menarche, menopause, parity, age of first pregnancy, breast/bottle feeding and use of contraceptive pill and hormone replacement therapy.

2.6.2 Imaging modalities and mammography

Diagnostic mammography is commonly used to identify possible breast cancers in women who present with signs or symptoms of the disease (Barlow, 2002). A diagnostic mammographic examination usually consists of standard screening views and additional views using spot compression and/or magnification of a specific area. Although mammography may be sufficient to evaluate the clinical finding, additional imaging with ultrasound, ductography, MRI or other imaging techniques may also be done (Barlow, 2002. Mammography may also show enlarged nodes in the axilla. Of note is that about 15% of cancers are not detected by mammography and nearly 4% are neither palpable nor visible on mammography (Kunkler, 2012).

According to Kunkler (2012), ultrasound of the breast has an important role in helping to distinguish benign from malignant lesions, particularly when mammography is normal or equivocal. Colour Doppler ultrasound may show changes caused by increased tumour vasculature both in primary tumours and in lymph nodes (Kunkler, 2012).

Computed tomography is mainly used in evaluating the extent of breast cancer spread to other organs. It is most important in advanced breast cancer assessment. A CT scan may be used to detect tumours in organs outside of the breast, such as the lung, liver, bone, and lymph nodes.

According to Yang, Cho and Moon (2007), a combination of Positron Emission Tomography (PET) and CT is very useful in determining tumour multiplicity, localising the primary tumour in those patients with metastases of a breast origin when the mammography is indeterminate, and for those patients whom biopsy is not a desirable option (Noh, Kang, Yun, Kim, Chung and Lee, 1999).

PET/CT has a potential advantage over PET for evaluating small lesions in which the uptake may be artifactually lowered due to the partial volume effect of PET because areas of mild hyperglycolytic activity can be reliably assigned to normal or abnormal anatomical structures (Noh et al.,1999).

2.6.3 Biopsy and histological diagnosis

DeVita et al. (2013) clearly indicated that a biopsy remains the standard technique for diagnosing both palpable and non-palpable breast abnormalities. A biopsy is done when mammograms, other imaging tests, or the physical exam shows a breast change that may be cancer. A biopsy is the only gold standard verification method of breast cancer. The available biopsy techniques are fine needle aspiration (FNA), core cutting needle biopsy, and excisional biopsy (DeVita et al., 2013).

Non- palpable lesions can be biopsied with image guided core needle biopsy or surgical excision after wire localization. Ultrasound is used for lesions that are visualised with this modality while most calcifications require stereotactic mammographic guidance for biopsy (Dillion , Hill, Quinn, McDermott and O'Higgins, 2005). The use of core biopsy for the diagnosis of mammographic abnormalities is cost effective and increases the likelihood that the patient will be able to undergo a single surgical procedure for definitive cancer treatment especially young women who want to preserve their breast (Dillion et al., 2005).

In conclusion, a biopsy is one of the main definitive diagnostic procedures that should be done in evaluating presence of malignancy and stage of breast cancer disease.

2.7 STAGING OF BREAST CANCER

Staging is important in assessing the local, regional and metastatic spread of breast cancer since management may differ significantly depending on the extent of the disease (Kunkler, 2012). The major types of breast cancer staging include the TNM staging system, staging by clinical findings and the complex American Joint committee on Cancer staging system. The staging system that is used in this study is staging by clinical findings as this is much simpler and more commonly used in Namibia. Below is a table that shows the clinical staging of breast cancer.

Table 2.1 Clinical staging of Breast cancer

Stage	**Clinical findings**
I	Tumour is freely movable (on underlying muscle). No suspicious nodes
II	As stage I but mobile axillary nodes on the same side
III	Primary tumour more extensive than stage I, e.g. skin invaded wide of the primary mass or fixation to muscle. Axillary nodes, if present, are fixed: or supraclavicular nodes involved
IV	Extension beyond the ipsilateral chest wall area, e.g. opposite breast or axilla; or distant metastases

Adapted from Walter &Miller's Textbook of radiotherapy 7th edition pg. 436

2.8 PATHOLOGY OF BREAST CANCER

Invasive breast cancers constitute a heterogeneous group of lesions that differ with regard to their clinical presentation, radiographic characteristics, pathologic features, and biological behaviour (DeVita et al., 2013). The most common classification is invasive ductal and lobular carcinomas but that does not mean "ductal" originates from ducts and "lobular" originates from lobules (DeVita et al., 2013). Premalignant in-situ carcinoma may occur confined to the lobules (LCIS, lobular carcinoma in situ) or ducts (DCIS, ductal carcinoma in situ) without evidence of penetration of the basement membrane (Kunkler,2012).

DCIS now accounts for approximately 20% of breast cancers diagnosed by mammography. Laboratory and patient data suggest that DCIS is a precursor lesion for invasive cancer (Olivotto &Levine, 2001).

According to Walter &Millers (2012), inactivation of the tumour suppressor gene, e-cadherin is also associated with the development of LCIS and loss of tumour suppressor gene; p-53 is associated with the development of poorly differentiated DCIS. LCIS is associated with an in increased risk of tumour in both breasts, particularly infiltrating ductal carcinoma (Walter &Millers, 2012).

According to Kunkler (2012), a lump in the breast may be benign or malignant and benign lesions include cysts, fibroadenomas and papillomas. Malignant tumours mainly arise from the glandular epithelium (adenocarcinomas). According to WHO Classification of Breast Tumours, 4th Edition, (2013) breast cancers are classified as of no special type and special type. The majority (80%) are of no special type.

The terminology for the most common type of breast cancer has changed from invasive ductal carcinoma, not otherwise specified (NOS) to invasive carcinoma of no special type (NST) (Lakhani, 2013.) This group of breast cancers comprises all tumours without the specific differentiating features that characterise the other categories of breast cancers. The special type are classified into five classes, which are tubular, mucoid, cribriform, papillary, medullary and classic lobular (Lakhani, 2013).

The knowledge of the histological grading of the tumour is important because it has prognostic significance and determines the effective management methods for the disease.

2.9 TREATMENT OF BREAST CANCER

A multidisciplinary approach with input from the patient, the surgeon, the diagnostic radiologist, the pathologist, the general practitioner, the radiation oncologist, the medical oncologist, nurses, and other health professionals should be employed for a complete and optimal treatment of breast cancer (Rahman, 2011). The primary goal in the treatment of breast cancer is to control the disease with the aim of achieving cure. The other desirable outcomes of treatment include: to improve survival, minimise the risk of distant metastases and / or local recurrence, cosmesis, relief of symptoms, and the return to a quality life as close as possible to the life before diagnosis (Rahman, 2011).

The different modalities of treatment include surgery, radiotherapy, systemic therapy (cytotoxic drugs and hormonal manipulation) and treatment targeted at HER2 (Rahman, 2011).

2.9.1 Surgery of the breast

Surgery is considered the primary treatment for breast cancer. Goals include complete resection of the primary tumour, with negative margins to reduce the risk of local recurrences, and pathologic staging of the tumour and axillary lymph nodes to provide necessary prognostic information (Chustecka, 2014). Several different types of operations are available. The two main surgical removal of breast cancer are lumpectomy and mastectomy.

- **Breast conservation surgery**

According to Burstein, Harris and Morrow (2011), breast-conserving surgery (also called a lumpectomy, quadrantectomy, partial mastectomy, or segmental mastectomy) is a conservative surgical method in which only the part of the breast containing the cancer is removed.

The goal is to remove the cancer as well as some surrounding normal tissue. How much of the breast is removed depends on the size and location of the tumour and other factors (Burstein et al., 2011). The most popular choice of conservative therapy is a wide excision to obtain clear histological margins. This involves excision of the tumour with a margin of 1-2cm. If the margins are found to be involved, a re-excision to clear the margins is recommended. Usually a combination with post-operative radiotherapy is recommended (Kunkler, 2011).

Relative contraindications of lumpectomy include small breast size, large tumour size (>5 cm), and collagen vascular disease and absolute contraindications include multifocal disease, history of previous radiation therapy to the area of treatment, inability to undergo radiation therapy for invasive disease, first or second trimester of pregnancy and persistent positive margins after attempts at conservation (CMAJ,

1998). According to Walter and Miller's (2011), about 25-30% of patients who undergo conservative surgery with clear margins will have residual tumour at the time of re-excision or mastectomy. There is evidence that local recurrence rates following breast-conserving surgery are higher in younger women. Women under the age of 35 have a two to four-fold higher risk of local recurrence after breast conserving surgery and radiotherapy. This may be in part due to the difficulty of identifying cancers by mammography in younger women who tend to have more radiodense breasts or more aggressive biology of the disease (Kunkler, 2011).

- **Mastectomy**

A mastectomy, defined as the complete removal of the breast tissue, is a surgical option for patients diagnosed with breast cancer as well as a prophylaxis to reduce the risk of breast cancer in high-risk women (Feigelson, James, Single, Onitilo and Barney, 2013).

This procedure is also called a simple mastectomy. Some of the lymph nodes under the arm may be removed and assessed for cancer. A modified radical mastectomy may also be done which is surgery to remove the whole breast that has cancer, many of the lymph nodes under the arm, the lining over the chest muscles, and sometimes, part of the chest-wall muscles (Roses, Harris, Porter & Gumport, 1981). Mastectomy is indicated for patients who are not candidates for breast conserving therapy, patients who prefer mastectomy, and for prophylactic purposes to reduce the risk of breast cancer (Feigelson et al., 2013). As mentioned earlier, mastectomy has an advantage of less recurrence as compared with partial mastectomy but has a disadvantage of being more extensive and permanent loss of the whole breast.

According to Jameson, Fauci, Kasper, Hauser and Longo (2001), mastectomy patients may not require radiotherapy after surgery. It may sometimes be recommended in women who are at high risk of the cancer returning in the chest wall.

- **Axillary dissection**

Axillary dissection refers to the removal of the lymph node in the armpit (axilla) on the same side as the affected breast (NBCC, 2001). This is done because axillary lymph nodes are one of the commonest first sites for breast cancer to spread to. By removing some of the axillary lymph nodes during surgery, it is possible to find out whether the cancer has spread to these nodes. This may help plan future treatment such as chemotherapy or radiotherapy. Axillary dissection can also help by removing nodes the cancer has already spread to, reducing the likelihood that cancer will grow in the axilla (Jameson et al., 2001). Axillary dissection is usually associated with stiffness of arm, numbness or tingling feeling of hand and lymphoedema (NBCC, 2011).

2.9.2 Radiotherapy treatment of breast cancer

Radiation therapy is a cancer treatment that uses high-energy x-rays or other types of radiation to kill cancer cells or keep them from growing. As mentioned by Yang and Ho (2013), radiation therapy plays an essential role in the management of breast cancer by eradicating subclinical disease after surgical removal of grossly evident tumour. Adjuvant radiation reduces local recurrence rates and increases breast cancer-specific survival in patients with early-stage breast cancer after breast-conserving surgery and in node-positive patients who have undergone mastectomy (Yang and Ho, 2013). Some recent data suggests that radiotherapy following mastectomy and or breast-conserving surgery has a beneficial effect on survival (Vin-Hungh and Verschraegen, 2004).

Three randomised clinical trials of post-mastectomy radiotherapy from Canada and Denmark have shown a 9 – 10% improvement in overall survival at 10 years for patients that received radiotherapy compared with those who did not receive radiotherapy (Ragaz, Jackson, Plenderleith, Spinelli and Basco, 1997).

According to Kunkler (2013), despite the evidence from clinical trials of a reduction in local recurrence after postoperative radiotherapy, there is no evidence from published trials of a survival advantage from the addition of radiotherapy.

The prognoses and clinical courses of patients with distant metastatic breast cancer vary considerably depending on host and tumour characteristics. Once distant metastases occur, breast cancer remains a treatable condition but is no longer considered curable (Cardoso, Harbeck, Fallowfield, Kyriakides & Senkus, 2012). In this situation, radiotherapy might be performed with palliative intention and the primary goals of treatment include prevention and palliation of symptoms, maintenance or improvement of quality of life and prolongation of survival (Cardoso et al., 2012).

2.9.3 Hormonal and Cytotoxic therapy

Walter and Millers (2012) indicated that it is generally accepted that a substantial number of patients with apparently localised breast cancer harbour systemic micrometastases. These are currently beyond the detection of the conventional staging. According to DeVita et al. (2013), the goal of adjuvant systemic therapy is to prevent the recurrence of breast cancer by eradicating micrometastatic deposits of tumour that are present at the time of diagnosis. In current practice, three systemic treatment modalities are widely used as adjuvant therapy for early-stage breast cancer.

These modalities are endocrine treatments such as tamoxifen, AIs, or ovarian suppression; anti-HER2 therapy with the humanized monoclonal antibody, trastuzumab; and chemotherapy.

The selection of adjuvant treatment is determined by the biological features of the breast cancer (Berry, Cronin, Pleviritis, Fryback, Clarke and Zelen, 2005). Patients with tumours that are hormone receptor positive (either for ER, PR or both) are candidates for adjuvant endocrine therapy and patients with tumours that are HER2 overexpressing are candidates for trastuzumab (Henry, Somerfield, Abramson, Allison , Anders and Chingos, 2016). Chemotherapy is used irrespective of tumour hormone receptor status or HER2 status, based largely on features such as tumour size, nodal status and the patient's other health considerations (Berry et al., 2005).

Tamoxifen is the historic standard for adjuvant endocrine therapy. Research done by The Early Breast Cancer Trialists' Group (2005) showed that tamoxifen administered for 5 years results in a 41% reduction in the annual rate of breast cancer recurrence and 34% reduction in the annual death rate for women with ER positive breast cancer. Based on this data, The National Institute of Health Consensus Development Conference on Adjuvant therapy for Breast Cancer (2001) recommended the use of adjuvant tamoxifen for 5 years as adjuvant hormonal therapy for all women with hormone receptor-positive breast cancer irrespective of age, menopausal status, tumour size or nodal status.

Kunkler (2012) talks about the efficacy of ovarian suppression as an adjuvant therapy, which can reduce the activity of breast cancer. Medical ovarian suppression by goserelin (3.6mg given subcutaneously monthly) provides a reversible means of stopping ovarian function.

According to DeVita et al. (2013), recent observations suggest that ovarian suppression is a critical question for younger women with hormone receptor positive cancer. Young women, typically those younger than 35years who do not routinely experience amenorrhea with adjuvant chemotherapy appear to have a substantial worse prognosis than patients who do enter menopause with chemotherapy.

Adjuvant chemotherapy consisting of multiple cycles of polychemotherapy is well established as an important strategy for lowering the risk of breast cancer recurrence and improving survival (DeVita et al., 2013). Clinical studies have shown that chemotherapy can be of benefit to women with node positive and node negative breast cancers, with tumours that are either hormone receptor –positive or negative (DeVita et al., 2013). The potential impact of patient age on benefit from chemotherapy is of interest to our understanding of the effects of endocrine therapy. Thus, a possible explanation as to why chemotherapy could be of particular benefit in young women is chemotherapy-induced loss of ovarian function in premenopausal women (Lonning, 2012).

2.10 BREAST CANCER OUTCOMES

2.10.1. Survival, prognostic and predictive factors

The aim of breast cancer treatment is to cure the disease or to relieve symptoms caused by the disease with the main aim of improving quality of life. The favourable survival outcome in breast cancer is mainly due to two factors which are; detection of disease at an early stage with screening mammography, which is in common use, and advances in adjuvant systemic treatment—including chemotherapy, hormone therapy, and HER2-targeted therapy—that eliminates micrometastases after definitive breast cancer surgery (Cheng &Ueno,2012).

It is estimated that about 30–50% of patients with early to locally advanced breast cancer at diagnosis have relapses despite the use of adjuvant systemic treatment after surgery. In addition, about 5–10% of patients with breast cancer present with metastatic disease at diagnosis (Cheng &Ueno, 2012). Patients with metastatic disease at either initial diagnosis or relapse have traditionally been considered incurable with conventional treatment. However, although the median survival of patients with metastatic breast cancer who undergo treatment is only 24 months, 5–10% of those patients survive more than 5 years, and 2–5% survive more than 10 years (Falkson, Gelman, Leone & Falkson, 1990).

Traditionally, cancer has been considered cured when the disease is totally eliminated from the patient and the patient has a normal life expectancy without the threat of recurrence. However, even with the most advanced radiologic imaging or laboratory monitoring methods, it is not easy to be certain that cancer has been totally eliminated (Haybittle, 1991). If one follows a strict definition of cure, a patient can be considered cured only when he or she has a normal life span and dies without any evidence of either macroscopic or microscopic disease (Cheng &Ueno, 2012).

According to Cianfrocca (2004), prognostic factor is any measurement available at the time of surgery that correlates with disease-free or overall survival in the absence of systemic adjuvant therapy and, as a result, is able to correlate with the natural history of the disease. In contrast, a predictive factor is any measurement associated with response to a given therapy. Some factors, such as hormone receptors and HER2/neu overexpression, are both prognostic and predictive factors (Nemoto, Natarajan, Bedwani,Vana and Murphy, 1983). The most significant prognostic indicator for patients with early-stage breast cancer is the presence or absence of axillary lymph node involvement.

Furthermore, there is a direct relationship between the number of involved axillary nodes and the risk for distant recurrence (Saez, McGuire and Clark, 1985).

Tumour size correlates with the presence and number of involved axillary lymph nodes and is also an independent prognostic factor, with distant recurrence rates increasing with larger tumour size (Koscienly, Tubiana, Valeron ,Mouriesse , Contesso and Sarrazin, 1984). For node-negative patients, tumour size is the most powerful prognostic factor and is routinely used to make adjuvant treatment decisions. In general, patients with a tumour size of >1–2 cm warrant consideration of adjuvant therapy since they may have a distant recurrence risk of ≥20% (Cianfrocca, 2004).

The pathologic characteristics of the tumour have prognostic significance. Certain subtypes such as tubular, mucinous, and medullary have a more favourable prognosis than unspecified breast cancer. In conclusion, tumour grade does have prognostic significance and is primarily used to make decisions for lymph node-negative patients with borderline tumour sizes (Carstens, Gfeenberg, Franci and Lyon, 1985).

Peritumoural lymphatic vessel and vascular invasion (LVI) has been demonstrated to have prognostic significance for the risk of local and distant recurrence.

Lymphatic and vascular invasion does have prognostic significance and is primarily used to make decisions for lymph node-negative patients with borderline tumour sizes (Neville, Bettelheim, Gelber and Reed, 1992).

Another important prognostic factor in breast cancer is ethnicity and patient age at diagnosis. According to Elledge , Clark, Chamness and Osborne (994), African American and Hispanic women have a decreased survival from breast cancer compared with white women. The source of this disparity is likely multifactorial, including issues such as lack of access to care resulting in a higher stage at diagnosis.

There is data, however, to suggest that survival may be worse for African American women, even after adjusting for disease stage. Many studies evaluating the influence of age on outcome in breast cancer have been small and have had conflicting results (Hibberd, Horwood & Wells, 1983). Two relatively large trials have however, demonstrated a worse prognosis for patients younger than 35 years of age, even after adjustment for other prognostic factors (Nixon,Neuberg, Hayes, Gelman , Connolly and Schnitt, 1994).

Ethnicity and age at diagnosis may be used to identify a group of patients who have a higher risk recurrence. They should be used however, as an adjunct to other prognostic factors that are better validated such as tumour size (Nixon et al., 1994).

2.10.2 Follow-up for breast cancer survivors

Following initial treatment for breast cancer, patients require surveillance for local-regional tumour recurrence, contralateral breast cancer, and the development of distant metastatic disease. According to Kunkler (2013), the main goals of follow-up are the detection of loco-regional or metastatic recurrence, secondary primary tumour and contralateral breast cancer as well assessment and treatment of complications of treatment. In addition, follow-ups encourage compliance with ongoing therapy such as adherence to tamoxifen drugs intake as well as psychosocial support. Another goal of follow-ups is to maintain and monitor response to treatment and treatment-induced morbidity and facilitate rehabilitation.

2.10.3 Survival of breast cancer in Africa

Breast cancer survivorship has become a major issue, particularly in the last decade, as early detection and more effective therapies have led to an ever-increasing number of those transitioning from patient to survivor.

Since 1980, the overall survival rates of breast cancer have been increasing maybe due to advancements in diagnoses and treatment methods (Bodai & Tuso, 2015). Breast cancer survival rates for Sub- Saharan Africa are the lowest in the world with an average survival rate of less than 50% as compared to nearly 90% in the United States. In addition to being diagnosed at an advanced stage of the disease, which limits treatment options, cancer patients in most parts of Africa have limited access to timely standard treatment, further diminishing their chance of survival. According to a World Health Organization government survey of national capacity for cancer control programs in 2001, anti-cancer drugs were only available in 22% and affordable in 11% of the 39 African countries that participated in the survey (WHO, 2002).

Studies done by Adebamowo, Famooto, Ongundiran, Aniagwu and Akang (2008) on the clinical characteristics of breast cancers diagnosed in Africa summarised that the average age at diagnosis in most studies was late 40's, about a decade younger than in the US or other Western populations.

The majority of studies reported a high frequency of poorly differentiated tumours, although there has been considerable variation across studies, with rates ranging from 16–83%. Tumours tend to be large, with the vast majority being >2 cm. In addition, the majority of studies showed greater than 70% of patients had node positive or Stage III tumours, likely reflecting a combination of a lack of organized screening/detection programs and potentially more aggressive tumour presentation.

All these factors contribute to low survivals in African women with breast cancer. (McCormack , Joffe, van den Berg, Broeze and Romieu, 2013)

Consistent with the reported high prevalence of poorly differentiated and early-onset tumours, many of the tumours have been reported as hormone receptor negative.

However, reported rates of both ER (oestrogen receptor) and PR (progesterone receptor) negativity have varied substantially across studies, with the respective rates ranging from 36–79% and 30–87 %(Brinton ,Figueroa, Awuah, Yanery and Wood, 2014). Fewer studies have reported on HER2 status, but tumours have largely been classified as not expressing this marker. As a result, the rates of triple negative cancers have been high, with a number of studies showing that the majority of African women are diagnosed with such tumours (Brinton et al., 2014).

In addition, low breast cancer survivals in Africa may also be because of the delay in seeking medical attention until tumours are quite advanced. Reasons for this delay include a lack of knowledge surrounding cancer diagnosis and treatment, fear of surgery, non-acceptance of hospital treatment and/or preferences for alternative care, and challenges to receiving treatment (Yarney, Donkor, Opoku, Agyeman-Duah and Abakah, 2013). Delays in seeking treatment may reflect a sense of hopelessness and fatalism, particularly given that many women's experience with breast cancer has involved a death by a close family member or friend (De Ver Dye, Bogale, Hobden and Deressa, 2011).

Fear of mastectomy remains a prominent barrier to timely treatment, particularly given that husbands often leave their wives following such surgery. These delays are unfortunate, as it has been estimated that earlier detection methods could increase survival rates in Sub-Saharan Africa for one third of cancer patients (Ferlay et al., 2012).

A survey from the Union for International Cancer Control (UICC) showed that approximately 25% of Africans surveyed believed that cancer had no cure and only 36% believed cancer was a major health issue (Maree, Wright and Lu, 2013).

In a low-resource community in South Africa over 80% of the women were unaware of the warning signs of breast cancer. In another South African study, over one third of women were unaware about tests for breast cancer, with lack of knowledge being more common among older and rural women (Suh, Atashili, Fuh and Eta, 2012).

Education is clearly an important component of breast cancer prevention; a Nigerian study found that participants with higher education were 3.6 times more likely to practice breast self-examination (BSE) than those with lower education levels. In many cases, effective treatment is hindered by women initially seeking care from traditional healers (Pillay, 2002). A study of breast cancer patients in Cameroon indicated that 55% went to traditional healers before presenting for medical consultation (Kemfang, Yomi, Kasia ,Mawamba, Ekortarh and Vlastos, 2011). In Enugu, Nigeria, 17.5% of patients first sought aid from traditional healers, and this was significantly associated with greater than three months delay to presentation at a modern health facility (Ezeome, 2010). There are also logistical issues affecting access to care, including transportation problems. One South African study showed that women living long distances from a medical centre have a greater likelihood of being diagnosed with advanced tumours (Dickens, Joffe, Jacobson, Venter and McCormack, 2014).

In addition to problems with personal resources, there are limited facilities for detection and treatment of cancer in most African countries. Mammography facilities are sparse and this may not be the best approach for detection among young women who have dense breasts.

While radiotherapy units have increased by almost a third in the previous decade, the supply only meets 18% of the demonstrated need. For instance, in Namibia there was only one centre offering radiotherapy treatment to the whole country since 2006.

There are now two radiotherapy centres offering cancer care in Namibia. Chemotherapeutic agents are also often not available and, even when available, targeted use may be hindered by unreliable access to IHC agents and inaccurate classification of tumours (Kingham, Alatise, Vanderpuye, Casper, Abantanga and Kamara, 2013).

Although the number of treatment facilities must increase to counter the rising breast cancer incidence in sub-Saharan African, this undoubtedly will be a long process (Sefan, Elzawawy, Khaled, Ntaganda, Asiimwe and Addai, 2013). Therefore, more attention is needed on primary and secondary preventive efforts.

