FACTORS ASSOCIATED WITH BREAST CANCER AMONG WOMEN PATIENTS ATTENDING KENYATTA NATIONAL HOSPITAL, KENYA - 2008

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Factors Associated with Breast Cancer among Women Patients Attending Kenyatta National Hospital, Kenya – 2008.

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DECLARATION

This thesis is my original work and has not been presented for a degree in any other University.

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This thesis has been submitted for examination with our approval as University supervisors.

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DEDICATION

I dedicate this work to my mother Esther Andeso for teaching me by example - that perseverance pays. Your enduring maternal dedication has continuously made me.

I also dedicate this thesis to my lovely wife Lorna Buhya Omumia, and my children Elsie Shitandi, Finch Juma and Roy Matsanza for their encouragement and perseverance.

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ABBREVIATIONS

ASWR	Age Standardized Mortality Rates
BMI	Body Mass Index
BRCA	Breast Cancer Gene
CIS	Carcinoma *In Situ*
DCIS	Ductal Carcinoma *in Situ*
DNA	Deoxy-ribo-nucleic acid
EE	Ethinyl estradiol
ER	Oestrogen Receptor
FFTB	First Full Term Pregnancy/Birth
HRT	Hormone Replacement Therapy
JKUAT	Jomo Kenyatta University of Agriculture and Technology
KEMRI	Kenya Medical Research Institute
KNH	Kenyatta National Hospital
LCIS	Lobular Carcinoma *in Situ*
OC	Oral Contraceptive
OR	Odds Ratio
PR	Progesterone Receptor
RR	Relative Risk

SBE	Self Breast Examination
SD	Standard Deviation
SEER	Surveillance Epidemiology and End Results
SHBG	Sex Hormone Binding Globulin
UK	United Kingdom
USA	United States of America

ABSTRACT

Breast cancer is the second most common cancer in the world. Its incidence in Kenya is increasing. Factors associated with breast cancer have been studied elsewhere. There, exists a knowledge gap on the factors associated with the disease in Kenya.

An age-matched case control study was carried out with the aim of determining factors associated with breast cancer in female patients at Kenyatta National Hospital in 2008. Cases were adult female breast cancer patients. Controls were adult female non-breast cancer patients.

Sixty four cases and sixty four controls were interviewed. Using univariate analysis, having primary or no formal education (mOR = 0.40), having the first conception at or before age 24 (mOR = 0.31), attaining menopause at age 49 or earlier (mOR = 0.10), and having 36 or less years of fertility (mOR = 0.09) were associated with a reduced chance of having breast cancer. Being overweight (BMI $\geq$ 25) (mOR = 6.60) or being in formal occupation (mOR = 5.00) were associated with an increased chance of having breast cancer.

The following factors were significantly associated with breast cancer in logistic regression: having regular monthly menstrual cycles (mOR = 19.24), having menstrual cycles of 28 days or less (mOR = 12.91), having conceived 3 times or less (mOR = 16.08), attaining menarche by age 14 (mOR = 9.39) and residing in a rural setting (mOR = 16.43).

There is need to revise and disseminate policy guidelines for women breast cancer health education, screening, care and treatment. Health workers should be updated on the factors found to be associated with breast cancer so as to enrich targeted screening. Escalating health education of women could advance early diagnosis.

CHAPTER 1: INTRODUCTION

1.1 Background

Cancer is a group of distinct diseases in which abnormal cells divide without control and invade other tissues abnormally. This result from damage of the genetic material -- called Deoxyribonucleic Acid (DNA) -- of a cell, producing mutations that affect normal cell division, growth and attrition. The resultant cells do not die when they should, and new cells form when the body does not need them. This often results in a tumour (swelling) in most cancers (*www.cancer.gov*, 2008).

Cancer cells travel either directly by local spread or indirectly through the bloodstream or the lymph system to other parts of the body where they continue to grow and replace normal tissue.

In developed countries, and with the changing lifestyles in most developing countries, cancers continue to be important causes of chronic morbidity. Cancer is the leading cause of death in the United States after heart disease, accounting for 1 in 4 deaths (Greenlee *et al.*, 2000).

There are more than 100 known different types of cancers originating from almost every organ and tissue in the body.

Breast cancer is a malignant tumour that starts in the tissues of the breast. Though occurring almost entirely in women, breast cancer can occur in men too (*http://www.cancer.org*, 2008).

Although the advancement of diagnostic techniques and treatment in the last decade has greatly contributed to the survival of cancer patients, breast cancer is still one of the leading causes of death in women worldwide (Teng *et al*., 2008). The incidence and mortality from breast cancer has been steadily decreasing after peaking in the year 2000. One of the factors responsible for this decrease is the early detection and management of non-invasive and pre-cancerous breast lesions through screening (Petra *et al.,* 2008).

There is approximately one reported case of breast cancer in males for every 100 reported breast cancer cases in women (Rai *et al., 2005*). Breast cancer in males predominantly affects the older populations, with a peak incidence at 60 years of age compared to 50 – 55 in females (Parkin *et al.*, 2005). This is due to the paucity of breast tissue in males. Exposure to ionizing radiation, a family history of breast cancer in first-degree relatives, single marital status, previous benign disease of the breast, and high oestrogen levels as occurs in liver cirrhosis are some of the known risk factors in the male (Rai *et al., 2005*).

1.2 Statement of the problem

About 5.3 million men and 4.7 million women were diagnosed with malignant tumours worldwide in the year 2000. In the same year, malignant tumours were responsible for 12% of the nearly 56 million deaths from all causes (*www.dep.iarc.fr/, 2008*).

Breast cancer is the second most common cancer in the world, accounting for just over 1 million new cases annually. It was the 6th leading cause of death in women in the United States of America (USA) for the period 1969-2004

(www.dep.iarc.fr/, 2008). It is the number one cause of cancer deaths in Hispanic women, and ranked second among white, black and Asian women (*www.cdc.gov/cancer/breast/statistics/, 2008)*.

The age standardised world rates (ASWR) of breast cancer morbidity in Kenya was 25.2 per 100,000 women in 2002. This was second only to Mauritius (ASWR 33.1 per 100,000 women) among the 16 eastern Africa countries (regional average 19.5 per 100,000 women). The breast cancer age standardised mortality rate for Kenya in the same year was 18.1 per 100,000 women. This was the highest for the region (*www.dep.iarc.fr/*, 2008). Age standardized rates take into account differences in the age structure of the populations being compared. This is necessary because the incidence and mortality rates of most cancers rapidly increase with age so that populations containing a high proportion of old people tend to have a high overall (crude) cancer rate than one with mainly young people (Parkin *et al.*, 2005).

Despite a paucity of sufficiently long-term series of high quality data in Kenya, increases in breast cancer incidence and mortality are seen in countries similar to Kenya, where such data is available (Freddie *et al.*, 2004, Parkin, 1994, Coleman *et al.*, 1993). There has been a two-fold increase in breast cancer incidence in Kampala, Uganda, (Wabinga *et al.*, 2000) and Ibadan, Nigeria (Parkin *et al.*, 2003) between the 1960s and the late 1990s, with a steady increase in breast cancer mortality rates of the same order. Uganda had an ASWR of Breast cancer morbidity of 18.3 per 100,000 women and an ASWR

breast cancer mortality of 13.4 per 100,000 women in 2002 (*www.dep.iarc.fr/*, 2008). Breast cancer in Kenya could also be on an upward trend.

As a consequence of a range of socio-economically correlated differences in the population prevalence of reproductive, hormonal and nutritional determinants over time, women are at increasingly high risks of breast cancer (Freddie *et al.,* 2004). The fastest rise is being witnessed in developing countries where changing of lifestyles such as childbearing, dietary habits and exposure to exogenous estrogens towards a distribution closer to that in industrialised countries is thought to be responsible (Freddie *et al*., 2004).

For women, breast cancer is a terrifying disease as it has a high mortality rate. Moreover, since the breast is considered as a symbol of womanhood and women's sexuality, having breast cancer and the knowledge of the possible deforming treatment is traumatic to women due to its impact on self image (Yankaskas, 2005). At Kenyatta National Hospital (KNH), the estimated cost of chemotherapy per patient is between Kshs 12,000 – 18,000 for the first course drugs and Kshs 53,000 – 76,500 for the second course drugs.

Cancer of the breast in women is therefore a disease of public health concern that is projected to exert more strain on the health care system in Kenya.

1.3 Justification of the study

Various factors of established or postulated relationship with breast cancer have been studied in other set-ups that are not similar with Kenya. However, there exists a knowledge gap on the association between reproductive, familial, lifestyle and other modifiable factors and breast cancer in Kenya.

There is at least a 10-fold variation in breast cancer incidence rates worldwide over regions (Freddie *et al*., 2004), a difference that is mainly attributable to a range of socio-economically correlated differences in the population prevalence of several reproductive, hormonal and nutritional factors. Studies of migrants have shown that environmental (rather than genetic) determinants are responsible for most of the observed international and inter-ethnic differences in breast cancer incidence. For instance, comparisons of breast cancer risk in low-risk Asian populations migrating to the high-risk USA reveal major increases in risk between successive generations (Ziegler *et al*., 1993). Increases in risk were also observed in populations from Italy and Poland -- European countries with relatively low incidence -- after migration to Australia, particularly if the migration took place in childhood.

As a consequence of changing exposures to reproductive and nutrition-related determinants over time, women even in traditionally low-risk set-ups are at increasingly high risk of breast cancer, with incidence rates increasing in most countries and regions of the world in the past few decades. The most rapid rises are seen in developing countries, where breast cancer risk has historically been low relative to industrialized countries (Freddie *et al*., 2004). There however have been few attempts to quantify the magnitude of risk differentials between populations that might be explained by population-unique factors (Parkin *et al*., 2005).

Consequently, even though the association of a number of factors with breast cancer has been evaluated elsewhere, the findings may not apply in Kenya

owing to the differences in the populations. There was therefore need to investigate the factors associated with breast cancer in women seeking services at Kenyatta National Hospital (KNH), a national referral hospital in Kenya. The strength of such associations also needed to be established.

This may help inform implementation of prevention strategies aimed at promoting practices that may be beneficial in reducing breast cancer incidence and mortality in women in Kenya (Collaborative Group on Hormonal Factors in Breast Cancer, 2002).

In addition, knowledge of the female population at risk will help target screening interventions for breast cancer and improve advocacy for protective practices against the disease. Screening for breast cancer is known to prevent up to a third of breast cancer deaths (*www.dep.iarc.fr, 2008*). This improved treatment outcome is possible especially in developing countries where 80% of breast cancer cases are first diagnosed in late stage of the disease.

The reduced breast cancer mortality from primary prevention together with increased awareness, wider implementation of screening, and continued improvements in treatment and management of cases are likely to improve the survival of women.

Therefore, this knowledge of the factors associated with breast cancer will provide insights into the possible causes of the disease and will strengthen the role of primary prevention, early diagnosis and treatment in the reduction of the burden of the disease to the healthcare system and the community.

1.4 Null hypothesis

There are no factors associated with breast cancer among female patients in Kenyatta National Hospital, Nairobi – Kenya.

1.5 Objectives of the study

1.5.1 General Objective

The study aimed to determine the factors associated with breast cancer in female patients in Kenyatta National Hospital, Nairobi – Kenya.

1.5.2 Specific Objectives

The specific objectives of the study were:

1. To determine any association between reproductive factors and breast cancer among female patients in Kenyatta National Hospital.
2. To determine any association between socio-demographic factors and breast cancer among female patients in Kenyatta National Hospital.
3. To investigate familial history in breast cancer among female patients in Kenyatta National Hospital.

CHAPTER 2: LITERATURE REVIEW

2.1 Global Breast Cancer Situation

Cancer of the breast in women is a major health burden worldwide. One in ten of all new cancers diagnosed worldwide each year is a cancer of the breast; it is responsible for over one million of the estimated ten million neoplasms that are diagnosed worldwide annually in both sexes (Freddie *et al.,* 2004). It is the second most common tumour after lung cancer (Ferlay *et al.,* 2001).

Breast cancer is also the most common cancer in women in both developing and developed countries, accounting for over a fifth of the estimated annual 4.7 million cancer diagnoses. Fifty five percent of the cases occur in developed countries where the age-standardised rates are three times higher than in developing countries (Ferlay *et al.,* 2001).

Breast cancer is also the principal cause of death from cancer among women globally. In the year 2000, it was responsible for about 375,000 deaths (Freddie *et al.,* 2004). In 2004, it was the sixth cause of death in the USA, responsible for 40,954 deaths in women and 362 deaths in men (*www.seer.cancer.gov*, 2008).

International comparisons of disease rates by area of diagnosis shows that there is at least a 10-fold variation in breast cancer incidence rates worldwide (Freddie *et al.,* 2004). This is mainly as a result of a range of socio-economic correlated differences in the population prevalence of several reproductive, hormonal and nutritional factors. As indicated in figure 1, the geographical

variation in breast cancer incidence worldwide as estimated for the year 2000 shows that the highest incidence rates occur in northern and western Europe, northern America, Australia and New Zealand, and in southern countries of South America, notably Uruguay and Argentina (Ferlay *et al*., 2001). Geographical differences in risk are apparent within Europe, with elevated rates in northern and Western Europe, whereas rates in most southern and eastern European countries are comparatively lower to intermediate. Incidence is comparatively lower throughout Africa, Asia and most of Central and South America.

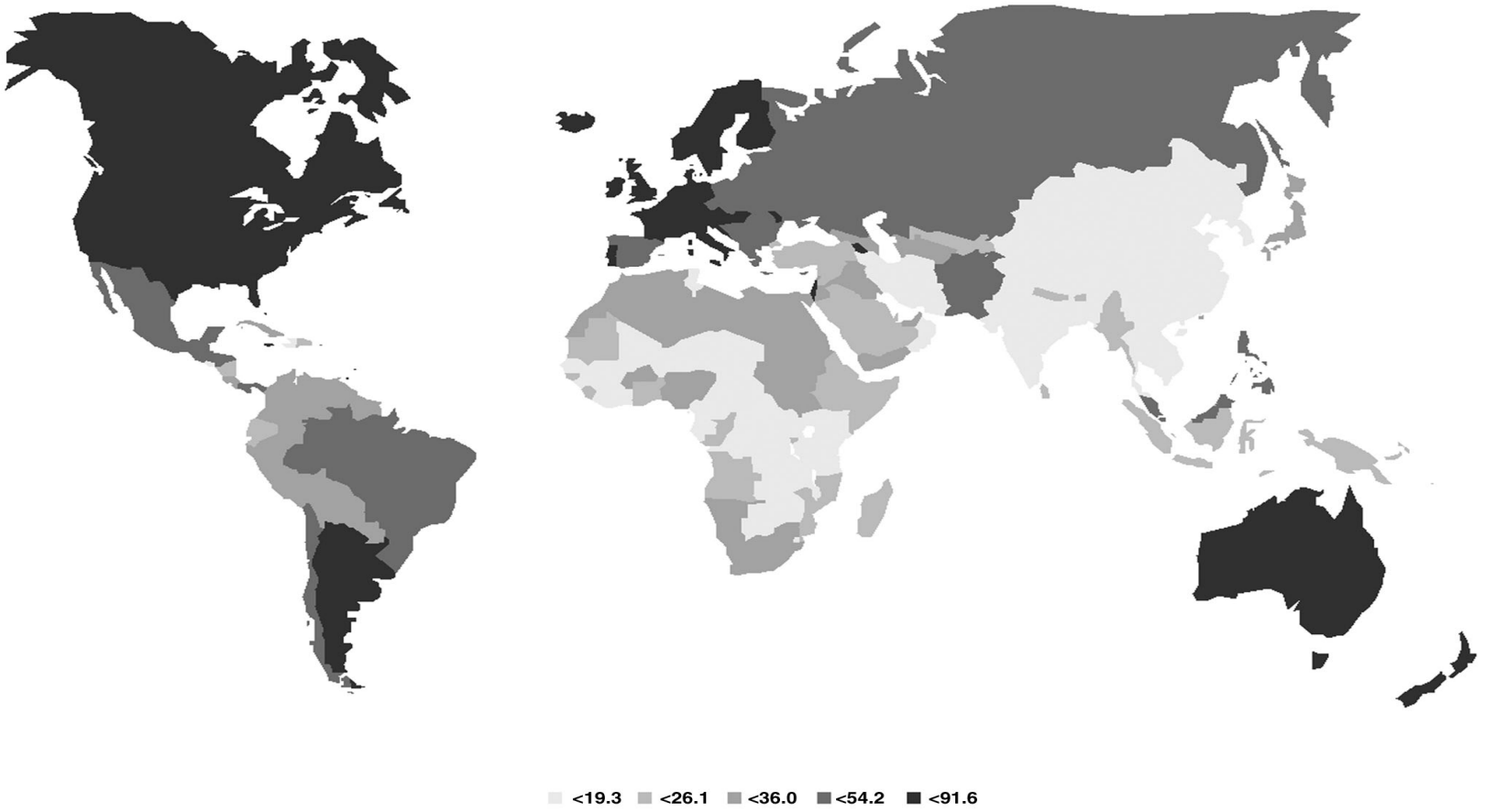

Figure 1: Breast cancer incidence worldwide: age-standardized rates (world population). Source: Ferlay *et al.*, 2001.

2.2 Breast Cancer Situation in Kenya

Kenya's age standardised world rates (ASWR) for breast cancer was 25.2 per 100,000 women in 2000, and was second only to Mauritius among the 16 eastern Africa countries with regional average 19.5 per 100,000 women. The breast cancer age standardised mortality rate for Kenya was 18.1 per 100,000 women in the same year and was the highest in the region (*www.dep.iarc.fr/*, 2008). Comparatively, Kenya has therefore been experiencing a high burden of breast cancer in the region.

The country reported 2,422 new cases of breast cancer in women in 2002 with a crude incidence rate (number of new cases per 100,000 women of reproductive age) of 15.2 per 100,000 women (*www.dep.iarc.fr/*, 2008). It was the second commonest cancer in women after cervical uteri cancer which had 2635 reported cases (16.5 cases per 100,000 women) (Curado *et al.*, 2007). It was also responsible for 1,699 reported deaths with a crude mortality rate of 10.6 per 100,000 women compared to cervical cancer which caused 2,111 deaths with a crude mortality rate of 13.2 per 100,000 women (*www.dep.iarc.fr/*, 2008).

A cancer registry maintained at the Kenya Medical Research Institute (KEMRI) was established in 2001 with the primary duty of collecting data on newly diagnosed cancer cases from hospitals, laboratories and radiotherapy units in Nairobi city for policy development and support in cancer research, treatment, control, prevention and surveillance (Mutuma and Rugut-Korir,

2006). The registry is therefore not comprehensive as it does not capture newly diagnosed cancer cases from the rest of the country.

Breast cancer was the most common cancer captured by the registry in women for the reporting period 2000 – 2002 with 419 (23.3%) cases followed by cervical uteri cancer with 359 (20%) cases. The trend was generally upward, with 149 cases in 2000, 117 cases in 2001 and 153 cases in 2002. Peak incidence was realised in the 50-54 (15%) age group followed by 40-44 (14.3%), 35-39 (12.9%), 45-49 (10.7%), 30-34 (10.3%), 55-59 (10%) and 65-69 (7.4%) age groups. About nine percent were aged below 30 or above 70 years.

KNH is the only public hospital in the country that offers comprehensive breast cancer diagnosis and treatment services in the country. These services, which include mammography, histopathology, surgery, chemotherapy, radiotherapy, radiotherapy and psychosocial support, are also offered at The Aga Khan Hospital, a privately owned hospital in Nairobi. KNH serves approximately 2 million patients annually from Kenya and the greater East Africa.

Moi Teaching and Referral Hospital in Eldoret (Kenya) offers all other services except radiotherapy. Regional and district hospitals therefore refer breast cancer patients to MTRH, KNH or The Aga Khan hospital for comprehensive care.

