

CHAPTER ONE

INTRODUCTION AND LITERATURE REVIEW

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1 Introduction:

Among women, breast cancer (BC) is the leading cancer and the most common cause of cancer-related death in subjects between 30 and 69 years old⁽¹⁾.

Prolactin hormone is also known as luteotropic hormone or luteotropin, is a protein that in humans is probably best known for its role in enabling female mammals to produce milk however it is influential over a large number of functions with over 300 separate actions of PRL having been reported in various vertebrates⁽²⁾.

The incidence of hyperprolactinemia was significantly higher in patients with metastatic breast cancer than in patients with non-metastatic breast cancer, or with mastopathy, or with advanced solid tumors of different histology⁽³⁾.

Lipoproteins are spherical particles with a hydrophobic core (TG and esterified cholesterol). Lipoprotein analysis (lipid profile) measure blood levels of total cholesterol, LDL cholesterol, HDL cholesterol, and TG. Plasma lipoproteins act as transport for cholesterol and TG in the human blood⁽⁴⁾.

Lifestyle and diet are frequently indicated as reasons for the global distribution of BC incidence. Nevertheless, while dyslipidemia [high LDL-C (low density lipoprotein cholesterol) and low HDL-C (high density lipoprotein cholesterol) levels] was already shown to play a major role in the etiopathogenesis of cardiovascular diseases⁽⁵⁾, mainly attributed to diet, the specific influence of dyslipidemia in BC initiation and progression is not completely understood.

Furthermore, cholesterol is also a steroid hormone precursor and the vast majority of BC is known to be hormone responsive⁽⁶⁾. The peak incidence of BC occurs in the perimenopausal age⁽⁷⁾, when women dyslipidemia prevalence also rises⁽⁸⁾.

Several authors have shown that lipoprotein fractions can induce cancer cells proliferation and migration *in vitro*⁽⁹⁾ and oxysterol 27-hydroxycholesterol, a primary metabolite of cholesterol was shown to promote estrogen receptor (ER-positive) and BC growth in *invivo* models⁽¹⁰⁾. Moreover, studies in genetic or diet induced hypercholesterolemic mouse models also demonstrated a clear association between high lipid levels and BC development ⁽¹¹⁾ and progression⁽¹²⁾.

1.1 Breast cancer:

The word cancer refers to more than 100 related diseases. Cancer can affect every part of body. Cancer that begins in the breast is called breast cancer. It occur when abnormal cell in the breast divide uncontrollably and form tumors⁽¹⁾.

1.1.1 Breast cancer epidemiology:

Breast cancer continues to remain the most lethal malignancy in women across the world. In 2008, approximately 1.4million women were diagnosed with breast cancer worldwide with corresponding 460000 deaths⁽¹³⁾. Of these, approximately450000 women were diagnosed with the disease in Europe with a corresponding 140000 deaths, while 68000women were reportedly diagnosed with the disease in Africa with a corresponding 37000 deaths⁽¹³⁾.A number of studies have suggested that there are epidemiological differences between breast cancers among women in Europe and Africa⁽¹³⁾⁽¹⁴⁾.

Risk factors such as menopause, oral contraceptive use, cigarette smoking, and family history of breast cancer have been shown to have different relations to breast cancer among blacks and whites⁽¹⁴⁾.

1.1.2 Incidence of breast cancer:

Breast cancer is a leading cause of death among women in West Africa with an approximately 30000 new cases in 2008 and more than 16000 deaths⁽¹³⁾. The incidence appears to be significantly lower in Eastern Africa with approximately 18000 new cases and a corresponding 10000 deaths during the same year⁽¹³⁾. In Western Europe, the incidence is five times higher than that in West Africa. Furthermore, approximately 40000 deaths from breast cancer were recorded in 2008⁽¹³⁾. The incidence is similar in Central and Eastern Europe with approximately 115000 new cases and more than 47000 deaths in 2008⁽¹³⁾. The incidence has also been shown to be significantly higher among women of European origin in the United States of America.

Fejerman and colleagues reported that Greater European ancestry is associated with increased risk of breast cancer⁽¹⁵⁾. They recorded a statistical significance when women² Journal of Cancer Epidemiology with 51% to 75% and 76% to 100% European ancestry were compared with women with 0% to 25% European ancestry⁽¹⁵⁾.

