



Risk factors for breast cancer in patients presenting at the Khartoum Teaching Hospital

By

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Dedication

This Work Is Dedicated to

My Family.

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Abbreviations

BMI	Body mass index
CBC	Contralateral breast cancer
FNAC	Fine needle aspiration cytology
GICMB	Gaziera institute for cancer treatment and molecular biology
HRT	Hormone replacement therapy
RICK	Radiation isotope Centre Khartoum
SMSB	Sudan Medical Specialization Board
OCs	Oral contraceptives
KTH	Khartoum teaching hospital
NCR	National population-based cancer registry
SPSS	Statistical package for social sciences
NSAIDS	Non-steroidal anti-inflammatory drugs
LCIS	Lobular carcinoma in situ
DCIS	Ductal carcinoma in situ
IARC	International agency for research on cancer
EPIC	Electronic privacy information center

Abstract

Female breast cancer is by far the leading cancer in the Sudan.

Studying risk factors for breast cancer are important for a reduction of the incidence.

Objectives: To study the risk factors for breast cancer at Khartoum teaching hospital in the study period and to compare them with the literature.

Patients and methods: It is prospective study conducted at Khartoum Teaching Hospital.

In this study, 110 patients with confirmed breast cancer were included.

The data collected using special data sheet and managed using Statistical packs of social sciences SPSS (SPSS).

Results: In these study 110 patients studied, 108 were female and 2 were male.

Their ages ranged between 25 and 85 years. The majority of patients fell in the average age group (45-54years) by 34.2%, the majority 38 patients (34.2%) originate from the North, the highest incidence was in Gaalia.

Sixty one patients (54.9%) develop menarche at or below the age of 13 years old, 57.6% of all females that have kids (71patients) had their first child below the age of 31 years old, 44.1% were pre-menopausal at presentation, 17.1% had a family history of breast cancer, and 25 patients (22.7%) ate diet rich in fat.

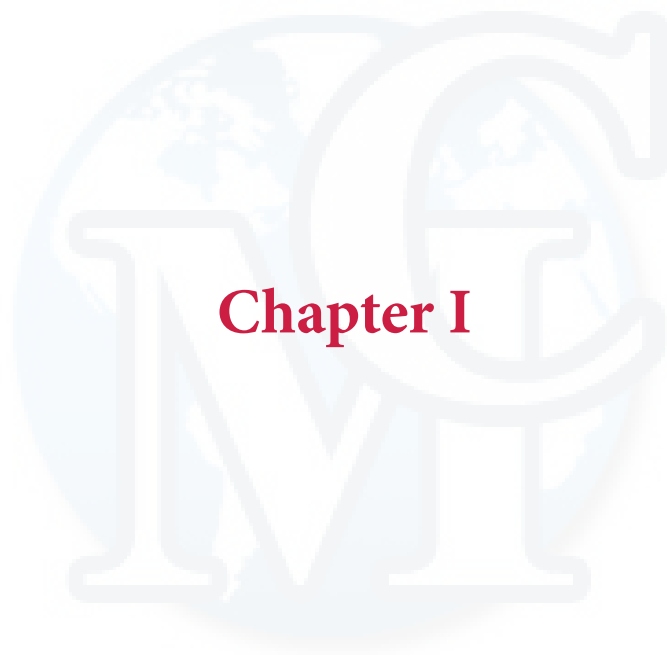
Conclusion: North was the commonest state of origin and the Gaalia, Shawaiga and Kwahla is the mostly affected tribes among 44 tribes; breast cancer occurs in a younger age group 45 – 54 years old, which is younger than in the west and Arabian.

In Sudan we need a lot of studies in all country focusing on the genetic and racial factors.

Family history of breast cancer, early menarche, contraceptive pills, and unmarried play important role risk factors and increase the incidence.

Diabetes, fatty diet, overweight and obesity and antihypertensive drugs also play a significant increasing risk.

Age at first child, menopausal status, breast feeding, education and socioeconomic status, parity, widow and alcohol is not risk factors for breast cancer in Sudanese females and against the literature in the west, at least in this study.



Chapter I

Introduction

Breast cancer, with its uncertain cause, has captured the attention of surgeons throughout the ages. Despite hundreds of studies, breast cancer remains one of the most difficult and frightening of human diseases.

In 2010, approximately one and three-quarter million new cases were diagnosed worldwide. In England and Wales, 1 in 12 women will develop the disease during their lifetime. The incidence is expected to continue rising as the population ages.¹

In 2009, the first National Population-based Cancer Registry (NCR) was established in Sudan. During 2009–2010, 6771 new cancer cases were registered. Of those, 3646 (53.8%) cases were in women and 3125 (46.2%) were in men. The most commonly diagnosed cancer among women was breast cancer, and among men it was prostate cancer.²

Female breast cancer is by far the leading cancer in the Sudan.

The alarmingly high frequency of women presenting with advanced breast cancer to the Radiation Isotope Center Khartoum (RICK) and Gaziera Institute for Cancer treatment and Molecular Biology (GICMB), were recorded in 1998 (38.4% of all female cancers), followed by the years, 1999, 2000 and 2001, which attended 36.03%, 35.2% and 32.4% respectively. Furthermore, the records from GICMB indicated the highest percentages (42%) of breast cancer.³

Recently there is oncology center in Shendi but there is no available published registration.

Risk factors for breast cancer are important for a reduction of the incidence of the disease if avoided and enable better prediction of risk and targeting of preventive measures if are not avoidable.

Literature review

Anatomy:

- The breast is a group of large glands derived from the epidermis.⁴
- The breast extends from the second rib above to the sixth below, and from the sternal border medially to the midaxillary line laterally.⁵
- Between the breast and the pectoral fascia is the retromammary space or bursa. A small part of the mammary gland may extend along the axillary fossa; the tail of Spence.
- The glands are firmly attached to the dermis, by skin ligaments (L. retinacula cutis), the suspensory ligaments (of Cooper). The breast contains 15–20 lobules of glandular tissues.⁶

Blood supply and venous drainage

The breasts are supplied by branches of the axillary artery, the internal thoracic artery, and some intercostal arteries.

Venous drainages accompany corresponding arteries.⁷

Lymphatic drainage:

From the subareolar lymphatic plexus lymph passes to: 75% to the axillary lymph nodes, the remaining drain to the parasternal, opposite breast or abdominal lymph nodes.⁶

Innervation:

The breast is innervated by branches of the fourth to sixth intercostal nerves, which carry sensory and sympathetic efferent fibers.⁸

Physiology of breast

Estrogen affects breast ducts development; progesterone affects the development of secretory alveoli.⁹

Pathology

Breast cancer may arise from the epithelium of the duct system anywhere from the nipple end of the major lactiferous ducts to the terminal duct unit. The disease may be entirely *in situ*, or may be invasive cancer.

The degree of differentiation of the tumor is usually described using three grades: well differentiated, moderately differentiated or poorly differentiated.

Histopathology of breast cancer

1. Carcinoma in situ

Cancer cells are *in situ* or invasive depending on whether or not they invade through the basement membrane.

Lobular carcinoma in situ (LCIS): LCIS is regarded as a marker of increased risk for invasive breast cancer rather than as an anatomic precursor.

Ductal carcinoma in situ (DCIS): DCIS is an anatomic precursor of invasive ductal carcinoma.