2.3 Breast Cancer Risk Factors

2.3.1 Pathogenesis background

Most breast cancers begin in the cells that line the ducts (tiny tubes that carry milk from the lobules to the nipple). Some however originate in the cells that line the lobules (milk-producing glands) and rarely in the stroma (fatty and connective tissue) of the breast.

Approximately 70% of human breast cancers express the oestrogen receptor (ER+) and are hormone dependent (Masood, 1992). It has been known for many years that sex steroid hormones play a role in the development, growth, and behavior of tumors of the breast, prostate, ovary and uterus. In order for sex steroid hormones to exert their effect, specific receptors should be present (Fisher *et al*., 1983). Studies done in American women show that 77% of breast cancer cases express ER (ER+) while 55% show progesterone receptors (PR+) (Thorpe, 1988). Tumors that are ER+ and PR + are regarded as being hormone responsive, while those that are hormonally non-responsive are often ER- and PR-. Tumors that are of a more dubious hormone responsive nature are either ER + and PR- or ER- and PR+. While estrogen directly binds on the receptors, influencing gene expression and cellular phenotype, it is recognized that PR is an expression of a fully functional ER mechanism as PR synthesis is usually an estrogen-dependent process. The increased mitotic activity due to estrogen activity replicates any abnormalities in genes which may phenotypically express as a tumor. It has been shown clinically that PR appears to be a more important prognosticator than ER.

It is acknowledged that compared to other times, the worst time for women to be exposed to any potential breast carcinogens takes place between the onset of menstruation and first full-term pregnancy (Russo *et al.,* 2000). This is thought to be due to the interaction of carcinogens with the rapidly dividing epithelium composing the undifferentiated ductal structures of the mammary tissue (Russo *et al.*, 2005). This interaction is thought to result in fixation of transformation in the cell's DNA make-up, leading to the initiation of cancer.

It has been proposed that the differentiation, and therefore the propensity for carcinogenesis of the human breast may be defined by the degree of complexity of the secretory lobules (Britt *et al.*, 2007). The breast tissue of normally cycling women contains types 1, 2, 3 and 4 lobules in the order of increasing complexity (defined as the number of clusters of ductules per lobule). The lobular composition of the breast of sexually mature women is influenced by numerous endogenous and exogenous factors. Principal among them are age, and hence the number and regularity of menstrual cycles, endocrine hormones, the use of exogenous hormones, environmental exposures that could act as endocrine disruptors, and the physiological condition of pregnancy.

The breast attains its maximum development during pregnancy (Figure 2). While type 1 and 2 lobules predominate in the nulliparous breast, type 3 and 4 lobules (with up to 80 ductules per lobule) develop at pregnancy and are the most abundant in the breasts of parous women (Russo *et al.*, 1992). It is known that 95% of breast cancer originates in type 1 and 2 lobules (Russo *et al.,*

2000). Type 1 and 2 lobules are matured by human chorionic gonadotrophin and human placenta lactogen into the cancer resistant type 3 and 4 lobules during normal pregnancy. At the end of a full term pregnancy, 85% of the lobules are Type 4.

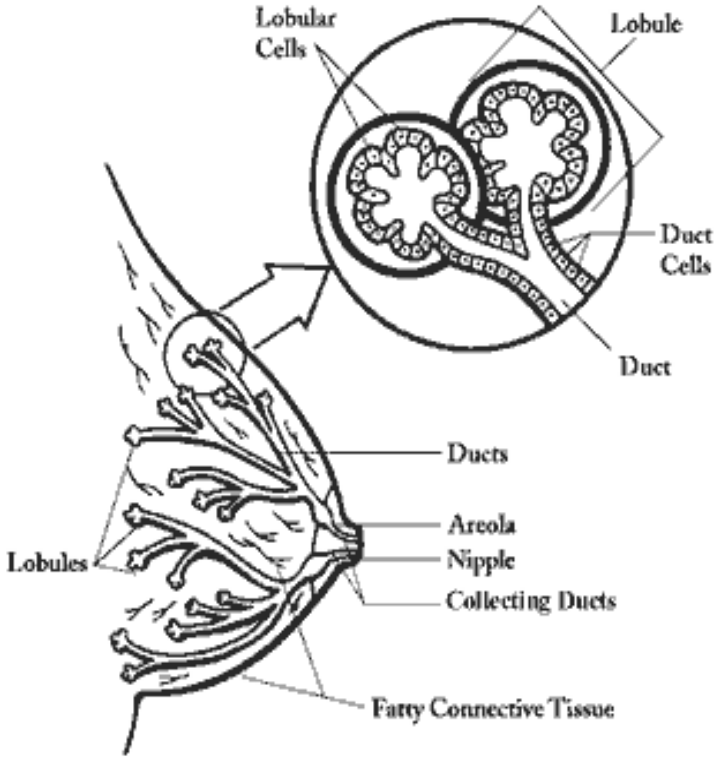

Figure 2: Structure of the female breast (Source: Britt *et al.,* 2007)

The breast regresses in both nulliparous and parous women after menopause. At the end of the fifth decade of life, the breast of both nulliparous and parous women contains predominantly Lob 1. Despite the similarity in the lobular composition of the breast, the fact that nulliparous women are at higher risk of developing breast cancer than parous women indicates that Lob 1 in these two

groups of women might be biologically different, or might exhibit different susceptibility to carcinogenesis.

The major influences on breast cancer appear to be certain reproductive factors, body size, alcohol, physical activity, exogenous hormones and possibly diet. There however have been few attempts to quantify the magnitude of risk differentials between populations that might be explained by such factors.

2.3.2 Hereditary factors

Family history has long been recognized as a potent risk factor for breast cancer (Steel *et al.*, 1991). Steel and co-researchers reckon that of all the factors contributing to breast cancer risk, a strong familial history of the disease is the most powerful. Familial clustering was noted by ancient Romans in the mid 19th century. Several studies have found that breast cancer is higher among women whose close relatives have had the disease. On average, 20-30% of women with breast cancer have a family member with the disease (*http://www.cancer.org*, 2008). Having a first degree relative (mother, sister, or daughter) doubles the risk of the disease while having two first degree relatives increases the risk 5-fold. Breast cancer in close male relatives also increases the risk of breast cancer in women offspring, though the exact risk is not clearly known.

Hereditary breast cancer accounts for about 10 – 14% of all breast cancers (Borresen, 1992). This is thought to be due to mutations inherited from a parent. While defects in several genes have been described, mutations in the BRCA1 and BRCA2 genes are the commonest and best understood.

BRCA1 is a tumour suppressor gene playing a role in surveillance of cell cycle and repair of DNA damage. BRCA2 which bears no gene homology to BRCA1 binds with BRCA1, participating in DNA damage response pathway associated with the activation of homologous recombination and double stranded break repair.

For their key role in maintaining DNA integrity, mutations affecting BRCA1 and BRCA2 increase the possibility of breast cell DNA aberrations which may lead to carcinogenesis. Carriage of these mutations is therefore strongly related to hereditary breast cancer. However, the type of mutation differs in distribution by ethnicity and geographical location. The prevalence of these mutations is higher in Ashkenazi (Eastern Europe) Jews, African American women, and Hispanic women, even though they can occur in any racial group (Teng *et al.,* 2008). The prevalence of BRCA1 mutations in Finish breast cancer patients is 0.4% while that in breast cancer patients in neighbouring Sweden is 7%. The prevalence rate in Kenyan women or any sub-Saharan country is no published.

In population-based studies, the risk of breast cancer by age 70 has been estimated to be about 65% in BRCA1 mutation carriers and 45% in BRCA2 carriers (Antoniou *et al*., 2003). When the women with such mutations in the BRCA1 and BRCA2 genes develop the cancer, they do so at a younger age -- often less than 50 years old -- than women with the normal genes (Ford *et al.,* 1994). The bearers of the mutated genes also have an increased risk of developing ovarian cancer.

Although the majority of BRCA1-associated breast cancers are oestrogen-receptor negative, factors that affect endogenous hormone levels appear to modify the breast cancer risk, as the risk of breast cancer in mutation carriers is decreased by oophorectomy (surgical removal of ovaries) (Rebbeck, 1999) and the risk of contra-lateral breast cancer decreased by tamoxifen (Narod *et al.*, 2000).

Besides serving as molecular markers for hereditary breast cancer risk screening, BRCA1 and BRCA2 mutations are also important indicators of breast cancer prevention, treatment and prognosis. Breast cancer carriers of the mutations have a poor outcome compared to non-carriers. A research program at collaborating centre in Norway and United Kingdom found that the 5-year survival in BRCA1 mutated patients was 73% compared to 92% in mutation negative patients (Moller *et al.*, 2007).

2.3.3 Reproductive factors

Epidemiological, clinical and experimental data indicate that the risk of developing breast cancer is strongly dependent on the ovary and on endocrine conditions modulated by ovarian function such as menarche, menopause and parity (Russo *et al.*, 2005). Of the multiple known and likely risk factors for the development of breast cancer, many are directly or indirectly related to endogenous or exogenous oestrogen exposure (McPherson *et al.*, 2000).

Oestrogen, a predominantly ovarian hormone, has important physiological effects on the growth and function of hormone-dependent tissues, including the epithelium of the breast. At birth, the mammary gland of intact animals

consists of a rudimentary ductal tree that develops and fills the stroma of the gland in response to increased ovarian oestrogen at puberty. Mammary glands of females that lack oestrogen receptors (ERα) do not grow beyond this rudimentary state (Russo *et al.,* 2005).

Besides, oestrogen influences gene expression and cellular phenotype by binding nuclear ER which in turn activates receptor dimerization and association with various co-activator and co-repressor proteins. This leads to gene transcription activation (Johnston, 2005). Evidence suggests that oestrogen acts as a mammary gland carcinogen. Two potential mechanisms that are thought to act independently, or in an additive or even synergistic way are responsible. First is the stimulation of ER-mediated transcription leading to cell proliferation. The second mechanism is direct carcinogenesis via metabolic activation and direct binding of DNA (Petra *et al.,* 2008).

2.3.3.1 Parity

Among well established reproductive risk factors, parity has been found to be associated with breast cancer (Britt *et al.,* 2007). Childbirth is the only factor known to consistently reduce breast cancer risk among all ethnic groups. Overall, compared with nulliparous women, parous women have been found to have a slightly lower risk of breast cancer. Andrieu *et al.* (2005) found that even among parous women, an increasing number of full-term pregnancies was associated with a decrease in the risk of breast cancer estimated at 14% for each additional birth for women aged more than 40 years. Among women who

were 40 years or younger, the risk per additional birth was unchanged (Andrieu *et al.,* 2005).

There is no consensus however on the effect of age at first full term pregnancy among parous women. Andrieu *et al.* (2005) found no statistically significant association between age at first full term pregnancy and the risk of breast cancer. However, in the same study, it was postulated that the association differed between the different BRCA1 and BRCA2 mutation carriers, suggesting an interaction between the mutation gene carriage status and age at first full term pregnancy. MacMahon *et al*. (1970) in a study in America, Europe and Asia, however found that women who had undergone a first full term pregnancy or birth (FFTB) before age 20 years had a 50% reduced lifetime risk of developing breast cancer compared with nulliparous women whereas Trichopoulos *et al*. (1983), re-analyzing the same data reported that first full-term births over 35 years of age led to an increased risk of developing breast cancer.

In a study carried out in Malaysia, a higher proportion of women in the breast cancer clinic were childless due to being single or infertile (Norsa'adah *et al.,* 2005). However, Garland *et al.,* (1998) elsewhere found that ovulatory infertility (infertility due to ovulatory dysfunction) was protective against breast cancer. This is thought to be due to lower exposure to ovulatory hormones. The possible failure to ovulate may be associated with reduced oestrogen and progesterone in the luteal (second half of menstrual cycle) phase of ovulatory menstrual cycle. Normally, following ovulation, there is an elevated estrogen and progesterone level, which has been biologically found to be associated

with higher mitotic activity of breast tissue. This is supported by the findings by Garland and co-researchers in the same study that there was no association between other types of infertility and breast cancer risk, which suggests that the observed inverse association is specific to ovulatory infertility. The ovulation inducing drug Clomiphene citrate which is an anti-oestrogen is associated with lower risk of breast cancer among infertile women (Garland *et al.*, 1998).

Ma *et al*. (2006) found that these parity-specific effects on breast cancer risk are limited to hormone-responsive breast cancer confined to oestrogen receptor positive/progesterone receptor positive (ER+/PR+) breast cancer and not ER-/PR- breast cancer.

There exist several schools of thought as to how pregnancy protects against breast cancer. First, protection may occur through pregnancy-induced changes in levels of circulating hormones such as estradiol, prolactin and growth hormone. Each of these has been associated with breast cancer risk (Henderson & Feigelson, 2000). Secondly, the extensive duct, lobule and alveoli development that occurs during pregnancy may result in epithelial cell differentiation, thereby maturing the gland in response to the first pregnancy. The parous mammary gland may, therefore, contain epithelial cells with a more differentiated and less proliferative type 3 and 4 lobules which are less susceptible to carcinogenesis (Britt *et al*., 2007). Finally, given that parity protects mainly against ER+ tumors, it is possible that parity protection may also be mediated via changes in the estrogen responsiveness of the mammary gland. These may take the form of changes in the response of hormone-sensing cells to estrogen.

2.3.3.2 Abortion

Andrieu *et al.* (2005) in their retrospective cohort study of 1601 women in the International BRCA1/2 Carrier Cohort Study in Europe did not find any association between having a miscarriage or an induced abortion and the risk of breast cancer. There was also no association between the timing of a miscarriage or an induced abortion with respect to the first full-term pregnancy and the risk of breast cancer. This is in agreement with the findings of Norsa'adah *et al.* (2005) in Malaysia who did not find a significant difference between cases and controls in the number of abortions.

However, in an ecological breast cancer modelling study in eight countries in Europe, Carrol showed that abortion is the "best predictor" of breast cancer (Carroll, 2007). He found that increase in breast cancer incidence appears to be best explained by an increase in abortion rates, especially nulliparous abortions, and lower fertility. And the social gradient, which is not explained by fertility alone, seems also attributable circumstantially to abortion.

The prospective study by Howe *et al*. (1989) also reported a statistically significant odds ratio of 1.9 (95% CI, 1.2-3) among women who had had abortions. Pike *et al.* (1981) in a case control study conducted in California, USA on 163 breast cancer cases also found that a first trimester abortion before FFTB, whether spontaneous or induced, was associated with a 2-fold increase in breast cancer risk. Daling and co-researchers also found that among women who had been pregnant at least once, the risk of breast cancer in those who had experienced an induced abortion was 50% higher than among other women

(Daling *et al.,* 1994). While this increased risk did not vary by the number of induced abortions or by the history of a completed pregnancy, it did vary according to the age at which the abortion occurred and the duration of that pregnancy. Highest risks were observed when the abortion occurred in women at ages younger than 18 years, particularly if it took place after 8 weeks' gestation, or at 30 years of age or older. No increased risk of breast cancer was associated with a spontaneous abortion in this study (Daling *et al.,* 1994).

It is possible that any loss of pregnancy in the first or second trimester leaves the mother with increased highly cancer susceptible Type 1 and 2 lobules due to the partial stimulating effect of the mitogen estradiol. Without loss of pregnancy, type 1 and 2 lobules would have been matured by human chorionic gonadotrophin and human placenta lactogen into the cancer resistant Type 4 lobules if the pregnancy went to term, reducing the risk of breast cancer.

The contradictions in findings of the association between abortion and miscarriage and breast cancer may be associated with the ability to collect accurate information on women's abortion histories. In societies where abortions may be moral issues, studies eliciting abortions by self-reporting stand a higher chance of under-reporting the incidence.

The study designs might also have contributed to these contradicting results. The investigators either reviewed existing data in government generated records (Andrieu *et al.,* 2005, Howe *et al.,* 1989, Pike *et al.,* 1981, Carroll, 2007) or conducted case control studies (Daling *et al.,* 1994, Norsa'adah *et al.,* (2005). Prospective cohort studies could possibly capture more accurate data.

2.3.3.3 Menstrual Factors

In 1985, Henderson *et* al. put forward the hypothesis that the risk of breast cancer is directly related to the cumulative number of regular ovulatory cycles (Henderson *et al.,* 1985). A woman's cumulative menstruation duration is determined by several factors, including the age at menarche and menopause and menstruation cycle duration and regularity.

It has been established that early age at menarche is an important risk factors for breast cancer. Hunter *et al*. (1997) found that a year's delay in onset of menarche was associated with a 5% reduction in the risk of developing breast cancer in later life. Besides, women who had an early menarche after age 15 years had a 28% reduced risk of developing breast cancer. In a large cohort study in the USA, Garland *et al*., (1998) also found that women with older ages at menarche after 12 years were at a reduced risk of developing breast cancer compared with women attaining menarche at earlier ages. In the case control study by Norsa'adah *et al*. (2005) in Malaysia however, no significant difference was found between cases and controls in the age attained at menarche. An early age at menarche increases the duration of breast tissue exposure to the cancer-inducing ovarian hormones.

A study carried out in Kenyan school children in 2003 found the average age at menarche to be 15 years (95% CI 14.9 – 15.1). This was reported to be 1.5 – 2 years later than that in the USA population (Leenstra *et al.,* 2003).

Garland and colleagues observed only a weak and insignificant increased association between the time from menarche to establishment of regular

menstrual cycles (Garland *et al*., 1998). In a large investigation in Northern Italy the breast cancer cases reported systematic menstrual irregularities significantly less frequently than controls (Parazzini *et al.*, 1993). In a prospective study by Tonkelaar and Waard (1996), irregular menstrual cycles were also found to be associated with decreased breast cancer risk. Among women with regular cycles, long cycles were not associated with decreased risk. The reason for this association is still not known, though it is postulated that since irregular cycles tend to have low estrogen and progesterone levels, the breast glandular tissue is exposed to low levels of these hormones in irregular cycles (Tonkelaar and Waard 1996).

Compared with women with a cycle length of 26-31 days, Garland *et al*. (1998) found that women who reported longer or shorter cycle lengths had a reduced risk of breast cancer. Other studies have variously indicated no association with cycle length (Parazzini *et al.*, 1993), an increased risk due to shorter cycles (Yuan *et* al., 1988) or a decreased risk (Soini, 1977). Biologically though, the risk of breast cancer is expected to be higher among women with shorter menstrual cycles owing to two reasons. First, the duration of the luteal phase of the menstrual cycle tends to vary less regardless of the duration of the entire menstrual cycle. Second, ovarian hormones during this phase are at higher levels than in the follicular phase. Women with shorter menstrual cycles tend to have a high number of cumulative cycles, exposing the breast tissue to high concentrations of the hormones.

Some reproductive characteristics in a woman's life affect her postmenopausal serum sex hormone levels. Mariana and co-workers in their study found that a lower cumulative number of menstrual cycles or a higher parity was associated with a higher level of Sex Hormone Binding Globulin (SHBG) (Mariana *et al.,* 2008) after menopause. By binding sex hormones like estradiol, SHBG engages them and reduces the proportion of the free circulating forms of these hormones that are able to enter cells and cause carcinogenic changes. Therefore, these findings suggest that having fewer menstrual cycles may be protective of breast cancer in the post-menopausal period by indirectly reducing free levels of estrogens and even androgens.

Even though several studies have not found an association between age at menopause and sex hormones--oestrogens, progestins and steroids -- a direct association between menopause and androstenedione (Madigan *et al.,* 1998) and estradiol (Chubak *et al.,* 2004) has been demonstrated. Madigan and co-researchers acknowledge that androgens have been associated with breast cancer risk; androstenedione is converted peripherally to estradiol, a known breast carcinogen (Madigan *et al.,* 1998).

Age at menopause has also been thought to be a risk factor of breast cancer. In one international multicentre case-control study, it was found that a delay of menopause by 5 years was associated with an increase in breast cancer risk of 17% during the post-menopausal period (Hsieh *et al*., 1990). In the case control study by Norsa'adah *et al*. (2005), no significant difference was found between cases and controls in the menopausal status and age attained at menopause.