1.1.3 Causes of Breast cancer:

There are several causes of breast cancer which include:

1.1.3.1 Heredity:

Being born with mutate, or damage breast cancer gene cause from 5 to 10 percent of breast cancer cause. The breast cancer genes breast cancer 1 (BRCA1) and breast cancer 2 (BECA2) are supposed to stop tumor growth. When these genes are abnormal, they can't carry out their function⁽¹⁾.

1.1.3.2 Radiation:

Radiation is particles send out from radioactive substances. Exposure to high dose of ionizing, or electrically charging radiation has been proven to increase cancer risk⁽¹⁾.

1.1.3.3 Environment:

Chemicals used in factories and on farms and chemicals in every day household products may cause breast cancer. Pesticides for killing bugs, as well as fuel, plastics, detergents, and other poisonous substance may damage breast cancer gene. These chemicals haven't been proven to cause breast cancer. However, studies are currently being done to determine their effect⁽¹⁾.

1.1.3.4 Estrogen:

Estrogen is a female sex hormone produced by ovaries. It triggers breast development and helps in menstrual cycle regulation. This is the time from one menstruation to the next. Estrogen increases the number of cells in the breasts during menstruation. It may stimulate growth of breast cancer cells⁽¹⁾.

1.1.3.5 Diet:

A high-fat diet may contribute to breast cancer by rising estrogen levels in the body.

As possible evidence, researchers point to Japan, where the rate of breast cancer is quite low. Women Japan typically eats less fat than women in the United States and Canada do⁽¹⁾.

1.1.4 Risk factors of breast cancer:

The major risk factors are as fallow:

1- Person's sex: Although men can develop breast cancer, it is predominantly a disease of women⁽¹⁶⁾.

2- Age: Breast cancer risk increases progressively as women aged. Two third of breast cancer cases occur in women over the age 50, after menopause. It does not occur often in women under the age of 30, but it increases sharply in the early forties. It levels off after age 45 and increase again after age 55. The yearly incidence in 70-years old women is three times greater than in 50-years-olds ⁽¹⁶⁾.

3- Family history: This may be the most important factor, especially in women who have a history of immediate relatives who have breast cancer. Women whose mothers or sisters have had breast cancer are two to three times more likely to develop it. If it is occurred in both breasts of these relative and before menopause, the risk is increased. A family history of breast cancer need not indicate a genetic cause ⁽¹⁶⁾.

4- Previous cancer: If a woman has had cancer in one breast, the risk of her developing it in other breast in the twenty years following the initial diagnosis between 10 and 15 percent⁽¹⁶⁾.

Other risk factors are pregnancy and menstrual history. Women who have not born a child or whose pregnancy occurred after age 30 have a highest risk. Early onset of the menstrual period along with late menopause also seems to increase the risk, whereas early menopause lessens it⁽¹⁶⁾.

1.1.5 Signs and symptoms of breast cancer:

The widespread use of screening mammograms has increased the number of breast cancers found before they cause any symptoms, but some are still missed. The most common sign of breast cancer is a new lump or mass. A lump that is painless, hard, and has uneven edges is more likely to be cancer. But some cancers are tender, soft, and rounded or even painful. So it's important to have anything new or unusual checked by a doctor ⁽¹⁷⁾.

1.1.6 Types of breast cancer:

There are several types of breast cancer, and cancer can be found in different areas of the breast. Generally, the cancer can be non invasive (in situ) or invasive (infiltrating) and can begin in the cells lining the ducts (ductal carcinoma) or the lobules (lobular carcinoma). Most commonly, breast cancer begins in one of the cells lining the ducts⁽¹⁸⁾.

Following are some of the main categories of breast cancer:

1.1.6.1 Infiltrating ductal carcinoma:

This is most common type of breast cancer and accounts for 65 to 85 percent of cases. This cancer starts in the cells lining the wall of a milk duct and spreads through the wall into the surrounding tissue. The cancer becomes surrounded by scar like material, which form the lump that is detected⁽¹⁸⁾.

1.1.6.2 Infiltrating lobular carcinoma:

This type of cancer accounts for 5 to 10 percent of cases. Here the cancer starts in the cells lining the lobules and spread through the lobule walls to the surrounding tissue. The cancer typically forms fingerlike projections rather than a lump and may be more difficult to distinguish and diagnose than infiltrating ductal carcinoma⁽¹⁸⁾.