Several epidemiologic studies are ongoing, which hopefully will identify risk factors that may be amenable to intervention. It will also be important for these studies to understand the barriers to women seeking medical care early enough for treatment to be effective (Brinton et al., 2014)

2.11 YOUNG AGE AND OLD AGE FEMALE BREAST CANCER

2.11.1 Africa versus Developed world.

Approximately 7% of women with breast cancer are diagnosed before the age of 40 , and this disease accounts for more than 40% of all cancer in women in this age group**.** The incidence of breast cancer in young women varies according to race and ethnicity. In women over 45, breast cancer is more common in whites than in blacks.

However, black women under age 35 have more than twice the incidence of invasive breast cancer and three times the breast cancer mortality of young white women (Shavers, Harlan and Stevens, 2003).

In contrast, Native American women aged 20-44 have a lower incidence of breast cancer (relative risk [RR] = 0.7) compared to the general population (Baquet, Mishra, Commiskey, Ellison and DeShields, 2008). Women of all ages with low socioeconomic status, as well as young black and Hispanic women, and Native American women have an increased likelihood of presenting with advanced disease.

The average age of diagnosis of breast cancers among African women tends to be young, with estimates that a majority of cancers develop among women of 50 years or younger, a considerably younger age than seen in Caucasian populations. Although this is likely due in part to the fact that fewer African women live past 65 years of age compared to women in developed countries, this may not entirely explain the younger breast cancer ages (Sighoko, Kamate, Traore, Mallw, Coulibaly and Karidiatou, 2013). The fact that African-American women also tend to develop breast cancers at younger ages than Caucasian women in the United States suggests that there may be additional factors involved, including either genetic or environmental factors or an interplay of the two (Brinton et al.,2014). In addition, the fact that African women may develop unique breast tumour subtypes could also be an important contributory factor to the unusual age distribution noted in Africa (Akarolo, Ogundiran & Adebamowo, 2010).

2.11.2 Epidemiological and Clinicopathological features of young and older female breast cancers.

Althuis, Brogan ,Coates, Daling, Malone and Brinton (2003) state that personal risk factors for the early onset of breast cancer differ in interesting ways from those for postmenopausal breast cancer.

A positive family history of cancer is a strong risk factor for women under 35 years of age (RR = 3.22) and suggests the presence of a familial cancer syndrome.

Breast cancer at an early age is more likely to be associated with an increased familial risk, especially in women harbouring a germline BRCA1 mutation. According to Silvera, Jain, Howe, Miller and Rohan (2006), there is evidence that breast cancer risk is positively associated with body mass index in postmenopausal women. A large population-based study evaluating approximately 50,000 women indicated that the combination of obesity, high-energy (caloric) intake, and sedentary lifestyle is a risk factor in premenopausal women (Silvera et al., 2006).

Hormonal risk factors are somewhat different for women aged younger than 35 years in comparison to older women. Recent oral contraceptive use is a risk factor for early-onset breast cancer (RR = 2.26), particularly for estrogenic receptor (ER)-negative tumours. For women aged younger than 35 years, early childbearing and multiparty are risk factors, due to a short-term elevation in breast cancer risk for several months immediately following a birth (Rodriguez, Chew, Cress, Xing, McElvy and Smith, 2008). Other risk factors of young age breast cancers are previous irradiation to chest-wall, early age at menarche, heavy alcohol consumption, and a high intake of red meat. Intense physical activity and a high intake of certain fruits and vegetables (e.g., tomatoes) have been associated with a decreased breast cancer risk in premenopausal women (Slattery, Edwards, Murtaugh, Sweeney and Byers et al., 2007).

The comparison of the clinocopathological features of young and old female breast cancers has been a subject of the last decade. Traditionally, breast cancer arising in a younger host is characterised by a more aggressive phenotype (Kollias, Elston, Ellis, Robertson and Blamey, 1997).

Despite discrepancies in adverse prognostic features, younger age has been shown in several studies to be an independent predictor of adverse outcome (Albain, Allred and Cark, 1994; Anders, et al., 2008).

Research done by Nixon et al.(1994) where they evaluated the relationship between age, typical prognostic factors, treatment, and patient outcome, concluded that age younger than 35 proved to be a powerful independent prognostic factor in multivariate analyses, including all potential patient, treatment, and pathology variables, and this was true for time to recurrence. This thought-provoking analysis illustrates that young age, after adjustment for all known prognostic factors, proves to be a powerful predictor of recurrence risk and survival (Nixon et al., 1994). A second retrospective study evaluating more than 200,000 women in the SEER database, who were diagnosed with breast cancer between the years of 1988-2003, revealed that those under the age of 40 were 39% more likely to die when compared to those age 40 or older (hazard ratio [HR] = 1.39; 95% CI, 1.34-1.45)(Margenthaler,2008). Moreover, the highest mortality disparity between younger (<40 years) and older women (≥40 years) was present in early stage, rather than later stage disease. Specifically, women aged less than 40 were 44% and 9% more likely to die of stage I (HR = 1.44; 95% CI, 1.27-1.64) and stage II breast cancer (HR = 1.09; 95% CI, 1.03-1.15), respectively (Margenthaler, 2008).

This research evidence provides one of the first substantiations that breast cancer arising in a younger host is a unique entity characterised not only by adverse prognostic features, but also by a diverse underlying biology against which novel therapeutics should be targeted.

2.11.3 Treatment and Management of the young female breast cancer

Although the principles of managing invasive breast cancer in young women are the same as in older women, there are a number of management and therapeutic issues requiring special consideration. According to Shannon and Smith (2003), adolescents and young women are at particular risk of emotional and psychosocial problems, and require appropriate support from age- and disease-specific psychosocial and medical multidisciplinary teams.

One of the most import risk factors for local recurrence after breast conservation surgery is young age (below 40 years) as these patients were found to have a nine times higher risk of local recurrence after conservative surgery than patients over 60 years of age (Voogd, Nielsen, Peterse Blichert-Toft, Bartelink and Overgaard, 2001). With that eluded, for many reasons including development, function, body image, and quality of life, breast-conserving surgery, whenever possible, is obviously desirable for most young women. However, the two principle considerations when deciding between breast-conserving surgery and mastectomy are the risk of local recurrence, as well as the overall cosmetic result (Voogd et al., 2001).

As mentioned earlier, that young age is an important prognostic factor in breast cancer, all young women should be considered at high risk due to age alone, and so adjuvant therapies should be considered during management discussions (Goldhirsch, 2005). The challenge with the use of adjuvant therapies in young women is it raises issues of long-term side effects, including the induction of an early menopause, fertility impairment, and adverse effects on bone mineral density with chemotherapy and endocrine therapies, and of the development of a second malignancy with radiotherapy (Goldhirsch, 2005).

In addition to the appropriate use of radiotherapy, the current choices of adjuvant therapies for premenopausal patients include cytotoxic chemotherapy, ovarian ablation (by surgery, irradiation, or chemical ovarian suppression), anti-oestrogen therapy, or any combination of these modalities (Anders et al., 2009).

2.11.4 Differences in outcomes between young and elderly breast cancer patients

According to a research done by Bleyer, Anders, Johnson, Litton, and Phillips (2006) in US, across all histologic subtypes and stages, breast cancer survival rates are comparatively lower for women younger than 40 years of age than for older women. The lowest overall rate of cancer survival for females diagnosed during 2000-2005 was in those aged 25-29 years (72% 5-year relative survival), followed by 20- to 24-year-olds and 30- to 34-year-olds (75% and 76%, respectively) and 35- to 39-year-olds (80%). In contrast, relative survival for women between age 45 and 80 years was 84%-86%.

Fifteen to 19 year olds diagnosed with breast cancer have an 80% survival rate at 5 years, but there is some suggestion that this group may have increased mortality at older ages (Bleyer et al., 2006). This research concluded that younger women in the United States have poorer outcomes as compared to older women.

One other important factor to consider as mentioned by Anders et al. (2006) is that not only has the survival of women with breast cancer been lower in those younger than 40 years at diagnosis, the improvement in survival since 1975 has been poorer in the younger women. Hence, the discrepancy in survival between younger and older women became progressively worse over the last quarter century.

The relative improvement in older women and lack of progress in younger women may be due to the age-dependent biological differences, in that most of the therapeutic efforts have been conducted in middle age and older women with gratifying success, and not in young women, whose cancers require a different treatment approach (Anders et al., 2006).

Young African American women, which might resemble Sub-Saharan African women, have a disproportionately high breast cancer mortality rate in comparison to other racial groups. One study by Newman, Bunner, Carolin, Bouwman, Kosir, White, and Schwartz (2002) found that black women aged below 40 had larger tumour size, higher rates of local and distant metastasis, a higher proportion of ER-negativity, and a higher rate of medullary tumours. Relative risk for death was 1.94 for localised disease, 1.58 for regional disease, and 2.32 for metastatic disease compared to white women. However, young black women with stages III and IV disease had a worse prognosis despite standard therapy (Newman et al., 2002).

Another study conducted in Egypt, on the effect of age on breast cancer outcome, indicated that recurrence rates were significantly higher among young women 44.2% compared to 34.5% in older women. Five- year disease free survival in young women was 38.9% ± 4.6% compared to 48.6% ± 2.5% with adjusted hazard ratio of 1.22 95% CI (0.91–1.64), p = 0.19. Although the difference in disease free survival between young and old was about 10%, these results still tally with the fact that younger women have generally poor outcomes (Alieldin et al., 2013). The relationship between age at diagnosis and outcome of treatment in Southern African women has not been done and little is known if age is an adverse prognostic factor but it is generally known that the overall survival rates of breast cancer is low disregarding age as compared to other regions.

After black women, the highest mortality in young women is seen in Latinas, followed closely by white, non-Hispanic; Native American; and Asian women. Interestingly, and in contrast to women in the United States, women below 40 years of age in Asia did not have worse outcomes compared to older women, despite more advanced disease at diagnosis and higher-grade tumours, suggesting an environmental role for outcome discrepancies (Foo, Su, Chong, Chng, Tay, Low and Tan, 2005).

A population-based study in Switzerland showed that young women presented with larger tumours and more aggressive tumours, but it found no effect of age on survival (Rapiti et al., 2005). Results of a study in 1992 in Saudi Arabia and another study in 2004 in Singapore did not report an adverse effect of age on survival (Al-Idrissi, Ibrahim & Kurashi, 1992). A recent study in Japan aimed at identifying the prognostic value of age in premenopausal women younger than 40 years of age, found that age at diagnosis was not an independent prognostic factor on survival (Yoshida et al., 2011).

2.11.5 Definitions of Age: "Young" and "Elderly" in breast cancer.

Establishing the definition of "young" patients with breast cancer has been the subject of some controversy. Breast cancer in women younger than 40 years of age is relatively uncommon, reflecting only 5% of new breast cancers from 2002 to 2006. As according to Zhou & Recht, (2004), women "35 to 40 years of age or younger" defined a group of patients in which age was an independent risk factor for higher rates of recurrence. Other series have also suggested that the age of 35 might be most appropriate with which to define a "young" age group. Although controversy still exists, most series recognise patients younger than 40 years old as a "young" population (Oh et al., 2006). In this study, the researcher also adapted the below 40 years of age as younger patients and the above 40 as older patients for classification.

2.11.6 Breast cancer in young women as a public health concern in Namibia

There has been a significant rise in breast cancers among young African women, as well as Namibian women, which are characterised by poor outcomes and very low survival rates. Young African women under the age of 40 have breast cancer rates that are two times higher than white women of the same age are (Brinton et al., 2014). Furthermore, young African American women are three times as likely to die from breast cancer as white women of the same age are. This is also true in the Namibian context and has become a public health concern in Namibia. Once diagnosed, young Namibian women face unique challenges that are not either present or are less severe for older women (Cancer Association of Namibia, 2016). Having a breast health course of action and discussing the significant implications of a breast cancer diagnosis is essential for young Namibian women in taking care of their health (Brinton et al., 2014).

This increased proportion of breast cancer cases in young women is important because their diagnoses and tumour behaviour are usually more aggressive than in their older counterparts, with a disproportionate number of life-years lost because of cancer (Justo, Wilking & Jönsson, 2011). In Namibia, the increased risk of loco-regional recurrence, optimal methods for fertility preservation, precise psychosocial interventions for these women, challenges related to a longer survival period, and associated costs for the already compromised health care system remain uncertain and unexplored. The principles of care and treatment for invasive breast cancer in young women are the same as those for older women, although there are several particularly challenging age-related issues in this group, such as fertility impairment after cancer treatment, impaired cognition, and effects on bone mineral density (Armes et al., 2009).

Furthermore, these women are recognised to be more vulnerable to emotional distress and psychosocial problems needing special supportive interventions (Shannon & Smith, 2003). Known causes that diminish quality of life for these women include premature menopause induced by treatment, body image disturbance caused by surgery, compromised sexual function, and the constant threat of disease recurrence and death (Avis, Crawford &Manuel, 2005). Moreover, this population represents an important economically active population that often serves as primary moral and financial support to their families. It is also the age at which the professional phases, social lives, and family projects of these women are consolidated. Other particular issues that young breast cancer patients might face in Namibia are marital problems, violence and abuse, child-care issues, economic loss, stigma, and a perception of discrimination (WHO, 2013). Intervention and special programmes must be put in place to reduce this breast cancer burden on young women.

SUMMARY

This chapter discussed breast cancer epidemiology in Africa and globally. The literature on the relationship between age and outcomes of breast cancer was reviewed as well. It was observed that from various studies conducted, in other regions, young age at diagnosis was found to be related to poor outcomes but little research was done in Africa to determine if this was true in Sub-Saharan women and Namibia in particular. The following chapter is an outline of how the research was conducted and a description of the research design, data collection procedure as well as the ethical aspects of the study.

CHAPTER 3

RESEARCH METHODOLOGY

3.1 INTRODUCTION

The previous chapter presented in detail the literature review of breast cancer in relation to the study objectives. In this chapter, the researcher explains the methodology used in determining the relationship between age at first diagnosis and outcome of breast cancer patients in Namibia. This section presents an overview of the research design, study setting, population, sampling, data collection, data analysis and important aspects on research ethics.

3.2 RESEARCH DESIGN

Van Der Walt & Van Rensburg (2006) describe research design as comprising of a set of logical steps taken by the researcher in order to answer a research question and therefore forms the blueprint of the study. It is the overall plan, structure and strategy of investigations of answering the research questions (Christensen, 2014; Brink, 2009). In this study, the researcher employed a quantitative analytical epidemiological study design. An epidemiological study is an analytical study designed to reach causal inferences about hypothesised relationships between risk factors and outcome. Analytical studies identify and quantify associations, test hypotheses, identify causes and determine whether an association exists between variables, such as between an exposure and a disease (Segen's, 2011). Quantitative research as defined by Burns and Grove (2005) is a formal, objective, systematic process in which numerical data are used to obtain information about the world, and it is used to describe variables, examine relationships among variables and to determine cause-and-effect interactions between variables.

The study was a retrospective cohort study, which involved an assessment of records of patients following them up from time of diagnosis to until end of the 5-year follow-up period. The key characteristic of a cohort study is that at the starting point of the study, the study population is defined and study subjects are identified and classified into exposure groups. Subsequently, the outcome, usually the incidence of disease or death over a certain time span, is measured and related to exposure status. In this way, the effect of exposure on outcome can be expressed as a relative risk (Noordzij, Dekker, Zoccalu and Jager, 2009). Similarly, in this study, the subjects where all breast cancer women diagnosed and treated of breast cancer between 2009 and 2011 in Namibia, exposure being young age (40 years and below) and outcomes being survival, metastases and recurrence after 5 years. The non- exposed group was defined as the older patients. According to Euser et.al (2009), a major disadvantage of cohort studies is that it is not possible to establish causal effects. The exposure has not been allocated randomly and there is always a possibility that the association found may be explained by other variables, so-called confounders that differ between exposed and non-exposed subjects and that have an association with the outcome studied. In respect to this, outcomes of the two groups were compared with respect to clinical characteristics and epidemiological factors in order to explain the differential effects of those factors on outcomes of young patients and older patients.

3.3 STUDY SETTING

The study was conducted in Namibia, which is part of the Southern Africa. According to the demographic results obtained from the 2013 Census, Namibia has a population of 2.3 million comprising 13 ethnic groups which are: The Herero, the Damara, the Nama, the San (Bushmen), the Rehoboth Basters, the Coloureds, the Whites, the Caprivian, the Kavango, the Topnaars, the Tswana, the Himba and the Owambo.

Urban population is around 46.7% of the total population, which means the majority of people in Namibia stay in the rural areas. According to the Namibia Demographics Profile (2016), there are 1.24 million women and 1.19 million men, meaning that there are more women than men.

Currently Namibia has only one Class A hospital, which is the Windhoek Central Hospital. It is a highly specialised hospital to which all hospitals in the country refer their patients. Dr A. B May Cancer Centre located at Windhoek Central Hospital offers radiotherapy treatment, Nuclear medicine facilities and chemotherapy treatment for cancer patients. Namibia currently has two Oncology centres, which are responsible for the holistic management of breast cancer patients. During the study period, there was only one centre, at Windhoek Central Hospital (Dr A. B May Cancer Centre), which carried the load of managing breast cancer all over Namibia until recently in 2015 when another private centre was established. All patients from all over Namibia, in need of cancer treatment are referred to this centre for treatment, as it is the only state cancer care centre available currently. New patients that are referred from all over Namibia are first seen by the doctors and medical examinations are done to verify cancer diagnosis and stage of cancer. Each patient's clinical information regarding the cancer is compiled in a single file labelled with the name of the patient and a reference hospital number of the patient. This file contains all the medical history of patients, diagnostic procedures, results, all the treatments received and all routine follow-up reviews. Information from these files was used for the entire study.

3.4 POPULATION OF THE STUDY

A study population is any defined group that is selected as a subject for research. It includes all the members or units, of a group that can be clearly defined in terms of its distinguishing criteria, whether they are people, objects or events and having some common characteristics (Brink, 2009). The target population for the study was all Namibian women diagnosed and treated of breast cancer. Windhoek Central hospital was the only centre providing a holistic treatment of cancer in Namibia until 2015; this therefore means that all patients who got treatment of breast cancer in Namibia were treated at Windhoek Central Hospital. This made the study more representative of the whole of Namibia

3.4.1 Inclusion and Exclusion criteria

Only patients diagnosed and treated of breast cancer at Windhoek Central Hospital between January 2009 and December 2011 were included in the study. All age groups were included in the study. Patients with missing medical records, incomplete treatments, diagnosed and partially treated elsewhere were excluded from the study. Non-Namibians were also excluded from the study. The nationality of the patient is usually recorded in the patient file, and this made it easy to identify if the patient was Namibian or non-Namibia. Men diagnosed and treated of breast cancer in Namibia were excluded from the study as this study only targeted female breast cancer.

3.5 SAMPLE AND SAMPLING

Sampling is the process, or technique of selecting a suitable sample, or a representative part of a population for the purpose of determining parameters or characteristics of the whole population (Patton, 1990). For the purposes of this study, the sampling frame consisted of all female breast cancer patients diagnosed and treated of breast cancer between January 2009 and December 2011. The researcher employed convenience sampling method in recruiting medical records of patients diagnosed and treated of breast cancer between January 2009 and December 2011 from all the records at the cancer centre, because the outcomes were to be measured to a period of 5-years after treatment, meaning the outcomes were to be determined after December 2016 for the last group of patients who were treated in December 2011. This was more convenient to the researcher since the study was conducted in 2017 giving an adequate 5-year follow-up period after treatment.

A sample had to be withdrawn from this population but in this study, all subjects who met the inclusion criteria were recruited since the population was small. Hence, total population sampling method was used. Total population sampling is a type of purposive sampling technique where you choose to examine the entire population (i.e., the total population) that have a particular set of characteristics ("Total Population Sampling, 2017"). According to the hospital records, 420 patients were treated of breast cancer between 2009 and 2011 at Windhoek Central Hospital. Out of these, those with missing medical records, non-Namibians and those diagnosed and partially treated elsewhere were excluded from the study.

Epi Info sample size calculator was used to determine the size of the population of the cohort study.

The parameters used in determining the population size were power 80%, 95% confidence interval, Ratio of unexposed to exposed 1, hazard/risk ratio of 1.4 and a 50% outcome in unexposed group. These parameters were obtained from a similar research by Alieldin et al. (2014), which investigated the relationship between age at diagnosis and survival of non-metastatic breast cancer. The sample size calculator obtained a sample size of 309. After the exclusions, the remaining population size from the total 420 was 334, which is more adequate for the study as it is more than 309 obtained from the Epi info sample size calculator for cohort studies. Therefore, the sample size was 334 patient files.

3.6 DATA COLLECTION

Data collection is the process of gathering and measuring information on variables of interest, in an established systematic fashion that enables one to answer stated research questions, test hypotheses, and evaluate outcomes (Whiteney, Lindi & Wahl, 1998). In this study, patient data on breast cancer was collected from patient files. Data collection in this study covered the data collection instrument, validity and reliability, pilot study and the data collection procedure.

3.6.1 Data collection Instruments

The researcher formulated a data extraction form using ideas and components of an existing data collection form for cohort studies by Cochrane Collaboration Glossary (2010). All required data was obtained solely from patient files archived at Windhoek central Hospital. The data extraction form was divided into two sections. Section 1 was for recording the socio-demographic data of the patient.

Socio-demographic variables on the data extraction form were age, residence (urban or rural), marital status, number of children and employment. Section 2 recorded patient clinical information based on the diagnosis, treatment and outcomes of the breast cancer for each patient. Section 2 was subdivided into Part A and Part B.

Part A recorded clinical variables below:

- Date at first diagnosis
- Date at first treatment
- Date of completion of treatment- state if patient did not complete the prescribed breast cancer treatment
- Stage of disease at diagnosis
- Family history of breast cancer
- Receptor status ER and PR
- History of chronic illness/ HIV?
- HRT/hormonal use
- Smoking and Alcohol intake of the patient

Table 3.1 Definition of socio-demographic variables and their categories

Variable	**Type/scale**	**Categories**
Age	Numeric	continuous
Residence	Nominal/categorical	Urban & Rural
Marital status	Nominal /categorical	Married, Divorced, Widowed & Single
No. of children	Numeric	Continuous
Employment	Nominal	Yes & No

Table 3.2 Definition of clinical variables and their categories

Variable	**Type/scale**	**Categories**
Date of diagnosis	Interval	Continuous-any date
Date of first treatment	Interval	Continuous -any date
Date completed treatment	Interval	Continuous-any date
Stage of disease	Ordinal scale	I,II,III&IV
Family history of breast cancer	Nominal	Yes & No
Breast cancer receptors	Nominal/categorical	ER+PR+, ER-PR- ,ER+PR-&ER-PR+
Chronic illness/HIV	Nominal	Yes & NO
Hormonal use/HRT	Nominal	Yes &NO
Smoking and Alcohol	Nominal/categorical	Smoke only, Smoke &Alcohol, Alcohol only, None.

Part B of Section 2 recorded the outcomes of treatment. The condition of the patient was recorded after each yearly review for up to 5 years. Information such as metastases, recurrences and deaths were recorded in this section as well. The variables for each yearly review are defined in the table below. The overall outcome for the year for the patient was recorded as good outcome if the patient was well and disease free at the time of review. If the patient has died, it was recorded as such. Metastases and recurrences were recorded as such as well.

Table 3.3 Definition of outcome variables

Variable	**Type/scale**	**Categories**
Yearly outcomes(Yr1-Yr5)	Nominal	Good , Metastases , Recurrence, Died

3.6.2 Validity

Validity is described as the degree to which a research study measures what it intends to measure (Gravetter and Forzano, 2009). According to De Vos (2011), validity is the degree to which an instrument actually measures what it is intended to measure. The two main types of validity are internal and external validity. The internal validity refers to whether the results of the study (e.g. mean differences between intervention and control groups) are legitimate based on the way in which the groups were selected, the data was recorded or the data analysis was performed (Last, 2001). In this study, the researcher ensured three types of internal validity, namely: content, criterion validity and predictive validity.

Content validity refers to whether the tool appears to others to be measuring what it purports to measure (Peat, 2002). Content validity is concerned with the sampling adequacy or representativeness of the content of an instrument and focuses on whether the instrument measures the concept that it is intended to measure (De Vos , 2011). In this study, the researcher consulted and referenced previous research literature on breast cancer survival and its relationship to age. The researcher also consulted cancer specialists at Windhoek Central Hospital for their input on the content covered by this study, thus ensuring content validity.

Criterion validity refers to the use of already existing and well-accepted measures against which the new measure is compared (Peat, 2002). For the purposes of this study, the researcher ensured criterion validity by using a data extraction form for cohort studies by Cochrane Collaboration Glossary (2010). The researcher modified the form to meet the requirements of the current study.

Predictive validity is an important assessment test for a cohort study since it is the extent to which a test predicts some future or desired outcome, for example in this study, being young may be a risk factor of poor outcome in breast cancer (Schmidt and Hunter,1993). Predictive validity involves testing a group of subjects for a certain construct, and then comparing them with results obtained at some point in the future. In order to be able to test for predictive validity, the new measurement procedure must be taken after the well-established measurement procedure (Haynes, Richard & Kubany, 1995). By after, we typically would expect there to be quite some time between the two measurements (i.e., weeks, if not months or years). In this study, this was done by measuring the outcomes of patients up to a period of 5 years after their initial treatment. This 5-year period is an adequate time for the measurement to be valid and is a standard waiting period for cancer survival determination.