This is in agreement with the findings in one large series of 1,187 BRCA1 and 414 BRCA2 carriers from the International BRCA1/2 Carrier Cohort Study that there is no association between breast cancer risk and ages at menopause in BRCA1 and BRCA2 carriers, though there was some evidence to support a protective effect of early oophorectomy on breast cancer risk (Chan-Claude *et al.,* 2007).

From this study, it is recommended that further large studies, preferably including population-based and/or prospective studies, will be required to provide more definitive risk estimates.

2.3.4 Breastfeeding

Although childbearing is known to protect against breast cancer, whether or not breastfeeding contributes to this protective effect is unclear. A number of researchers agree that there is no increased risk of breast cancer associated with prolonged breastfeeding (Norsa'adah *et al.,* 2005, Beral *et al.,* 2002, Martin *et al.,* 2005). Andrieu *et al.,* 2005 in their retrospective cohort study of 1,601 women who had a mutation in BRCA1 or BRCA2 found that the history of breast-feeding was not statistically significantly associated with the risk of breast cancer.

However, reanalyzing data for 50 302 women with invasive breast cancer and 96 973 controls from 47 epidemiological studies in 30 countries, The Collaborative Group on Hormonal Factors in Breast Cancer, (2002) found that fewer parous women with cancer than parous controls had ever breastfed. It was also found that the average lifetime duration of breastfeeding was shorter

for cases than for controls (9·8 *vs* 15·6 months). The relative risk of breast cancer decreased by 4·3% for every 12 months of breastfeeding, the size of the decline in the relative risk not differing significantly for women in developed and developing countries, by age, menopausal status, ethnic origin, the number of births a woman had or her age when her first child was born.

In a multicenter, population-based, case-control study, Newcomb *et al*. (1994) found that lactation was associated with a slight reduction in the risk of breast cancer among premenopausal women, as compared with the risk among women who were parous but had never lactated. It was also found that with an increasing cumulative duration of lactation, there was a decreasing risk of breast cancer among premenopausal women but not among postmenopausal, parous women.

Lokman and co-researchers in Kuala Lumpur also found out that breastfeeding reduces the risk of developing breast cancer (Lokman *et al.,* 2001).

These differences in findings could be partly due to near uniform breastfeeding practices among communities being investigated, as the average breastfeeding duration trends in a homogeneous community may be similar. The study designs could also play a role as mot studies that find some association are large multi-centre studies or meta-analyses.

While the exact mechanism by which breastfeeding confers protection is not known, lactation has a strong appeal as a potentially modifiable factor and is still under intense investigation (Newcomb *et al*., 1994).

2.3.5 Exogenous hormones

2.3.5.1 Oral Contraceptive (OC) use

Available information suggests that there is still no consensus on the association between OC use and breast cancer. Norsa'adah *et al.* (2005) in a case-control study found a significant association between oral contraceptive use and breast cancer in Malaysia. Oral contraceptive intake among nulliparous women was moderately associated with breast cancer. In his clinical review, McPherson *et al.,* (2000) noted that women on oral contraceptives and for 10 years after stopping these agents have a small increase in the relative risk of developing breast cancer. He also noted that there is no significantly increased risk of breast cancer 10 or more years following cessation of the oral contraceptive. This association was related to the duration, dosage, pattern of use, type of oral contraceptive and age of first use.

In 2005, the International Agency for Research in Cancer classified combined OCs as a group 1 carcinogen, the highest rating possible. This was based on noted increased risks of breast, cervical and liver cancer (Petra *et al.,* 2008).

The Oxford pooled analysis of 1996 (*Collaborative Group on Hormonal Factors in Breast Cancer, 1996*) probably contains the most comprehensive data that addressed the role of OC. The key findings were a 24% increased risk of breast cancer in current OC users (RR 1.24), a weaker but still elevated risk in those who had discontinued use for 1-9 years, and no increased risk 10 or more years after discontinuation of OC use. The risk was also found to be greater in women who used OC before 20 years, and in those who used OCs

before the birth of their first child. It is however worth noting that the RR is small and the population excess breast cancer cases due to OC exposure is very small.

Narod *et al*. (2002) found that among BRCA1 mutation carriers, women who first used oral contraceptives before 1975, who used them before age 30, or who used them for 5 or more years may have an increased risk of early-onset breast cancer. However, they also found that oral contraceptives did not appear to be associated with risk of breast cancer in BRCA2 carriers. This suggests that there could be a difference in the risks among the normal population, BRCA1 and BRCA2 carriers.

Shapiro *et al*. (2000) found that hormonal contraceptives did not increase the risk of breast cancer. This has lately received support from other investigators. Marchbanks *et al*. (2002) in a population-based, multi-centre case-control study on 4,575 women with breast cancer and 4682 controls at centers in USA found no breast cancer risk among current or former OC users regardless of the duration of use or the dose of the estrogens. Wingo *et al*. (2007) in a multicentre registry records review in USA found no association between breast cancer mortality and OC use, time since first use, age of first use, and use of specific formulations (Wingo *et al.*, 2007).

The lack of agreement by the various researchers could be attributed to differential in risk between BRCA1 and BRCA2 carriers (Narod *et al*., 2002). Furthermore, the studies are based on older data with higher dose oestrogen and older progestin OC preparations that may not be in use now. Since the

introduction of OCs 40 years ago, the progestin and estrogen components have been modified substantially to improve the adverse-effect profile and decrease hormone-associated risks. For instance, estrogen doses in the form of ethinyl estradiol (EE) in OCs have decreased from 150 µg in the 1960s to the current 20 to 35 µg of EE.

2.3.5.2 Hormone Replacement Therapy (HRT)

Ross *et al*. (2000) found that there exists a significant relationship between Hormone Replacement Therapy and breast cancer. These findings are in agreement with the findings of The Women Health Initiative Study (Writing Group for the Women's Health Initiative Investigators, 2002) which found that 5 years of combined HRT was associated with a 26% increased risk of invasive breast cancer in post-menopausal women.

Contrary to these findings, Norsa'adah *et al.* (2005) in a case-control study on 147 cases and 147 controls did not find any association between HRT and breast cancer. He however thought that, owing to the low HRT uptake in Malaysia--and most developing countries--it is often difficult to acquire significant numbers for statistical analysis of HRT.

It is important to note that since all estrogens are not alike, and that even though the doses might be the same between OC and HRT preparations, they are not biologically comparable. For instance, most OCs available today contain ethinyl estradiol. Compared to estradiol, the ethinyl group increases the estrogen's potency 4- to 18-fold and prolongs its half-life. Hormone replacement therapy contains either a mix of conjugated estrogens or 17-β-

estradiol. The conjugated types are not easily available for uptake into cells, while the estradiol types have a lower potency. Therefore, adverse effects attributable to OCs might not always occur with HRT and vice versa (Petra *et al.,* 2008).

2.3.6 Smoking

Smoking has been thought to be related to development of breast cancer (Yngve *et al.,* 2007). However, several epidemiologic studies show inconsistent results on the association between smoking and breast cancer risk.

In a review of some case-control studies, Terry and co-reviewers reported lack of positive associations (Terry *et al.,* 2002) between smoking and breast cancer. Tseng in his study also did not find significant association (Tseng, 2007).

In their cross-sectional study in Norway, Yngve and co-investigators found an inverse association between smoking and percentage mammographic density among 907 post-menopausal women. An inverse dose-response relation was also observed among current smokers. Women who had stopped smoking less than 24 years also had a significantly lower mean mammographic compared with those who had never smoked (Yngve *et al.,* 2007). Mammographic density is one of the strongest independent risk factors for breast cancer. Women with high mammographic density have a 4- to 6-fold increase in breast cancer risk compared with those with low mammographic density (Boyd *et al.,* 2007). This lower mammographic density could suggest a lowered risk of breast cancer.

Other recent cohort studies have indicated an increased breast cancer risk among women who are long-term smokers and also among those who start to smoke before their first birth (Al-Delaimy *et al.,* 2004, Ha *et al*., 2007). Ha and co-investigators reported an increased risk by 3% per smoked pack per year when done between menarche and first childbirth (Ha *et al.,* 2007). This high risk window is characterised by a predominance of the type 1 and 2 cancer susceptible lobules.

The inconsistency is explained by the fact that even though tobacco smoke constituents may have carcinogenic effects on breast tissue, tobacco smoking also has have anti-estrogenic effects that can reduce breast cancer risk, leading to opposing effects. Besides, most studies may have used crude measures of smoking exposure, for instance, ever/never categories which fail to determine the duration and intensity and frequency of their smoking habits (Yngve *et al.,* 2007).

2.3.7 Alcohol

There is substantial evidence that alcohol consumption increases breast cancer risk. In one pooled analysis of 6 largest cohort studies conducted in Canada, the Netherlands, Sweden, and the United States, (Smith-Warner *et al.,* 1998) the risk of breast cancer was found to increase with increasing alcohol intake. For a 10g/day (10g alcohol is equivalent to 30mls of spirits or 100mls of wine or 330mls of beer) increase in the alcohol taken, the risk increased by 9% (95% CI 4%-13%). Beer, wine and spirits all contributed to the association strongly suggesting that alcohol *per se* was responsible for the increased risk. In a

review of breast cancer risk assessment models, Gareth and Howell, 2007 reported that alcohol intake had only a fairly small effect on the risk of breast cancer. And in their recent re-analysis of 53 studies, Hamajima and co-workers found that about 4% of breast cancers in developed countries might be attributable to consumption of alcohol (Hamajima *et al.*, 2002).

The risk of breast cancer increases with the amount of alcohol consumed. Compared with non-drinkers, women who consume one alcoholic drink a day have a very small increase in risk. Those who have 2 to 5 drinks daily have about 1½ times the risk of women who drink no alcohol. Alcohol is also known to increase the risk of developing cancers of the mouth, throat, esophagus, and liver (*http://www.cancer.org*, 2008).

In one interventional study, consumption of 1-2 alcoholic drinks per day was found to increase oestrogen levels in both pre-menopausal and post-menopausal women, suggesting a possible mechanism by which alcohol might increase breast cancer risk (Reichman *et al.*, 1993).

2.3.8 Dietary factors

The role of specific dietary factor in breast cancer causation is not completely resolved (Holmes *et al.*, 2004). Trends show that breast cancer incidence rates vary widely around the world, and that the offsprings of those who migrate from lower-incidence countries to those with higher incidence take on the higher rates. These observations promote the hypothesis that nutrition is an environmental determinant of breast cancer.

In their study on 1,313 women that included 157 high-risk women for breast cancer, Tseng and co-workers found that only vitamin D was inversely associated with breast density, while protein and animal protein were positively associated with breast density (Tseng *et al.*, 2007). However, in a dietary review, it is reported that the consumption of red meat may not be associated with an altered breast cancer risk as breast cancer rates among UK nuns who ate little or no meat were similar to rates among women from the general population (Holmes and Willet, 2004).

Vitamin D might lower breast density through its anti-proliferative and proapoptotic effects of its biologically active form, 1.25-dihydrovitamin D, or through modulation of the immune system. Animal proteins may increase breast density by increasing circulating levels of insulin-like growth factor-1 which has been linked to higher breast density and breast cancer (Byrne *et al*., 2000).

Although there is a long established correlation between breast cancer and dietary fat intake, the true relation does not seem to be strong and consistent (Freddie *et* al., 2004). In cross-sectional studies, breast density has been both positively (Brisson *et al*., 1989) and inversely (Jakes *et al*., 2002) associated with fat intake. The effect of fats may be through affecting oestrogen levels or by directly affecting breast tissue structure directly (Brisson *et al*., 1989).

Breast density has also been inversely associated with carotenoid, fibre, calcium and folate (Brisson *et al*., 1989). Inverse associations between intakes of fruits and vegetables and breast cancer risk have been reported in a notably

large number of case–control studies (Fund, 2007). However, in the pooled analysis of eight large prospective studies of 7377 cases among 351,825 women, only weak and non-significant associations were seen with increasing consumption of fruit and vegetables (Smith-Warner *et al*., 2001). Vitamin A which may be of animal origin or in carotenoids from fruits and vegetables is a potent anti-oxidant that may provide a defense against reactive oxygen species that damage DNA.

The relevant time period of exposure to cause change in breast tissue is unknown (Tseng *et al*., 2007). While a low-fat, high-carbohydrate diet may reduce breast density in 2 years, the findings with other foods is inconsistent. However, Tseng *et al*. (2007) found that despite the possible fear that examining only recent diet may have limited their ability to evaluate the role of dietary intake, findings were not different when the average value of dietary intake reported at enrollment was used.

2.3.9 Body Mass Index (BMI) and exercise

High fat diets have long been known to increase the occurrence of breast cancer in rodents. In humans, national per capita fat consumption is highly correlated with breast cancer mortality rates. Secular trends show that both per capita fat consumption and breast cancer incidence rates increased substantially in the USA during the 20^{th} century (Holmes & Willet, 2004).

In their review, Holmes and Willet reported that while body fat has been inversely related to premenopausal breast cancer, it has been only weakly related to increased postmenopausal risk of breast cancer (Holmes & Willet,

2004). The reverse relationship of BMI and premenopausal breast cancer may be because heavier premenopausal women have more irregular menstrual cycles and anovulatory infertility, suggesting that the effect could be due to lower ovarian hormone exposure (Garland *et al.*, 1998). The association between BMI and postmenopausal breast cancer is surprising because obese postmenopausal women have endogenous oestrogen levels nearly double those of lean women (Hankinson *et al.*, 1995). In pre-menopausal women, the ovaries produce most of the estrogens. After menopause, most of a woman's estrogens come from fat tissue. This weakened association is thought to be due to the persisting early adult reduction in breast cancer risk due to being overweight, opposing the effect of the elevated estrogens after menopause, unless if the weight was gained in the postmenopausal period (Hankinson *et al.*, 1995).

Chang and co-workers in their study and Zhu and co-workers in a separate study found that an increasing number BMI was associated with an increased risk of breast cancer, an association that did not vary by menopausal status (Chang *et al.*, 1998, Zhu *et al*., 2005).

Observational studies report an inverse relationship between physical activity and breast cancer risk (Gago-Dominguez *et al*., 2007). The specific amounts of physical activity necessary to confer a reduction in risk is not fully known, though previous studies suggest 3 – 4 hours or more per week.

Physical activity influences certain menstrual characteristics, body size and hormone levels. It is therefore possible that physical activity reduces breast

cancer risk through hormonal-realted pathways, though the effect on the immune system and insulin resistance may also play a role (Gago-Dominguez *et al*., 2005, Smith *et al*., 2004).

2.3.10 X-rays

Ionizing radiation is an established cancer risk factor. In breast cancer, the risk increases linearly with the radiation dose (Cécile *et al.*, 2005). This has been seen with diagnostic, therapeutic and accidental exposures to ionizing radiation. Epidemiological studies of atomic bomb survivors and of medically irradiated populations show increased risk of female breast cancer with relative risks ranging from 1.0 – 4.3 per Gy. The risk is higher if the exposure occurs in childhood and adolescence rather than in adulthood; it is minimum to zero if exposure occurred in the post-menopausal period (Andrieu *et al.*, 2006).

In their retrospective study of 1,601 female BRCA1 and BRCA2 carriers, Andrieu and co-workers found diagnosing ionizing radiation exposure from chest x-rays may be associated with a significant breast cancer risk among women carrying a mutation in the BRCA genes (Andrieu *et al.*, 2006). There was also a dose-effect relationship, with a higher number of exposures being associated with a higher breast cancer risk. In a pooled analysis of 8 radiation exposed cohorts, a breast cancer relative risk of about 2.0 at a dose of radiation of 1Gy was estimated (Preston *et al*., 2002). Given the role of BRCA1 and BRCA2 in DNA repair and the potential causation and imprinting of DNA errors by irradiation, women with BRCA mutations are strong candidates for BCA following x-ray radiation.

Other etiologic factors for breast cancer, mainly age at first birth, parity and a history of benign breast disease influence the risk of radiation-related breast cancer. If chemotherapy was also given, the risk of breast cancer is lowered if the chemotherapy stopped ovarian hormone production.

2.3.11 Other factors

Just being female is the main risk factor for developing breast cancer. Although women have many more breast cancer cells than men, the main reason they develop breast cancer more is because their breast cells are constantly exposed to the growth-promoting effects of the female hormones oestrogen and progesterone (*http://www.cancer.org*, 2008).

A woman's age is another strong risk factor for breast cancer. Older women have a relative risk greater than 10 compared with younger women. While 1 in 8 invasive breast cancer diagnoses are made in women younger than 45 years, 2 in 3 with invasive breast cancer are older than 55 years at diagnosis (*http://www.cancer.org*, 2008).

The occurrence of cancer in one breast increases 3 to 4-fold the risk of developing a new cancer in the other breast, or in another part of the same breast. This is not a recurrence.

Even though white women are slightly more likely to develop breast cancer than African American women in the same set-up, the later are more likely to die from the disease. This is partly because African American women tend to have a more aggressive variant of the cancer, but also to lower rates of early detection and later stage at diagnosis (*http://www.cancer.org*, 2008).

2.4 Prevention of breast cancer

There is certainly a lot of interest in strategies to prevent breast cancer. The primary risk factors for breast cancer are not easily modifiable as they stem from prolonged hormonal exposures (Freddie *et al.*, 2004).

Primary prevention strategies may be aimed at the following (Freddie *et al.*, 2004):

- Prevention strategies involving lifestyle alteration are easier to implement, though their effectiveness is still under debate. A low fat diet, exercise regimes and abstinence from alcohol and smoking may play a role.
- Promoting breastfeeding for long durations of time should be adopted with guarded optimism as the role of breastfeeding in lowering breast cancer is still unclear.
- The use of tamoxifen is known to lower the breast cancer incidence by 30-40% in high risk women. Other pharmacological agents are under trial.
- Surgical intervention with total mastectomy may be used in women with known BRCA1 and BRCA2 mutations

Attitudes conducive to secondary prevention through screening, early detection and appropriate treatment are desired. Recommended screening strategies for breast cancer include monthly self breast examination (SBE), clinical breast examination and screening mammography. While SBE is of questionable

value, regular mammography and clinical breast examination decrease mortality from breast cancer by 26-30% in women older than 50 years (Humphrey *et al*., 2002). It is recommended that annual mammography for women older than 40 years be practiced.

In Kenya, the breast cancer preventive practices include:

- Health education on breast cancer presentation, screening and treatment in mass media and health facilities.
- Publicised screening in hospitals and during organised events. The screening methods used include clinical breast examination and mammography.

2.5 Classification/staging of breast cancer

Breast cancer is staged based on the size of the tumour and the spread of the cancer. Often, the stage is not known until after surgery to remove the tumour in the breast. Staging aids to plan breast cancer treatment as the different stages need different combinations of conservative and radical treatment.

The stages of breast cancer are (*www.cancer.gov*, 2008):

Stage 0: carcinoma in situ (CIS): Abnormal cells are found in the lining of a lobule (LCIS) or a duct (DCIS). However, having LCIS in one breast increases the risk of cancer for both breasts. While DCIS sometimes becomes invasive cancer if not treated, LCIS seldom becomes invasive cancer.

Stage I

This is an early stage of invasive breast cancer. The tumour is no more than 2 centimetres across and cancer cells have not spread beyond the breast.

Stage II

Stage IIA: encompasses any of the following:

- No tumour is found in the breast, but cancer is found in the axillary lymph nodes or
- The tumour is 2 centimetres or smaller and has spread to the axillary lymph nodes or
- The tumour is 2-5 centimetres but has not spread to the axillary lymph nodes.

Stage IIB: the tumour is either:

- 2-5 centimetres and has spread to the axillary lymph nodes or
- Larger than 5 centimetres but has not spread to the axillary lymph nodes.