1.1.6.3 Ductal Carcinoma in Situ (DCIS):

Combined with lobular Carcinoma in Situ, ductal carcinoma accounts for 15 to 20 percent of cases. It starts in the cells that line the duct walls but not spread outside the ducts. However it may eventually involve a large area of ducts. If not treated, it may spread outside the ducts. It is earliest stage of breast cancer⁽¹⁸⁾.

1.1.6.4 Lobular Carcinoma in Situ (LCIS):

Combined with ductal Carcinoma lobular carcinoma accounts for 15 to 20 percent of cases. LCIS originates in a lobular cell and grows within the lobule but has not spread to tissue outside the lobules. LCIS is considered a precancerous condition in

which a premalignant change has occurred in the lobular cells. The cells divide and multiply but do not always become invasive cancer. Thus, LCIS is considered a marker for having an increased risk of developing invasive breast cancer in either breast⁽¹⁸⁾.

1.1.6.5 Inflammatory breast cancer:

This is the rarest form of breast cancer and accounts for 1 to 4 percent of cases. It invades and blocks lymph vessels in the skin, which result in a red, warm, swollen breast⁽¹⁸⁾.

1.1.7 Stages of breast cancer:

Like other cancers, breast cancer is classified by stages. The stages indicate the size of tumor and how far the cancer has spread. Breast cancer has five stages. It is treated most successfully in the early stages⁽¹⁾.

Stage 0: this is non invasive breast cancer. The cancer cells haven't gone beyond the ducts or lobules⁽¹⁾.

Stage 1: the tumor is still within in the breast. It is two centimeters (about 3/4 inch) or less in diameter⁽¹⁾.

Stage 2: the tumor is larger than two centimeters but smaller than five centimeters (2inch), and the lymph node under the arm test positive for cancer⁽¹⁾.

Stage 3A and 3B: in stage 3A, the tumor is larger than five centimeters and spread to lymph node under the arm. In stage 3B the tumor spread to the skin, chest wall, or lymph node near to the sternum, or breastbone⁽¹⁾.

Stage 4: Cancer cells may be carried to places such as the bone, liver, lungs or brain. The spread of cancer from the original tumor to other body parts called metastasis⁽¹⁾.

1.1.8 Breast cancer treatment:

The main types of treatment for breast cancer are:

- Surgery
- Radiation
- Chemotherapy
- Hormone therapy

Treatments can be put into broad groups based on how they work and when they are used. Local treatment is used to treat a tumor without affecting the rest of the body⁽¹⁹⁾.

Surgery and radiation are examples of local treatment. Systemic treatment is given into the bloodstream or by mouth and goes throughout the body to reach cancer cells that may have spread beyond the breast. Chemotherapy and hormone therapy are systemic treatments⁽¹⁷⁾.

1.2 Prolactin hormone (PRL):

Also known as luteotropic hormone or luteotropin, is a protein that in humans is probably best known for its role in enabling female mammals to produce milk however it is influenced in various vertebrates⁽²⁾.

Discovered in non-human animals around 1930 by Oscar Riddle, and confirmed in humans in 1970 by Henry Friesen⁽²⁰⁾. prolactin is a peptide hormone, encoded by the *PRL* gene⁽²¹⁾.

Prolactin is secreted from the pituitary gland in response to eating, mating, estrogen treatment, ovulation, and nursing. Prolactin is secreted in a pulsatile fashion in between these events. Prolactin also plays an essential role in metabolism, regulation of the immune system and pancreatic development⁽²⁾.

1.2.1 Production and regulation of prolactin hormone:

In humans, prolactin is produced at least in the pituitary, decidua, myometrium, breast, lymphocytes, leukocytes and prostate⁽²²⁾⁽²³⁾.

Pituitary PRL is controlled by the Pit-1 transcription factor and ultimately dopamine, extrapituitary PRL is controlled by a superdistal promoter and apparently unaffected by dopamine⁽²³⁾.

In decidual cells and in lymphocytes the distal promoter and thus prolactin expression is stimulated by cAMP. Responsiveness to cAMP is mediated by an imperfect cAMP-responsive element and two Cytosine Adenosine Adenosine Thymine/enhancer binding proteins (CAAT/EBP)⁽²⁴⁾. Progesterone has been observed to upregulate prolactin synthesis in the endometrium but decreases it in myometrium and breast glandular tissue⁽²⁴⁾. However breast and other tissues may also express the Pit-1 promoter in addition to the distal promoter⁽²⁴⁾.