External validity refers to whether the results of the study are transferable to other groups (Last, 2001). The researcher in this study used the retrospective cohort study design in terms of which the study took place in the real-world environment. This created a relatively high external validity (Gravetter & Forzano, 2009). In addition, the research was done at the main and only hospital in Namibia where all breast cancer patients are referred. This meant that almost all breast cancer patients during the study period were included in the study, which therefore makes the results of the study more representative of the whole of the Namibian population.

3.6.3 Reliability

According to De Vos (2011), reliability can be defined as the accuracy or precision of an instrument. In general, reliability refers to the extent to which the independent administration of the same instrument consistently yields the same results when repeated, under comparable conditions. The researcher ensured the reliability of the data collection instrument by adopting a generic, slightly modified data extraction form for cohort studies. In addition, the exact similar data extraction form was used to collect data from all the patients' files.

3.6.4 Pilot Study

The term "pilot studies" refers to so-called feasibility studies, which are "small scale versions, or trial runs, done in preparation for the major study" (Polit et al., 2001). However, a pilot study can also be the pre-testing or "trying out" of a particular research instrument (Baker, 1994). One of the advantages of conducting a pilot study is that it might give advance warning about where the main research project could fail, where research protocols may not be followed, or whether proposed methods or instruments are inappropriate or too complicated. Accordingly, a pilot study may result in changes to the study methodology, data collection process and data analysis methods before the actual data collection starts (Booyens, 2001; Brink, 2006).

In this study, the pilot study was done with 10 patients who were diagnosed and treated of breast cancer during the year 2007 at Windhoek Central Hospital. The patients' files were drawn from the archives and data was recorded on the formulated data extraction tool.

The main goals of the pilot study were to determine if the sections in the data extraction form were adequate for the study, to evaluate the feasibility of the data collection within a certain timeframe and to identifying logistical problems, which might occur using proposed methods.

As a result of the pilot study, the researcher removed some unnecessary sections in the data extraction form such as employment specifics and left it as employed or non – employed.

During the pilot study, the researcher also noticed that sections which needed to be completed in the data extraction form, were a lot for each and every patient so the researcher had to look for an assistant who had to help in the real study data collection stage, as the work was overwhelming for one person. The pilot study also made the researcher aware of the fact that there were patient files which had missing information either on patient routine reviews or epidemiological data, so the researcher had to decide to exclude out of the study patient files which had more than 3 variables missing.

Results of the pilot study also forewarned the researcher that the general proportion of the younger cancer patients to the older cancer patient was low. There were no means of modifying the sampling techniques so as to make proportions almost equal as that is what it was, and would result in bias since we would have reduced size of the important study group.

3.6.5 Data collection procedure and process

The research was based solely on a document review of patient's files of breast cancer treated at Windhoek Central Hospital between 2009 and 2011.

The researcher did not have any contact with patient subjects and all the information used in the research was obtained solely from the patients' files archived at Dr A.B May Cancer Centre Oncology Department. The oncology department archives all oncology patients' files dating back 2007 up to now. Files of patients who were treated prior to 2007 were kept at a document warehouse outside the hospital.

The researcher sought the assistance of a research assistant, one of the radiation therapists working on Radiation and Oncology department as he was also knowledgeable on the whole procedure of the management of cancer patients at the hospital.

Data obtained from the patients' files was recorded on a data extraction form which had three sections, the socio-demographic data section, clinical data section and the post-treatment /outcomes reviews section.

Socio-demographic data section

Socio-demographic variables on the data extraction form were age, residence (urban or rural), marital status, number of children and employment status. This data was deemed necessary in view of the fact that the breast cancer diagnosis and or outcome are related to the number of pregnancies a woman had in her lifetime, activity lifestyle (linked to employment) and possibly lifestyle in the urban or rural area. All these variables can and may have confounding effects on the relationship between age and breast cancer survival among women.

Clinical data section

This section of the research instrument collected data on the clinical variables of the breast cancer patients.

Generally, patient clinical data is recorded during diagnoses and or before treatment has started on the patient. It forms the basis of the type of treatment, which will be given to the patient. Dates of first diagnosis and first treatment were recorded so as to enable the researcher to determine treatment delays that could have occurred during the course of treatment.

The stage of breast cancer at diagnosis for each patient was recorded as well in this section. Breast cancer stage is one of the determining factors in the outcome of treatment. Women diagnosed with early stage breast cancers tend to have higher overall survival rates than people diagnosed with stage III or IV breast cancers.

It has been determined that underlying tumour pathology such as higher tumour stage, nodal status, and presence of distant metastasis at diagnosis contribute to the worse outcome in breast cancer in women younger than 40 years of age (Chung ,Chang, Bland and Wanebo ,1996). Therefore, this was an important variable in the study since it affected the relationship between age at diagnosis and the survival of breast cancer women.

Under clinical data, the family history of the patients was recorded as well. This variable was important due to the fact that previous research indicate that women diagnosed of breast cancer at a younger age (age$\leq$ 40years) tend to present with aggressive tumours associated with mutation of BRCA1 and BRCA2 genes which are transferred genetically from their mothers. Thus familial breast cancer is very much associated with young female breast cancer. Thus in this study, this variable was important so that the researcher would be able to draw inferences on the association between familial breast cancer and age among Namibian women and then link it to the variances in survival between younger and older patients.

The data collection instrument also collected data on the receptor statuses of the breast cancer patients. This is an important variable as it is the cornerstone of breast cancer chemotherapy and hormone treatment. Tumours that are ER/PR-positive are much more likely to respond to hormone therapy than tumours that are ER/PR-negative (DeVita et al., 2013).

The researcher collected data on the history of chronic illness (not cancer) or HIV on each patient because HIV or any chronic illnesses like diabetes have a negative effect on the overall survival of breast cancer patients. This information was important in the analysis of the research results because other patients might have died because of chronic illnesses or HIV, and not of breast cancer.

Other variables that were recorded were alcohol intake, smoking and hormonal use/hormone replacement therapy. A research done by Bishop et al. (2014) indicated that among breast cancer patients treated with partial mastectomy and radiation therapy, current smokers have a significantly higher recurrence rate than prior smokers or never smokers. This shows that smoking is related to poor survival after breast cancer treatment, thus it was important to collect data on whether the patients were smokers or non-smokers.

With an increasing population of breast cancer survivors, there has been an emphasis on examining the effect of alcohol on breast cancer recurrence and survival. Thus far, studies of recurrence and mortality have shown mixed results, although this may be due to studies having few breast cancer specific mortality events and relatively low levels of alcohol consumption, making it difficult to observe a dose-response effect (Brooks & Zakhari, 2013; Patterson et al., 2010). With this information, the researcher deemed it necessary to collect data on alcohol intake of the study population.

Although hormone replacement therapy is associated with an increased incidence of breast cancer ((Holli, Isola and Cuzick, 2016), it has been associated with lower mortality from breast cancer or improved survival after a diagnosis of breast cancer in some (Hunt et al.,1987) but not all studies. In line with this, the researcher included the variable measuring hormone use or HRT in the data extraction so that inferences can made for study population.

Treatment outcome data and routine reviews

This section of the data extraction form collected data on the outcomes of the treatment. Treatment outcome was measured up to a universal period of 5 years post-treatment for each patient. The outcomes were measured individually by evaluating the survival of the patients up to a period of 5 years after treatment. In addition to survival, outcome was also measured by the assessment of occurrences of recurrences or metastases up to a period of five years after treatment. All cancer patients at Dr A. B. May Cancer Centre must come for routine reviews every three monthly after treatment for the first two years and then yearly after two years.

These routine reviews involve medical examinations, assessment of the patient for recurrences, post treatment complications and the general health condition of the patient. The doctor records all that information on the state of the patient in the patient's file on each routine review. Thus, the researcher was able to determine if the patient had recurrences, is still alive /date of death and any metastases that could have occurred within a period of 5 years after treatment.

STEP-BY-STEP DATA COLLECTION PROCESS

Step 1. Identify patients' book daily register

The nurses at the Oncology department record daily all the new breast cancer patients that come for treatment in a register book. The details of the patient recorded in the register are name, surname, date of birth, diagnosis, date of diagnosis and hospital identification number. The researcher identified all the patients who came between 2009 and 2011.

Step 2. Make a list of all the patients treated between 2009 and 2011

The researcher typed all the patients treated between 2009 and 2011 on the computer spreadsheet and automatically sorted them out in alphabetical order using Microsoft Excel out for easier access in the archives.

Step 3. Extract the files from the shelves where files are archived

The researcher withdrew the patients' files of all breast cancer patients treated between 2009 and 2011 according to the list from above. The files were arranged in alphabetical order in the shelves thus the researcher withdrew the files in alphabetical order as well, which made the procedure quicker. Files of deceased patients are kept in a separate storeroom from those who are still coming for their routine reviews, thus the researcher could easily get the information of deceased patients without having to visit Birth and Death registration offices. The files were returned to their respective shelves immediately after use.

Step 4. Prepare and enter patient information into a data extraction form

In this step, the researcher prepared a data extraction form for each patient file and used recorded information from the patients' files to enter data into the data collection instrument. Each patient's file had its own corresponding data extraction form. All sections were filled in, and those sections with missing data were recorded as such.

Step 5. Compile data from all the data extraction forms and create a line listing

A line listing was created from the data extraction forms for easier analysis. The line listing was created using SPSS and Epi Info since these statistical software packages were to be used for the analysis of the data. The next section presents the data analysis.

3.7 DATA ANALYSIS

The data analysis process was divided into two phases, the descriptive phase and the analytical phase. The descriptive phase revealed the patterns in the patients' data. A descriptive data analysis is performed to enable the researcher to present the quantitative descriptions of the data in a manageable form and to provide a meaningful summary that enables comparisons across groups or units (Aasland, 2008). In the descriptive phase, the study population was grouped into two groups, (those aged up to 40 years and those above 40 years), and their outcomes were described with regards to socio-demographic factors and clinical factors. The descriptions were stratified for both young patients and older patients to determine trends of outcomes with respect to socio-demographic factors and clinical factors. For the descriptive phase, overall outcomes were defined as either good outcome or poor outcome. Good outcome was specified as 5-year survival with no metastasis or recurrence and poor outcome as less than 5-year survival and or metastasis/recurrence developed within that period.

The comparative description of metastases, deaths and recurrences between the younger patients and the older patients were done as well in this phase. Graphs, pie charts and tables were used to describe the results of the study.

The analytic phase involved the determination of the statistical relationship between age at diagnosis and outcome of breast cancer patients. Age was dichotomised (40 years and below and above 40 years) for analysis. The older group (age>40years) was used as a control or baseline group as the younger group represented a special high-risk population (exposed group). Treatment outcomes were divided into two categories i.e. good outcome and poor outcome as defined above.

With the use of Epi Info software, the analysis was initiated by formulating 2x2 tables to determine risk ratios and 95% confidence interval. The exposed group were the young patients and the non –exposed group were the older patients. P-values and 95% Confidence intervals were calculated to determine if the relationships were statistically significant.

Secondly, comparative survival analysis involving the calculations and comparison of the overall survival proportions of the young group to the overall survival proportions of the older group was done. In addition, the disease-specific survival proportions were determined and compared between the two groups. Disease free survival rates (DFS) were determined for the young patients and compared to the older group. SPSS was used to plot the DFS curves for the younger group and the older group for comparison purposes.

The third stage involved the comparative analyses of occurrences of metastases and recurrences between the young patients and the older patients. Metastases and recurrences form part of outcomes as well.

Metastatic events were computed for both young and older patients separately and compared to evaluate which group had more metastatic occurrences after treatment. The mean period of onset of metastases was determined as well for both groups. This procedure was performed as well on the analysis of recurrences for both groups.

Since the relationship between age at diagnosis and treatment outcome might have been influenced by potential confounding factors (socio-demographic factors and clinical factors) such as stage of disease, receptor status, HIV/chronic illnesses, hormonal use and smoking, a stratification method was used to determine the effect of each factor on the relationship between age and outcome. This was done by comparing the risk ratio of that factor in each strata to the crude unadjusted risk ratio. The stratification method used in the study was more appropriate as it identified if the factor was a confounder or an effect modifier in the study. Another advantage of this method was that it could show the individual effect of that factor on the outcome of young and older patients. Lastly, the adjusted risk ratios and 95% confidence intervals were determined using the Mantel–Haenszel method. All these analyses were computed using Microsoft Excel, SPSS, and Epi info statistical software.

3.8 RESEARCH ETHICS

De Vos (2011) described research ethics as principles, rules and regulations that all researchers should follow and abide by while conducting research. A researcher is responsible to conduct a study in an ethical manner because any study involving human subjects is of special concern related to the protection of the rights of the human subjects.

The ethical considerations upheld in this study included submitting the research proposal to ethical review committees, obtaining permission to conduct the study at Windhoek Central Hospital, and confidentiality.

3.8.1 Ethical Review Committees

The research proposal was submitted to the Post-Graduate Studies Committee of the Faculty of Health Sciences as well as the Postgraduate Studies Committee of the University of Namibia. The University of Namibia Research Ethics Committee scrutinized the research if it met the required ethical standards and consideration and issued an Ethical Clearance Certificate to the researcher.

The researcher then applied for the approval and permission to conduct the study from the Research Ethical Committee of the Ministry of Health and Social Services. Permission was granted to carry out the research study.

3.8.2 Permission to use patients' files

After having obtained the approval from the Ministry of Health and Social Services, the researcher had to again apply for authorisation at Windhoek Central Hospital to use patients' documentation archived at Dr A B May Cancer Centre. Again, the Medical Superintendent granted permission to the researcher to use patients' files. With that done, the researcher approached Dr A B May Cancer Centre, Oncology department and asked the Matron and the Head of Department for permission to use patients' file for the research purposes. Permission was again granted.

3.8.3 Confidentiality

During the phase of data collection where the patients' documentation were reviewed, ethics were adhered to by marinating confidentiality of patients' information obtained from the archives. The Royal College of Physicians Committee (1999) advises that so long as the same strict code of confidentiality is observed when medical records are used for research purposes as in standard clinical practice, it may not always be necessary to ask for the patient's permission first. The college takes the view that in studies that would not otherwise involve contact with patients, access to medical records is acceptable without their individual consent provided that the medical officer or other appropriate official in the institution that holds the data gives written permission. In addition to maintaining participants' confidentiality, fake patient identification numbers were used on patients instead of their real names.

Patients' files were not taken out of the department, and data collection was conducted in the department. Patients' files were returned to their respective positions immediately after use so as to keep patients' information confidential.

Data was stored in an electronic format protected by an access password and the paper-based data in a lockable cabinet. In addition, the research results were presented as aggregated data and with no reference to specific names of patients.

3.9 SUMMARY

This chapter described in detail the research methodology and research design used in the research. In summary, the research was conducted using a retrospective cohort study of female breast cancer patients diagnosed and treated of breast cancer at Windhoek Central Hospital between 2009 and 2011. This chapter detailed the data collection procedure and steps, sampling, and how the raw data was analysed to obtain meaningful inferences from it. The important ethical aspects of the study were described as well at the end of the chapter.

CHAPTER 4

PRESENTATION OF FINDINGS AND DISCUSSION

4.1 INTRODUCTION

The preceding chapter outlined the methods used to conduct the study of the relationship between age and outcomes of women treated of breast cancer in Namibia. A retrospective cohort study design was deemed appropriate in the investigation of the relationship between age at diagnosis and outcomes of breast cancer patients. The researcher also explained the data collection procedure and steps, sampling, defined the study population and more importantly how the raw data was analysed to obtain meaningful inferences from it. Research data was collected from archived documents of 334 women treated of breast cancer between 2009 and 2011 at Windhoek Central Hospital and was recorded on data extraction forms as outlined in the previous chapter. All medical records of the sampled 334 patients meeting the inclusion criteria were available and assessed for study, giving a response rate of 100%.

This chapter focuses on presenting the findings obtained from the study. The findings are presented in two phases, the descriptive phase and the analytical phase. The descriptive phase reveals the patterns of the socio-demographic and clinical factors of the young and older women, relating them to treatment outcomes. The analytic phase involving the determination of the statistical relationship between age at diagnosis and outcome of breast cancer patients, as well as the effect of the socio-demographic and clinical factors on the relationship between age at diagnosis and outcome of breast cancer, is presented at the end. The discussion of the research findings will follow thereafter.

4.2 SOCIO-DEMOGRAPHIC DATA

4.2.1 DESCRIPTIVE PRESENTATION OF THE SOCIO-DEMOGRAPHIC DATA

The first discussion is the description of the socio-demographic data of the study group. The socio-demographic factors collected in the study were age, marital status, residence, employment status, number of children. These factors are described in the following graphs and tables.

4.2.1.1 Age distribution of the patients

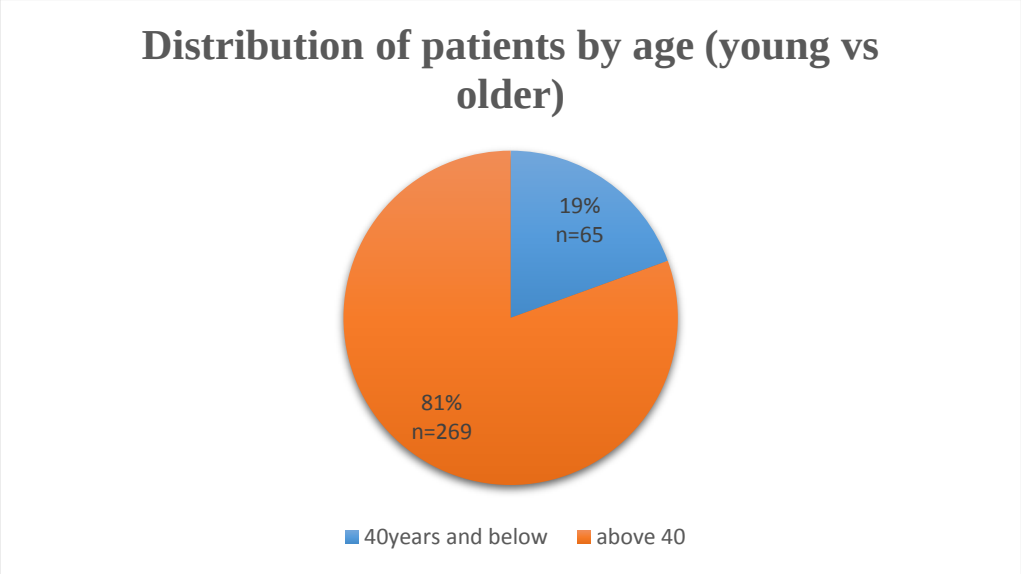


Figure 4.1 Distribution of the study population by age.

The pie chart above illustrates the proportions of the younger patients to the older patients in the study. A total of 334 patients were studied and 19% (n=65) were aged 40 and below whilst the majority, 81% (n=269) were above 40 years of age at first diagnosis of cancer.

The average age at diagnosis was 53.5 years and the mode being 61 years. The youngest patient was diagnosed at the age of 25 whilst the eldest patient was diagnosed at the age of 102.

4.2.1.2 Marital status, number of children, residence and employment status

Table 4.1: Marital status, number of children, residence and employment status of the young and older patients

Characteristics	**Young (≤ 40years)**			**Old (40 years)**	
Marital status	**Number**	**%**		**Number**	**%**
Married	35	53.8%		146	54.3%
Single	24	36.9%		84	31.2%
Divorced	4	6.2%		18	6.7%
Widowed	2	3.1%		21	7.8%
Total	65	100%		269	100%
Residence					
Urban	36	55.4%		158	58.7%
Rural	29	44.6%		111	41.3%
Total	65	100%		269	100%
No. of children					
0	1	1.5%		49	18.2%
1	0	0%		5	1.9%
2	12	18.5%		77	28.6%
3	23	35.4%		56	20.8%
4 or more	29	44.6%		82	30.5%
Total	65	100%		269	100%
Employment					
Employed	50	76.9%		187	69.5%
Not employed	15	23.1%		82	30.5%
Total	65	100%		269	100%

The table above shows that more than half of both young and older patients were married and about a third were single. Very few patients in both groups were either divorced or widowed. Concerning residence, a similar trend was seen between the young patients and the older patients. More patients were residing in the urban areas than in rural areas for both young and older patients. The mean, mode and median for the number of children for the older patients were three. Similarly, the mean number of children for the younger patients was three, median 3 as well but mode was 4 children. The majority of patients (more than 70%) in the study were employed at the time of diagnosis as indicated by table above.

4.2.2 DESCRIPTION AND ANALYSIS OF THE SOCIO-DEMOGRAPHIC FACTORS IN RELATION TO OUTCOMES.

In this section, the socio-demographic factors are described and analysed in relation to the outcomes of the young and older patients. Cross-tabulations will be used to analyse the relationship between each socio-demographic factor and outcome of treatment in both young and older patients.

Table 4.2: Cross-tabulations of socio-demographic factors and outcomes of young and older patient

	YOUNG PATIENTS (age≤40)			**OLDER PATIENTS (age >40)**		
	Outcomes		**$\chi 2$ p-value Fisher's exact**	**Outcomes**		**$\chi 2$ p-value Fisher's exact**
MARITAL STATUS	**good**	**poor**		**good**	**poor**	
Divorced	1 (25%)	3 (75%)	**$\chi 2$ =4.769**	11 (61.1%)	7 (38.9%)	**$\chi 2$=15.22**
Married	19 (54.3%)	16 (45.7%)	**p =0.19**	70 (47.9%)	76 (52.1%)	**p=0.002**
Single	8 (33.3%)	16 (66.7%)	**Fisher's= 4.27**	23 (27.4%)	61 (72.6%)	**Fisher's= 15.4**
Widowed	0 (0%)	2 (100%)		13 (61.9%)	8 (38.1%)	
Total	**28 (43.1%)**	**37 (56.9%)**		**117 (43.5%)**	**152 (56.5%**	
RESIDENCE			**$\chi 2$ =22.8**			**$\chi 2$= 5.3**
Rural	3 (10.3%)	26 (89.7%)	**p=0.00**	39 (35.1%)	72 (64.9%)	**p= 0.02**
Urban	25 (69.4%)	11 (30.6%)	**Fisher's= 0**	78 (49.4%)	80 (50.6%)	**Fisher's=0**
Total	**28 (43.1%)**	**37 (56.9%)**		**117 (43.5%)**	**152(56.5%**	
NUMBER OF CHILDREN						
0	0 (0%)	1 (100%)	**$\chi 2$ = 5.2**	20 (54.1%)	17 (45.9%)	**$\chi 2$=30.7**
1	0 (0%)	0 (0%)		0	0	
2	2 (16.7%)	10 (83.3%)	**p= 0.15**	29 (72.5%)	11 (27.5%)	**p=0.0**
3	12 (52.2%)	11 (47.8%)	**Fisher's= 5.18**	39 (41.1%)	56 (58.9%)	
4 or more	14 (48.3%)	15 (51.7%)		29 (29.8%)	68 (70.2%)	**Fisher's =21.2**
Total	**28 (43.1%)**	**37 (56.9%)**		**117 (43.5%)**	**152 (56.5%)**	
EMPLOYE MENT						
Unemployed	0 (0%)	15 (100%)	**$\chi 2$= 14.7**	14 (17.1%)	68 (82.9%)	**$\chi 2$= 35**
Employed	28 (56%)	22 (44%)	**p=0.0**	103 (55.1%)	84 (44.9%)	**p=0.0**
			Fisher's= 0			**Fisher's=0**
Total	**28 (43.1%)**	**37 (56.9%)**		**117 (43.5%)**	**152 (56.5%)**	

The highest percentage of young patients who had good outcomes were married (54%) and the highest percentage of patients who had poor outcomes were divorced, followed by the widowed. For older patients, the greatest percentage of patients who had poor outcomes were single. The table above shows that the relationship between marital status and outcome was not statistically significant for younger patients as presented by the chi-square test result of 4.769 and p value of 0.19. Contrary, a statistically significant relationship between marital status and outcomes was seen in the older patients ($\chi 2=15.22$, $p=0.002$).

Generally, for both groups, more patients residing in rural areas had poor outcomes than those residing in urban areas. According to the chi-square test results, the relationship between place of residence and outcome of breast cancer was statistically significant in both groups.

All young women who did not have any children in their life had poor outcomes whilst about 50% of women who had three or four pregnancies had good outcomes. For older patients, slightly more than half of women who had two pregnancies or less had good outcomes. The cross-tabulation obtained a chi-square value of 5.2 and a p-value of 0.15 for the young group. This means that there is no relationship between number of children and outcome of breast cancer for the young patients. For the older patients as illustrated by a p value of 0.0, there is a statistically significant relationship between number of children and outcomes of breast cancer.

The results of the cross tabulation between outcomes of treatment and employment status indicated that for both young and older patients, a greater number of employed patients had good outcomes and a greater proportion of unemployed patients had poor outcomes.