Stage III

In stage IIIA

- No tumour is found in the breast. Cancer is found in axillary lymph nodes that are attached to each other or to other structures, or cancer may be found in lymph nodes near the breastbone; or

- The tumour is 2 centimetres or smaller but cancer has spread to axillary lymph nodes that are attached to each other or to other structures, or cancer may have spread to lymph nodes near the breastbone; or
- The tumour is between 2 and 5 centimetres. Cancer has spread to axillary lymph nodes that are attached to each other or to other structures, or cancer may have spread to lymph nodes near the breastbone; or
- The tumour is larger than 5 centimetres. Cancer has spread to axillary lymph nodes that may be attached to each other or to other structures, or cancer may have spread to lymph nodes near the breastbone.

Stage IIIB: In this stage, the tumour may be any size and cancer:

- Has spread to the chest wall and/or the skin of the breast; and
- May have spread to axillary lymph nodes that may be attached to each other or to other structures or cancer may have spread to lymph nodes near the breastbone.
- Inflammatory breast cancer is a rare type of Stage IIIB where the breast looks red and swollen because cancer cells block the lymph vessels in the skin of the breast.

Stage IIIC: In this stage, there may be no sign of cancer in the breast or the tumour may be any size and may have spread to the chest wall and/or the skin of the breast. Also, cancer:

- Has spread to lymph nodes above or below the collarbone; and

- May have spread to axillary lymph nodes or to lymph nodes near the

Stage IV

This is distant metastatic cancer. The cancer has spread to other parts of the body, most often the bones, lungs, liver, or brain.

Recurrent cancer is cancer that has come back (recurred) after a period of time when it could not be detected. It may recur locally in the breast or chest wall. Or it may recur in any other part of the body, such as the bone, liver, or lungs.

2.6 Diagnosis of breast cancer

Breast cancer can be diagnosed by various methods (*www.cancer.gov*, 2008). These include:

a) Self examination: Breast self-examination in people who have had reproductive health education may help pick some cases of breast cancer. Breast cancer may be diagnosed this way at the different stages.

b) Clinical physical examination may be carried out during routine physical examination, during examination for other conditions, or when breast cancer is suspected.

c) During routine mammography unusual findings may be discovered that may point to the possible development of breast cancer. Mammography can also be used in situations when cancer is suspected due to suggestive symptoms such as a palpable mass, changes in breast contour, nipple or skin colour as reported by patients with advanced

disease. Fixed, hard and tender lumps at examination suggest breast cancer.

d) Ultrasound may also be used in situations where classical mammograms cannot be carried out.

e) Magnetic resonance Imaging (MRI) may also be used. It has the advantage of better soft tissue resolution.

f) Microscopy: A definitive diagnosis of breast cancer is only made by histological examination of biopsy specimen. The specimen may be obtained by fine needle or core needle biopsy, or by open surgical biopsy. Mammograms or ultrasound may be used to guide the needle when the target tissue is not obvious.

2.7 Treatment of breast cancer

Knowledge of a diagnosis of breast cancer can be traumatising. The initial management for breast cancer should include routine psychosocial counselling which is necessary for the newly diagnosed patients, and as a component of follow-up management (*www.cancer.gov*, 2008).

The strategy of breast cancer treatment that is adopted depends on many factors, including the type and stage of the disease. The following treatment modalities may be used in varying combinations:

- Most patients with breast cancer have surgery to remove the cancer from the breast. Total mastectomy, the surgical removal of the entire breast may

be performed, with varying degrees of chest wall surgery. Breast-conserving surgery may include the following:

  - Lumpectomy: Surgery that removes the tumour and a small amount of normal tissue around the tumour.
  - Partial mastectomy: Surgery that removes the part of the breast that has cancer and some normal tissue around the tumour.

- Adjuvant therapy may be given to some patients in the form of radiotherapy, chemotherapy or hormone therapy to kill any cancer cells that may have escaped surgical removal.

  - Radiation therapy using high-energy x-rays or other types of radiation may be used to kill cancer cells or stop the cells from growing or migrating to other parts of the body. This may be externally administered using a machine outside the body to send radiation toward the cancer, or internally administered using a radioactive substance that is placed directly into or near the cancer.
  - Chemotherapy is a cancer treatment that uses drugs to stop the growth of cancer cells, either by killing the cells or by stopping them from dividing. Specific cancer drugs are used. In KNH, chemotherapy is grossly under-used while tamoxifen is over-used especially in pre-menopausal (Othieno-Abinya *et al*., 2002).
  - Hormone therapy is another form of cancer treatment that removes certain hormones or blocks their action and stops cancer cells from

growing. Tamoxifen is a form of hormone therapy that is often given to patients with early stages of breast cancer and those with metastatic breast cancer. It reduces cancer recurrence and mortality by 47% and 26% respectively in oestrogen negative breast cancer. It has however been found to increase the chance of developing endometrial cancer. Women taking tamoxifen should have a pelvic exam every year to look for any signs of cancer.

- Ovarian ablation may be achieved surgically or by use of radiation or drugs. This causes stoppage of production of ovarian hormones.

2.8 Survival rate among breast cancer patients

In Europe, North America, Australia and New Zealand, mortality increased from the 1950s until at least the 1980s. This was followed by a levelling off and subsequent decline from the early 1990s. In USA, although the trends were similar from the 1970s to mid-1980s in both white and blacks, they diverged thereafter, with white women experiencing a levelling off and subsequent decline in mortality from the early 1990s whereas in contrast, mortality increased slightly in black women throughout the period up to 2000 (Freddie *et al.*, 2004).

The paucity of sufficient long time series of quality data in many developing countries has made it difficult to follow trends over time. Most countries in Latin America have had increasing mortality rates, doubling in some countries between the early 1970s and the mid 1990s (Coleman *et al.,* 1993). In China, mortality increased over the period 1987-1999 in both rural and urban areas,

the change being more evident in rural areas (Freddie *et al.,* 2004). The limited data from Africa shows that Mauritius reported steady 2-fold increases in breast cancer mortality rates from the early 1960s and the late 1990s (Parkin *et al.,* 2003).

Survival can be calculated by the "relative survival rate" which measures the survival of cancer patients in comparison to the general population to estimate the effect of cancer. The overall 5-year relative survival rate for the period 1996-2004 from 17 Surveillance, Epidemiology and End Results (SEER) Program geographic areas in the USA was 88.7%. The five-year relative survival rates by race were 89.9% for white women and 77.1% for black women (www.cancer.gov, 2008). SEER is a the U.S.A National Cancer Institute program that collects information on incidence, survival, prevalence and cancer mortality and compiles reports for the entire U.S.A.

In the U.S.A, projection based on stage shows that 61% of breast cancer cases are diagnosed while the cancer is still confined to the primary site (localized stage); 31% are diagnosed after the cancer has spread to regional lymph nodes or directly beyond the primary site; 6% are diagnosed after the cancer has already metastasized (distant stage) and for the remaining 2% the staging information is unknown. The corresponding 5-year relative survival rates are 98.1% for localized, 83.8% for regional; 27.1% for distant, and 56.9% for un-staged (www.cancer.gov, 2008).

Certain factors affecting prognosis (chance of recovery) include:

- The stage of the cancer: This is affected by early diagnosis either through screening or as a result of increasing individual awareness of the disease and its symptoms (Freddie *et al.*, 2004).
- In high-resource to medium-resource settings, advances in breast cancer therapy in recent years have made a considerable contribution to improved survival and the subsequent reduction or stabilization of breast cancer death rates (Freddie *et al.*, 2004).
- The type of breast cancer.
- Oestrogen and progesterone-receptor levels in the tumour tissue
- The speed of growth of the tumour
- The age of the patient and menopausal status
- Whether the cancer is newly diagnosed or it has recurred

CHAPTER 3: MATERIALS AND METHODS

3.1 Study site

The study was carried out at KNH, the older of the two National Referral Hospitals in Kenya. KNH is situated in Nairobi. Nairobi is situated along latitude 01^0 17'S and longitude 36^o 48'E.

This study site was selected for this study as it is the public hospital that receives the most number of breast cancer patients in Kenya. Breast cancer patients are referred here from most parts of the country. The hospital also manages patients referred with other medical, paediatric, surgical and obstetric/gynaecologic conditions. It is therefore expected that the patients attended to in the hospital have special or advanced disease. On average, 25 – 30 breast cancer patients are seen in the clinic every clinic day. The oncology department operates a breast cancer clinic on Tuesdays and a chemotherapy clinic on Wednesdays of every week.

3.2 Study Design

This was a case-control study. This study design allowed for the evaluation of association between reproductive factors and breast cancer to be made between cases and controls. Secondly, it was the most appropriate design as I had limited time and financial resources within which to conduct the study.

3.3 Study Population

The study population comprised of cases of breast cancer and controls as follows:

Cases: These were female breast cancer patients aged between 18 and 80 years who had been histologically confirmed to have breast cancer. Cases were recruited from the cancer clinic and the radiotherapy unit in the months of September 2008 to December 2008.

The following were excluded from the study:

- Male breast cancer patients: their hormonal exposure varies from that of females.
- Patients with mental disorders that affect cognition.
- Patients younger than 18 years.

Controls: These were female non-breast cancer patients who were identified in clinics or wards in the same hospital at the same time as cases. Controls were matched for age ± three years. The following were excluded from enrolment as controls:

- Male patients
- Patients with known malignant and/or cognitive disorders

3.4 Sample Size

Sixty four cases and sixty four controls were recruited into the study. The following formula (Fleiss, 1981) was used to determine the minimum sample size:

$$n = \frac{\left\{Z_{(1-\alpha/2)}\sqrt{[(r+1)P(1-P)]} + Z_{(1-\beta)}\sqrt{[rP_1q_1 + P_0q_0]}\right\}^2}{r(P_1 - P_0)^2}$$

Where:

- n = sample size of cases
- $Z_{(1-\alpha/2)}$ = 1.96 is the value of the standard normal distribution corresponding to a significant level of α (alpha) for a 2-sided test at the 0.05 level
- $Z_{(1-\beta)}$ = 1.28 is the value of the standard normal distribution corresponding to the desired level of power of 80%
- P_0 = 0.014*** is the estimated proportion of controls who are nulliparous**
- P_1 = 0.15*** is the estimated proportion of female cancer patients who are nulliparous**
- $q_0 = 1-P_0$
- $q_1 = 1-P_1$

- $P = \frac{1}{2}(P_1 + P_0)$
- r = 1, the ratio of controls to cases

** Parity was adopted as the prime independent variable of interest for calculating sample size

*** These proportions are adopted from the findings of Norsa'adah *et al.* (2005) in Malaysia. The proportions of parity among breast cancer patients and among non-breast cancer females could not be found for the Kenyan or other African population. The only published study conducted in Nigeria by Huo and co-workers (Huo *et al*., 2008) was not a matched case-control study. It did not therefore give a chance to try to normalize the distribution of the parity exposure among the study participants.

This formula gave a minimum sample size of 63 cases and 63 controls. Parity was used since childbirth is the only factor known to be consistently associated with a reduction in breast cancer risk among all ethnic groups (Britt *et al.,* 2007).

3.5 Sampling method

Breast cancer patients attending the cancer clinic or radiotherapy sessions at KNH were recruited into the study. All patients attending the clinic during the study duration who met the inclusion criteria and consented were recruited into the study. As patients walked into the clinic, their clinical records were examined to assess their eligibility. The number of patients attending the

clinics during the time of study was expected to be close to the minimum sample size.

Controls were recruited from the wards and medical outpatient clinics within the same period as the cases were recruited to meet the minimum control sample size. A visit was made to the medical wards 7 and 8 whenever 5 – 10 cases had been recruited. The details of all admitted patients in both wards were obtained from the nursing record card, in the wards. Age and the other inclusion criteria were checked and candidate controls short-listed. For every case, a suitable control was therefore selected. Whenever there was more than one suitable control per case, only one control was randomly selected by balloting. The wards were primarily used because being a public referral hospital, it was expected that patients admitted in the medical wards would be mainly referrals from peripheral facilities, just as much as breast cancer patients would be mostly referrals.

The clinic was only used if suitable controls for specific cases could not be obtained from the patients admitted in the wards. Suitable controls were selected by systematic sampling. The interviewer perused through the records of all attending patients as they came into the clinic. Controls who met the study inclusion criteria were identified and assessed for age-matching with already recruited cases; age-matched controls were then recruited into the study.

3.6 Data collection

A semi-structured interviewer-administered questionnaire was used to collect data from the study subjects. The questionnaire was administered in Kiswahili by the principal investigator. Data was collected on the following potential risk factors for breast cancer:

- Personal factors: Age, alcohol consumption and smoking.
- Hormonal/reproductive factors: Age at menarche, age at first live birth, menstrual cycle, parity status, number of children, abortion history, duration of breastfeeding, oral contraceptive pill use, hormone replacement therapy use, menopausal status and age at menopause,
- Familial history: History of breast or ovarian cancer in the family, history of male breast cancer in the family, age at onset of breast cancer and bilateral breast cancer
- Any history of exposure to ionizing radiation to the chest.
- Measurements: Weight and height were also measured to determine the BMI. Quetelet's Index was used to calculate the BMI as weight in kilograms divided by the square of height in meters (Eknoyan, 2007).

The questionnaire was pre-tested on seven cervical cancer patients and six cardiovascular clinic patients and changes duly made.

Neither cases nor controls were made aware of the research hypothesis upfront. Informed consent was obtained before commencing the administration of the questionnaire (appendix A).

3.7 Data management and analysis

3.7.1 Data Storage

Data was transferred from questionnaires to the computer using Epi info version 3.4.3. The data was coded, stored, pass-word protected and backed-up on alternate secure storage media. Filled questionnaires will be safely stored for at least 3 years.

3.7.2 Data analysis

Data was validated, cleaned and analysed using the Epi info 3.4.3 computer program for windows.

Univariate analysis: This was done for basic variables that describe the cases and controls to show the total number of responses and frequency of distributions.

Mean, median, mode and standard deviation was determined for continuous variables. Analysis of Variance (ANOVA) was used to measure the significance of the difference in the mean between cases and controls. A P-value equal to or less than 0.05 was taken to mean a statistically significant difference in the means. Bartlett's Test was used to assess for inequality of group variances (homoscedasticity). In situations when the Bartlett's Test P-value was less than 0.05, the groups' variances were considered to be unequal (exhibiting heteroscedasticity), and therefore the Kruskal-Wallis Test was used to measure the significance of the difference in the measure of the median between cases and controls. A P-value equal to or less than 0.05 was taken to mean a statistically significant difference in the medians (McDonald, 2008).

Bivariate analysis: This was done to compare two variables to each other in contingency tables to show the matched odds ratio (mOR) as a measure of association and confidence intervals. A mOR above one was considered to be associated with higher chances while a mOR below one was considered to be associated with a lower chance of having breast cancer. A significant level of 95% for a 2-sided test at the 0.05 level was adopted with the display of the corresponding confidence intervals.

Logistic regression: Variables which had yielded a P-value ≤ 0.1 in bivariate analysis were selected and taken into the logistic regression model. The scale-up method was used to build the model with progressive addition of a single variable at each stage, followed by the elimination of any variable with the highest P-value if the p value was ≥ 0.05. Conditional logistic regression was used.

3.8 Ethical issues

An administrative request for protocol approval was made through the Jomo Kenyatta University of Agriculture and Technology (JKUAT) to the Ministry of Higher Education. A request for approval to KNH ethical review committee was also made and clearance granted to carry out the study in the Hospital.

Written informed consent was sought from the study participants before enrolling them into the study. A prepared statement (appendix B) was read to the participants informing them of the study, anticipated risks and benefits, the right to opt out, confidentiality and anonymity before being asked if they wished to join the study.

CHAPTER 4: RESULTS

4.1 Demographic characteristics of the respondents

All the breast cancer patients were attending the breast cancer outpatient department (OPD) clinic while 63 (98.4%) controls were admitted in the medical wards. One (1.6%) control was attending the OPD medical clinic. Only one male with breast cancer was seen in the breast cancer clinic during the data collection period.

The mean age was 48.8 (SD 9.7) years for cases and 48.2 (SD 10.5) years for controls. There was no significant variation in the mean age of the cases and the controls (P = 0.7216).

Thirty five (54.7%) cases and twenty five (41.7%) controls resided in a rural area (Figure 3). Forty two (65.6%) cases and 46 (71.8%) controls were from Nairobi and Central Provinces combined (Figure 4).

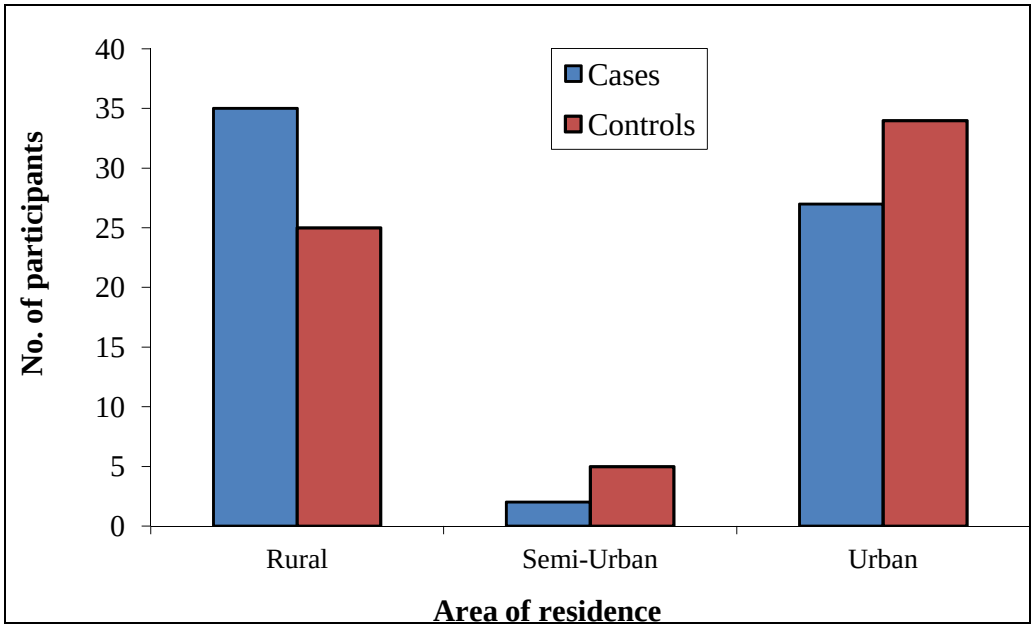

Figure 3: Area of residence for study participants

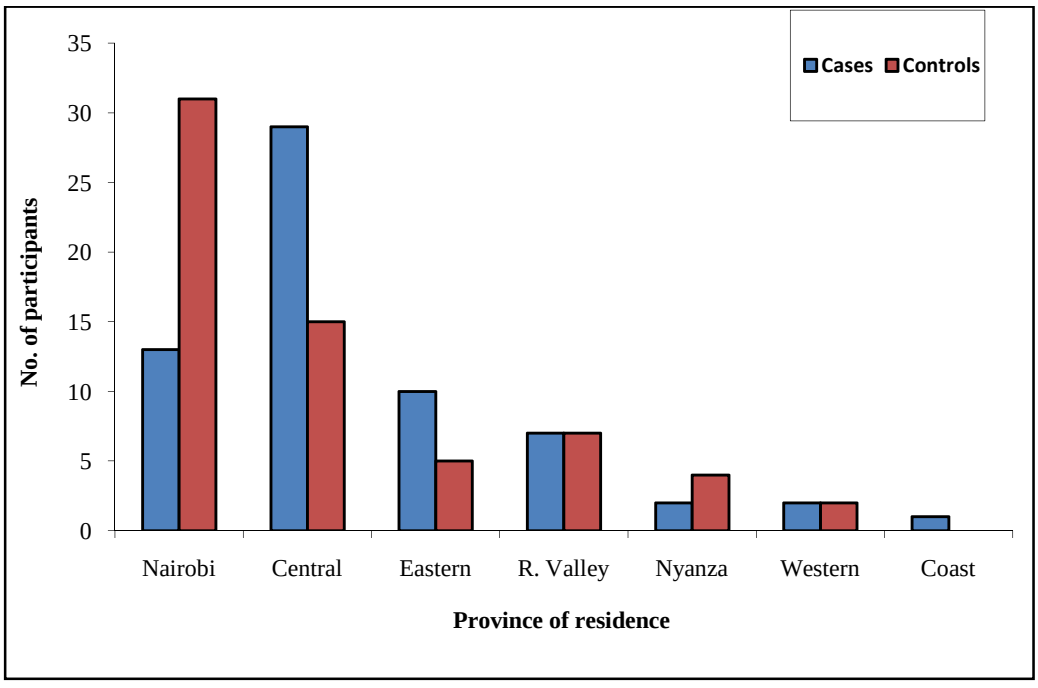

Figure 4: Province of residence of study participants

Thirty eight (59.4%) cases and 44 (68.8%) controls were married while 28 (43.7%) cases and 40 (62.5%) controls had primary or no formal education.