Extrapituitary production of prolactin is thought to be special to humans and primates and may serve mostly tissue specific paracrine and autocrine purposes. It has been hypothesized that in other vertebrates such as mice a similar tissue specific effect is achieved by a large family of prolactin like proteins controlled by at least 26 paralogous PRL genes not present in primates⁽²³⁾.

Vasoactive intestinal peptide and peptide histidine isoleucine help to regulate prolactin secretion in humans, but the functions of these hormones in birds can be quite different⁽²⁵⁾.

1.2.2 Diagnostic use of prolactin hormone:

Prolactin levels may be checked as part of a sex hormone workup, as elevated prolactin secretion can suppress the secretion of FSH and GnRH, leading to hypogonadism, and sometimes causing erectile dysfunction in men⁽²⁶⁾.

Prolactin levels may be of some use in distinguishing epileptic seizures from psychogenic non-epileptic seizures. The serum prolactin level usually rises following an epileptic seizure⁽²⁶⁾.

1.2.3 Reference ranges of prolactin hormone:

General guidelines for diagnosing prolactin excess (hyperprolactinemia) define the upper threshold of normal prolactin at 10.8 ng/ml for women, and 8 ng/ml for men⁽²⁷⁾. Similarly, guidelines for diagnosing prolactin deficiency (hypoprolactinemia) are defined as prolactin levels below 3 ng/ml in women⁽²⁸⁾, and 2 ng/ml in men⁽²⁷⁾. However, different assays and methods for measuring prolactin are employed by different laboratories, and as such the serum reference range for prolactin is often determined by the laboratory performing the measurement⁽³⁰⁾. The circumstances surrounding a given prolactin measurement (assay, patient condition, etc.) must therefore be considered before the measurement can be accurately interpreted⁽³⁰⁾.

1.2.4 Conditions associated with elevated levels:

Hyperprolactinaemia, or excess serum prolactin, is associated with hypoestrogenism, anovulatory infertility, oligomenorrhoea, amenorrhoea, unexpected lactation, and loss of libido in women, and erectile dysfunction and loss of libido in men⁽³¹⁾.

1. Physiological: which includes: coitus, exercise, lactation, pregnancy, sleep and stress.

2. Pharmacological: which includes: anesthetics, anticonvulsant, antihistamines (H2), antihypertensives, cholinergic agonist, drug-induced hypersecretion, catecholamine depletory, dopamine receptor blockers, dopamine synthesis inhibitor, estrogens(oral contraceptives and oral contraceptive withdrawal), neuroleptics, antipsychotics, neuropeptides, opiates and opiate antagonists.

3. Pathological: which includes: hypothalamic-pituitary stalk damage, granulomas, infiltrations, irradiation, rathke's cyst, trauma(pituitary stalk resection and suprasellar surgery), tumors(craniopharyngioma, germinoma, hypothalamic metastases, meningioma and suprasellar pituitary mass extension).

-Pituitary tumors(acromegaly, idiopathic, lymphocytic hypophysitis or parasellar mass, macroadenoma “compressive”, macroprolactinemia, plurihumoral adenoma and prolactinoma).

-Surgery.

-Systemic disorders (chest-neurologic chest wall trauma, herpes Zoster, chronic renal failure, cirrhosis, cranial radiation, epileptic seizures, polycystic ovarian disease and pseudocyesis) ⁽³¹⁾.

1.2.5 Conditions associated with decreased levels:

Hypoprolactinaemia, or serum prolactin deficiency, is associated with ovarian dysfunction in women ⁽²⁸⁾, and metabolic syndrome, anxiety, arteriogenic erectile dysfunction, premature ejaculation⁽²⁹⁾, oligozoospermia, asthenospermia, hypofunction of seminal vesicles, and hypoandrogenism⁽³²⁾ in men. In one study, normal sperm characteristics were restored when prolactin levels were brought up to normal values in hypoprolactinemic men ⁽³³⁾.