The chi-squared test results and the p –values (p=0.0 for both young and older patients) show that there was a statistically significant relationship between employment status and outcomes for both young and older patients. The next discussion is on the descriptive presentation of the clinical factors of the study group

4.3 CLINICAL DATA

4.3.1 DESCRIPTIVE PRESENTATION OF THE CLINICAL FACTORS

Clinical factors associated with the management of breast cancer were collected for both the older patients and the younger patients using the data extraction forms. The clinical factors that are discussed in this section are:

- Treatment commencement delays
- Stage of cancer
- Family history of breast cancer
- Breast cancer hormone receptor status
- Chronic illness or any other illness (not cancer)
- Hormonal use/Hormone Replacement Therapy
- Smoking and Alcohol intake

4.3.1.1 Treatment commencement delays

Table 4.3: Presentation of delays in commencement of treatment

Treatment Delay (Days)	Minimum	Maximum	Mean	Std. Deviation	Co-efficient of variation
Older Patients	1.00	349.00	72.1	71.9	99.7%
Young Patients	20	136.00	72.8	43.1	59.1%

Table 4.3 shows that, the minimum delay between first diagnosis of breast cancer and commencement of treatment was one day in older patients and 20 days in younger patients. An important point to note is that the mean treatment commencement delay for both young patients and older patients was almost the same, approximately 72 days as shown in the table above. Although the mean delay was identical between the two groups, older patients had a higher coefficient of variation meaning that delays were more varied than in younger patients.

4.3.1.2 Stage of disease at first diagnosis

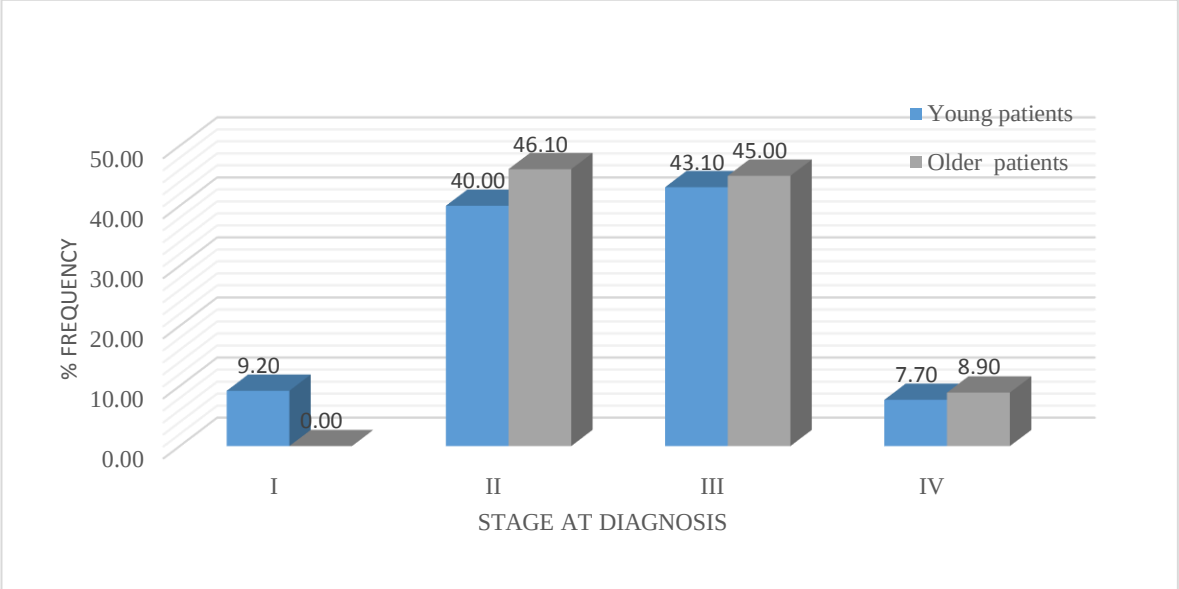


Fig 4.2 Percentage frequencies for stages at diagnosis of older and younger patients.

Fig 4.2 shows that the majority of patients were diagnosed with stage II and III breast cancer for both the older patients and the younger patients. Very few patients presented with stage I and IV breast cancer. None of the older patients presented with stage I breast cancer. The modal stage at first diagnosis of breast cancer for younger patients was stage III and stage II for older patients.

4.3.1.3 Breast cancer hormone receptor combinations

Table 4.4: Frequencies of Breast cancer hormone receptor combinations for both young and older patients

Receptor combinations	Older patients		Young patients	
	Frequency	Percentage	Frequency	Percentage
ER+PR+	170	63.2%	30	46.2%
ER+PR-	23	8.6%	10	15.4%
ER-PR-	60	22.3%	16	24.6%
Missing	16	5.9%	9	13.8%
Total	269	100.0%	65	100%

Table 4.4 compares the frequencies of breast cancer hormone receptors between the young patients and the older patients. The majority of the older patients (63.2%) had positive receptors for oestrogen and progesterone (ER+PR+), whilst the minority (8.6%) had oestrogen positive and progesterone negative. For the younger group, the highest percentage of patients (46.2%) had ER+PR+ as well, and the minority (15.4%) had ER+PR- .

4.3.1.4 Family history, chronic illness, hormonal use, smoking and alcohol

Table 4.5: Frequencies of family history, chronic illness, hormonal use, smoking and alcohol

Characteristics	**Young (≤ 40years)**			**Old (40 years)**	
Family history	**Number**	**%**		**Number**	**%**
Yes	23	64.6%		96	64.3%
No	42	35.4%		173	35.7%
Total	65	100%		269	100%
Chronic Illness/other illness					
Yes	13	20%		47	17.5%
No	52	80%		222	82.5%
Total	65	100%		269	100%
Hormonal use/HRT					
Yes	46	70.8%		166	61.7%
No	19	29.2%		91	33.8%
Missing	-	-		12	4.5%
Total	65	100%		269	100%
Smoking &Alcohol					
Smoking only	0	0%		4	1.5%
Alcohol only	22	33.8%		88	32.7%
Smoking and Alcohol	15	23.1%		71	26.4%
None	28	43.1%		106	39.4%

Table 4.5 above is a comparative presentation of the frequencies of family history, chronic illness, hormonal use, smoking and alcohol intake of the young and older patients. For both groups, the majority of patients did not have known family history of breast cancer. Regarding chronic illnesses, the larger proportion of the patients did not have any chronic illnesses, which were not cancer.

For both groups, only about 20% of the patients had chronic illnesses or other illnesses not breast cancer at the time of diagnosis of breast cancer.

The researcher recorded information of whether the patients were using any hormonal drugs or hormonal contraceptives before or at the time of diagnosis of breast cancer. Hormone replacement therapy and hormonal contraceptives are the most common forms of hormonal use amongst females. The majority (young, 70.8% and older 61.7%) were using hormones at the time of diagnosis of breast cancer. The percentage proportions of the young and older patients who smoked and drank alcohol were comparatively similar as shown in the table above. Very few patients smoked only and close to 40% did not smoke or drank alcohol in both groups.

4.3.2 DESCRIPTION AND ANALYSIS OF THE CLINICAL FACTORS IN RELATION TO OUTCOMES.

This section describes and analyses the relationship between the clinical characteristics of the patients and the outcomes of breast cancer treatment. The description and comparative analysis of the clinical characteristics in relation to outcomes is presented using cross-tabulations below.

Table 4.6: Cross-tabulation of stage of cancer, family history and receptors and outcomes of young and older patients**.**

	YOUNG PATIENTS (age≤40)			**OLDER PATIENTS (age >40)**		
	Outcomes		**χ2 p-value**	**Outcomes**		**χ2 p-value**
STAGE OF CANCER	**good**	**poor**		**good**	**poor**	
I	5 (83.3%)	1 (16.7%)	**χ2= 18.9 p=0.0 Fisher's =18.6**	0	0	**χ2= 20.2 p=0.0 Fisher' s =25**
II	5 (19.2%)	21(80.8 %)		59 (47.6%)	65 (52.4%)	
III	18 (64.3%)	10 (35.7%)		58 (47.9%)	63 (52.1%)	
IV	0 (0%)	5 (100%)		0(0%)	24 (100%)	
Total	28	37		117	152	
FAMILY HISTORY						
Yes	12 (52.2%)	11 (47.8%)	**χ2= 1.2 p=0.27 Fisher's =0**	41 (42.7%)	55 (57.3%)	**χ2= 0.04 p=0.84 6 Fisher' s=0**
No	16 (38.1%)	26 (61.9%)		76 (43.9%)	97 (56.1%)	
Total	28	37		117	152	
RECEPTOR COMBINATI						
ER+PR+	14 (46.7%)	16 (53.3%)	**χ2= 15.1 p=0.02 Fisher's = 16**	90 (52.9%)	80 (47.1%)	**χ2= 22.1 p=0.00 Fisher' s=24.7**
ER+PR-	8 (80%)	2 (20%)		1 (4.3%)	22 (95.7%)	
ER-PR-	1 (6.3%)	15 (93.8%)		21 (35%)	39 (65%)	
Missing	5 (55.6%)	4 (44.4%)		-	-	
Total	28	37		112	141	

For younger patients, a greater percentage of patients diagnosed with stage III cancer (64.3%) had good outcomes and a greater percentage of those diagnosed with stage II and IV had poor outcomes. For older patients, everyone diagnosed with stage IV had poor outcome and the outcomes of stage II and III patients were almost similar. The results of the chi-square test illustrate that the stage of cancer at diagnosis is statistically related to the outcomes for both young and older patients as indicated by the chi-square results (young group: $\chi 2$= 18.9, p=0.0, Fisher's exact test=18.6: older group $\chi 2$= 18.9, p=0.0), Fisher's exact =25.

According to the table above, a greater percentage, (61.9%) of young patients who did not have family history of breast cancer had poor outcomes and a lesser fraction (38.1%) had good outcomes. Table 4.6 above shows that there was no statistically significant relationship between family history of breast cancer and outcomes of treatment for both young and older patients.

According to the table above, there were no differences on outcomes of older patients and younger patients with ER+PR+. Almost all older patients (96%) with ER+PR- had poor outcomes. For younger patients, almost all patients with ER-PR- (93.8%) had poor outcomes. The relationship between breast cancer hormone receptor status and outcome was statistically significant for both groups as indicated by the p values which were less than 0.05.

Table 4.7: Cross-tabulation of chronic illnesses, hormonal use, HRT, smoking and alcohol and outcomes of young and older patients**.**

CHRONIC ILLNESSES						
Yes	3 (23.1%)	10 (76.9%)	**$\chi 2$= 2.7** **p=0.103 Fisher's =0**	17 (36.2%)	30 (63.8%)	**$\chi 2$= 1.2** **p=0.26 Fisher' s=0**
No	25 (48.1%)	27 (51.9%)		100 (45%)	122 (55%)	
Total	25	37		117	152	
HORMONAL USE/HRT						
Yes	25 (54.3%)	21 (45.7%)	**$\chi 2$= 8.1** **p=0.04 Fisher's =0**	69 (41.6%)	97 (58.4%)	**$\chi 2$= 1.** **p=0.49 Fisher' s=1.4**
No	3 (15.8%)	16 (84.2%)		41 (45.1%)	50 (54.9%)	
Missing	-	-		7 (58.3%)	5 (41.7%)	
Total	28	37		117	152	
SMOKING &ALCOHOL						
Alcohol only	9 (40.9%)	13 (59.1%)	**$\chi 2$ = 5.6** **p-value =0.06 Fisher's =5.4**	36 (40.9%)	52 (59.1%)	**$\chi 2$ =32.9** **p-value= 0.0 Fisher' s=33**
None	16 (57.1%	12 (42.9%)		66 (62.3%)	40 (37.7%)	
Smoke only	0	0		0	4 (100%)	
Smoke & Alcohol	3 (20%)	12 (80%)		15 (21.1%)	56 (78.9) %	
Total	28	37		117	152	

The greatest effect of chronic illnesses on the outcome of breast cancer was seen on young patients (76% of young patients who had chronic illness had poor outcomes and only 23.1% had good outcomes). In the older group, the differences on outcomes for those who had chronic illness were not as much as the younger patients.

The cross-tabulation obtained p-values of 0.1 for young patients and 0.26 for older patients. This means that the relationship between patient history of chronic illnesses, and outcome of breast cancer treatment was not statistically significant**.**

Table 4.7 above shows that a greater number of young patients using hormones had good outcomes (54.3%) and almost all patients who were not using hormones had poor outcomes (84.2%). Contrary, for older patients, hormonal use did not appear to change outcomes.

Hormonal use was significantly related to outcomes of treatment in young patients ($\chi 2$= 8.1; p=0.04). For older patients, the relationship between hormonal use/HRT with outcomes of treatment was not statistically significant ($\chi 2$= 1; p=0.49).

The table above shows that the majority of patients who had good outcomes in both groups were non-smokers and non-drinkers. A greater proportion of those who smoked and drank alcohol had poor outcomes. According to the chi-square test, the relationship between smoking or alcohol intake and outcomes of young patients was not statistically significant (p=0.06; $\chi 2$ =5.6) but the relationship was statistically significant in the older group (p=0.0; $\chi 2$ =32.9, Fisher's exact= 33).

4.4 DESCRIPTION OF THE OUTCOMES

This section is a descriptive presentation of the outcomes of treatment of the young and older patients. Outcomes were evaluated with respect to survival, metastasis occurrences and recurrences.

4.4.1 Proportions of those who survived after 5 years for young and older patients

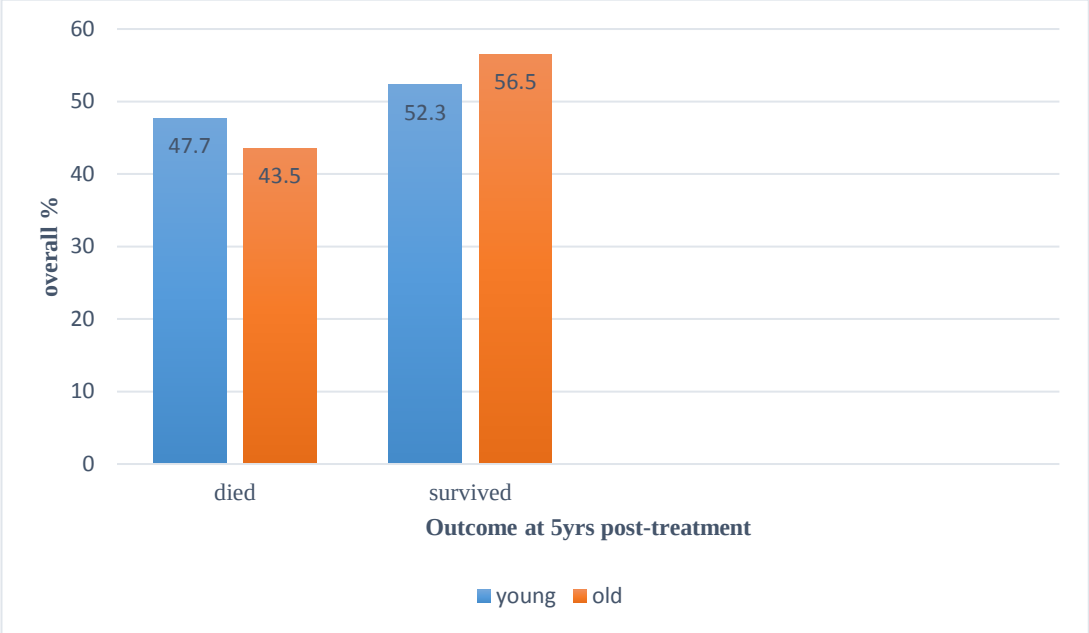


Fig 4.3: Survival proportions of the young and older patients after 5 years.

The graph above shows that 47.7% of the younger patients had died within 5 years after treatment and 43.5% of the older patients had died as well within 5 years after treatment. The percentage proportion of older patients who survived after years was marginally more than the proportion of young patients although the difference was not so significant.

4.4.2 Metastases

Table. 4.8: Comparison of the frequencies and onset of metastases between young and older patients

Period of onset of metastasis (Years.)	**AGE>40YEARS**		**AGE ≤40YEARS**	
	No. developed metastasis	**%**	**No. developed metastasis**	**%**
Less than 1 yr	18	6.7%	9	13.8%
1	62	23%	1	1.5%
2	16	5.9%	17	26.2%
3	10	3.7%	3	4.6%
4	-	-	2	3.1%
Total patients who had metastasis	**106**	**39.4%**	**32**	**49.2%**
No of patients who never developed metastasis within 5 years	**163**	**60.6%**	**33**	**50.8%**
Total	269	100%	65	100%
Measures of central tendency	Mean =1.16 yrs. Mode=1 yrs.		Mean = 1.62 yrs. Mode= 2 yrs.	

The table above shows that the majority of older patients who had metastases, developed them after the first year whilst younger patients developed them in the 2nd year. The average time of occurrence of metastases was 1.16 years for older patients and 1.62 years for younger patients. 36% of all older patients and 49.2% of younger patients developed metastasis after treatment.

4.4.3 Recurrences

Table 4.9: Comparison of frequencies and onset of recurrences between young and older patients

Period of onset of recurrences (Yrs.)	**AGE>40YEARS**		**AGE ≤40YEARS**	
	No. developed recurrences	**%**	**No. developed recurrences**	**%**
1-2 yrs.	0	0%	0	0%
3	3	1.1%	0	0%
4	8	3.0%	3	4.6%
5	1	0.4%	0	0%
Total patients who had recurrences	**12**	**4.5%**	**3**	**4.6%**
No of patients who never developed recurrences within 5 years	**257**	**95.5%**	**62**	**95.4%**
Total	**269**	**100%**	**65**	**100%**
Measures of central tendency(period of onset or recurrences)	Mean =3.8yrs. Mode=4 yrs.		Mean = 4 yrs. Mode= 4 yrs.	

Table 4.9 compares the occurrences of recurrences between the young patients and the older patients. Very few patients had recurrences after treatment in both groups (4.5% of the older patients and 4.6% of the young patients). The mean period of occurrence of recurrences for both older and young patients was about 4 years after treatment. No major differences were seen between the two groups regarding recurrences.

4.5 THE ANALYTICAL PRESENTATION OF THE OUTCOMES

This section presents the analysis of the outcomes of breast cancer treatment. The outcomes will be analysed and compared between the two groups (young vs. old). The analysis will be presented as follows; analysis of the overall outcomes of the two groups, comparative survival analysis, metastasis and recurrence and confounding factors.

4.5.1 ANALYSIS OF OVERALL OUTCOMES (GOOD OUTCOME VS POOR OUTCOME)

For the purposes of this study, the researcher defined good outcome as 5-year survival with no metastasis or recurrence and poor outcome as either death within 5 years or development of metastasis or recurrence within 5 years after treatment. Out of the 65 young patients, 28 had good outcomes and 37 had poor outcomes. Out of the 269 older patients, 128 had good outcomes and 141 had poor outcomes. In order to determine the relationship between young/old age and outcome, a 2x2 table was formulated and risk ratios were computed including the 95% confidence interval.

Table 4.10: 2X2 table for the relationship between age at diagnosis and outcome of breast cancer.

	OUTCOME			**Measures of association**
EXPOSURE	Poor outcome	Good outcome	Total	Crude Risk ratio=1.08 p- value= 0.5 95% CI (0.85 to 1.38)
Young	37 (56.9%)	28 (43.1%)	65 (100%)	
Old	141 (52.4%)	128 (47.6%)	269 (100%)	
Total	**178 (53.3%)**	**156 (46.7)%**	**334 (100%)**	

Without taking into consideration confounding factors, the table above shows that young patients had an 8% increased risk (Crude RR=1.08, 95% CI of 0.85 to 1.38) of having poor outcomes than older patients. The risk is relatively weak and can be considered as none, indicating that there is no association between age at diagnosis and outcome of treatment in women treated of breast cancer in Namibia. The association between age and outcomes obtained a p-value of 0.5 and 95% confidence interval of 0.85 to 1.38, which indicates that there is no statistically significant association.

4.5.2 ANALYSIS OF SURVIVAL POPORTIONS OF YOUNG AND OLDER PATIENTS

4.5.2.1 Overall survival rates

Overall survival rate is the actual percentage of patients still alive at some specified time after diagnosis of cancer. It considers deaths from all causes, cancer or otherwise. In this study, the overall survival was determined after a five-year period from date of diagnosis for both groups

Older patients (Above 40years)

Overall survival = $\frac{total\ number\ of\ patients\ alive\ after\ 5yrs}{total\ number\ of\ patients\ diagnosed\ of\ breast\ cancer}$ x 100%

=152/269*100%

=**56.5% (5-year overall survival rate)**

Young patients (40years and below)

Overall survival = $\frac{total\ number\ of\ patients\ alive\ after\ 5yrs}{total\ number\ of\ patients\ diagnosed\ of\ breast\ cancer}$ x 100%

=34/65 *100%

= 52.3% (5-year overall survival rate)

Fig 4.4: Calculations of overall survival rates of young and older patients

According to the results obtained from the calculations above, older patients had a higher 5-year overall survival rate than young patients

4.5.2.2 Net survival rates

Cause-specific survival is a net survival measure representing cancer survival in the absence of other causes of death. Disease-specific survival rate refers to "the percentage of people in a study or treatment group who have not died from a specific disease in a defined period of time. The time period usually begins at the time of diagnosis or at the start of treatment and ends at the time of death. Patients who died from causes other than the disease being studied are not counted in this measurement.

In this study, the researcher excluded all patients who had chronic illness which were not breast cancer and also all patients who died of other causes which were not cancer related.

Disease –specific survival estimates

Older patients= $\frac{total\ number\ of\ patients\ alive\ after\ 5yrs}{total\ number\ of\ patients\ diagnosed\ of\ breast\ cancer}$

$(excluding\ those\ who\ had\ chronic\ illness\ or\ other\ terminal\ illnesses)$

= 123/222*100%

= 55.4% (5-year disease specific survival rate)

Young patients = 30/52*100%

= **57.7 %(5-year disease specific survival rate)**

Fig 4.5: Calculations of disease specific survival estimates

Young patients had a higher disease specific survival rate but the difference between the two groups was very low (2.3%).

4.5.2.3 Disease Free Survival

Disease-free survival (DFS) is defined as the time between the beginning of the treatment and disease progression or death from any cause (Saad & Katz, 2009). DFS is usually used to analyse results of treatment for localized disease which renders the patient apparently disease free, such as surgery or surgery plus adjuvant therapy. In disease free survival, the event is relapse rather than death. People who relapse are still surviving but they are no longer disease-free (Earl et al., 2017). The table below (4.11) compares the DFS estimates measures up to 5 years after treatment of the older patient and younger patients.

Table 4.11: Disease free survival estimates of young and older patients.

DFS measure (Years)	**Older Patients**	**Young Patients**
Mean	2.7732	3.0923
Median	2.0000	3.0000
Mode	5.00	5.00
Std Deviation	2.08331	1.89344

The table above shows that the mean disease free survival for older patients was 2.77 years and 3.1 years for young patients. Thus, younger patients had a slightly higher mean disease free survival.

For comparison purposes, disease free survival curves were plotted using outcomes of older patients and young patients. The graph below (Fig4.6) illustrates the DFS curves for the two groups along a 5-year period after treatment. Time at zero was regarded as the date at first diagnosis of cancer.

The graph 4.6 below shows that the disease-free survival rates were generally higher for young patients than for older patients across the 5-year review period. The percentage of patients alive and diseases free for the older group significantly dropped as compared to the young patients between the 1st and the 3rd year after treatment. The percentage of patients alive and disease free after 5 years was almost similar between the older patients and the young patients.

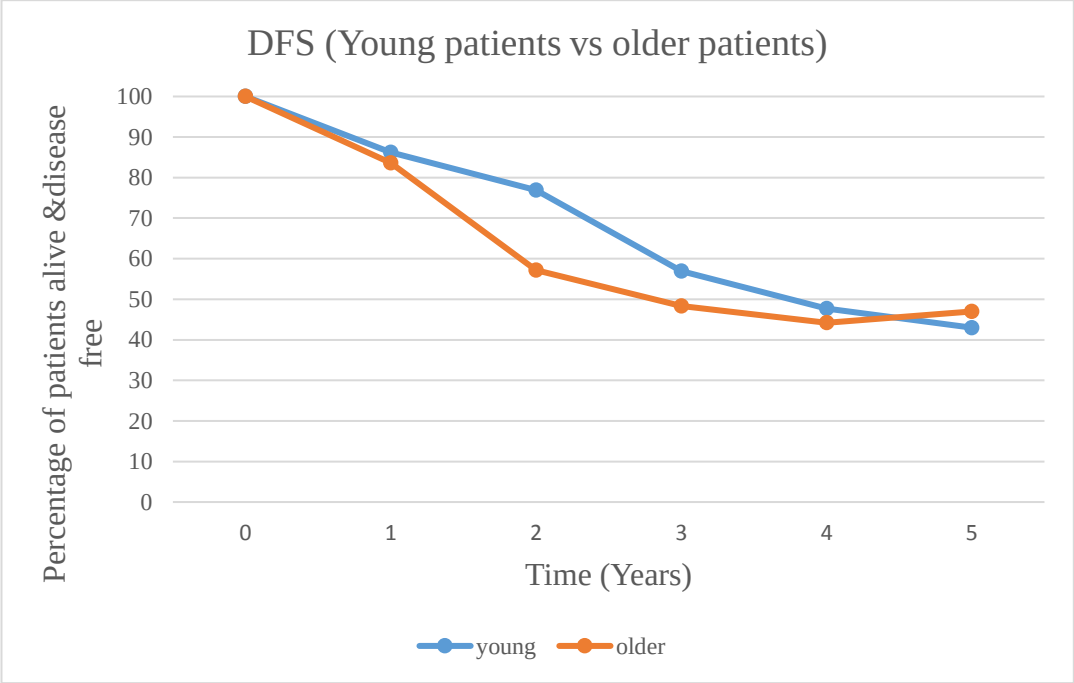


Fig 4.6: DFS curves of older patients and young patients over a 5-year period.