2. Invasive Breast Carcinoma

Ductal carcinoma is the most common variant with lobular carcinoma occurring in up to 15 per cent of cases.¹⁰

Risk factors of breast cancer

Gender:

Men have a much lower risk of developing breast cancer than women. In developed countries, about 99% of breast cancer cases are diagnosed in women; in a few African countries, which represent the highest incidence of male breast cancer, men account for 5–15% of breast cancer cases.¹¹

In Sudan, study of 170 patients with breast cancer in Wad Madani Teaching Hospital (March 2000–July 2004), all of them were female.¹²

Age:

The strongest risk factor for breast cancer (after gender) is age: the older the woman, the higher her risk.¹³ The average age at presentation of breast cancer in Arab countries appears to be a decade earlier than in western countries.¹⁴

Carcinoma of the breast is extremely rare below the age of 20 years but, thereafter, the incidence steadily rises so that by the age of 90 years nearly 20% of women are affected.¹

Women of African ancestry are younger at diagnosis than women of European ancestry, the populations with African ancestry are not homogeneous in terms of epidemiologic indicators of age-related breast cancer.¹⁵

Geographical distribution

Residence and Origin:

There is a 10-fold variation in breast cancer incidence among different countries worldwide. Cyprus and Malta have the highest age-adjusted mortality for breast cancer, whereas Haiti has the lowest.¹⁰

In South Africa and sub-saharan, high rate of incidence were found in cities like Abidjan and Harare (Robert son et al. 1971).

Khartoum State has an area of 22,122 km² and an estimated urban/rural population of approximately 7 million and it has structure similar to that of the entire country.

However, population-based data in cancer incidence, prevalence, and mortality in Sudan were not available and most published cancer cases were based on estimates from hospital-based information sources.

Tribe (Race):

A study was conducted in RICK targeting the breast cancer patients during 2010. A total of 60 breast cancer patients from northern states and 60 control breast cancer patients from other Sudan states, this study showed that risk factors of breast cancer do not differ significantly between northern states (Northern and River Nile) and other Sudan states in distribution.¹⁶

In another Sudanese study, the frequency of breast cancer was estimated in 200 patients with palpable breast lumps who were attended in a diagnostic center in Khartoum, 68 (34%) were malignant, the majority of malignant cases were found among Gaaleen tribe followed by Shaggy, Nubein and Baniamer, constituting 15 (22.7%), 12 (18.2%), 10 (15.2%) and 8 (12.1%) correspondingly.¹⁷

Also in another Sudanese study, breast cancer is distributed more frequently among Gaaleen tribe, 61(40.7%), while, tribes of Gohina, Koahla, Bija, African group and Nubian, constituted 20.7%, 5.3%, 1.3%, 14.7% and 17.3% respectively.³

Marital status:

- A study of 59,070 cancers newly diagnosed during the years 1978 through 1982 among black and white males and females was conducted to assess variations in age-adjusted incidence rates across four marital categories, single, married, divorced, and widowed.
- Among black females, more single and widowed women had higher age-adjusted incidence rates for the cancers analyzed than expected. Widowed white

females had the highest or second highest incidence rate for 16(include breast) of the 18 cancers analyzed.

- The most consistent finding is that single black men had the highest age-adjusted incidence rates for all 15 sites examined.
- For these cancers, incidence rates ranged from 1.2 to 1.4 times higher for breast cancer in single black women compared with widowed, married, or divorced black women.
- The lowest age-adjusted incidence rates across the cancer sites analyzed did not occur predominantly among the married in any of the race-gender groups.¹⁸
- In Sudan, study done by Hassan Ismail (MD. Thesis) found that 81.2% of the patients were married, 2.9% divorced, 5.4% widows and only 10% were single.¹²

Reproductive factors

Age at menarche:

Early age at menarche has been consistently associated with an increased risk of breast cancer. The estimated decrease in risk per five year delay in menarche is 22%.¹⁹ Average age of menarche in developed countries fell from around 16-17 years in the mid-19th century to 12-13 today.²⁰

Good nutrition in early life reduces the age of menarche.²¹

Age at first child:

Having a first child at an early age is protective, especially if associated with late menarche and early menopause.¹

The relative risk of developing breast cancer is estimated to increase by 3% for each year of delay.²²

In study of 1185 women with breast cancer, the risk of breast cancer increased with increasing age at first birth; this effect was not accounted for by parity. An early age at first birth appeared to reduce the risk relative to no pregnancy, whereas a late age at first birth was associated with a higher risk than not having a full-term pregnancy.²³

Parity:

- Childbearing reduces the risk of breast cancer and the higher the number of full-term pregnancies, the greater the protection. Risk of breast cancer reduces by 7% with each full-term pregnancy, and overall women who have had children have a 30% lower risk than nulliparous women.^{22,24}
- The terminal differentiation of breast epithelium associated with a full-term pregnancy is also protective, so older age at first live birth is associated with an increased risk of breast cancer.¹⁰
- High parity was associated with a reduction in the risk that was independent of that of age at first birth: for parity greater than or equal to 5, compared with parity 1-2, the relative risk estimate was 0.7.²³
- Women who carry pregnancy to full term at a young age have a *decreased* risk of developing breast cancer.

During pregnancy, maternal hormone levels change drastically. Studies show that some of these hormones may provide anti-estrogen effects, protecting individuals from the negative effects of estrogen. Examples of proteins thought to impact cancer risk include:

- i. Alpha-fetoprotein: Alpha-fetoprotein is a glycoprotein produced by the liver of a developing fetus. Since the protein is at its highest level during the third trimester, a pregnancy that is not carried to full term may not provide a protective effect.²⁵
- ii. Human Chorionic Gonadotropin (HCG): Human chorionic gonadotropin is a hormone produced by the placenta during pregnancy. The protein is elevated during the first trimester of pregnancy. Experiments with breast cancer cells suggest that the effects of HCG may partially explain the higher rate of breast cancer among nulliparous (non-child bearing) women.²⁶

A 15% risk reduction has been shown for women with a twin birth, compared to women giving birth to a singleton.²⁷

Breast feeding:

Breastfeeding in particular appears to be protective.¹ Longer lactation periods, factor that decrease the total number of menstrual cycles, are protective.¹⁰

Women who breastfeed reduce their risk compared with women who do not. The longer a woman breastfeeds, the greater the protection: risk is reduced by 4% for every 12 months of breastfeeding.²²

A study published in December 2011 estimated that, in 2010, around 3% of breast cancers in women in the UK were linked to women breastfeeding every child for fewer than six months.²⁸

Menopausal status:

Women who experience the onset of menopause at age 55 or older are at an *increased* risk of developing breast cancer.²⁹

Late menopause increases the risk of breast cancer. Women who have undergone the menopause have a lower risk of breast cancer than pre-menopausal women of the same age and childbearing pattern.³⁰

Risk increases by almost 3% for each year older at menopause (natural or induced by surgery), so that a woman who has the menopause at 55 rather than 45, has approximately 30% higher risk.³⁰

Endogenous hormones:

Higher levels of endogenous hormones have long been hypothesized to increase breast cancer risk. Studies show that post-menopausal women with the highest levels of estrogen and testosterone have 2-3 times the risk of women with the lowest levels.³¹

The link between these hormones and pre-menopausal breast cancer risk is less clear.³²