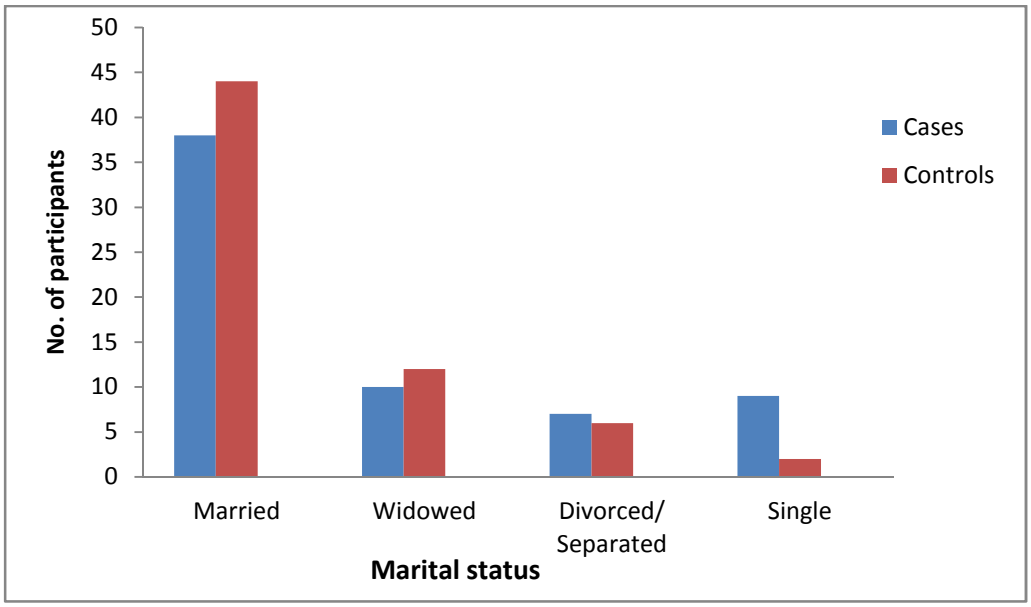

Figure 5: Marital status of participants

As shown in figure 7, 27 (42.2%) cases and 21 (32.9%) controls practiced subsistence farming. Christianity the most predominant religion among the participants, was practised by 62 (96.9%) cases and 60 (93.7%) controls.

The median age at which breast cancer was diagnosed was 47 years (range 25 – 70 years) with a mean time-lag of 6.5 months (SD 6.9) from the time the participants developed symptoms of breast cancer to the time of diagnosis.

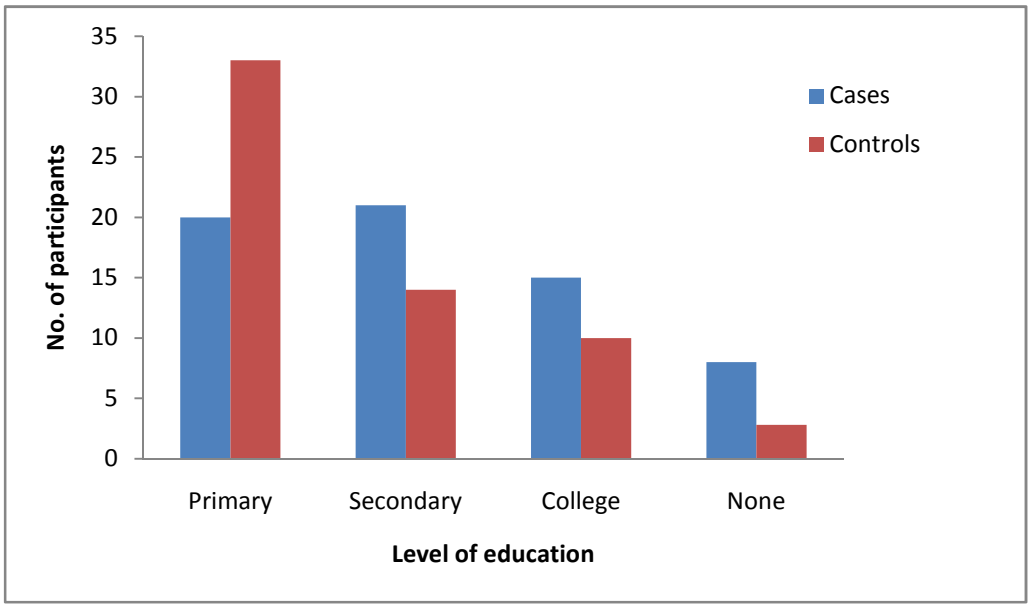

Figure 6: Highest level of education attained by participants

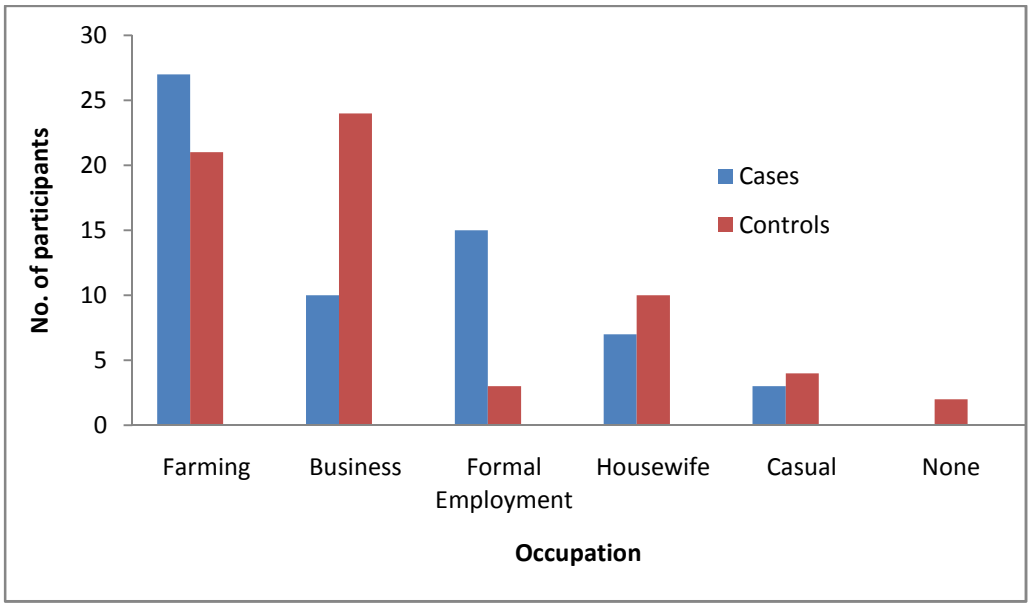

Figure 7: Occupation of study participants

4.2 Bivariate analysis: Reproductive factors

A total of 62 (96.9%) participants with breast cancer and 64 (100%) controls had ever conceived before; only 2 cases had never conceived. As shown in table 1, having had three or less conceptions was associated with a 5.5 times increase in the chance of having breast cancer ($P < 0.01$). Breast cancer participants had conceived on average 4.1 times (range 0 – 13) while controls had conceived 5.2 times (range 1 – 11) ($P = 0.02$).

Conceiving for the first time at the age of 24 years or earlier was associated with a 69% less chance of breast cancer ($P = 0.02$). The median age of first conception for cases was 21 years (range 15 – 34 years) versus 19 years (16 – 27 years) for controls (Kruskal-Wallis test $P = 0.01$).

Considering all the conceptions that a participant had, breast cancer participants had an average age of conception at 26.7 years (range 15 – 48 years) against 26.3 years (16 – 44 years) for controls, though the difference was not statistically significant.

Table 1: Pregnancy factors association with breast cancer – bivariate analysis

		Cases (%)	Controls (%)	mOR	95% C.I	P value
Conceived: ≤ 3 times		31	13 (20.3)	5.50	1.90 -15.96	0.001
Age at first conception	**≤ 18**	15	29 (45.3)	0.36	0.16 -0.82	0.006
	≤ 19	22	40 (62.5)	0.31	0.14 -0.68	0.001
	≤ 20	28	46 (71.9)	0.35	0.16 -0.74	0.002
	≤ 21	34	49 (76.6)	0.47	0.20 -0.87	0.010
	≤ 22	41	54 (84.4)	0.40	0.18 -0.91	0.014
	≤ 23	44	57 (89.1)	0.29	0.11 -0.80	0.006
	≤ 24	48	58 (90.6)	0.31	0.10 -0.94	0.015
Still birth gestations		2 (0.8)	16 (4.8)	0.17	0.04 – 0.73	0.003
Term gestations		244 (93.1)	319 (95.8)	0.51	0.24 – 1.10	0.053

As shown in figure 8, in 60 (93.8%) cases and 61 (95.3%) controls the first pregnancy reached term. Progression of the first pregnancy beyond 28 weeks gestation was not significantly associated with breast cancer P = 0.45). However, considering all the conceptions that a women had, term pregnancies had a borderline association with breast cancer (0.053). Likewise, having a stillbirth was associated with a reduced chance of having breast cancer (P < 0.01) (Table 1). Two (0.8%) breast cancer participants and 16 (4.8%) non-breast cancer participants had stillbirths.

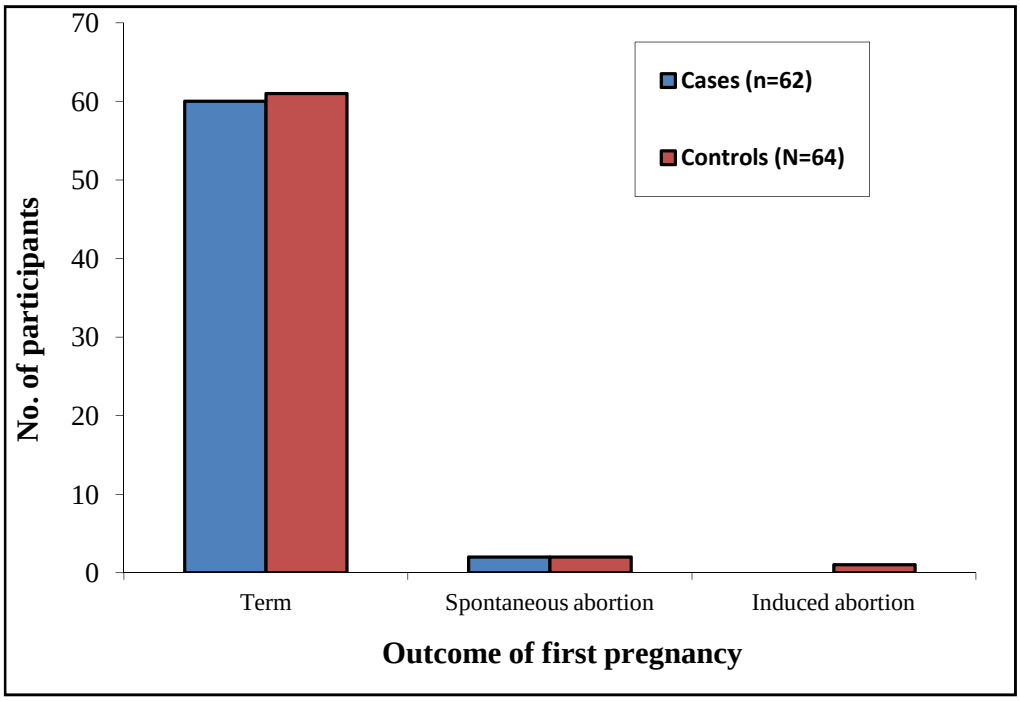

Figure 8: Outcome of first pregnancy

As shown in figure 9, forty nine (76.6%) cases and 52 (81.3%) controls had not had an abortion. Twelve (18.8) cases and ten (15.6) controls had one abortion while 3 (4.7) cases and 2 (3.1) controls had two abortions. Having had an abortion was not associated with the chance of having breast cancer (P = 0.38). There was also no significant difference between the mean number of abortions the cases (0.28) and controls (0.27) had (P = 0.46).

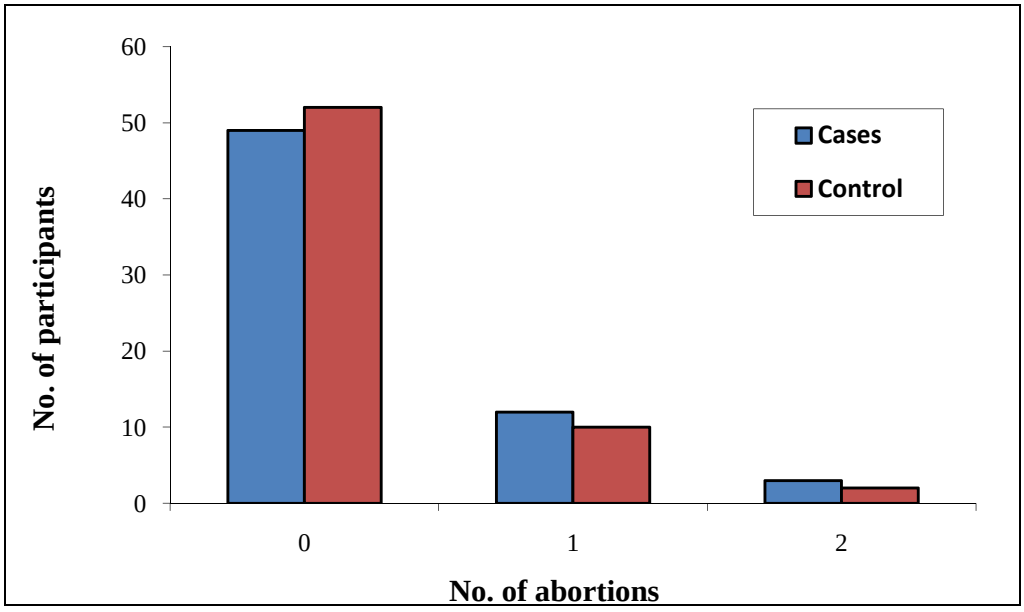

Figure 9: Number of abortions study participants had

The mean age for menarche for cases was 15.1 years (range 12 – 20) while that for controls was 15.9 years (range 13 – 21) ($P < 0.01$). This difference was significant. As shown in table 2, menarche attained at age 14 years or earlier was associated with a 3.8 increased chance of having breast cancer ($P = 0.01$). Menarche attained at age 15 or earlier ($P = 0.02$) or at age 16 years or earlier ($P = 0.03$) was also associated with an increased chance of having breast cancer.

Forty five (70.3%) cases and 28 (43.8%) controls had reached menopause. For the menopausal participants, 23 (50%) cases and 26 (92.9%) controls attained menopause naturally, while chemotherapeutic drugs (cancer treatment drugs) caused menopause in 20 (43.5%). The median age at natural menopause was 51 years (range 35 – 57) for cases and 49 years (range 40 – 51) for controls. This difference was significant ($P = 0.01$). Attaining menopause naturally at age 49 or earlier was associated with a 90% less chance of getting breast cancer ($P < 0.01$).

Table 2: Menstrual factors association with breast cancer

		Cases (%)	Controls (%)	mOR	95% C.I	P value
Age at menarche	< 14	24	10 (15.6)	3.80	1.42 -10.18	0.008
	< 15	38	23 (35.9)	2.67	1.24 -5.74	0.015
	< 16	56	45 (70.3)	3.20	1.17 -8.74	0.029
Menopause natural at age		6 (26.1)	18 (69.2)	0.10	0.01 – 0.78	0.003
Years of fertility	< 32	40	49 (76.6)	0.18	0.04 – 0.82	0.006
	< 33	42	55 (85.9)	0.19	0.05 – 0.64	0.001
	< 34	46	59 (92.2)	0.19	0.05 – 0.64	0.001
	< 35	50	61 (95.3)	0.15	0.03 – 0.68	0.002
	< 36	53	63 (98.4)	0.09	0.01 – 0.70	0.002

Having 36 or less fertility years was associated with a lower likelihood of breast cancer (P < 0.01). Cases had 29.8 (range 11 – 42) mean fertility years while controls had 28.0 (range 8 – 38) mean fertility years even though the difference in these means was not statistically significant.

As shown in table 3, having regular (predictable date of onset of the next menstrual flow) menstrual cycles was associated with a 7 times increased chance of breast cancer (P < 0.01) as compared to having irregular periods. Likewise, having had monthly cycles shorter than or equal to 28 days had a higher likelihood of having breast cancer (P < 0.01). The mean menstrual cycle length was associated with breast cancer (P < 0.01). Breast cancer patients had mean menstrual cycle length of 25.8 days (range 20 – 31 days) against 28.0 days (range 21 – 33 days) for controls. There was no significant difference in

the mean number of days of menstrual flow between cases (4.1 days) and controls (4.0 days).

Table 3: Menstrual cycle factors association with breast cancer

		Cases (%)	Controls (%)	mOR	95% C.I	P value
Regular periods		53	29 (45.3)	7.00	2.46 – 19.96	0.000
Menstrual cycle duration	< 21	15	2 (3.1)	7.50	1.71 – 32.80	0.004
	< 22	16	7 (10.9)	4.00	1.13 – 14.17	0.039
	< 23	17	7 (10.9)	4.33	1.23 – 15.21	0.025
	< 24	24	9 (14.1)	6.00	1.77 – 20.37	0.002
	< 25	25	9 (14.1)	6.33	1.87 – 21.40	0.001
	< 26	28	14 (21.9)	5.67	1.66 – 19.34	0.004
	< 27	34	23 (35.9)	2.38	1.04 – 5.43	0.054
	< 28	51	34 (53.1)	6.67	1.98 – 22.44	0.001
	< 29	55	38 (59.4)	5.25	1.80 – 15.29	0.001
	< 30	62	54 (84.4)	9.00	1.14 – 71.04	0.027

Sixty one (95.3%) cases and sixty four (100%) controls had breastfed. The average breastfeeding duration per baby for cases was 15.2 months while that for controls was 18.4 months. The duration of breastfeeding was associated with breast cancer ($P < 0.01$).

Forty one (64.1%) cases and forty seven (73.4%) controls had used some form of contraception (Figure 10). The mean duration of oral contraceptive use was 65.4 months for cases and 23.9 months for controls ($P < 0.01$). There was a significant difference in the duration of oral contraceptive use between cases and controls. Study participants uniformly could not remember the brands of oral pills taken. There was no association between other methods of

contraception used and breast cancer. Only one case (1.6%) reported having used hormone replacement therapy for 3 months.