4.5.3 ANALYSIS OF METASTASIS AND RECURRENCES

Table 4.12: Risks of developing metastasis within 5 years of treatment

	OUTCOME			**Measures of association**
EXPOSURE	Developed metastasis	Never had metastasis	Total	Relative Risk=1.25 P- value= 0.13 95%CI (0.94 to 1.7)
Young	32 (49.2%)	33 (50.1%)	65 (100%)	
Old	106 (39.4%)	163 (60.6%)	269 (100%)	
Total	**138**	**196**	**334**	

Young patients had a 25% increased risk of developing metastasis after treatment than older patients. The risks of developing metastasis after treatment were not statistically different between the two groups (p value =0.19).

Table 4.13: Risks of developing recurrences within 5 years of treatment

	OUTCOME			**Measures of association**
EXPOSURE	Developed recurrences	Never developed recurrences	Total	Relative Risk=1.03 P- value= 0.9 95%CI (0.3 to 3.5)
Young	3 (4.6%)	62 (95.4%)	65 (100%)	
Old	12 (4.5%)	257 (95.5%)	269 (100%)	
Total	**15**	**139**	**334**	

The risk of recurrences after treatment were basically the same for the young and older patients (RR =1.03, 95CI 0.3 to 3.5).

4.5.4 ANALYSIS OF CONFOUNDING FACTORS

This section analyses the effect of factors which were believed to be confounding or had an effect on the relationship between age and treatment outcome of the breast cancer patients. The factors that were analysed for their effect on the relationship of age and outcomes of breast cancer are residence, occupation, treatment delay, stage of disease, family history of breast cancer, receptor status, chronic illness, hormone use and smoking and alcohol intake. The factors were analysed using the stratification method and the adjusted relative risk was determined using the Cochran–Mantel–Haenszel method at the end.

4.5.4.1 Marital status

Table 4.14: Effect of marital status on the relationship between age and outcome of breast cancer

	Total		**Married**		**Single**	
	Poor outcome	Good outcome	Poor outcome	Good outcome	Poor outcome	Good outcome
Young	37	28	16	19	16	8
Old	141	128	76	70	61	23
RR	Crude RR = 1.086		Married RR = 0.87 95%CI (0.5 to 1.3)		Single RR=0.9 95%CI (0.6 to 1.2)	

Table 4.14 shows that the stratified RR for the married and single group were less than the crude meaning that marital status was confounding on the relationship between age and outcome of breast cancer. No statistically significant increased risk was seen in both groups as a result of marital status.

4.5.4.2 Residence

Table 4.15: Effect of residence on the relationship between age and outcome of breast cancer

	Total		**Urban**		**Rural**	
	Poor outcome	Good outcome	Poor outcome	Good outcome	Poor outcome	Good outcome
Young	37	28	11	25	26	3
Old	141	128	80	78	72	39
RR	Crude RR = 1.086		Urban RR = 0.6035 95%CI (0.36 to 1.01)		Rural RR=1.382 95%CI (1.1 to 1.6)	

Urban RR =0.6035 which is different from rural RR of 1.382 and crude RR of 1.0860. Therefore, residence was not confounding, but modified the effect of young age to outcome of treatment. The association was statistically significant in women from rural areas (95%CI of 1.1 to 1.6).

4.5.4.3 Occupation

Table 4.16: Effect of occupation on the relationship between age and outcome of breast cancer

	Total		**Occupied**		**Not occupied**	
	Poor outcome	Good outcome	Poor outcome	Good outcome	Poor outcome	Good outcome
Young	37	28	22	28	15	0
Old	141	128	84	103	68	14
RR	Crude RR = 1.086		Occupied RR = 0.979 95%CI (0.7 to 1.4)		Not occupied RR=1.2 95%CI (1.1 to 1.3)	

Occupation was not confounding but had a slight effect modification on the relationship between age and outcome of treatment. Young unemployed women had a 20% increased risk of poor outcomes than older unemployed women. The risk was statistically significant as indicated by the 95% confidence interval.

4.5.4.4 Delay

The researcher determined the average number of days between first diagnosis and treatment for the older patients and younger patients. The mean delay in days for the older patients was 72.1 days and for the younger patients it was 72.8 days. This means that the delays were the same between the older patients and younger patients, thus the researcher assumed that delay had no effect on the relationship between age and outcome of breast cancer.

4.5.4.5 Stage of Cancer

For stratification purposes, the researcher grouped stage I and II as early stages and stage III and IV as late stages.

Table 4.17: Effect of stage of disease at diagnosis on the relationship between age and outcome of breast cancer

	Total		**Early stages**		**Late stages**	
	Poor outcome	Good outcome	Poor outcome	Good outcome	Poor outcome	Good outcome
Young	37	28	22	10	15	18
Old	141	128	65	59	87	58
RR	Crude RR = 1.086		Early stage RR = 1.3 95%CI (0.9 to 1.7)		Stage 3 RR=0.76 95%CI (0.5 to 1.1)	

Young women diagnosed with early stage breast cancer had a 30% increased risk of having poor outcomes than older women although the risk was not statistically significant as indicated by the 95% confidence interval. Stage of disease was an effect modifier for the relationship between age and outcome

4.5.4.6 Family History

Table 4.18: Effect of family history of breast cancer on the relationship between age and outcome of breast cancer

	Total		**Family history**		**No Fam History**	
	Poor outcome	Good outcome	Poor outcome	Good outcome	Poor outcome	Good outcome
Young	37	28	11	12	26	16
Old	141	128	55	41	97	76
RR	**Crude RR = 1.086**		Family History RR=0.83 95%CI (0.5 to 1.3)		No Fam History RR=1.1 95%CI (0.8 to 1.4)	

According to the RR of the above table, absence or presence of family history of breast cancer did not alter the relationship between age and outcomes. The relationships were not statistically significant.

4.5.4.7 Receptors

Table 4.19: Effect of hormone receptor status on the relationship between age and outcome of breast cancer.

	Total		**Er+pr+**		**Er+pr-**		**Er-pr-**	
	Poor	Good	Poor	Good	Poor	Good	Poor	Good
Young	37	28	16	14	2	8	15	1
Old	141	128	80	90	22	1	39	21
RR	Crude RR =1.086		RR=1.133 95%CI(0.7 to 1.6)		RR=0.20 95 %(CI 0.6 to 0.7)		RR=1.4 95%CI (1.1 to 1.8)	

According to the relative risks obtained above, young women with ER+PR- receptor combinations had a statistically significant reduced risk of having poor outcomes than older patients with the same receptor combination (RR=0.2, 95%CI 0.6 to 0.7). Contrarily, young women with ER-PR- receptor combinations had a statistically significant 40% increased risk of having poor outcomes than older women with the same receptor combination (RR=1.4, 95%CI 1.1 to 1.8)

4.5.4.8 Chronic illness

Table 4.20: Effect of chronic illness/other illness not breast cancer on the relationship between age and outcome of breast cancer

	Total		**Chronic Illness**		**No Chronic Illness**	
	Poor outcome	Good outcome	Poor outcome	Good outcome	Poor outcome	Good outcome
Young	37	28	10	3	27	25
Old	141	128	30	17	122	100
RR	Crude RR = 1.086		RR=1.2 95% CI (0.8 to 1.7)		RR=0.94 95% CI (0.7 to 1.2)	

No statistically significant increased risk was seen for young women with chronic illnesses although they had a 20% increased risk of having poor outcomes than older patients.

4.5.4.9 Hormone use/HRT

Table 4.21: Effect of hormonal use on the relationship between age and outcome of breast cancer

	Total		**Hormonal Use**		**No Hormonal use**	
	Poor outcome	Good outcome	Poor outcome	Good outcome	Poor outcome	Good outcome
Young	37	28	21	25	16	3
Old	141	128	97	69	50	41
RR	Crude RR = 1.086		RR=0.781 95% CI (0.5 to 1.1) P=0.15		RR=1.53 95% CI (1.2 to 2)	

The stratified risk ratio of the group that was under hormonal use was 0.78 which is less than the crude risk ratio of 1.08. For the group which was not under any hormonal medication, the RR was higher than the crude, RR=1.53 and it was statistically significant. There is evidence of effect modification by hormonal use to the relationship between age and outcome of breast cancer.

4.5.4.10 Smoking and Alcohol intake

Table 4.22: Effect of smoking and alcohol intake on the relationship between age and outcome of breast cancer

	Total		**Smoking**		**Alcohol**		**None**	
	Poor	Good	Poor	Good	Poor	Good	Poor	Good
Young	37	28	12	3	25	12	12	16
Old	141	128	60	15	108	51	40	66
RR	Crude RR = 1.086		RR=1.00 95% (CI 0.7 to 1.3)		RR=0.99 95% CI (0.7 to 1.2)		RR=1.1 95%CI (0.6 to 1.8)	

The risk ratios of smoking and alcohol intake were almost similar to the crude risk ratio, thus smoking and alcohol did not confound the relationship. Neither smoking nor alcohol appeared to affect the outcomes.

4.5.4 .11 Determination of the adjusted relative risk using the Cochran–Mantel–Haenszel method

Table 4.22 obtained a crude risk ratio of 1.08 for the relationship between age at diagnosis and outcome of breast cancer in Namibian women. The following presents the results of the adjusted risk ratio after adjusting for confounding factors using the Cochran–Mantel–Haenszel method. The table below shows the results of the Cochran–Mantel–Haenszel method.

Table 4.23: Crude risk ratio and adjusted Risk ratio for the relationship between age at diagnosis and outcome of breast cancer

Crude Risk Ratio	Risk ratio = 1.08 95% CI (0.85 to 1.38)
Adjusted Risk Ratio	Risk Ratio = 1.03 95% CI (0.9 to 1.1)
Corrected Mantel–Haenszel Chi-square	$\chi 2 = 0.25$, $p = 0.47$

The adjusted risk ratio was close to 1 indicating that young age at diagnosis does not increase the risk of poor outcomes in women diagnosed and treated of breast cancer in Namibia. The relationship between age and outcome was not statistically significant.

4.6 DISCUSSION

4.6.1 INTRODUCTION

The previous section presented the results of the study in detail. The results were presented in a manner that tried to fulfil the objectives of the study. This section focuses on the discussion of the results in detail. The discussion is presented in sections, starting with age and outcomes of treatment, followed by socio-demographic factors and clinical factors.

4.6.2 AGE DISTRIBUTION OF PATIENTS

The main aim of the research was to determine the relationship between age at first diagnosis and outcomes of breast cancer in Namibia. This was done by dividing the study group into two groups, defined as the young group and the older group. The young group comprised of women diagnosed of breast cancer at the age of 40 or below, whilst the older group was defined as women diagnosed of breast cancer at any age above 40.

The study population comprised of 334 patients that were treated of breast cancer at Windhoek central hospital between 2009 and 2011. Sixty-five patients were aged 40 and below at the time of first diagnosis whilst 265 were above 40 at the time of first diagnosis. The percentage ratio of young patients was 19% and 81% for older patients (Fig 4.1). Breast cancer incidence increases with age, with the vast majority of women diagnosed after the age of 40 years (Breast Cancer Facts & Figures, 2009). Nevertheless, approximately 7% of women diagnosed with breast cancer between 2000 and 2005 were below the age of 40 (Anders et al., 2009).

The results of the study indicate that the percentage proportion of young patients diagnosed of breast cancer was relatively higher (about 18%) than the developed world estimates of 7%.

Anders et al. (2009) also indicated that overall, breast cancer is more common in Caucasian women than in Africans; however, in women under the age of 40, breast cancer is more than twice as common in African women. This was almost similar to the study results. The study results indicated that the mean age at diagnosis of breast cancer for the Namibia women was 53.5 years and the modal age was 61 years.

During the last decade, the worldwide median age at the time of breast cancer diagnosis was 61 years ((Kohler et al., 2015). The results of the study in Namibia were not too far; as the modal age at diagnosis was 61years and the mean was 53.5 years.

4.6.3 OUTCOMES OF BREAST CANCER TREATMENT FOR YOUNG AND OLDER PATIENTS IN NAMIBIA

Outcomes of treatment refer to the results after treatment of cancer. The results may be survival, death, metastases, recurrence or relapse. The outcomes of the treatment will be discussed and compared between the two groups with respect to survival rates, metastases occurrences and recurrences.

For the purposes of comparative analysis used in this study, the researcher defined good outcome as 5-year survival with no metastasis or recurrence and poor outcome as either death within 5 years or development of metastasis or recurrence within 5 years after treatment.

After the discussion of the outcomes with regards to the researcher's definition of good outcome and poor outcome, outcomes will be discussed as well with regards to overall survival rates, net survival rates, disease free survival, metastases and recurrences between the two study groups.

The study results showed that 47.6 % of the older patients and 43.1% of the young patients had good outcomes (Table 4.10). The differences between the two groups were marginal. Without taking into consideration confounding factors or any other modifying factors such as stage of disease, treatment delays etc., statistical analyses indicated that the risk of younger patients to having poor outcomes than older patients was about 8% (crude RR=1.08, 95%CI of 0.85 to 1.38) and about 3% after adjusting for potential confounders (adjusted RR=1.03, 95%CI 0.9 to 1.1).

These results show that there was no statistical difference (95%CI 0.9 to 1.1) between the outcomes of younger patients and older patients in the study (Table 4.23). The adjusted risk ratio was 1.03, which is regarded as null since it is way below 1.5. According to Grimes (1992), in epidemiology, relative risks or odds ratios in the range of 1.0 to 1.5 ("weak associations") are difficult to interpret; bias can easily account for them.

Although the measures of association between age and outcomes of breast cancer resulted in weak associations (RR of 1.03 and odds ratio or 1.19), the fact that the risk is still above 1 even though it is marginal, indicates that younger women in Namibia might have poor outcomes as compared to older women. Based on various prospective and retrospective studies performed in the last two decades, it has been generally accepted that young age at diagnosis correlates with a worse clinical outcome compared to their older counterparts (El Saghir et al., 2006).

In addition, breast cancer survival rates are comparatively lower for women less than 40 years of age than for older women across all histological subtypes and stages (Anders et al.,2009), but however in this study the results showed a marginal risk of poor outcome amongst younger patients than older patients.

In determining differences between survival rates of the two groups, overall survival rates and disease specific survivals were estimated. Overall survival rate is the actual percentage of patients still alive at some specified time after diagnosis of cancer. It considers deaths from all causes, cancer or otherwise (Seer, 2017). Predictively, older patients had higher overall 5- year survival rate of 56.5% compared to 52.3% of younger patients (Fig 4.4). This is again a marginal difference between the two groups but older patients had a slight edge in having better overall survival rates than younger patients. This is in line with what Anders et al. (2009) indicated.

The overall survival rates were higher than the percentages of patients with good outcomes as indicated above because overall survival rates take into consideration patients who are still alive even if they are not disease- free or metastases- free whereas good/bad outcome took into consideration recurrences, and metastases.

Net survival rates were determined for the study group as well. Disease-specific survival is a net survival measure representing cancer survival in the absence of other causes of death. Disease-specific survival rate refers to the percentage of people in a study or treatment group who have not died from a specific disease in a defined period of time (Kohler et al., 2015). The 5 year-disease- specific survival rate for older patients was 55.4% and 57.7% for the young patients (Fig 4.5).

Surprisingly, the disease specific survival rate for younger patients was slightly higher than that of older patients as opposed to overall survival rates, possibly because a greater number of younger patients might have died because of other illnesses, which were not breast cancer. This is supported by the fact that chronic illnesses such as TB and HIV are more common in younger women than in older patients in Namibia (Kwame , Antony and Louis, 2010). Kwame , Antony and Louis (2010) mentioned that, "In the countries of sub-Saharan Africa, AIDS has raised death rates and lowered life expectancy among adults between the ages of 20 and 49 by about twenty years".

Disease-free survival (DFS) is defined as the time between the beginning of the treatment and disease progression or death from any cause (Saad & Katz, 2009). DFS is usually used to analyse results of treatment for localized disease which renders the patient apparently disease free, such as surgery or surgery plus adjuvant therapy. Figure 4.6 described the disease-free survival rates across the five-year period of both young and older patients.

The results of the study indicated that older patients had a slightly higher mean disease-free survival period of 3.1years as compared to 2.8years for younger patients (Table 4.11). Disease-free survival curves across the 5-year post-treatment period show that there was a significant difference in survival during the 2nd and 3rd years after treatment between the older patients and the younger patients (Fig 4.6). This was because of noticeable fluctuations of the percentages of young patients alive and disease free between the 2nd and the 3rd year. This might mean that the majority of young patients die or have relapses or recurrences between the 2nd and 3rd year after treatment. At the end of the 5-year period, the disease-free survival rates of both the older patients and the young patients were more or less similar (43% 5-year disease free survival for the young patients and 47% for the older patients).

Interestingly, in a similar research that was done in Egypt, the five-year disease free survival in young women was 38.9% ± 4.6% compared to 48.6% ± 2.5% for older patients with adjusted hazard ratio of 1.22 95% CI (0.91–1.64), p = 0.19 (Alieldin et al.,2014).

The results of the study show that in Namibia, the younger patients have slightly better outcomes (DFS of 43%) than younger patients in Egypt who had a 5-year disease - free survival rate of 38.9%.

The 5-year disease-free survival rates for older patients were almost similar between Namibia and Egypt (47% and 48.6% respectively).

Regarding metastases, Table 4.8 showed that 39.4% of the older patients and 49.2% of the young patients had metastases within 5 years after treatment. The mean period of occurrence of metastasis was 1 year for the older patients and 2 years for the younger patients. This means that older patients had less metastatic events than younger patients and metastases appeared to occur earlier in older patients than in young patients.

Previous research has indicated that young female breast cancer follows a more aggressive course and is highly metastatic than in their elderly counterparts (Colleoni et al., 2002). Similarly, in this study, although not statistically significant, young patients had a 25% increased risk of developing metastasis after treatment than older patients (Table 4.12)

Risk of local recurrence of breast cancer has been shown to be increased in young patients in two separate analyses of clinical trials, namely the EORTC group trials and NSABP group trials (de Bock et.al. 2006; Wapnir et al., 2006).

The former showed a hazard ratio of 2.8 (95% CI, 1.4-5.6) for local recurrence in patients less than 35 years compared to those above 50 years. A study by Bharat et al. (2009) estimated the risk of breast cancer recurrence for women diagnosed below the age of 40 to be 1.53 (95% CI, 1.37-1.74) times higher than in those diagnosed above 40 years.

Contrary to that, the results obtained in the study did not find any differences in risks of recurrence after treatment between the young patients and the older patients (4.6% for the young and 4.5% for the older group, (RR =1.03, 95CI 0.3 to 3.5) (Table 4.13). The mean period of recurrence was about 4 years after treatment for both groups.

4.6.4 SOCIO-DEMOGRAPHIC FACTORS IN RELATION TO OUTCOMES

The next discussion will be on socio-demographic factors of the study group. The socio-demographic factors collected in the study were age, marital status, residence, employment status, number of pregnancies. Age has already been discussed above.

4.6.4.1 Marital status

More than half of the younger patients (54%) were married and about 37% were single (Table 4.1).

The highest percentage of patients who had good outcomes were married and the highest percentage of patients who had poor outcomes were the single and divorced patients (Table 4.2). This result is in line with what Martinez et al., (2016) researched. Martinez et al., (2016) indicated that mortality following a cancer diagnosis is higher in unmarried than married patients.

Another population-based study published in 2005 showed that compared to married breast cancer patients, unmarried women were more likely to be diagnosed with later stage disease and to die of breast cancer, and were less likely to receive definitive treatment, even after controlling for stage, treatment, socioeconomic factors, and comorbidities (Osborne et al.,2005). Similarly, for the older group, the majority of the patients who had good outcomes were married (55%) but as opposed to the younger patients, slightly less than half of the married patients (48%) had good outcomes.

In both groups, being single was associated with poor outcomes (RR=1.4; p=0.002 for older patients, and RR =1.45, p=0.18 for younger patients). The effect of marital status on outcomes was more statistically significant on older patients (Table 4.2).

4.6.4.2 Residence

Results of the study show that there were more patients coming from urban areas than rural areas for both young and older patients (Fig 4.4). This might mean that the incidence of breast cancer was more in women who stay in urban areas than in rural areas for both young and older patients. Table 4.2 showed that there was a statistically significant relationship between residence and outcomes of breast cancer in both young and older patients (p=0.00 in both groups). With regards to the effect of residence on the relationship between age at diagnosis and outcome of breast cancer treatment, cross tabulation done (Table 4.15) indicated that the place of residence modified the relationship of age and outcomes of patients. For the urban dwellers, younger patients were more likely to have good outcomes than older patients (RR =0.06; 95%CI 0.36 to 1.01). This might be because younger patients in urban areas have access to advanced diagnostic and treatment facilities than those in rural areas and thus have an advantage of early diagnosis and early treatment than those from rural areas.

For rural dwellers, younger patients were more likely to have poor outcomes than older patients (RR=1.38, 95%CI 1.1 to 1.6)). The 95% CI obtained showed that the risk was statistically significant.

With that said, according to a study by Henry et al. (2011) , findings related to cancer mortality in patients with melanoma, lung, and breast cancer from studies utilizing individual-level methods and Census tract definitions of rural have been relatively consistent in concluding that after adjusting for individual factors like demographics, comorbidity, treatment and stage, rural residence does not directly influence cancer-related mortality, rather patient-level factors (i.e., poverty, age, race) play more of a role.

4.6.4.3 Employment status

Table 4.1 indicates that the majority (more than 70%) of all the patients (both young and old) were employed at the time of diagnosis of breast cancer. No previous research has indicated an association between employment and risk of breast cancer but some studies have indicated that the link might be because employment is associated with certain behavioural lifestyles that might be risk factors of breast cancer (Achat et al., 2000). Cross tabulation between occupation and outcomes of older and young patients showed that there was a statistically significant relationship between employment status and outcomes for both young and older patients (p=0.00 in both groups). Occupational status did not confound the relationship between age and outcome of treatment but modified the effect of the relationship (Table 4.16).

In this study, being unoccupied increased the risk of younger patients to have poorer outcomes than older patients by 20% (RR=1.20; 95%CI 1.1 to 1.3)).

Substantial evidence indicates that the socioeconomic status (SES) of breast cancer patients has a significant impact on prognosis through its associated influence on the cancer stage at diagnosis. Previous findings suggest people with lower incomes/ those who do not have an income at all, have a later cancer stage at point of diagnosis and a worse overall prognosis (Macleod et.al, 2000). Socioeconomic status is also significantly associated with education level and occupation, both of which can greatly influence patients' perception of the tumour, thereby affecting the level of early detection, diagnosis, and treatment. This can be an explanation to this study as well.

4.6.4.4 Number of children

All young women who did not have any children in their life had poor outcomes whilst about 50% of women who had three or four pregnancies had good outcomes. For older patients, slightly more than half of women who had two pregnancies or less had good outcomes. The cross-tabulation obtained a chi-square value of 5.2 and a p- value of 0.15 for the young group. This means that there is no statistically significant relationship between number of children and outcome of breast cancer for the young patients. A study by Butt et al. (2009) showed positive association between high parity and breast cancer death in all strata, although only statistically significant among women older than 45 years of age or postmenopausal. Nulliparity was associated with breast cancer death in women that were younger than 45 years of age (RR=1.28) or premenopausal (RR=1.30), but these associations did not reach statistical significance. In this study, all young women who did not have any children in their life had poor outcomes. This was comparatively similar to what was indicated by Butt et al (2009) that nulliparity was associated with poor survival.

However, Butt et al. (2009) concluded that women with four or more children have a poor breast cancer survival as compared to women with one child, but this was not found in the current study.

4.6.5 CLINICAL FACTORS IN RELATION TO OUTCOMES

4.6.5.1 Treatment commencement delays

There was no significant difference between young and older patients regarding treatment commencement delays. The mean delay was about 72days for both young and older patients (Table 4.3). This can mean that treatment delays had a similar effect on both older and young patients with regards to outcomes of treatment thus no confounding was evident on the relationship between age and outcomes of breast cancer. According to McLaughlin et al. (2012) the average delay in western countries is between 23-46 days and another study indicated that when younger (< 40 years) patients underwent surgery as their initial treatment, women with a delay in surgical treatment of over 6 weeks had 10% decreased overall survival compared to women with a delay in surgical treatment of 2 weeks or shorter. Yoo et al., (2016), concluded that a delay of treatment initiation at any cut-off point within 60 days after biopsy confirmation had no impact on DFS and overall survival in breast cancer. Although with shorter interval, these results are consistent with the recent study by Brazda et al., (2010). The mean delay amongst Namibian women was 72days as obtained from the study, which is more than the recommended 60days. This may be one of the reasons why the overall survival rates of breast cancer were low in the study as compared to other countries.