Higher levels of the hormone, prolactin, have been associated with an increased risk of breast cancer, particularly estrogen-receptor-positive tumors.³³

Having higher levels of insulin has been associated with an increased risk of post-menopausal breast cancer in women not taking hormone replacement therapy.³⁴

A link between high insulin levels and breast cancer might explain the 20% increased risk of breast cancer for women with diabetes shown in a meta-analysis. Insulin-like growth factor 1 is positively associated with breast cancer risk.³⁵

Exogenous hormones:

Recent studies have clarified the role of exogenous hormones, in particular the oral contraceptive pills and HRT, in the development of breast cancer. However, long-term exposure to the combined preparation of HRT does significantly increase the risk of developing breast cancer. The recent fall in use of HRT in USA and UK has seen a reduction in the incidence of breast cancer in the 50- to 60-year-old cohort.¹

Oral contraceptive pills:

The use of oral contraceptives (OCs) increases the risk of breast cancer in current and recent users, but there is no significant excess risk ten or more years after stopping use.³⁶

Cancers diagnosed in women who have used OCs tend to be less clinically advanced than those detected in never-users.³⁶

The risk associated with oral contraceptive use in women is similar regardless of a woman's family history, ethnic origin, years of education, age at menarche, height, menopausal status, weight, and alcohol consumption. A study published in December 2011 estimated that around 1% of breast cancers in women in the UK in 2010 were linked to OCs.³⁷

Hormone Replacement Therapy (HRT):

Women currently taking HRT have a 66% increased risk of breast cancer compared to non-users.³⁸

The risk increase is temporary, with risk returning to that of a never-user within five years. A woman's BMI modifies the effect of HRT, with a stronger effect in women with a lower BMI.³⁹

The risk is larger for use of Estrogen-progestagen therapy compared to estrogen-only.^{39,40}

A study published in December 2011 estimated that just over 3% of breast cancers in women in the UK (around 1,530 cases) in 2010 were linked to HRT use.⁴¹

According to an earlier study, three-quarters of these additional breast cancers are linked to the use of Estrogen-progestagen HRT.⁴²

Previous breast disease

- a) Benign breast disease is a generic term describing all non-malignant breast conditions, some of which carry

an increased risk for breast cancer while others do not. Women with proliferative breast disease without atypia have a two-fold increased risk, whilst those with atypical hyperplasia have a more than four-fold increased risk.⁴³

- b) Women with a strong family history and nonproliferative breast lesions have a 60% increase in risk of breast cancer, but there is no risk increase for women without a family history.⁴³
- c) Women are more likely to develop breast cancer in the same breast as the benign breast lesion than in the opposite breast.^{43,44}
- d) Ductal carcinoma *in situ* (DCIS) and lobular carcinoma *in situ* (LCIS) are non-invasive conditions of the breast, which can in some cases develop into invasive cancer. Although women with *in situ* disease are more likely to develop invasive disease, it is difficult to know which are going to, although it is more likely to occur with high grade than low grade DCIS lesions.⁴⁵
- e) Overall, women with a previous *in situ* tumor have double the risk of invasive breast cancer compared to the general population, higher in the same breast as the carcinoma *in situ* than in the other breast.⁴⁶
- f) A previous diagnosis of breast cancer raises the risk of developing a second primary breast cancer. Risk ratios vary from a 40% risk increase^{47,48} to almost five-fold risk increase.^{49,50}
- g) A recent analysis suggests that a substantial proportion of contralateral breast cancers (CBC) diagnosed within two years of the first breast cancer may be in actual fact tumor spread from the primary breast cancer, and two years may be an appropriate cut-off for separating independent breast cancers from those that have spread from a previous breast cancer.⁵⁰
- h) Nonetheless, risk of CBC remains higher two or more years after a primary breast cancer, particularly where the first breast cancer was diagnosed before the age of 40.⁵⁰
- i) Risk of CBC is higher for women whose first tumor was hormone-receptor negative compared to those with a previous hormone-receptor-positive tumor, according to a recent study.⁵¹
- j) A recent randomized trial has shown that taking Tamoxifen for five years, rather than two, can reduce risk of CBC by 30%.⁵²

Family history

- a) A woman with one affected first-degree relative (mother or sister) has approximately double the risk of breast cancer of a woman with no family history of the disease; if two (or more) relatives are affected, her risk increases further,^{53,54} risk is higher if the relative is diagnosed aged under 50 years old.
- b) However, over 85% of women who have a close relative with breast cancer will never develop the disease, and

more than 85% of women with breast cancer have no family history of it.⁵³

- c) In developed countries it is estimated that hereditary factors contribute around a quarter of inter-individual differences in susceptibility to breast cancer, while environmental and lifestyle factors contribute the remaining three-quarters.⁵⁵
- d) Small proportions of women have a particularly strong family history of breast cancer and are at very high risk. Mutations in the breast cancer susceptibility genes BRCA1 and BRCA2 account for the majority of families with four or more affected members.⁵⁶ Women carrying such a mutation have a 45-65% chance of developing the disease by the age of 70.⁵⁷
- e) The estimated prevalence of BRCA1 and BRCA2 mutation carriers in the general population is 0.11% and 0.12% respectively, meaning that around 1 in 450 women carries a fault in one of these genes.⁵⁸
- f) These mutations probably account for around 2% of all breast cancers, 59 and up to 20% of the familial or inherited genetic component of disease risk.⁶⁰
- g) Mutations in the BRCA genes are known as high-penetrance, and confer a greater than 10-fold increase in breast cancer risk. TP53 (Li Fraumeni syndrome) also falls into this category, but is thought to account for a very low proportion of familial breast cancer due to its rarity.⁶¹
- h) Intermediate-penetrance gene variants that confer a 2-3-fold increase in risk have been found in genes such as CHEK2, ATM, BRIP1 and PALB2. Some low-penetrance gene variants have also been identified.⁶¹

Since the lifetime risk of breast cancer for women in the UK in 2008 is 1 in 8, there will be many women who have a mother or sister with the disease. But only if there are several family members with early onset breast cancer is there a likelihood of a significant inherited predisposition to the disease.⁶²

Non-reproductive lifestyle

Bodyweight:

- a) Overweight and obesity, as measured by high body mass index (BMI), moderately increases the risk of post-menopausal breast cancer and is one of the few modifiable risk factors for breast cancer. (BMI is calculated by dividing weight in Kg by height in meters squared. A BMI under 18.5 is classified as underweight, 18.5-24.9 as healthy weight, 25-29.9 as overweight and 30 or over as obese) Compared to lean (BMI 22.5-24.9) women, overweight post-menopausal women have a 10-20% increased risk of breast cancer, and obese post-menopausal women a 30% increase in risk. Women with a BMI under 22.5 have a 15% reduction in risk compared to women with a BMI of 22.5-24.9. In contrast, obese pre-menopausal women have a 20% reduction in breast cancer risk.⁶³

- b) A study published in December 2011 estimated that around 9% of breast cancers in women in the UK in 2010 were linked to excess bodyweight.⁶⁴
- c) The link between BMI and breast cancer risk is likely to be due to hormones. In post-menopausal women, the main endogenous source of estrogen is the conversion of hormones in fatty tissue. This is likely to explain the higher risk in overweight post-menopausal women.⁶⁵
- d) The reduction in risk in obese pre-menopausal women may be due to the increased likelihood of anovulatory menstrual cycles in this group.⁶⁶