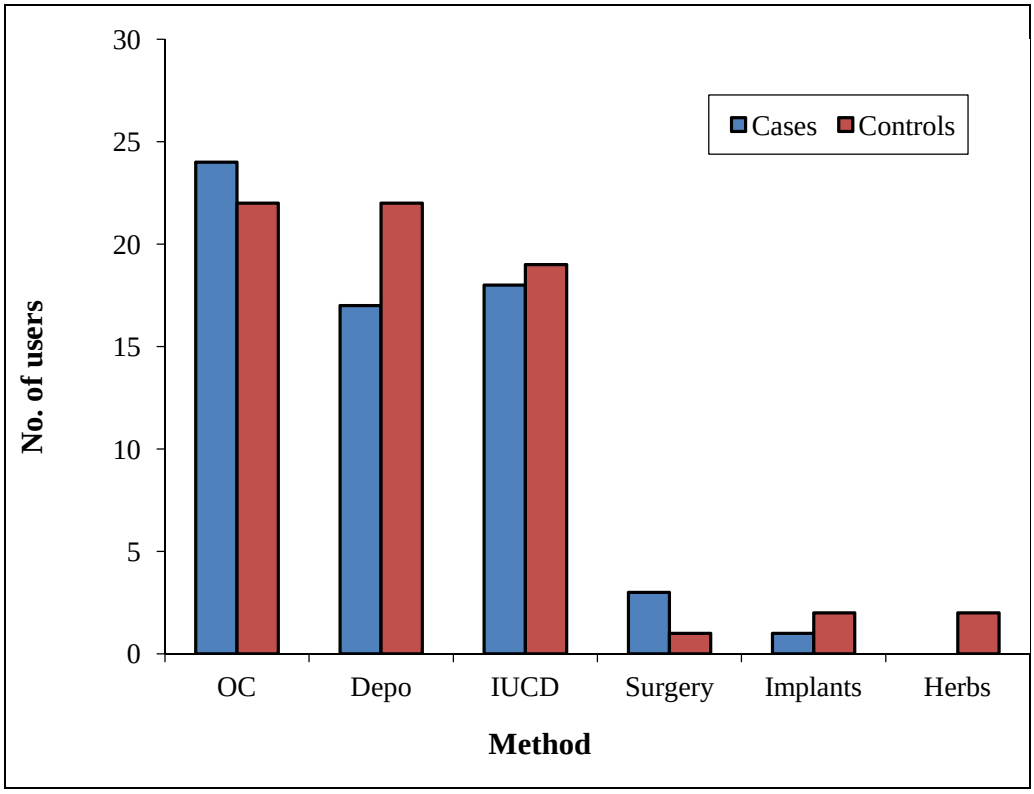

Figure 10: Contraceptive methods used by participants

4.3 Bivariate analysis: Lifestyle factors

Two (3.1%) cases and 1 (1.6%) control reported having smoked tobacco. As shown in table 4, smoking was not associated with having breast cancer (P = 1.00) irrespective of the duration of smoking or the average number of sticks smoked per day.

Sixteen (25%) cases and 13 (20.3%) controls had ever taken alcohol. Taking alcohol was not associated with a chance of having breast cancer (P = 0.68) irrespective of the duration of drinking, the average alcohol measures taken per month, or the cumulative measures of alcohol taken.

Table 4: Lifestyle and radiation factors association with breast cancer

Factors	Cases (%)	Controls (%)	mOR	95% CI	P-value
Eating vegetables ≤ 12	21 (32.8)	4 (6.3)	9.50	2.21–40.79	< 0.01
Being overweight (BMI ≥ 25)	46 (71.9)	18 (28.1)	6.60	2.58– 16.91	< 0.01
Eating deep fried foods > once/month	26 (40.6)	14 (21.9)	2.33	1.07– 5.09	0.04
Undergoing diagnostic radiation	6 (9.4)	10 15.6)	0.56	0.19– 1.66	0.18
Ever taken alcohol	16 (25)	13 (20.3)	1.30	0.57– 2.96	0.68
Ever smoked cigarettes	2 (3.1)	1 (1.6)	2.00	0.18–22.06	1.00

The average number of times cases ate vegetables in a month was 23 while that for controls was 28 (P < 0.01). As shown in table 4 above, eating vegetables less than 12 times a month was associated with an increased chance of having breast cancer (P < 0.01). There was no difference in the average number of times per month that cases (14 times) and controls (11 times) ate fruits (P = 0.21). Cases ate deep fried foods on average 3.4 times a month versus 2.5 times for controls (P = 0.96). Eating deep fried foods more than once a month was associated with an elevated chance of having breast cancer (P = 0.04).

Thirty one (48.4%) breast cancer participants had experienced weight change since diagnosis out of which 4 (12.9%) reported weight gain while 27 (87.1%) reported weight loss. Eleven participants quantified their weight change; 2 participants reported a mean weight gain of 7.5kg (SD 3.5) while 9 participants reported a mean weight loss of 9kg (SD 7.6).

Breast cancer participants had an average body mass index (BMI) of 28.2 (SD 5.2) while that for controls was 23.3 (SD 3.5) ($P < 0.01$). Being overweight ($BMI \geq 25$) was associated with an elevated chance of breast cancer ($P < 0.01$). Figure 11 shows the weight categories for the study participants.

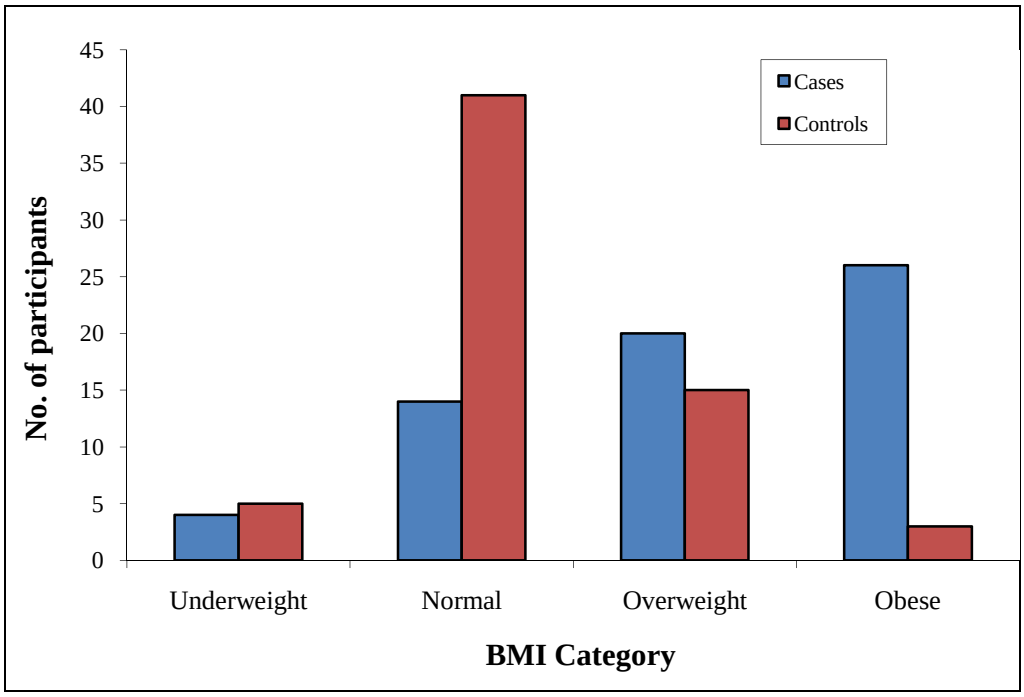

Figure 11: Weight categories of study participants

4.4 Bivariate analysis: Cancer in relative

Sixteen cases (25%) and seven controls (10.9%) had a relative who had been diagnosed with a cancer. Having a relative with any cancer was related with an increased chance of having breast cancer (mOR = 2.8; P = 0.0665). Cases reported cancers more in a father (33.3%), first cousin (23.8%), aunt (23.8%) and mother (14.3%). Figure 12 shows the summary of the distribution of the relatives among the study participants.

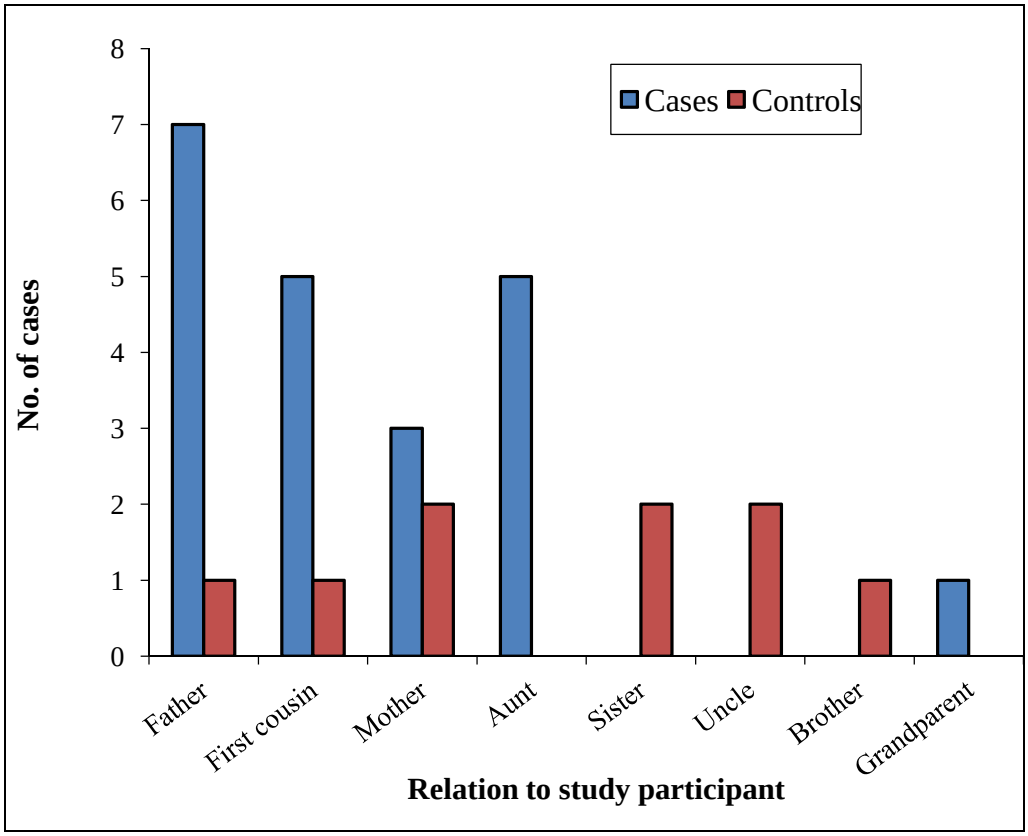

Figure12: Cancer relatives of study participants

As shown in table 5 stomach cancer (38.1%), breast cancer (23.8) and throat cancer (9.5%) were the most diagnosed cancers in relatives to cases, while breast cancer (33.3%) was the most diagnosed cancer in relatives to controls.

Table 5: The types of cancer in relatives of study participants

Type of cancer	Cases (%)	Controls (%)
Breast cancer	5 (23.8)	3 (33.3)
Stomach cancer	8 (38.1)	0 (0)
Throat	2 (9.5)	1 (11.1)
Liver	1 (4.8)	1 (11.1)
Cervical	1 (4.8)	0 (0)
Prostate	1 (4.8)	0 (0)
Pelvic	1 (4.8)	0 (0)
Leukemia	1 (4.8)	0 (0)
Leg	1 (4.8)	0 (0)
Bone	0 (0)	1 (11.1)
Lung	0 (0)	1 (11.1)
Intestinal	0 (0)	1 (11.1)
Other	0 (0)	1 (11.1)

4.5 Bivariate analysis: Radiation factors

Six (9.4%) cases and 10 (15.6%) controls had been exposed to diagnostic x-ray radiation before (P = 0.18). The mean number of times of diagnostic radiation exposure was 1.5 for cases and 2.1 for controls (P = 0.78). There was no association between exposure to diagnostic radiation and breast cancer, irrespective of the number of times of exposure. The mean time lag from radiation exposure to interview was 21 years for cases and 6.2 years for controls (P = 0.04). Only one (1.6%) case had had therapeutic exposure to radiation.

4.6 Bivariate analysis: Other factors

As shown in table 6, being in formal employment was associated with a 5 times higher chance of breast cancer (P = 0.01) in comparison with being unemployed or being in other types of employment. Conversely, not having any formal education or having primary education only was associated with a lower chance of breast cancer (P = 0.01).

There was no significant association between the marital status or religion and breast cancer.

Table 6: Other factors associated with breast cancer

	Cases (%)	**Controls (%)**	**mOR**	**95% C.I**	**P value**
Education ≤ Primary	28	40 (62.5)	0.40	0.18 -0.91	0.014
Formal employment	15	3 (4.7)	5.00	1.45 -17.27	0.010

4.7 Logistical regression

In logistical regression, attaining menarche at or before age 14, having regular monthly cycles, having menstrual cycle lengths of 28 or less days, and having conceived three or less times were found to be associated with a higher chance of breast cancer. Likewise, rural residence was associated with 16 times higher likelihood of having breast cancer as shown in table 7.

Table 7: Factors associated with breast cancer (Logistic regression)

Factors	**mOR**	**95% CI**	**P value**
Regular monthly menstrual	19.24	2.21 – 167.37	0.0074
Conceived ≤ 3 times	16.08	1.96 – 131.77	0.0096
Rural residence	16.43	1.87 – 143.93	0.0115
Menstrual cycle length ≤ 28 days	12.91	1.96 – 84.98	0.0078
Menarche age ≤ 14 years	9.39	1.67 – 52.80	0.0110

CHAPTER 5: DISCUSSION

5.1 Study assumptions and limitations

One of the major strengths of this study was the study design which gave an opportunity for comparison to be made between cases of breast cancer and non cases regarding the factors associated with the chance of having breast cancer.

In using parity proportions from Malaysia to calculate the sample size, it was assumed that the parity profile of the source community resembled that of Kenya. The second assumption made was that the controls did not have latent breast cancer. Even though controls were examined to rule out this possibility, physical examination is not a sensitive method of detecting breast cancer. However, it was established from literature that the ASWR of breast cancer morbidity for Kenya was 25.2 per 100,000 women. This prevalence is low, to the extent that the number of possible latent breast cancer cases among the controls would equally be negligibly low.

Another assumption made was that the potential control patients came from the entire catchment area of the national referral hospital as much as the cases did, as patients attended to in the hospital are referrals from lower health facilities.

However the study had potential limitations. Self reporting on some sensitive events could have resulted in under-reporting. Study participants would report less if asked to disclose events that arouse moral conscience, like induced abortions.

It is also possible that recall bias existed as some events of interest had happened years or decades before. If such bias existed, it was expected to be distributed among both cases and controls.

5.2 Parity

This study found that the proportion of nulliparity in the case and control population studied was much lower than anticipated. It was therefore not possible to determine statistically the association between nulliparity and breast cancer. However, it was found that women who had conceived three or less times had a high likelihood of having breast cancer. This is in agreement with the findings of Andrieu *et al,* (2005) that among parous women, an increasing number of pregnancies are associated with a decreased risk of breast cancer. This was also supported in this study by the finding that cases were likely to have had fewer conceptions than controls.

The finding that having the first conception at age 24 or earlier is associated with a 69% reduction in breast cancer is consistent with the findings of MacMahon *et al*. (1970) in America, Europe and Asia, and Trichopoulos *et al*. (1983) following analysis of the same data who reported that an earlier age of conception lowers the risk of breast cancer. The findings in this study are however in contrast to the findings of Andrieu *et al*. (2005) in Europe that there was no statistically significant association. There was also a significant difference in the median age of first conception between cases (21 years) and controls (19 years). However, this study did not find a significant difference in the means of the age of conception for all conceptions by cases and controls.

This could be explained by the knowledge that of all pregnancies, significance in breast cancer association is noted more with the first pregnancy more than the subsequent pregnancies. MacMahon found the critical age of significance to be 20 years. This study however has found that significant variation is maximal at age 24 years. This could be attributed to the fact that menarche in the Kenyan set-up occurs on average 2 years later than in the communities studied by MacMahon.

Considering all pregnancies, term pregnancies were found to be associated with a lower risk of breast cancer. This was true for both still births and normal term deliveries as still births and normal term pregnancies were associated with an 83% and 49% less chance respectively of having breast cancer. This is in agreement with the findings of MacMahon *et al*. (1970), though their findings were limited to first pregnancies. This however is in agreement with the postulations by Britt *et al*., (2007) that term pregnancies mature breast tissue cells to cancer resistant cell types.

This study did not find a significant association between the occurrence and number of abortions and breast cancer. This is in agreement with the findings by Andrieu *et al*. (2005) in Europe and Norsa'adah *et al*. (2005) in Malaysia that abortion is not associated with breast cancer. It however goes against the findings of Carroll (2007) in Europe and Pike *et al*. (1981) in America that both induced and spontaneous abortions were associated with an increased risk of breast cancer. Carroll, (2007) concurs that self-reporting on abortion often underestimates the incidence.

The level of self-reporting about abortions – especially when induced – in the study setup could be low. This is because induced abortions are illegal in Kenya, and respondents may fear being viewed negatively if they admit to having procured an abortion. It is therefore not surprising that only 15 cases and 12 controls reported having had abortions; only one participant reported having had an induced abortion. The study designs employed too may contribute to inconsistent findings. Previous investigators either reviewed existing data in government generated records (Andrieu *et al.*, 2005, Howe *et al*., 1989, Pike *et al.*, 1981, Carroll, 2007) or conducted case control studies (Daling *et al.*, 1994, Norsa'adah *et al.*, (2005). Prospective studies could possibly capture more accurate data.

5.3 Menstruation factors

The finding that attaining menarche at age 14 or earlier was associated with higher odds of breast cancer while attaining menopause by age 49 was associated with a lower chance is in agreement with the findings of Hunter *et al*. (1997) among women in the U.S.A. There was also a notable reduction in the risk from age 14 to age 16. Having 36 or less years of fertility was associated with a lower chance of breast cancer. This I in agreement with the findings of Henderson *et al*. (1985) that an early menarche and/or a late menopause increase the risk of breast cancer. The more the years of fertility that a woman goes through, the higher the exposure levels to ovulatory cycles and therefore the higher the risk of breast cancer.

Most (67.1%) of the menopausal participants had attained menopause naturally. Significantly, however, 43.5% of the breast cancer cases attained it as a side-effect of the chemotherapeutic agents used in the treatment of the disease. It is known that anti-cancer drugs ablate the ovaries, thereby stopping hormone production. Surgical operations accounted for menopause in a few participants.

This study also found that having had regular menstrual cycles was associated with a 7 times higher odds of breast cancer. This agrees with findings of Parazzini *et* al. (1993) in a study carried out in Italy, and Tonkelaar and Waard (1996) in a prospective study that breast cancer cases reported systematic menstrual irregularities less than controls. While the reason for this is still unknown, it is postulated that this could be due to the fact that irregular cycles tend to have low estrogen and progesterone levels, putting the breast glandular tissue at reduced insult levels (Tonkelaar and Waard, 19960.

However, the finding that cycles shorter than or equal to 28 days were associated with a higher odds of breast cancer supports the findings of a study that has reported an increased risk due to shorter cycles (Yuan *et* al., 1988) though Soini, (1977) reported a decreased risk. The findings of this study are supported by biological knowledge that the risk of breast cancer is expected to be higher among women with shorter menstrual cycles owing to the high ovarian hormones in the frequently occurring luteal phase.

This study did not find any significant difference in the mean of the number of menstrual flow days between cases and controls, similar to the findings of Nora'adah *et al.* (2005) in Malaysia.

5.4 Breastfeeding

Comprehensive assessment of breastfeeding was not possible in this study since all controls (100%) and 61cases (95.3%) had had a history of breastfeeding; in the entire study group, only three participants had not breastfed. However, there was a significant difference in the means of the duration of breastfeeding between the two study groups. The lack of the ability to statistically assess the association between the different levels of breastfeeding and breast cancer makes it impossible to add an opinion against the findings by other researchers that there is no increased or decreased risk of breast cancer with prolonged breastfeeding (Andrieu *et al.,* 2005, Norsa'adah *et al*., 2005, Beral *et al*., 2002 and Martin *et al*., 2005).