4.6.5.2 Stage of cancer

Stage II and III were the most frequent stages at the time of first diagnosis for both young and older patients in Namibia according to the study results (Fig 4.2).Previous studies indicated that more breast cancer patients with a known stage are diagnosed at an early stage (79-87% are diagnosed at stage I or II), than a late stage (13-21% are diagnosed at stage III or IV). Between 6% and 7% of people have metastases at diagnosis (stage IV) (NCIN, 2016). In this study, as shown by Fig 4.2, about half of the younger patients were diagnosed at an earlier stage and the other half at a later stage. Older patients showed a similar pattern as well. This shows that Namibian women still present with later stages of breast cancer as compared to western countries. Cross- tabulations (Table 4.6) illustrated that the stage of cancer at diagnosis is statistically related to the outcomes for both young and older patients (young group: $\chi 2= 18.9$, p=0.0: older group $\chi 2= 18.9$, p=0.0). Analyses of the effect of stage on the relationship between age and outcomes showed that earlier stages (Stage 1 and II) at diagnosis were associated with worse outcomes for younger patients than older patients (RR=1.3; 95%CI 0.9 to 1.7)). These results tallied with what Fredholm et al. (2009) concluded in a similar study. The study findings by Fredholm et al. (2009) concluded that the excess risk for young women was only seen in early stages of disease and was most pronounced in women with small tumours. Young women affected by breast cancer have a high risk of dying compared to their middle-aged counterparts even if diagnosed early and receiving an intense treatment.

4.6.5.3 Family history of breast cancer

The majority of cases of breast cancer arise in women with no apparent close family history. Between 6-19% of women with breast cancer will have a family history of the disease (Department of Health, 2000; Hill et al., 1997).

Results of the current study show that about 35% of breast cancer patients had family history of breast cancer (Table 4.6). This is higher than the average worldwide percentages as stated above. Antoniou et.al (2003) mentioned that breast cancer at an early age is more likely to be associated with an increased familial risk, especially in women harbouring a germline BRCA1 mutation.

This was not true in Namibian women as both young and older patients had similar proportions of familial breast cancer. Table 4.6 & 4.18 showed that there was no statistically significant relationship between family history of breast cancer and outcomes of treatment for both young and older patients. These results were similar to the study done by Veronesi et al., (2005) which concluded that there are no significant differences between outcomes of familial breast cancer and non-familial breast cancer.

4.6.5.4 Receptor status

The results of the study, as presented in Table 4.4 showed that a greater percentage (63%) of the older group had ER+PR+ receptors. Less than 50% of the young patents had ER+PR+ receptors. These results resembled what is known about young female breast cancer. Anders et.al (2009) indicated that young female breast cancer is associated with higher oestrogen and progesterone negativity and lower oestrogen and progesterone positivity as compared to their elderly counterparts**.** In addition, the "triple-negative" phenotype (ER−, PR−, and HER2−) of breast cancer, which is regarded as the most lethal type of the disease, is most prevalent in young women, particularly in African Americans. In one study, triple-negative breast cancer was found in 56% of black and 42% of white women aged 20-34 years (Lund et.al, 2009). Study results among Namibian women showed that ER-PR- tumours constituted about 24% in the younger patients and 22% in the older patients, which were not significantly high as indicated by Lund et.al(2009).

Young women with ER-PR- receptor combinations had a statistically significant 40% increased risk of having poor outcomes than older women with the same receptor combination (RR=1.4, 95%CI 1.1 to 1.8) (Table 4.19). This was because the young group had a higher proportion of ER-PR- tumours which are lethal and are associated with poor outcomes.

4.6.5.5 Chronic illness

Presence of other illnesses concurrently with breast cancer generally reduces the outcomes of treatment of breast cancer. In this study, the researcher noted that about 20% of the young patients and 17% of the older patients had other illnesses which were not breast cancer (Table 4.5). Illnesses common in younger patients are HIV, TB, Malaria and older patients usually have arthritis, lung disease, oral health, hypertension and stroke. In a retrospective cohort of 220 breast cancer cases in Uganda, HIV infected patients had twice the 1-year mortality of uninfected patients (Coghill et.al, 2013). Similarly, in this study, both young and older women who had other illnesses had poor outcomes as compared to those that did not have any other illnesses. The greatest effect of chronic illnesses on the outcome of breast cancer was seen on young patients (76% of young patients who had chronic illness had poor outcomes and only 23.1% had good outcomes) (Table 4.7). Chronic illness/other illness not breast cancer increased the risk of younger patients to having poorer outcomes than older patients by 20% although the risk was not significant. (RR=1.2, p=0.5) (Table 4.20).

The effect was more pronounced in younger women maybe because of the high prevalence of infectious diseases such as HIV amongst young sexually active women. In addition, chronic illnesses could have been the cause of death on some patients, thus resulting in reduced overall survival rates.

4.6.5.6 Hormonal use

The most common forms of hormonal intake or use for young patients are oral contraceptives and hormone replacement therapy for the older patients.

Namibian women aged 40years and below are still sexually active and still premenopausal so HRT is uncommon in this age group. On the other hand, older women more commonly use HRT than oral contraceptives because they would have reached menopause and will be no longer sexually active. Table 4.5 showed that about 70% of the younger women were using hormonal contraceptives and about 61% of the older patients were also under hormonal therapy or contraceptives. Hormonal use was significantly related to good outcomes of treatment in young patients ($\chi 2$= 8.1; p=0.04). For older patients, the relationship between hormonal use/HRT with outcomes of treatment was not statistically significant ($\chi 2$= 1; p=0.49). Regarding the effect of hormonal use on the relationship between age at diagnosis and outcomes of breast cancer, stratified analysis showed that hormonal use, either HRT or oral contraception was associated with better outcomes of younger patients than older patients (RR=0.78 , p=0.13). The results were not so statistically significant. On the other hand, not using any form of hormonal medication increased the risk of younger patients to having poorer outcomes than older patients (RR=1.53. 95% CI 1.2-1.2). In a study by Nilsson ,Olsson, Thorlacius and Butt (2016), similar results were obtained, indicating that breast cancer-specific survival in women who ever had used oral contraceptive was better when adjusting for BMI, socioeconomic status as well as tumour characteristics.

However, when adjusting for age at diagnosis, the results did not remain significant and conclusions that oral contraceptives had no effect on outcome of breast cancer were drawn.

Regarding HRT for older patients with breast cancer, a study by Ellen et.al (2001) observed that women who used HRT had lower risks of recurrence than women who did not.

Although residual confounding may exist, the results suggested that HRT after breast cancer had no adverse impact on outcome of breast cancer.

4.6.5.7 Smoking and Alcohol Intake

Some studies have suggested that smoking may also be associated with increased mortality from breast cancer. However, while some studies observed such an increase in post-diagnosis breast cancer-specific mortality in smokers, this increase was statistically significant in five studies (Warren et al., 2013, Fentiman et al., 2005, Manjer et al., 2000, Yu et al.,1997,& Dal Maso et al., 2008) but some studies showed little or no association between smoking and breast cancer survival(Hellman et al.,2010 & Sagiv et al.,2007). Although a greater proportion of young patients who smoked had poor outcomes (Table 4.5) in this study, stratified analyses of the study results as illustrated by table 4.22 indicate that smoking did not alter the relationship between age and outcome of breast cancer (RR=1). This was similar to other studies mentioned above, that concluded that there was no association between smoking and survival of breast cancer.

Some findings suggest breast cancer survivors who drink alcohol after diagnosis have an increased risk of recurrence and breast cancer mortality (death from breast cancer) (Lowry et al., 2016). Other studies have shown no difference in recurrence or breast cancer mortality between survivors who drink alcohol in moderation (less than 1 drink a day for women) and survivors who are non-drinkers (Fuchs et al., 1995 & Forman et al., 2009).

Table 4.7 showed that 60% of the older women consumed alcohol and about 76% of these had poor outcomes. Similarly, for the younger patients, it was noted that about 68% of the patients that drank alcohol had poor outcomes. This may indicate that alcohol consumption had a negative impact on the outcome of breast cancer patients (both young and old).

Stratified analyses to determine if alcohol consumption had an effect on the relationship between age at diagnosis and outcome of breast cancer concluded that alcohol did not alter the relationship (RR=0.99) (Table 4.22).

4.7 SUMMARY

This chapter presented the findings of the research in a descriptive and analytical manner. The findings were presented using graphs, tables and all relationships and associations determined statistically were shown as well. The research findings were then discussed with reference to literature and previous research. It was established that the relationship between age at diagnosis and outcome of breast cancer in Namibian women was not statistically significant. There was no difference between the outcomes of the young and older patients. Thus, diagnosis of breast cancer at a young age did not increase the risk of poor outcomes among Namibian women. A variety of clinical factors and socio-demographic factors of the study population were shown to affect the outcomes of young patients and older patients in different ways as stated above, thus affecting the relationship between age and outcomes of breast cancer among Namibian women.

CHAPTER 5

CONCLUSIONS, RECOMMENDATIONS AND LIMITATIONS

5.1 INTRODUCTION

The previous chapter presented the study findings and a discussion of the findings. This chapter focuses on the conclusions derived from the study findings, recommendations of the study, suggestions for further research studies, the study's contribution to the existing body of knowledge and the limitations of the study. The conclusion will be based on the primary objectives of the study.

5.2 CONCLUSIONS DRAWN FROM THE STUDY

Previous research results from the developed world have shown that young age at first diagnosis of breast cancer is associated with worst outcomes and across all histologic subtypes and stages, breast cancer survival rates are comparatively lower for women less than 40 years of age than for older women. Research studies conducted in Asia did not show any significant differences in outcomes between young patients and elderly patients. Little has been researched regarding the relationship between age and outcomes of breast cancer in African women. The purpose of this study was to determine the relationship between age at first diagnosis and treatment outcome in Namibian women and to verify whether breast cancer patients diagnosed at 40 years and below have poorer treatment outcome than those diagnosed above 40 years. In line with the purpose stated above, the objectives of the study were:

- To describe the frequency of treatment outcomes of breast cancer by socio-demographic and medical/clinical characteristics of the study population
- To determine the association between age and outcome of breast cancer treatment.

5.2.1 Objective 1: To describe the frequencies of treatment outcomes of breast cancer by socio-demographic and medical/clinical characteristics of the study population

This objective sought to describe the frequencies of treatment outcomes in relation to socio-demographic and clinical characteristics of both young patients and elderly patients. The socio-demographic factors were age, marital status, residence, employment status and number of pregnancies. Regarding the age distribution of the study population, the results of the study indicated that about 19% were aged 40 and below whilst the majority, 81% were above 40 years of age at first diagnosis of cancer. This revealed that the majority of women in Namibia are diagnosed of breast cancer at ages above 40, whilst a few are diagnosed at a younger age. In addition, it was concluded that the average age at diagnosis of breast cancer was between 53 and 61 years among Namibian women.

The majority of patients were married and being married was linked to good outcomes of breast cancer in both young patients and older patients, but it was concluded that the relationship between marital status and outcomes was statistically significant only in older patients.

For both groups, it was concluded that more patients who are diagnosed of breast cancer reside in the urban areas than in rural areas (58% of the older patients and 55% of the young patients). It was concluded that women who reside in urban areas had better outcomes than those residing in rural areas in both groups.

Regarding parity, for younger patients, it was concluded that having had more children was linked to good outcomes but the relationship was not statistically significant.

There was no definitive link between number of children and outcomes of breast cancer in older women.

In terms of employment status, the majority of patients who were diagnosed of breast cancer were employed. The percentage of younger patients who were employed was generally higher than those of older patients. There was a statistically significant relationship between employment status and outcomes for both young and older patients and being unoccupied increased the risk of poor outcomes in younger patients. The results of the study concluded that for both young and older patients, employed patients had better outcomes than unemployed patients in Namibia.

Clinical factors measured in the study were, treatment delays, stage of cancer, family history, receptor status, chronic illnesses/other illnesses, hormonal use, smoking and alcohol intake. The results of the study showed that the mean delay between diagnosis and treatment commencement was approximately 72days for both young and older patients. Since the delay was similar for both groups, it was concluded that treatment delays did not affect the relationship between age and outcomes of treatment. A 72 delay period was regarded as way too long comparing with other developed countries which have treatment delay periods of 23-40 days. This may be one of the reasons why the overall survival rates of breast cancer are low in Namibia as compared to other countries.

Stages II and III were the most common stages at diagnosis in both young and older patients. Earlier stages (Stage 1 and II) at diagnosis were associated with worse outcomes in younger patients than in older patients.

Family history of breast cancer was found in about 35% of elderly patients and 36% of young patients. It was concluded that the prevalence of familial breast cancer in

Namibian was higher than the worldwide averages ranging between 6-19% of all breast cancer patients. There was no statistically significant relationship between family history of breast cancer and outcomes of treatment for both young and older patients

Hormone receptor positive breast cancer (ER+PR+) was more common in older patients than in younger patients. Young women with ER-PR- receptor combinations had a statistically significant 40% increased risk of having poor outcomes than older women with the same receptor combination .ER-PR- breast cancer tumour receptors appeared to be more common in younger women than in older women.

The study concluded that other chronic illnesses had an adverse impact on breast cancer survival and the effects are more pronounced in younger patients.

The majority of patients were under hormonal medication or were using hormonal contraceptives. Hormonal intake/HRT was associated with good outcomes in younger patients than in older patients. Young women who did not have any form of hormonal intake had a 53% increased risk of poor outcomes than older patients.

A greater proportion of young and older patients who smoked and consumed alcohol had poorer outcomes than non-smokers/drinkers but stratified analyses did not find any association between smoking and or drinking with outcomes in both groups.

5.2.2 Objective 2. To determine the association between age and outcome of breast cancer treatment

The main objective of the study was to determine the association between age at diagnosis and treatment outcomes of breast cancer in Namibia. Without taking into consideration confounding factors, and other factors, younger patients had an 8% increased risk of having poor outcomes than older patients (Crude RR=1.08, 95%CI of 0.85 to 1.38). After adjusting for potential confounding factors, it was concluded that there was no significant difference between the outcomes of younger patients and older patients treated of breast cancer in Namibia (adjusted RR=1.03, 95%CI 0.9 to 1.1). Therefore, according to the results of the study, diagnosis of breast cancer at a younger age (below 40yrs) does not significantly reduce the outcome. With respect to survival, it can be concluded that older patients in Namibia have slightly higher overall survival rates than their younger counterparts although the difference is marginal.

Older patients had less metastatic events than younger patients but metastases appeared to occur earlier in older patients than in young patients. Regarding the risk of local recurrences after treatment, this study concluded that there were no differences in risks of recurrence after treatment between the young patients and the older patients. An important conclusion drawn from the study is that recurrences usually occur during the fourth year after treatment for both young and older patients in Namibia.

5.3 RECOMMENDATIONS

Although the research study findings and the conclusions drawn reflect no significant effect of young age on the outcome of treatment of breast cancer among Namibian women, the following recommendations are aimed at improving outcomes of treatment of young patients treated of breast cancer. The recommendations can also be used to improve survival of all breast cancer patients in Namibia.

Overall survival rates of patients treated of breast cancer in Namibia can be increased by reducing time delays between first diagnosis and treatment of breast cancer. In most cases, cancer is diagnosed at an earlier stage but because of delays in treatment commencement, the disease will be treated when it's already in later advanced stages. This is so common in Namibia as well.

Delays can be reduced by increasing the number of health services offering treatment of cancer so that the waiting period of patients is reduced. Currently in Namibia there are only two oncology centres catering for the whole of Namibia of which these two are overwhelmed with the continual increase in number of breast cancer patients. Hence there is need in setting up of more decentralized oncology centres in Namibia.

One major challenge in Namibia is that breast cancer usually present with advanced stages as indicated by the study. This might be because the majority of patients are not aware of breast cancer and how it presents, resulting in advancement of the disease as they seek other types of treatment such as traditional methods. Cancer awareness programs must be spearheaded by the MOHSS to improve cancer awareness to the population. An example of a cancer awareness program that can be implemented is an advocacy program.

The program can be conducted by bringing the media professionals, health care professionals, cancer survivors and advocates together.

The objectives may be to

- Promote information exchange.
- Educate journalists (broadcast and print) about breast cancer early detection, treatment and survivorship issues.
- Increase the frequency of media reporting on breast health, such as breast self-examination, clinical breast examination, and mammograms.
- Secure the commitment of media professionals on breast and other cancer information dissemination.
- Create awareness about breast cancer survivorship and support

5.4 LIMITATIONS OF THE STUDY

Since this research was conducted retrospectively, and involved analyses of patients' records, exposure status may not be very clear when old records are used, because the data that was saved was not designed to be used in the study. Even if it was clear that the exposed group were young patients (age≤ 40years) it was important to take into account (or adjust for) other differences that could have influenced outcomes (all potential confounding factors). Although the researcher collected data on some confounding factors in the study, not all confounding factors were collected in the study because of the unavailability of that information in the documents. Studies like the current are better and more accurate when conducted prospectively than retrospectively.

In analysing the effect of confounding factors on the relationship between age at diagnosis and outcomes of treatment, the researcher used stratification method and the Mantel Hansel method. Stratification method is more useful and accurate if the confounding factors are not many but in this study there were more than two confounding factors, thus multivariate regression analysis using Cox statistical method was deemed to have been more appropriate

Regarding recordings of outcomes, patients who died because of other causes which were not breast cancer were assumed to have died because of breast cancer since information of death was only obtained from the patients' cancer treatment files at Dr A. B May cancer centre. It would have been more accurate if the true causes of death were recorded other than assumptions.

5.5 CONCLUDING REMARKS

The study to determine the relationship between age at diagnosis and outcomes of breast cancer in Namibia was carried out at Windhoek Central Hospital. The study was a retrospective cohort study design involving a document review of a total of 334 breast cancer patients treated between January 2009 and December 2011.The study aimed to determine if younger patients had poorer outcomes as hypothesized by previous studies from other developed countries. The study concluded that there was no significant difference between the outcomes of younger patients and older patients treated of breast cancer in Namibia. Therefore, according to the results of the study, diagnosis of breast cancer at a younger age (below 40yrs) does not significantly reduce the outcome although younger patients had a slight increased risk of about 3% than older patients.

Factors such as rural residence, nulliparity, unemployment and being single were linked to poor outcomes among younger patients. Clinical factors such as non-familial breast cancer, Stage II breast cancer, hormone receptor negative tumours and chronic /other illnesses were linked to poorer outcomes in younger patients as well. Treatment commencement delays were more than 70days amongst all patients in Namibia, which could have resulted in very low overall survival rates of all patients.

Recommendations aimed at improving survival of breast cancer patients were outlined at the end. The importance of the reduction of treatment delays, psychosocial support of young women diagnosed of breast cancer, and breast cancer awareness strategies were outlined in the recommendations so as to improve management of breast cancer patients especially the younger patients.

REFERENCES

Abdulkareem, I. H. (2013). Aetio-pathogenesis of breast cancer. *Nigerian Medical Journal : Journal of the Nigeria Medical Association, 54(6), 371–375.*

Achat, H., Kawachi, I., Byrne, C., Hankinson, S., & Colditz, G. (2000). A prospective study of job strain and risk of breast cancer. *International Journal Of Epidemiology, 29(4),* 622-628. http://dx.doi.org/10.1093/ije/29.4.622

Adebamowo, C., Famooto, A., Ogundiran, T., Aniagwu, T., Nkwodimmah, C., & Akang, E. (2007). Immunohistochemical and molecular subtypes of breast cancer in Nigeria. *Breast Cancer Research And Treatment, 110(1*), 183-188.

Águas, F., Martins, A., Gomes, T., Sousa, M., & Silva, D. (2005). Prophylaxis approach to a-symptomatic post-menopausal women: *Breast cancer. Maturitas, 52*, 23-31.

Akarolo-Anthony, S., Ogundiran, T., & Adebamowo, C. (2010). Emerging breast cancer epidemic: evidence from Africa. *Breast Cancer Research, 12(S4).* http://dx.doi.org/10.1186/bcr2737

Albain K, S., Allred D, C., Clark, G.M (1994). Breast cancer outcome and predictors of outcome: are there age differentials*? J Natl Cancer Inst Monogr*. 1994; (16):35-42.

Alexander, D., Morimoto, L., Mink, P., & Lowe, K. (2010). Summary and meta-analysis of prospective studies of animal fat intake and breast cancer. *Nutrition Research Reviews, 23(01*), 169-179.

Al-Idrissi, H., Ibrahim, E., Kurashi, N., & Sowayan, S. (1992). Breast cancer in a low-risk population. The influence of age and menstrual status on disease pattern and survival in Saudi Arabia. *International Journal Of Cancer, 52(1*), 48-51.

Alieldin, N., Abo-Elazm, O., Bilal, D., Salem, S., Gouda, E., Elmongy, M., & Ibrahim, A. (2014). Age at diagnosis in women with non-metastatic breast cancer: Is it related to prognosis*?. Journal Of The Egyptian National Cancer Institute, 26(1*), 23-30. http://dx.doi.org/10.1016/j.jnci.2013.08.005

Althuis, M., Brogan, D., Coates, R., Daling, J., Gammon, M., Malone, K., Brinton, L. (2003). Breast Cancers among Very Young Premenopausal Women (United States). Cancer

Causes & Control, 14(2), 151-160. Retrieved from http://www.jstor.org/stable/3553627

Anders, C. K., Johnson, R., Litton, J., Phillips, M., & Bleyer, A. (2009). Breast cancer before age 40 years. *Seminars in Oncology, 36(3), 237–49.*

Anders, C., Hsu, D., Broadwater, G., Acharya, C., Foekens, J., & Zhang, Y. et al. (2008). Young Age at Diagnosis Correlates With Worse Prognosis and Defines a Subset of Breast Cancers With Shared Patterns of Gene Expression. *Journal Of Clinical Oncology*, 26(20), 3324-3330.

Antoniou, A., Pharoah, P., Narod, S., Risch, H., Eyfjord, J., & Hopper, J. et al. (2003). Average Risks of Breast and Ovarian Cancer Associated with BRCA1 or BRCA2 Mutations Detected in Case Series Unselected for Family History: A Combined Analysis of 22 Studies. *The American Journal Of Human Genetics, 72(5),* 1117-1130. http://dx.doi.org/10.1086/375033

Armes, J., Crowe, M., Colbourne, L., Morgan, H., Murrells, T., & Oakley, C. et al. (2009). Patients' Supportive Care Needs Beyond the End of Cancer Treatment: A Prospective, Longitudinal Survey. *Journal Of Clinical Oncology, 27(36),* 6172-6179.

Avis, N., Crawford, S., & Manuel, J. (2005). Quality of Life Among Younger Women With *B*reast Cancer. *Journal Of Clinical Oncology*, 23(15), 3322-3330.

Baker, T.L. (1994). Doing Social Research (2nd Edn.), New York: McGraw-Hill Inc.

Baquet, C., Mishra, S., Commiskey, P., Ellison, G., & DeShields, M. (2008). Breast Cancer Epidemiology in Blacks and Whites: Disparities in Incidence, Mortality, Survival Rates and Histology. *Journal Of The National Medical Association, 100(5), 480-489.* http://dx.doi.org/10.1016/s0027-9684(15)31294-3

Barlow, W. (2002). Performance of Diagnostic Mammography for Women with Signs or Symptoms of Breast Cancer. Cancer spectrum Knowledge Environment, 94(15), 1151-1159.

Beral, V. (2002). Breast cancer and hormone replacement therapy (HRT): collaborative reanalysis of data from 51 epidemiological studies of 52,705 women with breast

cancer and 108,411 women without breast cancer. *Breast Cancer Research, 4(S1).* http://dx.doi.org/10.1186/bcr486

Berry, D., Cronin, K., Plevritis, S., Fryback, D., Clarke, L., & Zelen, M. et al. (2005). Effect of Screening and Adjuvant Therapy on Mortality from Breast Cancer. *New England Journal Of Medicine*, 353(17), 1784-1792. http://dx.doi.org/10.1056/nejmoa050518

Bharat, A., Aft, R., Gao, F., & Margenthaler, J. (2009). Patient and tumor characteristics associated with increased mortality in young women (≤40 years) with breast cancer. *Journal Of Surgical Oncology, 100(3*), 248-251.

Bishop, J., Killelea, B., Chagpar, A., Horowitz, N., & Lannin, D. (2014). Smoking and Breast Cancer Recurrence after Breast Conservation Therapy. *International Journal Of Breast Cance*r, 2014, 1-5. http://dx.doi.org/10.1155/2014/327081

Bleyer, A., Anders, C. K., Johnson, R., Litton, J., Phillips, M. (2009). Breast cancer before age 40 years. *Seminars in Oncology, 36(3*), 237–49

Bodai, B. I., & Tuso, P. (2015). Breast Cancer Survivorship: A Comprehensive Review of Long-Term Medical Issues and Lifestyle Recommendations. *The Permanente Journal, 19(2), 48–79.*

Boscoe FP, Schymura M.J.(2006). Solar ultraviolet-B exposure and cancer incidence and mortality in the United States, 1993- 2002. *BMC Cancer .6*:264-75

Boyd, N., Guo, H., Martin, L., Sun, L., Stone, J., & Fishell, E. et al. (2007). Mammographic Density and the Risk and Detection of Breast Cancer. *New England Journal Of Medicine, 3*56(3), 227-236.