Physical activity:

About 50 studies have looked at the association between physical activity and breast cancer, showing a 15-20% risk reduction for the most active women, with the strongest association shown for post-menopausal women.⁶⁷ The effect of physical activity on breast cancer risk may be due to how it affects hormone levels, with a recent European Prospective Investigation of Cancer (EPIC) study showing lower levels of estrogen and testosterone in post-menopausal women who reported higher levels of physical activity.⁶⁸

A study published in December 2011 estimated that more than 3% of breast cancers in women in the UK in 2010 were linked to inadequate physical activity (less than 150 minutes moderate physical activity per week).⁶⁹

Alcohol consumption:

Epidemiological studies have consistently shown a significant association between alcohol consumption and breast cancer and a recent IARC report concluded that this association is causal, 70 estimates of the relative risk associated with every additional drink (~ 10g of alcohol) consumed on a daily basis range from about 7-12%.^{71,72}

This is possibly due to the higher levels of some sex hormones in the bloodstream of alcohol consumers than non-consumers.⁷³

A study published in December 2011 estimated that more than 6% of breast cancers in women in the UK in 2010 were linked to alcohol consumption.⁷⁴

Diet:

- a) There has been a lot of research into the effects of dietary factors on breast cancer risk, but findings are generally inconsistent and inconclusive. The strongest evidence seems to be for fat intake: a meta-analysis of 45 studies⁷⁵ reported that higher total fat intake increased breast cancer risk by 13% while a recent cohort study showed a small but significant risk increase for higher intakes of saturated, monounsaturated and polyunsaturated fat.⁷⁶
- b) The EPIC study showed that women who ate the most saturated fat had twice the risk of breast cancer, compared to those eating the least.⁷⁷
- c) The main types of phyto-estrogens consumed in the

west are lignans, found in a range of foodstuffs. A meta-analysis showed a 15% reduction in breast cancer risk for post-menopausal women with the highest intakes.⁷⁸ The other type of phyto-estrogens is isoflavones, found in soybeans. Consumption of soy-based foods is highest in parts of Asia, and a recent meta-analysis found a reduced risk for women with the highest intakes in studies conducted in Asian populations, but not in western populations.⁷⁹

- d) A meta-analysis showed a slight reduction in breast cancer risk for a higher intake of dietary fiber, although risk reductions were not shown for the main subtypes of fiber, and were only seen when intake of fiber was at least 25g/day.⁸⁰
- e) Higher intake of fruit is associated with a small decrease in breast cancer risk, a meta-analysis showed; both the fiber and the antioxidants contained in fruit may be responsible for this effect.⁸¹

Shift work:

- a) There is some evidence that women who do night shift work have an increased risk of breast cancer,⁸² and other studies show that sleeping longer reduces risk of breast cancer.^{83,84}
- b) One theory is that disrupted or shorter duration of sleep leads to reduced levels of the hormone melatonin which has been shown to have anti-carcinogenic properties. Melatonin also suppresses the production of other hormones that have been linked to an increased risk of breast cancer. A recent study showed a 38% reduction in risk of breast cancer in women with the highest levels of the major melatonin metabolite, 6-sulfatoxymelatonin.⁸⁵
- c) In 2007, the International Agency for Research on Cancer (IARC) classified night-time shift work as "probably carcinogenic to humans",⁸⁶ it has been estimated that more than 4% of breast cancers in women in the UK are linked to shift work.⁸⁷

Level of education and socioeconomic status:

The patients with breast cancer had a better education, the women with more than 7 to 12 years of education had 4.84 times risk of breast cancer as compared with the illiterate women.⁸⁸

Twelve or more years of education are associated with an increased risk of breast cancer.⁸⁹

Incidence and mortality vary with race and social status. Incidence rises with improving economic situation, while mortality is tied to low economic status. In the US incidence is significantly lower and mortality higher among black women.⁹⁰

Smoking and second-hand smoking:

In 2004, IARC concluded on the basis of the existing evidence that smoking and secondhand smoke do not cause breast cancer,⁹¹ since that evaluation, however, the

largest studies have shown an increased risk of breast cancer in women who began smoking before the age of 20 or before first birth^{92,93} and IARC now states that there is limited evidence that tobacco smoking causes breast cancer.⁹⁴ The risk increase for women who smoke compared to never-smokers in these studies was around 10-20%.^{92,93} However, evidence remains inconsistent as to whether smoking causes breast cancer after as well as before the menopause.⁹³

The latest meta-analysis found no association between secondhand smoke and breast cancer in studies that collected information on exposure prior to the development of breast cancer.⁹⁵

However, this study did not examine the effect of secondhand smoke exposure in relation to menopausal status or level of exposure, and more research is needed.

Tea drinking:

Tea consumption was not related to breast cancer risk overall. However, when stratified by age, an inverse association was observed among women less than 50 years: those consuming three or more cups per day had a 37% reduced breast cancer risk when compared with women reporting no tea consumption.⁹⁶

In-utero exposure:

A meta-analysis showed that women with higher birth-weight or birth-length or older maternal age at conception had a small (30%) raised risk of breast cancer and this has been associated with higher levels of estrogen in maternal blood.⁹⁷

Conversely, some studies suggest that breast cancer risk among offspring of mothers with pre-eclampsia or eclampsia may be reduced by as much as half and this has been connected to lower levels of maternal estrogen.⁹⁷

Medical radiation exposure:

Ionizing radiation is an established risk factor for breast cancer.⁹⁸ The effect is strongly related to age at exposure, that is, the younger the woman is exposed, the greater the excess risk. Studies show 12- to 25-fold increases for secondary breast cancer for women treated with mantle radiation therapy to the chest for Hodgkin's lymphoma before the age of 30.^{99,100}

Women who received diagnostic x-rays to the chest for

tuberculosis or pneumonia between the ages of 10 to 29 have a three-fold increased risk of breast cancer.⁹⁸ A much lower, 9%, risk increase has been shown for contralateral breast cancer in women treated with radiotherapy for a previous breast cancer (compared to women treated with surgery alone).¹⁰¹

It has been estimated that exposure to diagnostic x-rays (much lower in dose than radiotherapy) may be responsible for 29 female breast cancer cases before the age of 75 each year in the UK, an attributable risk of 0.1%.¹⁰²

A study published in December 2011 estimated that around 1% of breast cancers in women in the UK in 2010 were linked to radiation exposure. About 46% of these attributable cases were linked to medical radiation and most of the remainder to natural (background) radiation.¹⁰³

Breast screening mammograms (imaging of the breast using X-ray) are associated with a very small number of breast cancers: of 10,000 women who are screened every three years between ages 47 and 73, between three and six will develop cancer during their lifetime because of mammogram radiation.¹⁰⁴

Medications and medical conditions:

A risk reduction of up to 25% has been shown for women regularly using aspirin or other non-steroidal anti-inflammatory drugs (NSAIDs),^{105,106} two studies have shown that post-menopausal NSAID users have lower levels of estradiol than non-users.¹⁰⁷ However, because of the potential adverse consequences of high intake of aspirin, such as gastrointestinal hemorrhage, it would not be recommended as a prophylactic measure.