1.3 Association of PRL with breast cancer:

The function of PRL in the etiology and progression of human breast cancer is not yet clear, and literature data are not consistent but, are even contradictory. However, there is significant evidence that PRL may play a role in human breast cancer.

The incidence of hyperprolactinemia was significantly higher in patients with metastatic breast cancer than in patients with non-metastatic breast cancer, or with mastopathy, or with advanced solid tumors of different histology ⁽³⁾. Hyperprolactinemia was almost exclusively found in patients with metastatic breast cancer during the course of the disease⁽³⁴⁾. Hyperprolactinemia was found to be an important indicator of unfavorable prognosis in node-positive breast cancer patients⁽³⁵⁾. Results of another study indicated the possible association of hyperprolactinemia and overexpression of p53 with aggressiveness of the tumor, early disease relapse or metastases, and poor overall survival in node-negative breast cancer patients ⁽³⁶⁾. In primary tumors of stage II and stage III breast cancer patients, there was a significant increase in the frequency of PRL-positive tumors upon increase in the number of involved lymph nodes⁽³⁷⁾. With increasing tumor size, a significantly increased incidence of hyperprolactinemia was observed, hyperprolactinemic patients had a significantly increased risk of developing recurrent/metastatic disease, and seventy-eight percent of their tumors showed positive immunoreactivity with PRL antibody indicating that breast tumors produce PRL which may act as a major local growth promoter⁽³⁸⁾. Results of some other studies are in agreement with those mentioned above. Circulating levels of PRL might be very useful diagnostic and prognostic marker in breast cancer patients ⁽³⁹⁾, and a valuable parameter to assess treatment efficacy in breast

carcinoma patients ⁽⁴⁰⁾. Hyperprolactinemia is an indicator of disease progression and poor prognosis in metastatic breast cancer patients⁽⁴¹⁾. Serum levels of PRL probably directly depend on the size of primary tumor in breast cancer patients, especially in those with hyperprolactinemia, but this is not a differentiation-dependent phenomenon ⁽⁴²⁾.

1.4 Lipids and Lipoproteins:

Lipids are heterogeneous group of many different substances having low polarity and very limited solubility ⁽⁴⁾.

Lipids are water insoluble but soluble in fat solvents (ether, alcohol, chloroform...etc).

Plasma lipoproteins act as transport for cholesterol and TG in the human blood.

Lipoproteins are spherical particles with a hydrophobic core (TG and esterified cholesterol). Lipoprotein analysis (lipid profile) measure blood levels of total cholesterol, LDL- cholesterol, HDL- cholesterol, and TG⁽⁴⁾.

1.4.1 Cholesterol:

The cholesterol molecule is asteroid lipid, found in the cell membrane of all body tissues, and transported in the blood plasma, of all animals. Most cholesterol is produced internally, not dietary in origin ⁽⁴⁾.

1.4.1.1 Functions of cholesterol:

1. It is important component of the membrane of cells.
2. It is the major precursor for the synthesis of vitamin D.
3. It is the major precursor of the steroid hormones, including cortisol, cortisone, and aldosterone in the adrenal glands.
4. It is the major precursor of the sex hormone; progesterone, estrogen, and testosterone.

5. Cholesterol molecule has an important role for the brain synapses as well as in the immune system ⁽⁴⁾.

1.4.1.2 Normal range:

Total cholesterol: Less than 200 mg/dl

Border line: 200-240 mg/dl

High risky: > 240 mg/dl ⁽⁴⁾.

1.4.1.3 Causes of hypercholesterolemia:

-Arteriosclerosis, nephrotic syndrome, familial hyperlipidemia, coronary artery disease (CAD), high intake, pancreatitis, hypothyroidism and early stage of hepatitis.

1.4.1.4 Causes of hypocholesterolemia:

-Malnutrition, malabsorption, hyperthyroidism, liver disease, pernicious anemia and sepsis ⁽⁴⁾.

1.4.1.5 Methods of estimation:

1. Chemical method: which include:

-Libermann-Burchard method: - this method measured the cholesterol extracted into cold chloroform and then treated with acetic anhydride, acetic acid, and concentrated sulphuric acid to form a green color complex.

-Zak's ferric chloride method.

-Henly method ⁽⁴⁾.