Boyle, P. (2005). Cancer incidence and mortality in Europe, 2004. *Annals Of Oncology, 16(3), 481-48*8. http://dx.doi.org/10.1093/annonc/mdi098

Bray F, Ren JS, Masuyer E, Ferlay J (2013). Global estimates of cancer prevalence for 27 sites in Africa

Brandt, J., Garne, J., Tengrup, I. and Manjer, J. (2015). Age at diagnosis in relation to survival following breast cancer: a cohort study. *World Journal of Surgical Oncology, 13(1), p.33.*

Brazda, A., Estroff, J., Euhus, D., Leitch, A., Huth, J., & Andrews, V. et al. (2010). Delays in Time to Treatment and Survival Impact in Breast Cancer. *Annals Of Surgical Oncology, 17(S3), 291*-296. http://dx.doi.org/10.1245/s10434-010-1250-6

Breast Cancer Risk and Prevention. (2017). Cancer.org. Retrieved 13 July 2017, from https://www.cancer.org/cancer/breast-cancer/risk-and-prevention.html

Breast Cancer Risk Factors. (2016). Breastcancer.org. Retrieved 13 July 2016, from http://www.breastcancer.org/risk/factors

Breast MRI. (2017). Cancer.Net. Retrieved 14 July 2017, from http://www.cancer.net/navigating-cancer-care/diagnosing-cancer/tests-and-procedures/breast-mri-early-detection-breast-cancer

Brink, H. I. (2009). Fundamentals of research methodology for health care professionals.(2nd ed.).Cape Town: Cerda Press.

Brink, H., Van der Walt, C., & Van Rensburg, G. (2012). Fundamentals of research methodology for health care professionals. Cape Town, South Africa: Juta.

Brinton, L. A., Figueroa, J. D., Awuah, B., Yarney, J., Wiafe, S., Wood, S., Clegg-Lamptey, J. N. (2014). Breast Cancer in Sub-Saharan Africa: Opportunities for Prevention. *Breast Cancer Research and Treatment, 144(*3), 467–478.

Brinton, L., Figueroa, J., Awuah, B., Yarney, J., Wiafe, S., & Wood, S. et al. (2014). Breast cancer in Sub-Saharan Africa: opportunities for prevention. *Breast Cancer Research And Treatment*, 144(3), 467-478.

Brinton, L., Hoover, R., & Fraumeni, J. (1983). Reproductive factors in the aetiology of breast cancer. *British Journal Of Cancer*, 47(6), 757-762.

Brooks, P., & Zakhari, S. (2012). Moderate Alcohol Consumption and Breast Cancer in Women: From Epidemiology to Mechanisms and Interventions. Alcoholism*: Clinical And Experimental Research*, 37(1), 23-30. http://dx.doi.org/10.1111/j.1530-0277.2012.01888.x

Burns, N. & Grove, S. K. (2005). The practice of nursing research: Conduct critique, and utilization, (5th Ed.). St. Louis, M.O: Elsevier Saunders conducts.

Burstein H. J, Harris J.R, Morrow .M (2011). Malignant tumors of the breast. In: DeVita V.T, Lawrence T.S, Rosenberg S.A. Principles and Practice of Oncology. 9th ed. Philadelphia, Pa: Lippincott Williams & Wilkins: 1401–1456

Butt, S., Borgquist, S., Garne, J., Landberg, G., Tengrup, I., Olsson, Å., & Manjer, J. (2009). Parity in relation to survival following breast cancer. *European Journal Of Surgical Oncology (EJSO)*, 35(7), 702-708.

Cancer Association Namibia. (2014). Can.org.na. Retrieved 18 July 2016, from http://www.can.org.na/

Cancer Association Namibia. (2016). Can.org.na. Retrieved 18 July 2016, from http://www.can.org.na/

Cancer Association Namibia. (2017). Can.org.na. Retrieved 12 July 2017, from http://www.can.org.na/

Cancer Survival Statistics - SEER Cancer Statistics. (2017). Seer.cancer.gov. Retrieved 20 July 2017, from https://seer.cancer.gov/statistics/types/survival.html

Cancer. (2017). World Health Organization. Retrieved 9 July 2017, from http://www.who.int/mediacentre/factsheets/fs297/en/

CancerGuide: Statistics and Cancer Section Home. (2017). Cancerguide.org. By Steve Dunn. Retrieved 18 July 2017, from http://cancerguide.org/stats_home.html

Cardoso, F., Harbeck, N., Fallowfield, L., Kyriakides, S., & Senkus, E. (2012). Locally recurrent or metastatic breast cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Annals Of Oncology, 23(suppl 7)*, vii11-vii19. http://dx.doi.org/10.1093/annonc/mds232

Carsterns, P., Gfeenberg, R., Francis, D., & Lyon, H. (1985). Tubular carcinoma of the breast. A long term follow-up. Histopathology, 9(3), 271-280.

Cheng, Y., & Ueno, N. (2011). Improvement of survival and prospect of cure in patients with metastatic breast cancer. *Breast Cancer, 19(3)*, 191-199.

Chlebowski, R., Hendrix, S., Langer, R., Stefanick, M., Gass, M., & Lane, D. et al. (2003). Influence of Estrogen Plus Progestin on Breast Cancer and Mammography in Healthy

Postmenopausal Women: The Women's Health Initiative Randomized Trial. Obstetrical & Gynecological Survey, 58(11), 735-737. http://dx.doi.org/10.1097/01.ogx.0000093674.44946.d6

Chokunonga E., Levy L. M., Bassett M. T., Mauchaza B. G., Thomas D. B., Parkin D. M.(2000). Cancer Incidence in the African Population of Harare, Zimbabwe: Second Results from the Cancer Registry 1993–1995. *International Journal of Cancer. 85(1):54–59*

Christensen, J. (2014). Research Methods, Design and analysis. England: 11th Edition. Pearson Education Limited.

Chustecka, Z (2014). ASCO Updates Node Dissection Early Breast Cancer Guideline. Medscape.

Chung, M., Chang, H., Bland, K. and Wanebo, H. (1996). Younger women with breast carcinoma have a poorer prognosis than older women. *Cancer*, 77(1), pp.97-103.

Cianfrocca, M. (2004). Prognostic and Predictive Factors in Early-Stage Breast Cancer. *The Oncologist*, 9(6), 606-616.

CMAJ. (1998) .Mastectomy or lumpectomy? The choice of operation for clinical stages I and II breast cancer. The Steering Committee on Clinical Practice Guidelines for the Care and Treatment of Breast Cancer. *Canadian Association of Radiation Oncologists. 10; 158 Suppl 3:S15-21*.

Coghill, A., Newcomb, P., Madeleine, M., Richardson, B., Mutyaba, I., & Okuku, F. et al. (2013). Contribution of HIV infection to mortality among cancer patients in Uganda. AIDS, 27(18), 2933-2942.

Colleoni, M., Rotmensz, N., Robertson, C., Orlando, L., Viale, G., & Renne, G. et al. (2002). Very young women (<35 years) with operable breast cancer: features of disease at presentation. *Annals Of Oncology*, 13(2), 273-279.

Croce, C. (2008). Oncogenes and Cancer. *New England Journal Of Medicine*, *358*(5), 502-511. http://dx.doi.org/10.1056/nejmra072367

Dal Maso, L., Zucchetto, A., Talamini, R., Serraino, D., Stocco, C., & Vercelli, M. et al. (2008). Effect of obesity and other lifestyle factors on mortality in women with breast cancer. *International Journal Of Cancer*, 123(9), 2188-2194. http://dx.doi.org/10.1002/ijc.23747

de Bock, G., van der Hage, J., Putter, H., Bonnema, J., Bartelink, H., & van de Velde, C. (2006). Isolated loco-regional recurrence of breast cancer is more common in young patients and following breast conserving therapy: Long-term results of European Organisation for Research and Treatment of Cancer studies. *European Journal Of Cancer*, 42(3), 351-356. http://dx.doi.org/10.1016/j.ejca.2005.10.006

De Ver Dye, T., Bogale, S., Hobden, C., Tilahun, Y., Hechter, V., & Deressa, T. et al. (2011). A mixed-method assessment of beliefs and practice around breast cancer in Ethiopia: Implications for public health programming and cancer control. Global Public Health, 6(7), 719-731. http://dx.doi.org/10.1080/17441692.2010.510479

De Vos, A. (2011). Research at grass roots. Pretoria: Van Schaik.

Department of Health (2000). Interim advice to GPs on familial breast cancer. London: Department of Health.

DeVita, V., Lawrence, T., & Rosenberg, S. (2011). Devita, Hellman & Rosenberg's Cancer. Philadelphia: Wolters Kluwer Health/Lippincott Williams & Wilkins.

Dickens, C., Joffe, M., Jacobson, J., Venter, F., Schüz, J., Cubasch, H., & McCormack, V. (2014). Stage at breast cancer diagnosis and distance from diagnostic hospital in a periurban setting: A South African public hospital case series of over 1,000 women. *International Journal Of Cancer*, *135(9)*, 2173-2182. http://dx.doi.org/10.1002/ijc.28861

Dillon, M. F., Hill, A. D. K., Quinn, C. M., O'Doherty, A., McDermott, E. W., & O'Higgins, N. (2005). The Accuracy of Ultrasound, Stereotactic, and Clinical Core Biopsies in the Diagnosis of Breast Cancer, With an Analysis of False-Negative Cases. *Annals of Surgery*, *242(5*), 701–707. http://doi.org/10.1097/01.sla.0000186186.05971.e0

Dumitrescu, R., & Cotarla, I. (2005). Understanding breast cancer risk - where do we stand in 2005? *Journal Of Cellular And Molecular Medicine*, *9(1*), 208-221.

Earl, H., Hiller, L., Dunn, J., Blenkinsop, C., Grybowicz, L., Vallier, A., Gounaris, I., Abraham, J., Hughes-Davies, L., McAdam, K., Chan, S., Ahmad, R., Hickish, T., Rea, D., Caldas, C., Bartlett, J., Cameron, D., Provenzano, E., Thomas, J. and Hayward, R. (2017). Disease-free and overall survival at 3.5 years for neoadjuvant bevacizumab added to docetaxel followed by fluorouracil, epirubicin and cyclophosphamide, for women with HER2 negative early breast cancer: ARTemis Trial. *Annals of Oncology*.

El Saghir, N., Seoud, M., Khalil, M., Charafeddine, M., Salem, Z., Geara, F., & Shamseddine, A. (2006). Effects of young age at presentation on survival in breast cancer. *BMC Cancer, 6(1).*

Elledge, R., Clark, G., Chamness, G., & Osborne, C. (1994). Tumor Biologic Factors and Breast Cancer Prognosis Among White, Hispanic, and Black Women in the United States. *JNCI Journal Of The National Cancer Institute*, 86(9), 705-712.

Euser A, M, Zoccali C, Jager K, J., Dekker F, W. (2009). Cohort Studies: Prospective versus Retrospective. Nephron Clin Pract; 113:c214-c217

Ezeome, E.R. (2010). Delays in presentation and treatment of breast cancer in Enugu, Nigeria. *Niger J Clin Pract*. 2010 Sep; 13(3):311-6.

Fact Sheets by Cancer. (2017). Globocan.iarc.fr. Retrieved 9 July 2017, from http://globocan.iarc.fr/Pages/fact_sheets_cancer.aspx

Falkson, G., Gelman, R., Leone, L., & Falkson, C. (1990). Survival of premenopausal women with metastatic breast cancer. Long-term follow-up of eastern cooperative group and cancer and leukemia group B studies. *Cancer, 66*(7), 1621-1629.

Fattore, E. (2002). Persistent organic pollutants in food: public health implications. *Journal Of Epidemiology & Community Health, 56(11*), 831-832.

Feigelson, H., James, T., Single, R., Onitilo, A., Aiello Bowles, E., & Barney, T. et al. (2013). Factors Associated with the Frequency of Initial Total Mastectomy: Results of a Multi-Institutional Study. *Journal Of The American College Of Surgeons*, 216(5), 966-975. http://dx.doi.org/10.1016/j.jamcollsurg.2013.01.011

Fentiman I.S., Allen, D.S, Hamed. H (2005). Smoking and prognosis in women with breast cancer. *Int J Clin Pract.* 59: 1051-1054

Ferlay, J., Shin, H.-R., Bray, F., Forman, D., Mathers, C., & Parkin, D. M. (2010). Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008. International Journal of Cancer. *Journal International Du Cancer, 127*(12), 2893–917.

Ferlay, J., Soerjomataram, I., Dikshit, R., Eser, S., Mathers, C., & Rebelo, M. et al. (2013). Cancer incidence and mortality worldwide: Sources, methods and major patterns in GLOBOCAN 2012. *International Journal Of Cancer, 136(5),* E359-E386. http://dx.doi.org/10.1002/ijc.29210

Foo, C., Su, D., Chong, C., Chng, H., Tay, K., Low, S., & Tan, S. (2005). Breast cancer in young Asian women: Study on survival. *ANZ Journal Of Surgery, 75(*7), 566-572. http://dx.doi.org/10.1111/j.1445-2197.2005.03431.x

Forman, J.P., Stampfer, M.J., Curhan, G.C. (2009). Diet and lifestyle risk factors associated with incident hypertension in women. *JAMA. 302*(4):401-11.

Fredholm, H., Eaker, S., Frisell, J., Holmberg, L., Fredriksson, I., & Lindman, H. (2009). Breast Cancer in Young Women: Poor Survival Despite Intensive Treatment. PLoS ONE, 4(11), e7695. http://doi.org/10.1371/journal.pone.0007695

Fuchs CS, Stampfer MJ, Colditz GA, et al. (1995). Alcohol consumption and mortality among women. *N Engl J Med. 332*(19):1245-50.

Fulton,S. & Krainovich-Miller, B. (2010). Gathering and Appraising the Literature, in Nursing Research: Methods and Critical Appraisal for Evidence-Based Practice *(*7th ed), USA: Mosby, Inc.

Gnerlich, J., Deshpande, A., Jeffe, D., Sweet, A., White, N., & Margenthaler, J. (2009). Elevated Breast Cancer Mortality in Women Younger than Age 40 Years Compared with Older Women Is Attributed to Poorer Survival in Early-Stage Disease. *Journal Of The American College Of Surgeons, 208(3),* 341-347. http://dx.doi.org/10.1016/j.jamcollsurg.2008.12.001

Goldhirsch, A. (2005). Meeting Highlights: International Expert Consensus on the Primary Therapy of Early Breast Cancer 2005. *Annals Of Oncology, 16(10*), 1569-1583. http://dx.doi.org/10.1093/annonc/mdi326

Gravetter, F. J. & Forzano, L. B. (2009). Research methods for behavioural sciences. (4th ed) Belmont, CA: Wadsworth Cengage Learning.

Grimes, D. (1992). Progestins, breast cancer, and the limitations of epidemiology. Fertility And Sterility, 57(3), 492-494.

Hardin, J., Bertoni, G., Kleinsmith, L., & Becker, W. (2012). Becker's world of the cell. Boston: Benjamin Cummings.

Haybittle, J. (1991). Curability of breast cancer. British Medical Bulletin, 47(2), 319-323.

Haynes, S. N., Richard, D. C. S., & Kubany, E. S. (1995). Content validity in psychological assessment: A functional approach to concepts and methods. Psychological Assessment, 7(3): 238-247.

Hellmann, S., Thygesen, L., Tolstrup, J., & Grønbæk, M. (2010). Modifiable risk factors and survival in women diagnosed with primary breast cancer: results from a prospective cohort study. *European Journal Of Cancer Prevention, 19*(5), 366-373. http://dx.doi.org/10.1097/cej.0b013e32833b4828

Henry, K., Boscoe, F., Johnson, C., Goldberg, D., Sherman, R., & Cockburn, M. (2011). Breast Cancer Stage at Diagnosis: Is Travel Time Important?. *Journal Of Community Health, 36(6)*, 933-942. http://dx.doi.org/10.1007/s10900-011-9392-4

Henry, N., Somerfield, M., Abramson, V., Allison, K., Anders, C., & Chingos, D. et al. (2016). Role of Patient and Disease Factors in Adjuvant Systemic Therapy Decision Making for Early-Stage, Operable Breast Cancer: American Society of Clinical Oncology Endorsement of Cancer Care Ontario Guideline Recommendations. *Journal Of Clinical Oncology*, 34(19), 2303-2311. http://dx.doi.org/10.1200/jco.2015.65.8609

Hibberd, A., Horwood, L., & Wells, J. (1983). Long term prognosis of women with breast cancer in New Zealand: study of survival to 30 years. *BMJ, 286(6380)*, 1777-1779.

Higgins, J., & Green, S (2010). Cochrane handbook for systematic reviews of interventions.

Hill, A.D.K., Doyle, J.M., McDermott, E.W., O'Higgins, N.J (1997). Hereditary breast cancer. *British Journal of Surgery.84 (*10):1334–1339

Hill, M., Giacosa, A., & Caygill, C. (1994). Epidemiology of diet and cancer. New York: E. Horwood.

Holli, K., Isola, J. and Cuzick, J. (2018). Hormone replacement therapy and biological aggressiveness of breast cancer.

Hunt, K., Vessey, M., McPherson, K., & Coleman, M. (1988). Long-term surveillance of mortality and cancer incidence in women receiving hormone replacement therapy. *International Journal Of Gynecology & Obstetrics, 26(3),* 477-478. http://dx.doi.org/10.1016/0020-7292(88)90394-3

IARC. (2013). Iarc.fr. Retrieved 13 July 2017, from http://www.iarc.fr/en/media-centre/iarcnews/index1.php?year=2013

Institute of Medicine Staff. (2001). Health and Behavior: The Interplay of Biological, Behavioral, and Societal Influences. Washington, DC, USA: National Academies Press.

Jameson, J., Fauci, A., Kasper, D., Hauser, S., Longo, D., & Jameson, J. et al (2001). Harrison's principles of internal medicine.

Janerich, D., & Hoff, M. (1982). Evidence for a crossover in breast cancer risk factor. *American Journal Of Epidemiology*, *116*(5), 737-742.

Jemal, A., Bray, F., Center, M., Ferlay, J., Ward, E., & Forman, D. (2011). Global cancer statistics. CA: A *Cancer Journal For Clinicians*, 61(2), 69-90.

Justo, N., Wilking, N., & Jönsson, B. (2011). PHP3 A Review of Breast Cancer (BC) Care and Outcomes in Latin America & Caribbean (LAC). Value In Health, 14(7), A549. http://dx.doi.org/10.1016/j.jval.2011.08.1602

Kauff, N., Satagopan, J., Robson, M., Scheuer, L., Hensley, M., & Hudis, C. et al. (2002). Risk-Reducing Salpingo-Oophorectomy in Women With a BRCA1 or BRCA2 Mutation. Obstetrical & Gynecological Survey, 57(9), 574-575.

Kemfang Ngowa, J., Yomi, J., Kasia, J., Mawamba, Y., Ekortarh, A., & Vlastos, G. (2011). Breast Cancer Profile in a Group of Patients Followed up at the Radiation Therapy

Unit of the Yaounde General Hospital, Cameroon. *Obstetrics And Gynecology International*, 2011, 1-5.

Kharazmi, E., Chen, T., Narod, S., Sundquist, K., & Hemminki, K. (2014). Effect of multiplicity, laterality, and age at onset of breast cancer on familial risk of breast cancer: a nationwide prospective cohort study. *Breast Cancer Research And Treatment, 144(*1), 185-192.

Kingham, T., Alatise, O., Vanderpuye, V., Casper, C., Abantanga, F., & Kamara, T. et al. (2013). Treatment of cancer in sub-Saharan Africa. Retrieved 17 July 2017, from http://www.thelancet.com/journals/lanonc/article/PIIS1470-2045(12)70472-2/abstract

Knight, J., Lesosky, M., Barnett, H., Raboud, J., & Vieth, R. (2007). Vitamin D and Reduced Risk of Breast Cancer: A Population-Based Case-Control Study. Cancer Epidemiology Biomarkers & Prevention, 16(3), 422-429.

Kohler, B., Sherman, R., Howlader, N., Jemal, A., Ryerson, A., Henry, K., Boscoe, F., Cronin, K., Lake, A., Noone, A., Henley, S., Eheman, C., Anderson, R. and Penberthy, L. (2015). Annual Report to the Nation on the Status of Cancer, 1975-2011, Featuring Incidence of Breast Cancer Subtypes by Race/Ethnicity, Poverty, and State. *JNCI: Journal of the National Cancer Institute*, 107(6).

Kollias, J., Elston, C., Ellis, I., Robertson, J., & Blamey, R. (1997). Early-onset breast cancer – histopathological and prognostic considerations. *British Journal Of Cancer, 75(9*), 1318-1323. http://dx.doi.org/10.1038/bjc.1997.223

Koscielny, S., Tubiana, M., Lê, M., Valleron, A., Mouriesse, H., Contesso, G., & Sarrazin, D. (1984). Breast cancer: Relationship between the size of the primary tumour and the probability of metastatic dissemination. *British Journal Of Cancer, 49*(6), 709-715.

Kunkler, I. (2012). Radiotherapy Issues in Elderly Breast Cancer Patients. *Breast Care*, 7(6), pp.453-459.

Kwame, G., Anthony, A.,Louis, H. (2010). Encyclopedia of Africa. Oxford University Press

Labrèche, F., Goldberg, M., Valois, M., Nadon, L., Richardson, L., Lakhani, R., & Latreille, B. (2003). Occupational exposures to extremely low frequency magnetic fields and

postmenopausal breast cancer. *American Journal Of Industrial Medicine, 44*(6), 643-652.

Lakhani, S (2013). WHO classification of tumours of the breast.

Lambe M, Hsieh CC, Tsaih SW, Ekbom A, Trichopoulos D & Adami H O.(1998). Parity, age at first birth and the risk of carcinoma in situ of the breast. *International Journal of Cancer*. 77330–332.

Last, J. (Ed.). (2001). International Epidemiological Association: A dictionary of epidemiology (4th ed.). New York: Oxford University Press

Levin, C., El Gueddari, B., & Meghzifene, A. (1999). Radiation therapy in Africa: distribution and equipment. Radiotherapy And Oncology, 52(1), 79-83. http://dx.doi.org/10.1016/s0167-8140(99)00069-9

Louvet, C. (1998). Adjuvant radiotherapy and chemotherapy in node-positive premenopausal women with breast cancer. La Revue De Médecine Interne, 19(1), 73.

Lowry, S.J., Kapphahn, K., Chlebowski, R., Li CI. (2016). Alcohol use and breast cancer survival among participants in the Women's Health Initiative. Cancer Epidemiol Biomarkers Prev. 25(8):1268-73.

Lund, M., Trivers, K., Porter, P., Coates, R., Leyland-Jones, B., & Brawley, O. et al. (2008). Race and triple negative threats to breast cancer survival: a population-based study in Atlanta, GA. *Breast Cancer Research And Treatment*, 113(2), 357-370.

Macleod, U., Ross, S., Gillis, C., McConnachie, A., Twelves, C., & Watt, G. (2000). Socio-economic deprivation and stage of disease at presentation in women with breast cancer *Annals Of Oncology*, 11(1), 105-107.

MacMahon, B., Cole, P., Lin, T. M., Lowe, C. R., Mirra, A. P., Ravnihar, B. … Yuasa, S. (1970). Age at first birth and breast cancer risk. Bulletin of the World Health Organization, 43(2), 209–221.

Manjer J, Andersson I, Berglund G, Bondesson L, Garne JP, Janzon L, Malina J, Matson S. (2000). Survival of women with breast cancer in relation to smoking. *Eur J Surg: 166: 852-858*

Maree, J., Wright, S., & Lu, X. (2013). Breast Cancer Risks and Screening Practices among Women Living in a Resource Poor Community in Tshwane, South Africa. The Breast Journal, 19(4), 453-454. http://dx.doi.org/10.1111/tbj.12143

Margenthaler, J.(2008). Younger women diagnosed with early-stage breast cancer more likely to die than older women. American College of Surgeons Clinical Congress; October 12-16, 2008; San Francisco, CA

Marketing, I. (2015). 'Cancer patients need love and support' - Health - Namibian Sun. Namibiansun.com. Retrieved 12 July 2015, from https://www.namibiansun.com/news/cancer-patients-need-love-and-support.

Martin, A. (2000). Genetic and Hormonal Risk Factors in Breast Cancer. *Journal Of The National Cancer Institute*, 92(14), 1126-1135.

Martínez, M., Anderson, K., Murphy, J., Hurley, S., Canchola, A., & Keegan, T. et al. (2016). Differences in marital status and mortality by race/ethnicity and nativity among California cancer patients. *Cancer*, 122(10), 1570-1578.

McCormack, V., Joffe, M., van den Berg, E., Broeze, N., dos Santos Silva, I., & Romieu, I. et al. (2013). Breast cancer receptor status and stage at diagnosis in over 1,200 consecutive public hospital patients in Soweto, South Africa: a case series. *Breast Cancer Research, 15(5).*

McLaughlin, J., Anderson, R., Ferketich, A., Seiber, E., Balkrishnan, R., & Paskett, E. (2012). Effect on Survival of Longer Intervals Between Confirmed Diagnosis and Treatment Initiation Among Low-Income Women With Breast Cancer. *Journal Of Clinical Oncology*, 30(36), 4493-4500.