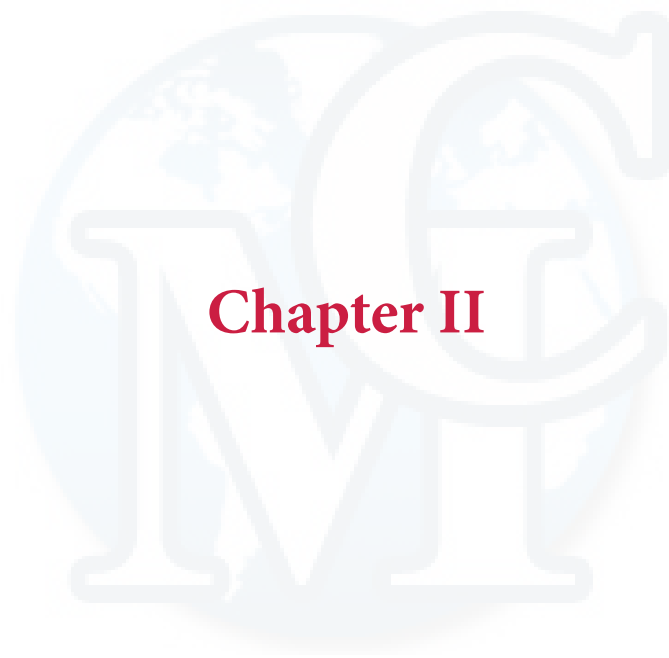
The largest study to date of breast cancer risk in relation to anti-hypertensive medications suggests that taking them for five years or longer increases risk by around 20%.¹⁰⁸

A 12% higher risk of breast cancer has been shown for people treated for Graves' disease (hyperthyroidism).¹⁰⁹

People with the autoimmune condition, coeliac disease, have been shown to have a *reduced* risk of breast cancer, although mechanisms are unclear.¹¹⁰

Objectives

This study aims to study and update the risk factors for breast cancer in Khartoum teaching hospital in the study period and to compare them with the literature.



Chapter II

Methodology

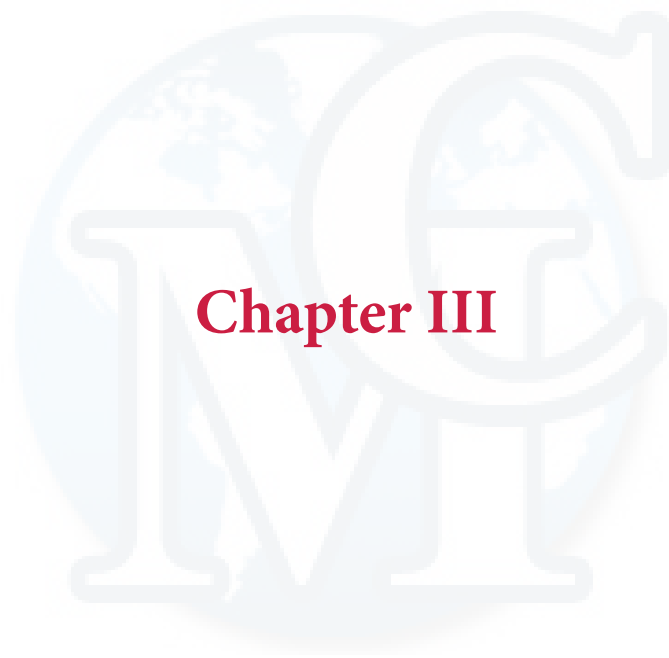
During a 1 year period (November 2013 – November 2014) a total number of 110 patients with breast cancer at K.T.H were studied in this hospital based-prospective descriptive study.

All patients presented to K.T.H with breast cancer and histologically proven in all surgical units were included in this study period without exclusion criteria.

All patients were interviewed, and all of them were consented verbally and special patient data sheet was designed to record the information of the patient regarding the known breast cancer risk factors like, personal data, reproductive factors, medications and medical conditions, previous breast diseases, family history, non-reproductive life style, etc.

At the end of the study the data processed using Statistical packs of social sciences SPSS computer system for analysis and relevant results were obtained.





Chapter III

Results

This study include 110 patients, 108 of them were females (98.2%) and 2 were males (1.8%) presented to K.T.H and diagnosed as breast cancer by histopathology in the period from November 2013 to November 2014.

Age distribution:

The age ranged from 25 to 85 years old and the majority of patients fell in the age group 45 -54 years: 38 pts. (34.2%) followed by age group 35-44 years: 22 patients (19.8%), age group 55-64 years: 20 patients (18%), age group 65-74 years: 15 patients (13.5%), age group 25-34 years: 13 patients (11.7%) and age 75-85 years: 2 patients (1.8%) (Figure 1).

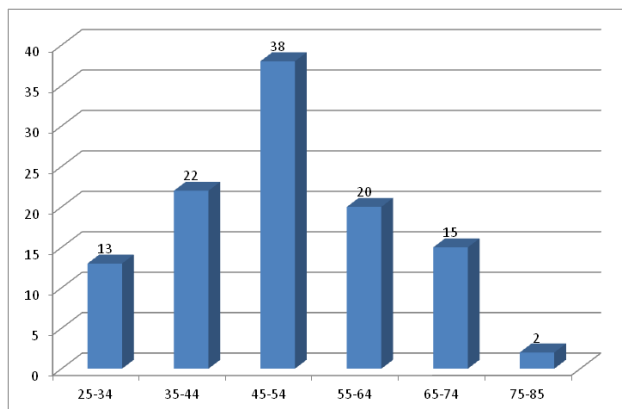


Figure 1 Age distribution.

Geographical distribution:

Fifty three patients (47.7%) were residing in Khartoum, followed by North 22 patients (19.8%), Central 13 patients (11.7%), West 15 patients (13.5%) and East 7 patients (6.3%).

Regarding the origin, 38 patients (34.2%) originate from the North, 27 patients (24.3%) from the West, 25 patients (22.5%) from the Central, 10 patients (9%) from the East, 7 patients (6.3%) from Khartoum, and 3 patients (2.7%) from south (Figure 2).

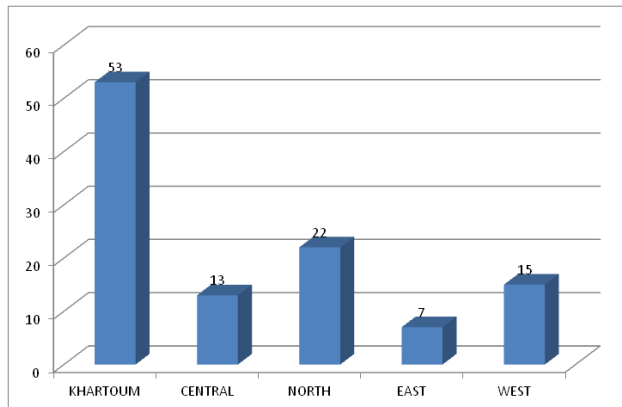


Figure 2A Geographical distribution A-residence.

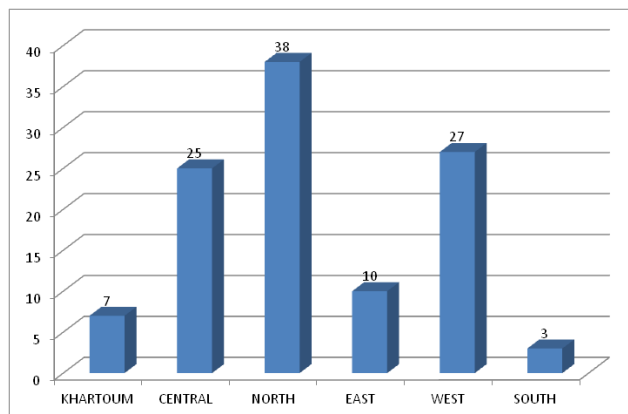


Figure 2B Geographical distribution B-origin.