5.5 Oral contraception

Even though the level of use of the different types of contraceptives among the study participants was high, no significant association was found between those who used or did not use oral contraceptives, or any other contraceptive method and breast cancer. There was however a significant difference in the average duration of oral contraceptive use between cases and controls. This finding is in agreement with findings by McPherson *et al*. (2000) in his clinical review and Norsa'adah *et al*. (2005) in Malaysia that there is an association between the duration of OC use and breast cancer although they don't agree

with the findings of Marchbanks *et al.* (2002) in a multicentre study and Wingo *et al.* (2007) in another multicentre study in the U.S.A that there is no association between the duration of use of OC and breast cancer.

Although the data collection tool was designed to also collect data on the individual contraceptive brands taken, a significantly high proportion of the study participants did not know the brand names taken, making it impossible to carry out statistical analysis. It would have been desirable to know if the brands take affected the level of association as it has been reported that the brand of OC used affects the association due to the type of estrogens or progestins in the preparations used.

The level of hormone replacement therapy use in the catchment community is low. The enrolment of only one participant who had used hormone replacement therapy could not permit statistical analysis.

5.6 Lifestyle factors

Even though smoking appeared to be associated with an increased chance of having breast cancer, this association was not statistically significant. Cases and controls did not differ in their duration of smoking or the number of cigarettes smoked per day. This is in agreement with the knowledge that even though smoking is associated with other cancers (Yngve *et al*., 2007), there is no association with breast cancer (Terry *et al*., 2002, Tseng, 2007). This is contrary to the findings by Al-Delaimy *et al*., (2004) in a cohort study that there was increased risk of breast cancer among women who are long-term

smokers. It is acknowledged that even though tobacco smoke has carcinogens, it also has an anti-estrogenic activity that can reduce breast cancer risk.

Likewise, this study did not find a significant association between alcohol intake and breast cancer. There was no variation among cases and controls in the daily measures of alcohol taken, the duration of drinking and the computed total measures of alcohol taken by the participants. This finding contradicts that of Smith-Warner *et al*. (1998) in a study in Canada, U.S.A, Sweden and the Netherlands which found that the risk of breast cancer increased with increasing intake of alcohol. It will be interesting to find out the true association between alcohol intake and breast cancer and the mechanism of association as it is only postulated that alcohol intake is associated with an increase in estrogen (Reichman *et al*., 1993).

Several dietary components were found to be associated with breast cancer. The finding that cases were more likely to eat vegetables than controls while controls were more likely to eat deep fried foods more often than cases supports the findings of Freddie *et al*. (2004) and Fund (2007) that fats are associated with increased breast density while the vitamin A and possibly other substances in fibres are associated with breast density. The surprising finding in this study was the lack of significant association between fruits and breast cancer since most fruits are known to have anti-oxidants that are thought to lower breast cancer risk (Smith-Warner *et al*., 1998).

The study supports the long known association between weight and breast cancer. The odd of breast cancer among the overweight participants was

significantly high. This could be through the oestrogen retaining ability of fat tissue. The strength of association could even be higher as 31 (48.4%) reported weight change since diagnosis out of which 27 (87.1%) was weight loss.

Being in formal employment was associated with a higher chance of breast cancer while having had primary level or no formal education was associated with a lower chance of breast cancer. These may be proxy indicators of other factors that may be directly associated with the odds of developing breast cancer. Such factors might be parity-related, or socio-economic. Women with higher levels of education are more likely to be in formal employment. Owing to the demands on their time, they are more likely to postpone childbearing, to breastfeed less, and have diets that are associated with breast cancer.

5.7 Family history of cancer as a risk factor

It has long been known that breast cancer is higher among women whose relatives have had the disease (Steel *et al*., 1991). This study found that having a relative with any cancer was associated with an increased chance of having breast cancer. However, owing to the small numbers realized in the study, it was not possible to evaluate the strength of association of breast cancer specifically in a relative to the participants and the chance of the participant having breast cancer. However, it is unusual that there was no cancer reported among the sisters to the cases.

Since the presence of other cancers in the family was associated with an increased chance, it appears that the familial susceptibility is not only limited to related types of cancers.

CHAPTER 6: CONCLUSIONS AND RECOMMENDATIONS

6.1 Conclusions

The study made significant findings regarding factors associated with breast cancer. First, parity of up to three times was associated with an increased chance of breast cancer. An increasing number of conceptions was inversely related with breast cancer. Maternal age at first conception of 24 years or below was associated with a reduced chance.

The occurrence of an abortion and the number of abortion episodes was not associated with breast cancer. However, term pregnancies regardless of the foetal viability were associated with a lower chance of having breast cancer.

The onset of menarche at age 14 or earlier was associated with higher chance of breast cancer while attaining menopause at age 49 or earlier was associated with lower chance of having breast cancer. The total number of fertility years was likewise a significant predictor.

Regular menstrual cycles and cycles shorter than or equal to 28 days were associated with higher odds of breast cancer. However, the duration of menstrual flow per cycle did not have any bearing on breast cancer.

While the duration of breastfeeding was inversely related with breast cancer, the duration of oral contraceptive use was directly associated with breast cancer.

While tobacco smoking and alcohol use were not related with breast cancer, vegetables in diet were associated with a reduced chance and eating deep fried foods was associated with an increased chance.

Being overweight, being in formal employment, or having a family relative with breast cancer were associated with an increased chance breast cancer. Conversely, not having formal education or having primary level formal education only were associated with a lower chance of having breast cancer.

Exposure to diagnostic radiation was not associated with breast cancer.

I therefore do not agree with the null hypothesis that there are no factors associated with breast cancer among breast cancer patients at KNH.

6.2 Recommendations

6.2.1 Policy formulation

There is need for the Ministry of Public Health and Sanitation and Medical Services to revise policy to guide health education on the known factors that are associated with breast cancer. Such policy should emphasize appropriate reproductive behaviour, yet encourage early screening practices among groups known to be at a higher risk of developing breast cancer, like women with low parity, those attaining menarche early, and those who delay conception. Policies should aim at disseminating guidelines, adopting vigorous health education, and establishing and publicizing more screening centres.

6.2.2 Health care implementation

The health-care system should start conducting targeted health education and screening of the high risk groups as established by this study. There is need to update health workers on the established factors that are associated with breast cancer. All health facilities with trained clinicians could start routine health education programs on breast cancer, and screening of clients known to be at a higher than normal risk factor of breast cancer.

6.2.3 Research

The areas of breastfeeding, abortion and contraception need further research to provide more information. Subsequent studies will need to develop appropriate methodologies and recruit study participants in adequate numbers and composition to enable studying the association of these factors with breast cancer.

REFERENCES

Al-Delaimy W. K, Cho E, Chen W. Y, Colditz G, Willet W. C. (2004). A prospective study of smoking and risk of breast cancer in young adult women. *Cancer Epidemiol Biomarkers Prev*, 13:398-404.

Andrieu N, David E. G, Douglas F, Matti R, Richard B, Antonis C. A, Susan P, Gareth E, Diana E, Fiona D, Catherine N, Marion G, Agnès C, GENEPSO, Flora E. V, Irma K, GEO-HEBON, Javier B, Brita A, Edith O, IBCCS Collaborators Group, Jenny C. (2005). Pregnancies, breastfeeding, and breast cancer risk in the International BRCA1/2 Carrier Cohort Study (IBCCS). *Singapore Med J*, 46(12) : 698.

Andrieu N, Easton D. F, Chang-Claude J, Rookus M. A, Brohet R, Cardis E, Antoniou A. C, Wagner T, Simard J, Evans G, Peock S, Fricker J, Nogues C, Veer L, Van Leeuwen F, Goldgar D. E. (2006). Effect of chest X-rays on the risk of breast cancer among *BRCA1/2* mutation carriers in the international *BRCA1/2b* carrier cohort study. *J Clin Oncol*, 10.1200/JCO.2005.03.3126.

Antoniou A, Pharoah P. D, Narod S, Risch H. A, Eyfjord J. E, Hopper J. L, Loman N, Olsson H, Johannsson O, Borg A, Pasini B, Radice P, Manoukian S, Eccles D. M, Tang N, Olah E, Anton-Culver H, Warner E, Lubinski J, Gronwald J, Gorski B, Tulinius H, Thorlacius S, Eerola H, Nevanlinna H, Syrjäkoski K, Kallioniemi O. P, Thompson D, Evans C, Peto J, Lalloo F, Evans D. G, Easton D. F. (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. *Am J Hum Genet,* 72:1117 – 30.

Beral V, Bull D, Doll D, Peto R. Reeves G. (2002). Breast cancer and breastfeeding: collaborative reanalysis of individual data from 47 epidemiological studies in 30 countries, including 50,302 women with breast cancer and 96 973 women without the disease. *Lancet,* 360:187–195.

Børresen A. L. (1992). Role of genetic factors in breast cancer susceptibility. *Acta Oncol,* 31(2):151-5.

Boyd N. F, Guo H, Martin L. J, Sun L, Stone J, Fishell E, Jong R. A, Hislop G, Chiarelli A, Minkin S. (2007). Mammographic density and the risk and detection of breast cancer. *N Engl J Med,* 356:227-236.

Brisson J, Verreault R, Morrison A. S, Tennina S, Meyer F. (1989). Diet, mammographic features of breast tissue, and breast cancer risk. *Am J Epidemiol*, 130:14-24.

Britt K., Ashworth A, Smalley M. (2007). Pregnancy and the risk of breast cancer. *Endocrine-Related Cancer* , 14: 907–933

Byrne C, Colditz G. A, Willett W. C, Speizer F. E, Pollak M, Hankinson S. E. (2000). Plasma insulin- like growth factor I, insulin-like growth factor-binding protein-3 and mammographic density. *Cancer Res*, 60:3744-3748.

Carroll P. (2007). The breast cancer epidemic: modelling and forecasts based on abortion and other risk factors. J Am Phys Surg, 12:72-78.

Cécile M. R, Erdmann C, Land C. L. (2005). Radiation and breast cancer: a review of current evidence. *Breast Cancer Res*, 7:21-32.

Chang-Claude J, Andrieu N, Rookus M, Brohet R, Antoniou A. C, Peock S, Davidson R, Izatt L, Cole T, Nogue C, Luporsi E, Huiart L, Hoogerbrugge N, Van Leeuwen F. E, Osorio A, Eyfjord J, Radice P, Goldgar D. E, Easton D. F, Epidemiological Study of Familial Breast Cancer (EMBRACE), Gene Etude Prospective Sein Ovaire (GENEPSO), Genen Omgeving studie van de werkgroep Hereditiair Borstkanker Onderzoek Nederland (GEO-HEBON), the International BRCA1/2 Carrier Cohort Study (IBCCS) collaborators group. (2007). Age at menarche and menopause and breast cancer risk in the International BRCA1/2 Carrier Cohort Study. *Cancer Epidemiol Biomarkers Prev*,16(4). April 2007.

Chang S, Buzdar A. U, Hursting S. D. (1998). Inflammatory breast cancer and body mass index. *J Clin Oncol*, Vol 16, 3731-3735.

Chubak J, Tworoger S. S, Yasui Y, **Ulrich C. M, Stanczyk F. Z, McTiernan A.** (2004). Associations between reproductive and menstrual factors and postmenopausal sex hormone concentrations. *Cancer Epidemiol Biomarkers Prev*, 13(8):1296–1301

Coleman M. P, Esteve J, Damiecki P, Arslan A, Renard H. (1993). Trends in Cancer Incidence and Mortality. *Lyon: IARC*.

Collaborative Group on Hormonal Factors in Breast Cancer. (2002). Breast cancer and breastfeeding: collaborative reanalysis of individual data

from 47 epidemiological studies in 30 countries, including 50302 women with breast cancer and 96,973 women without the disease. *Lancet*, 360:187-195.

Collaborative Group on Hormonal Factors in Breast Cancer. (1996). Breast cancer and hormonal contraceptives: collaborative reanalysis of individual data on 53,297 women with breast cancer and 100 239 women without breast cancer from 54 epidemiological studies. *Lancet*. 347(9017):1713-1727.

Curado M. P, Edwards B, Shin. H. R, Storm. H, Ferlay. J, Heanue. M, Boyle. P, (2007). Cancer Incidence in Five Continents, Vol. IX IARC Scientific Publications No. 160. *Lyon, IARC.*

Daling J. R, Malone K. E, Voigt L. F, White E, Weiss N. S. (1994). Risk of breast cancer among young women: relationship to induced abortion. *J Natl Cancer Inst*, 86(21):1584-92.

Eknoyan Garabed. (2007). Adolphe Quetelet (1796-1874) – the average man and indices of obesity. *Nephrol Dial Transplant*, 1 of 5.

Ferlay J, Bray F, Pisani P, Parkin D. M. (2001). GLOBOCAN 2000: Cancer Incidence, Mortality and Prevalence Worldwide. IARC Cancer Base No. 5. [1.0]. *Lyon, France: IARC.*

Fisher B, Redmond C, Brown A. (1983). Influence of tumor estrogen and progesterone levels on the response to tamoxifen and chemotherapy in breast cancer. *J Clin Oncol*, 1(4):22741.

Fleiss J. L. (1981). Statistical Methods for Rates and Proportions, 2nd Edition, Wiley: New York.

Ford D, Easton D. F, Bishop D. T, Narod S. A, Goldgar D. E. (1994) Risks of cancer in BRCA1-mutation carriers. *Lancet*, 343:692–5.

Freddie B, Peter M, Maxwell P. (2004). The changing global patterns of female breast cancer incidence and mortality. *Breast Cancer Res*, 6:229-239 (DOI 10.1186/bcr932).

Fund WCRL. (1997). Food, Nutrition and the Prevention of Cancer: Global Perspective. *Washington, DC: American Institutue for Cancer Research*.

Gago-Dominguez M, Castelao J, Pike M. C, Sevanian A, Haile R. W. (2005). Role of lipid peroxidation in the epidemiology and prevention of breast cancer. *Cancer Epidemiol Biomarkers Prev*, 14:2829–39.

Gago-Dominguez M, Jiang, X. J, Castelao E. (2007). Lipid peroxidation and the protective effect of physical exercise on breast cancer. *Medical Hypotheses*, 68: 1138–1143

Gareth D. R, Howell A. (2007). Breast cancer risk-assessment models. *Breast Cancer Research*, 9:213 (doi:10.1186/bcr1750)

Garland M, Hunter D. J, Colditz G. A, Manson J. E, Stampfer M. J, Spiegel D, Speizer F, Willet W. C. (1998). Menstrual cycle characteristics and history of ovulatory infertility in relation to breast cancer risk in a large cohort of US women. *Am J Epidemiol*, 147:636-43.

Greenlee R. T, Murray T, Bolden S, Wingo P. A. (2000). Cancer statistics, 2000. *CA Cancer J Clin* 50:7**.**

Ha M, Mabuchi K, Sigurdson A. J, Freedman D. M, Linet M. S, Doody M. M, Hauptmann M. (2007). Smoking cigarettes before first childbirth and risk of breast cancer. *Am J Epidemiol* 2007, 166:55-61.

Hamajima N, Hirose K, Tajima K, Rohan T, Calle E. E, Heath C. W, Coates R. J, Liff J. M, Talamini R, Chantarakul N, (2002). Alcohol, tobacco and breast cancer – collaborative reanalysis of individual data from 53 epidemiological studies, including 58,515 women with breast cancer and 95,067 women without the disease. *Br J Cancer*, 87:1234-1245.

Hankinson S. E, Willett W. C, Manson J. E, Hunter D. J, Colditz G. A, Stampfer M. J, Longcope C, Speizer F. E. (1995). Alcohol, height, and adiposity in relation to estrogen and prolactin levels in postmenopausal women. *J Natl Cancer Inst*, 87:1297-1302.

Henderson B. E, Feigelson H. S. (2000). Hormonal carcinogenesis. *Carcinogenesis*, 21 427–433.

Henderson B. E, Ross R. K, Judd H, Krailo M. D, Pike M. C. (1985). Do regular ovulatory cycles increase breast cancer risk? *Cancer* 56: 1206-1208.

Hirose K, Tajima K, Hamajima N, Takezaki T, Inoue M, Kuroishi T, Miura S, Tokudome S. (1999). Effect of body size on breast- cancer risk among Japanese women. *Int J Cancer*, 80:349-55.

Holmes M. D, Willett W. C. (2004). Review: Does diet affect breast cancer risk? *Breast Cancer Research*, Vol 6 No 4.

Howe H. L., Senie R. T., Bzduch H, Herzfeld P. (1989). Early abortion and breast cancer risk among women under age 40. *Int J Epidemiol*, 18:300-304.

Hsieh C, Trichopoulos D, Katsouyanni C, Yuasa S. (1990). Age at menarche, age at menopause, height and obesity as risk factors for breast cancer: associations and interactions in an international case-control study. *Int. J. Cancer:* 46, 796-800.

Humphrey L. L, Helfand M, Chan B. K. S, Woolf S. H. (2002). Breast cancer screening: A summary of the evidence for the U.S. Preventive Services Task Force. *Annal of Internal Med*, Volume 137, Number 5 (Part 1).

Hunter D. J, Spiegelman D, Adami H. O, Brandt P. A, Folsom A. R, Goldbohm R. A, Graham S, Howe R, Kushi L. H, Marshall J. R, Miller A. B, Speizer F. E, Willett W, Wolk A, Yaun S. (1997). Non-dietary factors as risk factors for breast cancer, and as effect modifiers of the association of fat intake and risk of breast cancer. *Cancer Causes Control* 8(1):49–56.

Huo D, Adebamowo C. A, Ogundiran T. O, Akang E. E, Campbell O, Adenipekun A, Cummings S, Fackenthal J, Ademuyiwa F, Ahsan H, Olopade O. I. (2008). Parity and breastfeeding are protective against breast cancer in Nigerian women. *British J Cancer,* 98, 992 – 996.

Jakes R. W, Duffy S. W, Ng F. C, Gao F, Ng E. H, Seow A, Lee H. P, Yu M. C. (2002). Mammographic parenchymal patterns and self-reported soy intake

in Singapore Chinese women. *Cancer Epidemiol Biomarkers Prev*, 11:608-613.

Johnston R. D Stephen. (2005). Review: Endocrinology and hormone therapy in breast cancer: Selective oestrogen receptor modulators and down-regulators for breast cancer – have they lost their way? *Breast Cancer Research*, 7:119-130.

Leenstra T, Petersen L. T, Kariuki S. K, Oloo A. J, Kager P. A, Kuile F. O. (2005). Prevalence and severity of malnutrition and age at menarche; cross-sectional studies in adolescent schoolgirls in western Kenya. 2003. *European J Clin Nutrition*, 59:41–48.

Lokman R, Dayang A. A., Hasni M. J, Noor Hassim I. (2001). Selenium blood level and other risk factors of breast cancer among patients in HKL. VIII National Public Health Qolloquium. Kuala Lumpur: Community Health Department, Medical Faculty UKM.

Ma H. Bernstein L. Pike M. C. Ursin G. (2006). Reproductive factors and breast cancer risk according to joint estrogen and progesterone receptor status: a meta-analysis of epidemiological studies. *Breast Cancer Res*. 8(4):R43.

MacMahon B, Cole P, Lin T. M, Lowe C. R, Mirra A. P, Ravnihar B, Salber E. J, Valaoras V. G, Yuasa S. (1970). Age at first birth and breast cancer risk. *Bull World Health Organ*, 43(2):209-21.

Madigan M. P, Troisi R, Potischman N, Dorgan J. F, Brinton L. A, Hoover R. N. (1998). Serum hormone levels in relation to reproductive and lifestyle

factors in postmenopausal women (United States). *Cancer Causes Control,* 9(2):199–207

Marchbanks P .A, McDonald J. A, Wilson H. G, Folger S. G, Mandel M. G, Daling J. R, Bernstein L, Malone K. E, Ursin G, Strom B. L, Norman S. A, Wingo P. A, Burkman R. T, Berlin J. A, Simon M. S, Spirtas R, Weiss L. K. (2002). Oral contraceptives and the risk of breast cancer. *N Engl J Med,* 346(26):2025-2032.

Margolin Sara. (2006). Family history and breast cancer susceptibility. ISBN 91-7140-868-1.