Metcalfe, K., Gershman, S., Lynch, H., Ghadirian, P., Tung, N., & Kim-Sing, C. et al. (2011). Predictors of contralateral breast cancer in BRCA1 and BRCA2 mutation carriers. *British Journal Of Cancer*, 104(9), 1384-1392. http://dx.doi.org/10.1038/bjc.2011.120

National Breast Cancer Centre. (2001). 'Clinical practice guidelines for the management of early breast cancer: Second edition'. National Breast Cancer Centre, Camperdown, NSW.

National Institutes of Health Consensus Development Conference Statement: Adjuvant Therapy for Breast Cancer, November 1-3, 2000. (2001). *JNCI Monographs*, 2001(30), 5-15. http://dx.doi.org/10.1093/oxfordjournals.jncimonographs.a003460

NCIN. (2016). National Cancer Registration and Analysis Service. Stage Breakdown by CCG. London

Nemoto, T., Natarajan, N., Bedwani, R., Vana, J., & Murphy, G. (1983). Breast cancer in the medial half. Results of 1978 national survey of the American College of surgeons. Cancer, 51(8), 1333-1338.

Neville, A., Bettelheim, R., Gelber, R., Säve-Söderbergh, J., Davis, B., & Reed, R. et al. (1992). Factors predicting treatment responsiveness and prognosis in node-negative breast cancer. The International (Ludwig) Breast Cancer Study Group. *Journal Of Clinical Oncology*, 10(5), 696-705.

Newman, L., Bunner, S., Carolin, K., Bouwman, D., Kosir, M., White, M., & Schwartz, A. (2002). Ethnicity related differences in the survival of young breast carcinoma patients. *Cancer*, 95(1), 21-27. http://dx.doi.org/10.1002/cncr.10639

Nilsson E, Olsson S, Thorlacius H, Butt Tuna S (2016) Use of Oral Contraceptives and Breast Cancer Survival. *Int J Womens Health Wellness 2:039*.

Nixon, A., Neuberg, D., Hayes, D., Gelman, R., Connolly, J., & Schnitt, S. et al. (1994). Relationship of patient age to pathologic features of the tumor and prognosis for patients with stage I or II breast cancer. *Journal Of Clinical Oncology, 12(5)*, 888-894.

Noh, D., Kang, H., Yun, I., Kim, J., Chung, J., & Lee, D. et al. (1999). The Detection of Cancer in Augmented Breast by Positron Emission Tomography. *Journal Of Korean Breast Cancer Societ*y, 2(1), 44.

Noordzij, M., Dekker F,W., Zoccali ,C., Jager K.J(2009): Study designs in clinical research. Nephron Clin Pract .113:c218–c221.

Oettlé A. G., Higginson J. (1966). Age Specific Cancer Incidence Rates in the South African Bantu: 1953–1955. *South African Journal of Medical Science*. Johannesburg .31:21–41

Oh, J., Bonnen, M., Outlaw, E., Schechter, N., Perkins, G., & Strom, E. et al. (2006). The impact of young age on locoregional recurrence after doxorubicin-based breast conservation therapy in patients 40 years old or younger: How young is "young"?. *International Journal Of Radiation Oncology*Biology*Physics, 65(5), 1345-1352.* http://dx.doi.org/10.1016/j.ijrobp.2006.03.028

Olivotto, I. Levine M. (2001). Clinical practice guidelines for the care and treatment of breast cancer: the management of ductal carcinoma in situ. CMAJ 165:912–3

O'Meara, E., Rossing, M., Daling, J., Elmore, J., Barlow, W., & Weiss, N. (2001). Hormone Replacement Therapy After a Diagnosis of Breast Cancer in Relation to Recurrence and Mortality. *JNCI Journal Of The National Cancer Institute*, 93(10), 754-761. http://dx.doi.org/10.1093/jnci/93.10.754

Osborne, C., Ostir, G., Du, X., Peek, M., & Goodwin, J. (2005). The Influence of Marital Status on the Stage at Diagnosis, Treatment, and Survival of Older Women with Breast Cancer. *Breast Cancer Research And Treatment*, 93(1), 41-47.

Patterson, R., Cadmus, L., Emond, J., & Pierce, J. (2010). Physical activity, diet, adiposity and female breast cancer prognosis: A review of the epidemiologic literature. Maturitas, 66(1), 5-15. http://dx.doi.org/10.1016/j.maturitas.2010.01.004

Patton, M.Q. (1990). Qualitative evaluation and research methods. SAGE Publications. Newbury Park London New Delhi.

Peat, J. (2002). Health services research: A handbook of quantitative methods. London: Sage Publications.

Pike MC., Gerkins VR., Casagrande JT., Gray GE., Brown .J., Henderson B.E. (1979). The hormonal basis of breast cancer. *Natl Cancer Inst Monogr* .53:187–93.

Pillay, A. (2002). Rural and Urban South African Women's Awareness of Cancers of the Breast and Cervix. Ethnicity & Health, 7(2), 103-114. http://dx.doi.org/10.1080/1355785022000038588

Polit, D.F., Beck, C.T. and Hungler, B.P. (2001), Essentials of Nursing Research: Methods, Appraisal and Utilization. 5th Ed., Philadelphia: Lippincott Williams & Wilkins

Ragaz, J., Jackson, S., Le, N., Plenderleith, I., Spinelli, J., & Basco, V. et al. (1997). Adjuvant Radiotherapy and Chemotherapy in Node-Positive Premenopausal Women with Breast Cancer. *New England Journal Of Medicine, 337*(14), 956-962.

Ragunath, P., Reddy, B. V., Abhinand, P., & Ahmed, S. S. (2012). Relevance of systems biological approach in the differential diagnosis of invasive lobular carcinoma & invasive ductal carcinoma. Bioinformation, 8(8), 359–364. http://doi.org/10.6026/97320630008359

Ragunath, P., Reddy, B., Abhinand, P., & Ahmed, S. (2012). Relevance of systems biological approach in the differential diagnosis of invasive lobular carcinoma & invasive ductal carcinoma. Bioinformation, 8(8), 359-364. http://dx.doi.org/10.6026/97320630008359

Rahman, G. A. (2011). Breast Conserving Therapy: A surgical Technique where Little can Mean More. *Journal of Surgical Technique and Case Report*, 3(1), 1–4. http://doi.org/10.4103/2006-8808.78459

Rapiti, E., Fioretta, G., Verkooijen, H., Vlastos, G., Schäfer, P., & Sappino, A. et al. (2005). Survival of young and older breast cancer patients in Geneva from 1990 to 2001. *European Journal Of Cancer, 41*(10), 1446-1452.

Robertson, C., & Boyle, P. (1998). Age at any birth and breast cancer risk. *Statistics In Medicine, 17(4*), 431-445.

Rodriguez, A., Chew, H., Cress, R., Xing, G., McElvy, S., Danielsen, B., & Smith, L. (2008). Evidence of Poorer Survival in Pregnancy-Associated Breast Cancer. Obstetrics & Gynecology, 112(1), 71-78. http://dx.doi.org/10.1097/aog.0b013e31817c4ebc

Ronckers, C., Erdmann, C., & Land, C. (2004). Radiation and breast cancer: a review of current evidence. *Breast Cancer Research, 7(1*).

Roses, D., Harris, M., Potter, D., & Gumport, S. (1981). Total Mastectomy with Complete Axillary Dissection. *Annals Of Surgery, 194(*1), 4-8. http://dx.doi.org/10.1097/00000658-198107000-00002

Saad, E .D. Katz, A. (2009). Progression-free survival and time to progression as primary end points in advanced breast cancer: often used, sometimes loosely defined. *Ann Oncol. 20(3):460-4*

Saez, R.A., McGuire W.L., Clark G.M. (1989). Prognostic factors in breast cancer. *Semin Surg Oncol 198*9;5:102–110.

Schedin, P. (2006). Pregnancy-associated breast cancer and metastasis. Nature Reviews Cancer, 6(4), 281-291.

Schmidt, F. L., & Hunter, J. E. (1993). Employment testing: Old theories and new research findings. American Psychologist, 36, 1128-1137.

Schonland M., Bradshaw E. (1968). Cancer in the Natal African and Indian, 1964–1966. *International Journal of Cancer. 3*:304–16

Segen's Medical Dictionary. (2011). Retrieved January 4 2017 from http://medical-dictionary.thefreedictionary.com/analytical+study

Shannon, C., & Smith, I. (2003). Breast cancer in adolescents and young women. *European Journal Of Cancer*, 39(18), 2632-2642. http://dx.doi.org/10.1016/s0959-8049(03)00669-5

Sharp, L., McDevitt, J., Brown, C., Carsin, A., & Comber, H. (2017). Association between smoking at diagnosis and cause-specific survival in patients with rectal cancer: Results from a population-based analysis of 10,794 cases. *Cancer, 123(13)*, 2543-2550. http://dx.doi.org/10.1002/cncr.30583

Shavers, V., Harlan, L., & Stevens, J. (2002). Racial/ethnic variation in clinical presentation, treatment, and survival among breast cancer patients under age 35. *Cancer, 97(1)*, 134-147. http://dx.doi.org/10.1002/cncr.11051

Sighoko, D., Kamaté, B., Traore, C., Mallé, B., Coulibaly, B., & Karidiatou, A. et al. (2013). Breast cancer in pre-menopausal women in West Africa: Analysis of temporal trends and evaluation of risk factors associated with reproductive life. The Breast, 22(5), 828-835. http://dx.doi.org/10.1016/j.breast.2013.02.011

Silvera, S., Jain, M., Howe, G., Miller, A., & Rohan, T. (2005). Energy balance and breast cancer risk: a prospective cohort study. *Breast Cancer Research And Treatment*, 97(1), 97-106. http://dx.doi.org/10.1007/s10549-005-9098-3

Simon, S. (2013). Cancer.org. Smoking linked to breast cancer .Retrieved 13 July 2017, from http://www.cancer.org/cancer/news/study-links-smoking-to-breast-cancer-risk.

Singletary, K., & Gapstur, S. (2001). Alcohol and Breast Cancer. JAMA, 286(17), 2143.

Sitas, F., Parkin, M., Chirenje, Z., Stein, L., Mqoqi, N., & Wabinga, H. (2006). Cancers. Ncbi.nlm.nih.gov. Retrieved 12 July 2017, from https://www.ncbi.nlm.nih.gov/books/NBK2293

Slattery, M., Edwards, S., Murtaugh, M., Sweeney, C., Herrick, J., & Byers, T. et al. (2007). Physical Activity and Breast Cancer Risk Among Women in the Southwestern United States. *Annals Of Epidemiology*, *17(*5), 342-353. http://dx.doi.org/10.1016/j.annepidem.2006.10.017

Stefan, D., Elzawawy, A., Khaled, H., Ntaganda, F., Asiimwe, A., & Addai, B. et al. (2013). Developing cancer control plans in Africa: examples from five countries. *The Lancet Oncology*, 14(4), e189-e195. http://dx.doi.org/10.1016/s1470-2045(13)70100-1

Suh, M., Atashili, J., Fuh, E., & Eta, V. (2012). Breast Self-Examination and breast cancer awareness in women in developing countries: a survey of women in Buea, Cameroon. BMC Research Notes, 5(1), 627. http://dx.doi.org/10.1186/1756-0500-5-627

Symonds, P., Deehan, C., Mills, J., & Meredith, C. (2012). Walter and Miller's textbook of radiotherapy. Edinburgh: Elsevier Churchhill Livingstone.

The Early Breast Cancer Trialists' Group. (2005.) Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: an overview of the randomised trials. (2005). The Lancet, 365(9472), 1687-1717. http://dx.doi.org/10.1016/s0140-6736 (05)66544-0

Thomas HV, Reeves G.K, Key T.J (1997). Endogenous estrogen and postmenopausal breast cancer: a quantitative review. Cancer Causes Control. 8:922–8.

Thun, M. J., DeLancey, J. O., Center, M. M., Jemal, A., & Ward, E. M. (2010). The global burden of cancer: priorities for prevention. Carcinogenesis, 31(1), 100–110. http://doi.org/10.1093/carcin/bgp263

Total population sampling | Lærd Dissertation. (2017). Dissertation.laerd.com. Retrieved 18 July 2017, from http://dissertation.laerd.com/total-population-sampling.php

Trichopoulos D, MacMahon B, Cole P (1972). Menopause and breast cancer risk. *J Natl Cancer Inst . ; 48*:605–13.

Velikova, G., Booth, L., Johnston, C., Forman, D. and Selby, P. (2004). Breast cancer outcomes in South Asian population of West Yorkshire. *British Journal of Cancer, 90(10), p*p.1926-1932.

van Leeuwen, F., Klokman, W., Stovall, M., Dahler, E., van't Veer, M., & Noordijk, E. et al. (2003). Roles of Radiation Dose, Chemotherapy, and Hormonal Factors in Breast Cancer Following Hodgkin's Disease. *JNCI Journal Of The National Cancer Institute*, 95(13), 971-980.

Veronesi, A., Giacomi, C., Magri, M., Lombardi, D., Zanetti, M., Scuderi, C., Dolcetti, R., Viel, A., Crivellari, D., Bidoli, E. and Boiocchi, M. (2005). Familial breast cancer: characteristics and outcome of BRCA 1–2 positive and negative cases. *BMC Cancer*, 5(1).

Vinh-Hung, V., & Verschraegen, C. (2004). Breast-Conserving Surgery With or Without Radiotherapy: Pooled-Analysis for Risks of Ipsilateral Breast Tumor Recurrence and Mortality. *JNCI Journal Of The National Cancer Institute, 96(2*), 115-121. http://dx.doi.org/10.1093/jnci/djh013

Voogd, A., Nielsen, M., Peterse, J., Blichert-Toft, M., Bartelink, H., & Overgaard, M. et al. (2001). Differences in Risk Factors for Local and Distant Recurrence After Breast-Conserving Therapy or Mastectomy for Stage I and II Breast Cancer: Pooled Results of Two Large European Randomized Trials. *Journal Of Clinical Oncology, 19(6),* 1688-1697. http://dx.doi.org/10.1200/jco.2001.19.6.1688

Walter .R & Miller's , J(2012). Textbook of Radiotherapy (5th edn). *British Journal of Cancer*, 69(6), 1198

Wapnir, I., Anderson, S., Mamounas, E., Geyer, C., Jeong, J., & Tan-Chiu, E. et al. (2006). Prognosis After Ipsilateral Breast Tumor Recurrence and Locoregional Recurrences in Five National Surgical Adjuvant Breast and Bowel Project Node-Positive Adjuvant Breast Cancer Trials. *Journal Of Clinical Oncology*, *24(*13), 2028-2037. http://dx.doi.org/10.1200/jco.2005.04.3273

Whitney, C.W., Lind, B.K., Wahl, P.W. (1998). Quality assurance and quality control in longitudinal studies. Epidemiologic Reviews, 20(1): 71-80.

Williams, N., Bulstrode, C., & O'Connell, P. (2013). Bailey & Love's Short Practice of Surgery 26E. Hoboken: CRC Press.

World Health Organization (2002). National cancer control programmes. Geneva: World Health Organization.

Yaghjyan, L., Colditz, G., Collins, L., Schnitt, S., Rosner, B., Vachon, C., & Tamimi, R. (2011). Mammographic Breast Density and Subsequent Risk of Breast Cancer in Postmenopausal Women According to Tumor Characteristics. *JNCI Journal Of The National Cancer Institute, 103*(15), 1179-1189.

Yang, S. K., Cho, N., & Moon, W. K. (2007). The Role of PET/CT for Evaluating Breast Cancer. *Korean Journal of Radiology, 8(5),* 429–437.

Yang, T., & Ho, A. (2013). Radiation Therapy in the Management of Breast Cancer. Surgical Clinics Of North America, 93(2), 455-471. http://dx.doi.org/10.1016/j.suc.2013.01.002

Yarney, J., Donkor, A., Opoku, S., Yarney, L., Agyeman-Duah, I., Abakah, A., & Asampong, E. (2013). Characteristics of users and implications for the use of complementary and alternative medicine in Ghanaian cancer patients undergoing radiotherapy and chemotherapy: a cross- sectional study. *BMC Complementary And Alternative Medicine,* 13(1). http://dx.doi.org/10.1186/1472-6882-13-16

Yoo, T.-K., Han, W., Moon, H.-G., Kim, J., Lee, J. W., Kim, M. K. … Noh, D.-Y. (2016). Delay of Treatment Initiation Does Not Adversely Affect Survival Outcome in Breast Cancer. Cancer Research and Treatment : *Official Journal of Korean Cancer Association*, 48(3), 962–969.

Yoshida, M., Shimizu, C., Fukutomi, T., Tsuda, H., Kinoshita, T., & Akashi-Tanaka, S. et al. (2010). Prognostic Factors in Young Japanese Women with Breast Cancer: Prognostic Value of Age at Diagnosis. *Japanese Journal Of Clinical Oncology*, 41(2), 180-189.

Yu GP, Ostroff JS, Zhang ZF, Tang J, Schantz SP (1997). Smoking history and cancer patient survival: a hospital cancer registry study. Cancer Detect Prev. pg21: 497-509.

Zhou, P., & Recht, A. (2004). Young age and outcome for women with early-stage invasive breast carcinoma. *Cancer, 101(6),* 1264-1274.

APPENDICES

Appendix 1: Ethical clearance certificate

UNAM
UNIVERSITY OF NAMIBIA

ETHICAL CLEARANCE CERTIFICATE

Ethical Clearance Reference Number: SONPH/124/2016 **Date: 9 September, 2016**

This Ethical Clearance Certificate is issued by the University of Namibia Research Ethics Committee (UREC) in accordance with the University of Namibia's Research Ethics Policy and Guidelines. Ethical approval is given in respect of undertakings contained in the Research Project outlined below. This Certificate is issued on the recommendations of the ethical evaluation done by the Faculty/Centre/Campus Research & Publications Committee sitting with the Postgraduate Studies Committee.

Title of Project: The Relationship Between Age At First Diagnoses And Treatment Outcome Of Breast Cancer in Namibia

Nature/Level of Project: Masters

Researcher: S. Chiridza

Student Number: 201401635

Faculty: School of Nursing and Public Health

Supervisor: Dr. S. Yigeremu
Take note of the following:

(a) Any significant changes in the conditions or undertakings outlined in the approved Proposal must be communicated to the UREC. An application to make amendments may be necessary.
(b) Any breaches of ethical undertakings or practices that have an impact on ethical conduct of the research must be reported to the UREC.
(c) The Principal Researcher must report issues of ethical compliance to the UREC (through the Chairperson of the Faculty/Centre/Campus Research & Publications Committee) at the end of the Project or as may be requested by UREC.
(d) The UREC retains the right to:
  (i). withdraw or amend this Ethical Clearance if any unethical practices (as outlined in the Research Ethics Policy) have been detected or suspected, request for an ethical compliance report at any point during the course of the research.

UREC wishes you the best in your research.

Dr. H. Kapenda
Director –Centre for Research and Publications
ON BEHALF OF UREC

Appendix 2: Letter of permission to conduct the research study from the Ministry of Health and Social Services

REPUBLIC OF NAMIBIA

Ministry of Health and Social Services

Private Bag 13198
Windhoek
Namibia

Ministerial Building
Harvey Street
Windhoek

Tel: 061 – 203 2562
Fax: 061 – 222558
E-mail: hnangombe@mhss.gov.na

OFFICE OF THE PERMANENT SECRETARY

Ref: 17/3/3
Enquiries: Ms. H. Nangombe

Date: 08 September 2016

Mr Simbarashe Chiridza
School of Public Health
University of Namibia
P.O. Box 50805
Bachbrecht
Windhoek

Dear Mr Chiridza

Re: The relationship between age at first diagnosis and outcome of breast cancer in Namibia

1. Reference is made to your application to conduct the above-mentioned study.

2. The proposal has been evaluated and found to have merit.

3. **Kindly be informed that permission to conduct the study has been granted under the following conditions:**

3.1 The data to be collected must only be used for academic purpose;

3.2 No other data should be collected other than the data stated in the proposal;

3.3 Stipulated ethical considerations in the protocol related to the protection of Human Subjects should be observed and adhered to, any violation thereof will lead to termination of the study at any stage;

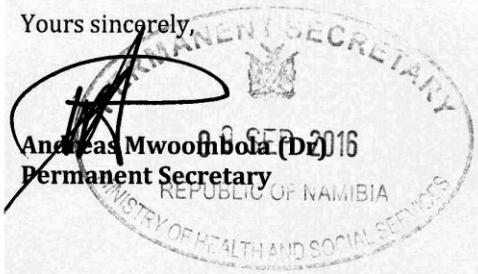
3.4 A quarterly report to be submitted to the Ministry's Research Unit;

3.5 Preliminary findings to be submitted upon completion of the study;

3.6 Final report to be submitted upon completion of the study;

3.7 Separate permission should be sought from the Ministry for the publication of the findings

Yours sincerely,



Andreas Mwoombola (Dr)
Permanent Secretary

"Health for All"

Appendix 3: Letter of permission/approval to conduct the research study from the Windhoek Central hospital

9 - 0/0001

REPUBLIC OF NAMIBIA

Ministry of Health and Social Services

Private Bag 13215 Windhoek Namibia	Harvey Street Windhoek Central Hospital	Tel. No: (061) 203 3024 Fax No: (061) 222886
Enquiries: Mrs. A.MOOTU	Ref.	Date : 21 September 2016

OFFICE OF THE MEDICAL SUPERINTENDENT

WINDHOEK CENTRAL HOSPITAL

Mr. Simbarashe Chiridza
School of Public Health
University of Namibia
Windhoek
0817195616

Dear Mr.Chiridza

RE: PERMISSION TO CONDUCT THE STUDY ON RELATIONSHIP BETWEEN AGE AT FIRST DIAGNOSE AND OUTCOME OF BREAST CANCER IN NAMIBIA.

Kindly be informed that permission has been granted for you to conduct a research on the above mentioned subject:

1.1 Patients /clients information should be kept confidential at all times
1.2 The purpose for research is only for your study purposes as you have requested and it does not include any remuneration.

Thank you for your kind gesture.

Yours sincerely

DR. S. SHALONGO
MEDICAL SUPERINTENDENT

"Health for All"

Appendix 4: Research permission letter from UNAM

University of Namibia, Private Bag 13301, Windhoek, Namibia
340 Mandume Ndemufayo Avenue, Pioneerspark
☎ +264 61 206 3111, URL : http://www.unam.edu.na

UNAM
UNIVERSITY OF NAMIBIA

RESEARCH PERMISSION LETTER

Date: 20/06/2016

TO WHOM IT MAY CONCERN

RE: RESEARCH PERMISSION LETTER

1. This letter serves to inform you that student: **SIMBARASHE CHIRIDZA** (Student number: **201401635**) is a registered student in the SCHOOL of PUBLIC HEALTH for the **MASTER IN PUBLIC HEALTH** degree at the University of Namibia. His/her research proposal was reviewed and successfully met the University of Namibia requirements.
2. The purpose of this letter is to kindly notify you that the student has been granted permission to carry out postgraduate studies research. The School of Postgraduate Studies has approved the research to be carried out by the student for purposes of fulfilling the requirements of the degree being pursued.
3. The proposal adheres to ethical principles

Kind regards

Signed: pp. Mulenga, HoD, PGS, Fac. of Health Sciences

Name of Main Supervisor: Dr. Solomon Yigeremu

Signed: pp.
Dr. M. Hedimbi
Director: School of Postgraduate Studies
Tel: 2063523
E-mail: mhedimbi@unam.na

Centre for Postgraduate Stu
Office of the Director
2016 -07- 04
University of Namibia
UNAM

Appendix 5: **Data Collection Tool**

DATA EXTRACTION FORM

THE RELATIONSHIP BETWEEN AGE AT FIRST DIAGNOSIS AND TREATMENT OUTCOME OF BREAST CANCER IN NAMIBIA

A data extraction form will be used to collect the data from the patients' files since the research is based on previous recorded data in the patent's files. No questionnaires or interviews will be used in the study for the collection of data. The data extraction form will be used to collect epidemiological variables and clinical variables. Socio-demographic variables on the data extraction form will include age, residence, marital status, number of children. Clinical variables will include disease stage at diagnosis, family history of cancer, receptor status, and other diseases such as HIV, diabetes mellitus, hypertension known to the patient, HRT/hormonal use, smoking and alcohol intake. The health condition of patient (absence or presence of metastases and survival) after a 5year post treatment period will be recorded as well.

SECTION 1

Socio-demographic data collection form of the patient

1. Date form completed	
2. Patient ID	
3. Age at first diagnosis of breast cancer	
4. Residence Urban /rural	
5. Marital Status of patient	
6. Number of children	
7. Employment status	

SECTION 2

Clinical data collection form

Part A

Pt ID	
Date at first diagnosis	
Date at first treatment	
Date of completion of treatment- state if patient did not complete the prescribed breast cancer treatment	
Stage of disease at diagnosis	
Family history of breast cancer	
Receptor status (negative/positive receptors) ER,PR	
Does patient have a history of chronic illness/ HIV?	
HRT/hormonal use	
Is the patient a smoker?	
Alcohol intake?	

Part B OUTCOME OF TREATMENT DATA OBTAINED FROM POST-TREATMENT REVIEWS						
Condition of patient on each yearly review post treatment (Metastases, recurrences, and deaths should be stated here.)	**12 months**	**24 months**	**36 months**	**48 months**	**60 months**	**Overall outcome good/bad?**