Tribe:

Concerning the tribe, the highest incidence was in Gaalia, 20 patients (18.2%), followed by shaigia 10 patients (9.1%), and the kawahla 8 patients (7.3%) (Table 1).

Table 1 Age at menarche/years

Age	Frequency	Percent
9	4	3.6
10	6	5.5
11	9	8.2
12	21	19.1
13	21	19.1
14	21	19.1
15	16	14.5
16	6	5.5
17	2	1.8
18	2	1.8
Total	108	98.2

Marital status:

Eighty-two patients (73.8%) were married, 25 patients (22.7%) were single and 3 patients (2.7%) widows.

Age at menarche:

Sixty one patients (54.9%) develop menarche at or below the age of 13 years old, while 4 patients (3.6%) develop it in the age more than 16 years old (Table 2).

Table 2 Previous breasts diseases

Diagnosis	Frequency	Percent
Abscess	10	9.1
Breast Trauma	1	0.9
Fibrosis	3	2.7
Malignant Fibrosis	1	0.9
Mass	1	0.9
Mastectomy	1	0.9
Mastitis	1	0.9
Total	18	16.20%

Age at first birth:

Sixty four patients (57.6%) of all females that have kids (71) had their first child below the age of 31 years old (Table 3).

Table 3 Chronic illnesses

Diagnosis	Frequency	Percent
Asthma	1	0.9
DM	16	14.5
DM, HTN	1	0.9
HTN	7	6.4
HTN, Hyperlipidemia	1	0.9
HTV,DM	1	0.9
TBS	1	0.9
TBS, Peptic Ulcer	1	0.9
Thyroid	2	1.8
Total	31	27.90%

Parity:

Seventy-one patients (63.9%) have children, 9 patients (8.1%) were nulliparous and 55 patients (49.5%) have 3 or more of children.

Sixty five patients (58.5%) have a full term pregnancies and 5 patients (4.5%) have a twins.

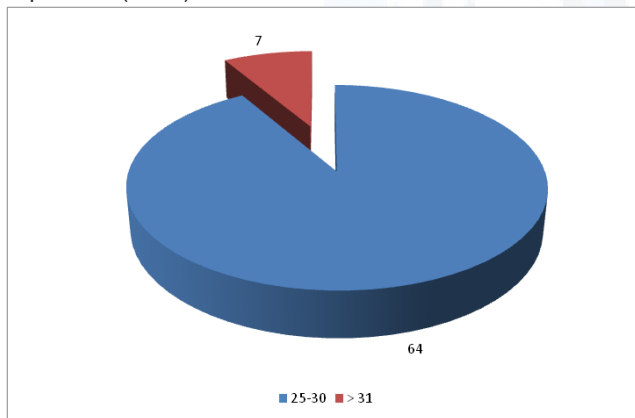


Figure 3 Age at first child.

Breast feeding:

Breast feeding was recorded in 68 patients (61.2%), only 3 patients (2.7%) did not breast fed.

Sixty five patients breastfed more than 6 month and 60 patients breast fed for 12 month or more and 3 patients less than 6 months.

Menopausal status:

Forty nine patients (44.1%) were pre-menopausal at presentation, 51 patients (45.9%) had menopause at the age less than 55 years old, while just 8 patients (7.2%) had menopause at 55 years old or more.

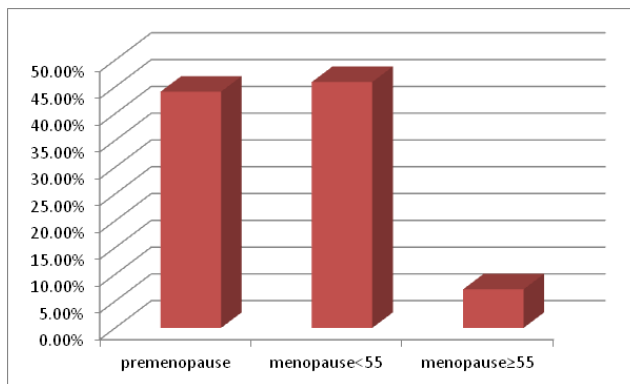


Figure 4 Menopausal status.

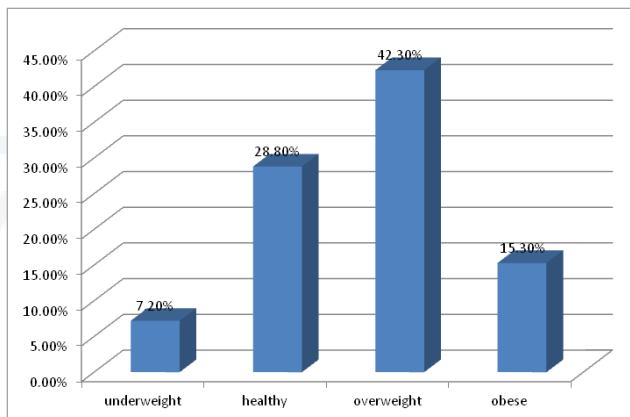


Figure 5 Body weight.

Endogenous hormones:

No patient has had a hyperprolactinemia.

Nineteen 19 patients (17.1%) were diabetic.

Exogenous hormones:

No body of the patients receives HRH.

Seventeen patients (15.3%) receive oral contraceptive pills, of them 13 patients used combined OCs, 2 patients ER and another 2 patients used PR pills.

Previous breast disease:

Table (5) shows that 18 patients (16.2%) had a previous breast disease with their diagnosis.

Twelve of them had a non-proliferative disease and 4 with proliferative disease.

No body known to have a previous diagnosis of DCIS or LCIS.

Family history:

Nineteen 19 patients (17.1%) had a family history of breast cancer.

Fourteen patients of them in the 1st degree (12 patients have one member and 2 patients have 3 members)

Five patients in the 2nd degree (3 patients with one member and 2 patients with 2 members).

The patients have 9 mothers affected, 2 of them diagnosed before 50 years old and 7 at age 50 and more.

Of the 1st degree 50% diseased relatives diagnosed ≥50 years old and 50% before the age of 50 years old

Of the 2nd degree 42.8 % diseased relatives diagnosed ≥50 years old and 57.2% diagnosed <50 years old.

Non reproductive life style factors:

Bodyweight

Fig (3) shows that the majority were overweight 47 patients (42.3%), while 17 patients (15.3%) obese, 32 patients (28.8%) healthy and 8 patients (7.2%) underweight.

Occupation and Physical activity:

Ninety-eight patients (89.1%) were housewives (not employed), while 12 patients (10.9%) were employed.

Sixty one patients (55.5%), had a physical activity less than 50 minutes per week, 39 patients (35.5%) had 150-450 minutes per week and 10 patients (9.1%) more than 450 minutes.

Regarding post-menopausal women (59 patients), 39 patients had a physical activity <150 minutes/week, 17 patients had a physical activity 150-450 minutes/week and just 3 patients with a physical activity more than 450 minutes/week.

Alcohol consumption:

One patient was alcohol consumer.