Mariana C, Carla H, Yvonne T, Monninkhof E, Noord P. A. H, Peeters P. H. M. (2008). Lifetime cumulative number of menstrual cycles and serum sex hormone levels in postmenopausal women. *Breast Cancer Res Treat*, 108:101–112.

Martin R. M, Middleton N, Gunnell D, Owen C. G, Smith G. D. (2005). Breast-feeding and cancer: the Boyd Orr cohort and a systematic review with meta-analysis. *J Nat Cancer Inst*, 97:1446-1457.

Masood S. (1992). Estrogen and progesterone receptors in cytology: a comprehensive review. *Diagn Cytopathol*, 8(5):475-91.

McDonald, J. H. (2008). Handbook of Biological Statistics. Sparky House Publishing, Baltimore, Maryland. (Pages 94, 151).

McPherson K, Steel C. M, Dixon J. M. (2000). ABC of breast diseases: Breast cancer – epidemiology, risk factors, and genetics. *BMJ*, 321:624-8.

Moller, P, Evans D. G, Reis M. M, Gregory, H, Anderson, E, Maehle, L, Lalloo, F, Howell, A, Apold, J, Clark, N. (2007). Surveillance for familial breast cancer: Differences in outcome according to *BRCA* mutation status. *Int. J. Cancer*, 121(5):1017-1020.

Mutuma G. Z, Rugutt – Korir A. (2006). Nairobi cancer registry: Cancer incidence report – Nairobi 2000 – 2002. KEMRI.

Narod S. A, Brunet J. S, Ghadirian P, Robson M, Heimdal K, Neuhausen S, Dominique Stoppa-Lyonnet D, Lerman C, Pasini B, Rios P, Weber B, Lynch H. (2000). Tamoxifen and the risk of contralateral breast cancer in BRCA1 and BRCA2 carriers. *Lancet*, 356:1876–81.

Narod S. A, Dube´ M, Klijn J, Lubinski J, Lynch H, Ghadirian P, Provencher D, Heimdal D, Moller P, Robson M, Offit K, Isaacs C, Weber B, Friedman E, Gershoni-Baruch R, Rennert G, Pasini B, Wagner T, Daly M, Garber J. E, Neuhausen S. L, Ainsworth P, Olsson H, Evans G, Osborne M, Couch F, Foulkes W. D, Warner E, Kim-Sing C, Olopade O, Tung N, Saal H. M, Weitzel J, Merajver S, Gauthier-Villars M, Jernstrom H, Sun P, Brunet J. S. (2002). Oral Contraceptives and the Risk of Breast Cancer in BRCA1 and BRCA2 Mutation Carriers. *J Natl Cancer Inst*, 94:1773–9.

National cancer institute (www.cancer.gov, 2nd April 2008).

Newcomb P. A, Storer B. E, Longnecker M. P, Mittendorf R, Greenberg E. R, Clapp R. W, Burke K. P, Willett W. C, MacMahon B. (1994). Lactation and a reduced risk of premenopausal breast cancer. *N Eng J Med* 330(2):81-87.

Norsa'adah B, Rusli B. N, Imran A. K, Naing I, Winn T. (2005). Risk factors of breast cancer in women in Kelantan, Malaysia. *Singapore Med J*, 46(12): 698.

Parazzini F, La Vecchia C, Negri E, Franceschi S, Tozzi L. (1993). Lifelong menstrual pattern and risk of breast cancer. *Oncology*, 50: 222-225.

Parkin D. M. (1994). Cancer in developing countries. *Cancer Surveys*, 19/20:519-561.

Parkin D. M, Bay F, Pisani P. (2005). Global cancer statistics, 2002. *CA Cancer J Clin*, 55:74-108

Parkin D. M, Ferlay J, Hamdi-Cherif M, Sitas F, Thomas J. O, Wabinga H, Whelan S. L. (2003). Cancer in Africa: Epidemiology and Prevention. *Lyon: IARC*.

Petra M. C, James R. C, Sandhya P. (2008). Oral Contraceptive Use and the Risk of Breast Cancer. *Mayo Clin. Proc*, 83(1):86-91.

Pike M. C, Henderson B. E, Casagrande J. T, Rosario I, Gray G. E. (1981). Oral contraceptive use and early abortion as risk factors for breast cancer in young women. *Br J Cancer*, 43(1):72-6.

Preston D. L, Mattsson A, Holmberg E. (2002). Radiation effects on breast cancer risks: A pooled analysis of eight cohorts. *Radiat Res*, 158:220-235.

Rai B, Dip N. B, Sushmita G., Suresh C. S. (2005). Breast cancer in males: A PGIMER experience. *J Cancer Res Ther* – March 2005 – Volume 1 – Issue 1.

Rebbeck T. R, Levin A. M, Eisen A, Snyder C, Watson P, Lynch H. T, Cannon-Albright L, Isaacs C, Olopade O, Garber J. E, Godwin A. K, Daly M. B, Narod S. A, Neuhausen S. L, Weber B. L. (1999). Reduction in breast cancer risk after bilateral prophylactic oophorectomy in BRCA1 mutation carriers. *J Natl Cancer Inst*, 91:1475–9.

Reichman M. E, Judd J. T, Longcope C, Schatzkin A, Clevidence B. A, Nair P. P, Campbell W. S, Taylor P. R. (1993). Effects of alcohol consumption on plasma and urinary hormone concentrations in premenopausal women. *J Natl Cancer Inst*, 85:722-727.

Ross R. K, Paganini-Hill A, Wan P. C, Pike M. C. (2000). Effect of hormone replacement therapy on breast cancer risk: Estrogen versus estrogen plus progestin. *J Natl Cancer Inst*, 92:328-32.

Russo J, Hu Y. F, Yang X, Russo I. H. (2000). Developmental, cellular, and molecular basis of human breast cancer. *J Natl Cancer Inst*, (27):17-37.

Russo J, Moral R, Balogh G. A, Mailo D, Russo H. I. (2005). Review: The protective role of pregnancy in breast cancer. *Breast Cancer Res*, 7:131-142.

Russo J, Rivera R, Russo I. H. (1992). Influence of age and parity on the development of the human breast. *Breast Cancer Res Treat*, 23 211–218.

Shapiro S, Rosenberg L, Hoffman M, Truter H, Cooper D, Rao S, Dent D, Gudgeon A, van Zyl J, Katzenellenbogen J, Baillie R. (2000). Risk of breast cancer in relation to the use of injectable progestogen contraceptives and combined estrogen/progestogen contraceptives. *Am J Epidemiol*, 151:396-403. Erratum in: Am J Epidemol 2000; 151:1134.

Smith T. P, Kennedy S. L, Fleshner M. (2004). Influence of age and physical activity on the primary in vivo antibody and T cellmediated responses in men. *J Appl Physiol,* 97:491–8.

Smith-Warner S. A, Spiegelman D, Yaun S. S, Adami H. O, Beeson W. L, van den Brandt P. A, Folsom A. R, Fraser G. E, Freudenheim J. L,Goldbohm R. A, Graham S, Miller A. B, Potter J. D, Rohan T. E,Speizer F. E, Toniolo P, Willett W. C, Wolk A, Zeleniuch-Jacquotte A, Hunter D. J. (2001). Intake of fruits and vegetables and risk of breast cancer: a pooled analysis of cohort studies. *JAMA,* 285: 769-776.

Smith-Warner S. A, Spiegelman D, Yaun S. S, van den Brandt P. A, Folsom A. R, Goldbohm R. A, Graham S, Holmberg L, Howe G. R, Marshall J. R, Miller A. B, Potter J. D, Speizer F. E, Willett W. C, Wolk A, Hunter D. J. (1998). Alcohol and breast cancer in women: a pooled analysis of cohort studies. *JAMA,* 279:535-540.

Soini I. (1977). Risk factors of breast cancer in Finland. *Int J Epidemiol,* 6:365-73.

Steel M, Thompson A, Clayton J. (1991). Genetic aspects of breast cancer. *Br Med Bull,* 47(2):504-18.

Steinberg K. K, Thacker S. B, Smith S. J, Stroup D. F, Zack M. M, Flanders W. D, Berkelman R. L. (1991). A meta-analysis of the effect of estrogen replacement therapy on the risk of breast cancer. *JAMA,* 265:1985-1990.

Teng L, Yi Z, Hao-hao W. (2008). BRCA1/2 associated hereditary breast cancer *J Zhejiang Univ Sci, 2008 9(2):85-89* 85.

Terry P. D, Rohan T. E. (2002). Cigarette smoking and the risk of breast cancer in women: a review of the literature. *Cancer Epidemiol Biomarkers Prev,* 11:953-971.

Thorpe S. M. (1988). Estrogen and progesterone receptor determinates in breast cancer. *Acta Oncol,* 27:1-19.

Trichopoulos D, Hsieh C. C, MacMahon B, Lin T. M, Lowe C. R, Mirra A. P, Ravnihar B, Salber E. J, Valaoras V. G, Yuasa S. (1983). Age at any birth and breast cancer risk. *Int J Cancer*, 15;31(6):701-4.

Tseng M, Byrne C, Evers K. A, Daly M. B. (2007). Dietary intake and breast density in high-risk women: a cross-sectional study. *Breast Cancer Research,* 9:R72 doi:10.1186/bcr1781.

United States Cancer statistics: 2004 incidence and mortality (http://apps.nccd.cdc.gov/uscs/) (Dated 18th February 2008)

Wabinga H. R, Parkin D. M, Wabwire-Mangen F, Nambooze S. (2000). Trends in cancer incidence in Kyadondo County, Uganda, 1960–1997. *Br J Cancer*, 82:1585-1592.

Wingo P. A, Austin H, Marchbanks P. A. (2007). Oral contraceptives and the risk of death from breast cancer. *Obstet Gynecol,* 110(4):793-800.

Writing Group for the Women's Health Initiative Investigators. (2002). Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results from the Women's Health Initiative randomized controlled trial. *JAMA,*288(3):321-333.

www.cancer.org/docroot/CRI/content/CRI_2_4_2X_what_are_the_risk_factors_for_breast_cancer_5.asp Dated 2nd June 2008.

www.cdc.gov/cancer/breast/statistics/ (Dated 19th February 2008)

www-dep.iarc.fr/ (Dated 21st February 2008)

www.seer.cancer.gov (Dated 20th February 2008)

Yankaskas B. C. (2005). Epidemiology of breast cancer in young women. *Breast Dis*, 23: 3-8.

Yngve B, Ursin G, Bjurstam N, Gram I. T. (2007). Different measures of smoking exposure and mammographic density in postmenopausal Norwegian women: a cross-sectional study. *Breast Cancer Research*, 9:R73 doi:10.1186/bcr1782

Yuan J. M, Yu M. C, Ross R. K**,** Gao Y, Henderson B. E. (1988). Risk factors for breast cancer in Chinese women in Shanghai. *Cancer Res*, 48: 1949-53.

Zhu, K. M, Caulfield, J, Hunter, S, Roland, C. L, Payne-Wilks, K, Texter, L. (2005). Body mass index and breast cancer risk in African American women. *J Annals of Epidemiol*, 15(2):123-128.

Ziegler R. G, Hoover R. N, Pike M. C, Hildesheim A, Nomura A. M, West D. W, Wu-Williams A. H, Kolonel L. N, Horn-Ross P. L, Rosenthal J. F. (1993). Migration patterns and breast cancer risk in Asian-American women. *J Natl Cancer Inst*, 85:1819-1827.

APPENDICES

Appendix A: Interview questionnaire

Questionnaire Factors in Breast Cancer

Identifying Information

1. Date of interview: DD ☐ MM ☐ YYYY ☐
2. Name of interviewer:

   ☐
3. Hospital Department/Clinic:

   ☐
4. Identification No: ☐ Case Status: ☐ ***(0 = case: 1= control)***
5. OPD No: ☐ IPD No:

   ☐
6. Area of residence: Urban ☐ Semi-urban ☐

   Rural ☐
7. Location of residence ☐
8. District of residence: ☐
9. Province of residence: ☐

Demographic Information

1. Year of birth: ☐ Age ☐

2. Marital status:

i. Single ☐

ii. Married ☐

iii. Divorced/Separated ☐

iv. Widowed ☐

3. Highest level of education:

i. None ☐

ii. Lower primary (≤ 4) ☐

iii. Primary ☐

iv. Secondary ☐

v. College/University ☐

4. Profession (specify):

_____

5. Occupation (specify):

_____

6. Religion

i. Protestant

ii. Catholic

iii. Islam

iv. Other (specify):

_____

7. Height (cm): ☐ Weight (Kg): ☐

Reproductive Data

1. When was the clinical condition discovered by Doctors? MM ☐

   YYYY ☐

2. When did you start experiencing the symptoms that you attribute to this condition?

   MM ☐ YYYY ☐

3. Have you noticed any change in your weight since the condition was discovered? Yes ☐ No ☐

   If yes,

   i. What has the weight change been? Gain ☐ Loss ☐

      Don't know ☐

   ii. By how many Kilos has the weight change been? ☐

      Don't know ☐

4. Have you ever conceived? Yes ☐ No ☐

   (If no, please skip to question 7)

5. How many times have you conceived? ☐

6. For each conception, please give the following details:

Order of conception	Maternal age at conception	Outcome of pregnancy (LB,	Gestation at	Comments **

NB:

* - LB: Live birth after 28 completed weeks (6 completed months) of pregnancy

- SB: Baby delivered dead after 28 completed weeks (6 completed months) of pregnancy

- Abortion: Loss of pregnancy ≤ 28 completed weeks (6 completed months) of pregnancy

** For abortion, indicate if spontaneous or induced

7. How old were you when you first had your monthly periods? ☐

8. Do you still get monthly periods? Yes ☐ No ☐

If no,

i. Which year did you last get your periods? ☐

ii. How did they stop? (Please specify)

– ☐ Naturally _____

– ☐ Surgery on the womb

_____

– ☐ Family Planning

_____

– ☐ Don't know

_____

9. Are/were your periods regular? Yes ☐ No ☐

   Don't know ☐

10. What is/was the average length of your menstrual cycle in days?

    ☐

11. On average, how many days do/did you experience menstrual flow per month? ☐

Breast-Feeding

1. Have you ever breast-fed a baby? Yes ☐ No ☐
2. If yes, please provide the following details for every baby that you breast-fed

No.	**Duration of breastfeeding (in months)**		
	Exclusive	Non-exclusive	Total

Family Planning

1. Have you ever used a family planning method? Yes ☐ No ☐

   If yes, please provide the following details:

Family planning method	Brand-name	Duration of (In months)

2. Have you ever used hormone replacement therapy? Yes ☐ No ☐

   If yes,

   i. What was the brand name?

      _____

   ii. What was the dosage? _____

   iii. For how long (in months) did you use it? ☐

Other Factors

1. What was your stable food before this condition? ***(Name two in order of priority)***

   i. _____

   ii. _____

2. How often did you eat vegetables before this condition (days)?

   ☐

3. How often did you eat fruits before this condition (days)?

   ☐

4. How often did you eat deep fried foods e.g. chips before this condition?

   ☐

5. Have you ever smoked cigarettes? Yes ☐ No ☐

   If yes,

   i. For how long (in years **OR** months) did you smoke before this condition?

      - Months ☐ or

      - Years ☐

   ii. On average, how many sticks of cigarettes did you smoke per day?

      ☐

6. Have you ever taken alcoholic drinks? Yes ☐ No ☐

   If yes,

   i. For how long (in years **OR** months) did you take alcohol before this condition?

      - Months ☐ or

      - Years ☐

7. On average, how many measures of the following drinks did you take per week?

   - Beer (330ml) ☐
   - Wine (100Ml) ☐
   - Spirits (30ml) ☐

8. Do you have a **blood** relative who has had cancer before? Yes ☐

   No ☐

   If yes,

   i. What is the relationship with the person?

   ☐

   ii. What is the relative's gender? Male ☐ Female ☐

   iii. What type of cancer was it?

   ☐

   iv. What was the approximate age of the patient at diagnosis?

   ☐

9. Have you ever undergone chest X-ray before this condition was discovered? Yes ☐ No ☐

   If yes,

   i. How many times? ☐

   ii. When

   ☐

10. Have you ever undergone treatment with X-ray radiation before this condition was discovered? Yes ☐ No ☐

    If yes,

    i. For what condition(s)?

    ☐

    ii. What part of the body was exposed?

    ☐

iii. How many times? ☐

iv. When?

☐

11. Have you ever had an exercise program before this condition was discovered? Yes ☐ No ☐

If yes,

i. When did you start? ☐

ii. How many hours per day did /do you exercise? ☐

iii. How many days per week did /do you exercise? ☐

iv. Do you still exercise? Yes ☐ No ☐

Thank you.

Appendix B: Consent Form

Consent Form

Title of Study: Reproductive factors associated with breast cancer among breast cancer patients at Kenyatta National Hospital.

Investigator: Dr. Shikanga Reuben O-tipo

Institution: Jomo Kenyatta University of Agriculture and Technology/KEMRI

Sponsor: FELTP – Kenya

Request: I am Dr. Shikanga O-tipo. I am a Masters student at JKUAT. I am carrying out a study for academic reasons. I request you to take part in the study. The study aims to determine factors associated with breast cancer.

Breast cancer is a common cancer in women in Kenya. It is often discovered late. An understanding of factors associated with the disease may enable us to prevent it, or discover it early. This is expected to improve the outcome among breast cancer patients.

The study session with you will last only about 30 minutes. During this time, you will be asked some questions about the current illness and previous practices & experiences, and your responses written down. The study will not interfere with your current treatment as determined by your Doctors.

Risks and benefits: The study will not pose any physical risks to you; however, some of the questions could cause you some discomfort. This

study may help to improve our understanding, prevention and treatment of breast cancer in future. There will be no costs to you for taking part in this study.

Confidentiality: Information obtained about you for this study will be kept confidential and will be used only for the purposes of the study. Your name will not be required. The results of the study may be published or disseminated without revealing your identity.

Consent: Your taking part in the study is your choice. You are free to withdraw from the study at any time. If you choose not to participate, or to withdraw from the study, there will be no penalty.

Questions: If you have any questions, concerns or complaints about the study, please contact me on **0722-343341** or **0734-343341**.

Signatures: Your signature below indicates that you agree to participate in this study. You will receive a copy of this signed document.

_____

Signature of interviewee Date

_____

Signature of investigator Date

Appendix C: Letter of Study Approval

KENYATTA NATIONAL HOSPITAL
Hospital Rd. along, Ngong Rd.
P.O. Box 20723, Nairobi.
Tel: 726300-9
Fax: 725272
Telegrams: MEDSUP", Nairobi.
Email: KNHplan@Ken.Healthnet.org

Ref: KNH/UON-ERC/ A/75

23rd September 2008

Dr. Shikanga O-tipo
TM 312-0027/2007
JKUAT

Dear Dr. O-tipo

RESEARCH PROPOSAL: "REPRODUCTIVE FACTORS ASSOCIATED WITH BREAST CANCER AMONG BREAST CANCER PATIENTS AT KENYATTA NATIONAL HOSPITAL"(P255/9/2008)

This is to inform you that the Kenyatta National Hospital Ethics and Research Committee has reviewed and **approved** your above cited research proposal for the period 23rd September 2008 – 22nd September 2009.

You will be required to request for a renewal of the approval if you intend to continue with the study beyond the deadline given. Clearance for export of biological specimen must also be obtained from KNH-ERC for each batch.

On behalf of the Committee, I wish you fruitful research and look forward to receiving a summary of the research findings upon completion of the study.

This information will form part of database that will be consulted in future when processing related research study so as to minimize chances of study duplication.

Yours sincerely

PROF. A N GUANTAI
SECRETARY, KNH/UON-ERC

c.c. Prof. K.M. Bhatt, Chairperson, KNH-ERC
The Deputy Director CS, KNH
Supervisors: Dr. Erick Muchiri
Dr. Makokha Anzelimo
Dr. Muttunga James
Dr. David Mutonga