Diet:

Twenty-five 25 patients (22.7%) ate diet rich in fat, 61 patients (55.5%) rich in carbohydrate, 18 patients (16.4%) rich in carbohydrate and 6 patients (5.5%) rich in fibers.

Shift work:

Only 1 patient (0.9%) did shift work.

Level of education and socioeconomic status:

Forty three patients (39.1%) were educated to primary school level, illiterate were 30 patients (27.3%), 26 patients (23.6%) educated to secondary school level, and 11 patients (15.1%) to university level.

Sixty patients (54.5%) were poor patients fell in class III, 38(34.5%) patients in class II and just 12 (10.9%) in class I.

Smoking and secondhand smoking:

Just 1 patient (.9%) was smoker and start smoking at age 40 years old.

Secondhand smokers were 14 pts.

Tea drinking:

Forty four patients (39.6%) always drink Tea, 24 patients (21.6%) usually, 32 patients (28.8%) sometimes and only 10 patients (0.9%) never.

In utero-exposure:

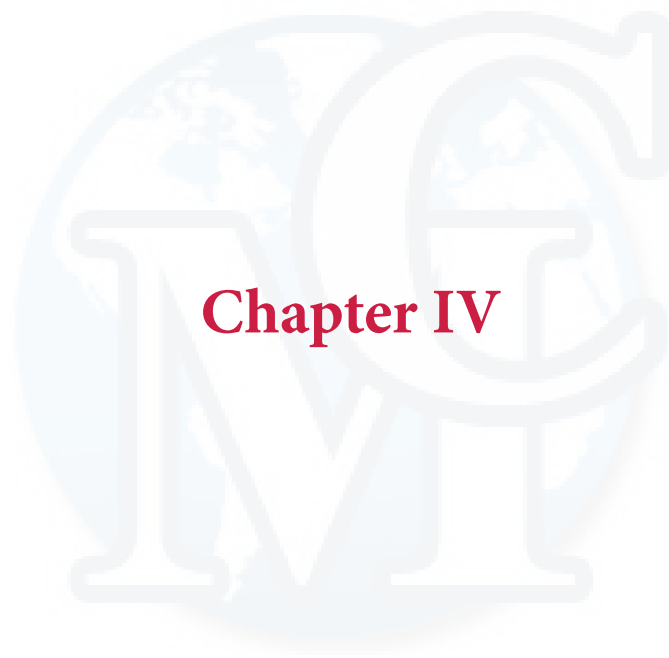
Only one patient (0.9%) developed malignancy during pregnancy, the age of mother was 38 years old, the weight and height of child was not known.

Radiation:

Twenty-seven 27 patients (24.5%) were exposed to x-ray; age according to first time exposure was 12 patients in age 35-45 years old, 6 patients in age 25-35 years old, and 5 patients < 25 years old, 4 patients more than 45 years. Three 3 patients (2.7%) were exposed to mammography radiation, all of them ≥50 years old at exposure. Two patients (1.8%) were exposed to radiotherapy; they were more than 50 years old at radiation and already they were have had a breast cancer.

Medications and medical conditions:

Twenty-two patients (20%) were taking aspirin regularly, and 13 patients (11.8%) were using NSAIDs regularly. Fourteen patients (12.7%) were using antihypertensive drugs regularly; 8 patients of them use it more than 5 years. Table 6 shows that 31 patients (28%) had chronic illness, 18 patients (16.2%) had D.M and 10 patients (9%) had HTN.



Chapter IV

Discussion

Breast cancer is the dominant cancer in the female in Sudan, Percentages of the breast cancers represented 38.4% to 42% of all female cancers.¹⁷ At global level it accounted for 11.4 million new cases and 7.4 million deaths (around 13% of all deaths) in 2004. In this study the percentage of male was 1.8%, (1% in west) which is consistent with that, male breast percentage is high in African, but it is not much as high as 5 -15%.¹¹ The majority of patients fell in the average age group (45-54years) by 34.2%, which consistent with the literature in that, the higher incidence of breast cancer in African women occur in a younger age.¹⁵ A higher incidence of breast cancer in younger women has also been observed in women of African descent living in western countries, in a recent study conducted to examine data collected from British women, it has been shown that black British women were diagnosed with breast cancer at a much younger age (average age 21 years) compared to their white counterparts. In our study the average age is 18.45 which is more lower than black British women.

In another study Palmer et al. reported that multiparity increased breast cancer risk prior to age 45 but offer a protective effect after age 45 years. These factors may explain the age distribution of breast cancer in African women who tend to have multiple children at a younger age.

The reasons for the younger age distribution of African women with breast cancer deserve additional study. The majority of patients (48.2%) were living in Khartoum; this is acceptable because the Khartoum state include people from all other states of Sudan {pts. those have Khartoum as origin and residence are just 7 patients (6.3 %)}. Many risk factors associated with urbanization and economic development were cited to contribute to increase in breast cancer and these include early menarche, late childbearing, having fewer children, obesity, and increased awareness and detection.

Regarding the origin 34.2% originate from the North, and Khartoum just 6.3%. If we compare the estimates of population distribution in percentage { North 5.8%, Khartoum 17.7% (Central Bureau of Statistics-2012)}, we will find the percentage of cancer incidence is very high in north, may be due to environmental or genetic factors. The tribe that has most high incidence was the Gaali (18%), shaigi (9%) and kwahal (7.2%), these variables clearly signify the risk of tribe in the incidence of breast cancer in Sudan. It's consistent of most previous studies.^{3,17} Also previous Sudanese study done by AmiraZino (MD.thesis) found that, the highest incidence was among Gaalia, shaigi, Danagla and Mahas which are all in the North.

Genetic or environmental factors may play a role.

The marital status in correlation to breast cancer has been reported in several studies, with the higher risk is in black single and widowed female, and white widowed, in our study 73.8% were married, 22.7% were single, 2.7% were widows. Ernsteret et al. observed, there appears to be no protective effect of marriage for cancer incidence.

This may indicate that marriage influences survivorship among cancer patients but plays no role in the etiology of cancer. Exposure to endogenous estrogens increases the risk of breast cancer. In regard to early menarche there is strong relation as a risk factor, since 54.9% of the patients get the menarche at or before the 13 years old. The study conducted by Abbasi, *et al.*, reported significant association between age at menarche and breast cancer.¹¹¹

In Sudan, early menarche was observed in 43.5%.¹¹²

The study shows that, 57.6% of the patients have had their first child before the age of 31 years old which and report weak or no association with breast cancer (no protective effect of early first child), especially with the high percentage of early menarche.

In current study 71 patients (63.9%) have children, 9 patients (8.1%) were nulliparous and 56 patients (50.4%) have 3 or more of children. 65 patients (58.5%) have a full term pregnancies and 5 patients (4.5%) have twins. The higher age group incidence (45-54), has the higher rate of nulliparity, this observation is consistent with the strong positive correlation of breast cancer and nulliparity, although the percentage is not high as the western countries, may be related to the different culture.

It seems that there is weak correlation between number of children, full term pregnancies and twins and the breast cancer in African women.

The majority breastfed for long duration, (58.5% more than 6 months and 54% more than 12 months) and just 3 patients did not breastfed.

In large –case study control in Cape town. Coogan et al. (1999) found no effect of lactation on the risk. The study suggests weak or even no protective effect of breast feeding in African women. Although breast cancer is suggested to increase by early menarche and late menopause, study done in Kampala of 86 cases and match hospital control most cases was premenopausal. This is consistent with our study, 44.1% were pre-menopausal at presentation, 45.9% had menopause at the age less than 55 years old, while just 7.2% had menopause at 55 years old or more.

In this study no body have a hyperprolactinemia, whereas 17.1% were diabetic. This is similar to Sudanese study done by Musa abarshi (MD Thesis) who found 20% incidence of DM through his cases of breast cancer.

No body receives HRH after menopause.

The proliferation of cells is essential for carcinogenesis because the risk of errors during DNA replication is increased during cell division, which if not corrected, can lead to cancer. In the current study 15.3% of patients receives OCs, it is very high relatively than western.³⁷ Even it is high relative to previous Sudanese studies 2.9%.¹²

Future separate researches should focus at this issue.

No body known to have a previous diagnosis of DCIS or LCIS, this most likely due to a poor screening in Sudan.

Although 18 patients 16.2% had a previous history breast disease, it is not to be a significant because 12 of them presented with a nonproliferative lesions and just 4 of nonproliferative lesions had a family history of breast cancer, similarly just 2 patients of the proliferative lesions had a family history of breast cancer, just one patient 0.9% had a cancer.

Our study has a very high positive family history 17.1% in comparison to literature, about 2%,⁵⁹ or even local studies, also 2%.¹² It is consistent with our overall current study, since the highest age group 45-54 years (less than 50) old has the highest rate of family history (7 patients), also in that 7 patients is from tribes, Gaaleen and Shaigi.

There is significant percentage of overweight (42.3%) and obese (15.3%), our culture still making it as indicator of beauty, and this can be modified. Physical exercise appears to protect against breast cancer in both premenopausal and postmenopausal women. 89.1% were housewives and 55.5% do inadequate physical activity, again it is related to our culture and can be modified. Alcohol consumption appears to have no risk factor, just one patient (0.9%). The non-vegetarian diet was observed an important risk factor; higher intake of fruit is associated with a small decrease in breast cancer risk. In this study 22.7% ate high fat diet.

Harrison *et al.* noted that diet was significantly associated with breast cancer. Hence education and awareness about the beneficial effects of consuming fresh vegetables and fruits will be helpful in controlling Breast Cancer. It is likely that, shift work does not affect breast cancer in Sudanese ladies, only 1 patient 0.9%. Education and socio-economic status is higher in breast cancer cases in international literature, but in our study 27.3% were illiterate, 39.1% educated up to primary school, just 15.1% get university education, also 54.5% of patients were poor, they are not a risk factor, but it can be a relative through populations.

Just one patient (0.9%) was smoker, 14 patients passive smokers, it appear that smoking is not risk factor in our study, regarding passive smoking there is no study confirm the relation. Tea and other beverages did not prove association with risk cancer and in our study only 0.9% did not drink tea. There is risk factor of in-utero exposure in our study, 0.9%.

Radiation is well known risk factor, but it is related to the age at first exposure, although in our study there is significant percentage 24.3% of exposure but just 5 patients (4.5%) exposed before the age of 30 years old, it show weak effect but still important. In current study 19.8% and 11.7% uses aspirin and NSAIDs respectively regularly; it is consistent with the international literature but the autoimmune disease is by far lower, and it seems does not protective. Significant proportion and a lot patient that had chronic illnesses is diabetic or hypertensive with more than 5 years in their regular treatment and with percentage consistent with the local previous studies.¹²

Conclusion

North was the commonest state of origin and the Gaalia, Shawaiga and Kwahla is the mostly affected tribes among

44 tribes; breast cancer occurs in a younger age group 45 – 54 years old, which is younger than in the west and Arabian. In Sudan we need a lot of studies in all country focusing on the genetic and racial factors. Family history of breast cancer, early menarche, contraceptive pills, and unmarried play important role risk factors and increase the incidence. Diabetes, fatty diet, overweight and obesity and antihypertensive drugs also play a significant increasing risk. Age at first child, menopausal status, breast feeding, education and socioeconomic status, parity, widow and alcohol is not risk factors for breast cancer in Sudanese females and against the literature in the west, at least in this study.

Recommendations

- Future studies should be focus on the genetic background.
- Increase the awareness of population about the risk factors that can be changed like the use of contraceptive pills and fatty food.
- Encourage the early marriage.
- Advanced registration of breast cancer in all states of Sudan.

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Appendix

Questionnaire

Review of breast cancer risk factors in Khartoum teaching hospital (1/11/2013 - 1/11/2014)

Personal data

NO () name Date..... /..... /.....

Birth day: (...../...../.....) Sex (.....) Residence (.....)

Origin (.....)

Race/Tribe: (.....) Occupation (.....)

Level of education:

Primary school (...) secondary school (...) university (...)

Social class: I (...) II (...) III (...)

Single (.....) Married (.....) Divorced (.....) Widow (.....)

Reproductive factors:

-Age at menarche.....years

-Age at first birth.....years

-Nulliparous (...)

-have children (... Number....) Number of full term pregnancies (.....)

-Twin (...)

-Breast feeding: no (...) yes (...) duration Months /kid.

-Age at menopauseyears

Endogenous hormones:

-D.M (...) Prolactinemia (...)

Exogenous Hormones:

-ER (.....duration.....) PR (.....duration.....)

-OCP (.....duration.....) HRT (.....duration.....)

Previous Breast Diseases : No (.....) yes (.....)

Diagnosis

Not diagnosed (.....)

Previous diagnosis of breast cancer: yes (...) no (...)

Previous diagnosis of: DCIS yes (...) NO (...) LCIS yes (...) NO (...)

Family History: No (...) yes (...)

1st degree: mother (age at diagnosis.....years)

Sister (age at diagnosis.....years)

Sister (age at diagnosis.....years)

2nd degree: (1) Age at diagnosis.....years

(2)Age at diagnosis.....years

(3)Age at diagnosis.....years

Family history of ovarian cancer (.....age at onset...years)

Non-reproductive lifestyle:

- Body weight (.....kg) body height (.....cm)
- Physical activity: less than 150 min/week (..) moderate 150-450 (..) Hard more than 450(..)
- Smoking: no (...) yes (...) duration (age.....to age.....)
- Alcohol: no (...) yes (...) duration
- Diet rich in: fats (...) protein (...) fibers (...) carbohydrates (...) fruits (...)
- Shift work: yes (...) no (...)

In Utero Exposure:

- Maternal age at conception (...years) birth weight (....kg/not known.....)
- Birth length (.....cm/ not known.....)

Medical Radiation Exposure:

- X.RAY: NO (...) YES
- 1st at age..... 2nd at age..... 3rd at age
- Mammography: no (...) YES
- 1st at age..... 2nd at age..... 3rd at age
- Radiotherapy: no (...) yes
- 1st at age.....2nd at age.....3rd at age

Medications and Medical Condition:

- Regular using of:
- Aspirin (.....) NSAID (.....)
- Antihypertensive medications (.....duration.....year)
- Chronic disease (1).....
- (2).....
- (3).....

Smoking and second hand smoking:

- Smoking (.....duration.....)
- Secondhand (.....duration.....)
- Previous breast disease:
- Diagnosis (.....) duration (.....) age (....)
- Diagnosis (.....) duration (.....) age (....)
- Tel. NO