2. Enzymatic method:

Principle:

Cholesterol esters are hydrolyzed by cholesterol esterase enzyme to free cholesterol and free fatty acids. Free cholesterol is oxidized by cholesterol oxidase enzyme to form cholesta-4-ene-3-one and hydrogen peroxide. The hydrogen peroxide is reduced by hydrogen peroxidase enzyme to water and oxygen that is

received by oxygen receptor (4-amino antipyrine), and in the presence of phenol as indicator- quinonimine red is formed and it is measured at 515nm green filter ⁽⁴⁾.

1.4.2 Triglyceride (TG):

The class of a cylglycerol “glyceride” is determined by the number of alcohol groups that are esterified to produce monoacylglycerol “monoglyceride “, diacylglycerol “diglyceride” and triacylglycerol “triglyceride”.

Triglyceride is the main form of the dietary lipid. It is the form of storage fat. It's consist of glycerol esterified with 3 long chains fatty acid through the three separate dehydration steps ⁽⁴⁾.

The increased level of TG is often associated with insulin resistance, obesity, and diabetes mellitus (DM). The high level of TG may be responsible for the development of blood clot that block the arteries resulting in myocardial infarction (MI). Having a high triglyceride level with high LDL cholesterol may increase chances of having heart disease more than having only a high LDL cholesterol level ⁽⁴⁾.

1.4.2.1 Normal range:

Normal: <150 mg/dl

Border line: 150-199mg/dl

High: 200-499 mg/dl

Very high: >500 mg/dl.

1.4.2.2 Causes of high result:

1. Genetic: about 0.2% of hypertriglyceridemic patients are due to genetic affect.
2. Acquired: such as; DM, obesity, high level of lipoprotein, alcohol abuse, Hypothyroidism, nephrotic syndrome, hyperparathyroidism and renal failure.

1.4.2.3 Causes of low result:

Malnutrition, malabsorption, and some drugs.

1.4.2.4 Methods of estimation:

The old methods of estimation of TG were long, hazardous, and tedious procedures. So the enzymatic method represent greater cost reagents saving the technologist time and hazards.

Enzymatic method:

Principle:

TG are broken down by lipase enzyme to glycerol and free fatty acids. And in the presence of ATP, the glycerol is phosphorylated by glycerol kinase enzyme to glycerol-3-phosphate.

Then, the reaction can be completed by one of the following methods:

1. glycerol-3-phosphate reduces NAD^+ catalyzed by glucose-6-phosphate dehydrogenase enzyme to give dihydroxyacetone phosphate (DHAP), hydrogen ions and NADH that read at 340nm.
2. glycerol-3-phosphate by an enzyme that called L-glycerophosphate oxidase enzyme gives dihydroxyacetone phosphate (DHAP) and hydrogen peroxide. The hydrogen peroxide is reduced by hydrogen peroxidase enzyme to water and oxygen that is received by oxygen receptor (4-amino antipyrine), and in the presence of phenol as indicator- quinonimine red is formed and it is measured at 515nm green filter ⁽⁴⁾.

1.4.3 High Density Lipoprotein (HDL-cholesterol):

High density lipoproteins form a class of lipoproteins, varying somewhat in their size (8-11 nm in diameter) and contents that carry cholesterol from the body's tissues to the liver. Because HDL can remove cholesterol from atheroma within arteries, and transport it back to the liver for excretion, they are seen as "good" lipoproteins.

The major apoproteins in HDL are A-1 and A-2 in ratio A-1: A-2 as 3:1 by weight. HDL is synthesized primarily in the liver and small intestine ⁽⁴⁾.

1.4.3.1 Measurement of HDL-cholesterol:

Principle:

HDL-C is measured –as cholesterol- in the supernatant of samples following the precipitation of apoB-containing lipoproteins by several methods.

Polyanion precipitation methods:

Polyanion precipitation was most commonly used to remove apoB-containing lipoproteins prior to analysis HDL-C. It required a sample pretreatment and was not fully automate. Most clinical laboratories have replaced precipitation techniques with automated homogeneous assay for HDL-C and LDL-C. HDL-C has been measured in the supernatant of samples following the precipitation of apoB-containing lipoproteins by poly anion (as heparin sulphate, dextran sulphate, phosphotungstate)-divalent cations(Ca^{2+} , Mg^{2+} and Mn^{2+}) ⁽⁴⁾.

1.4.3.2 Normal level:

Male: 29-62 mg/dl

Female: 34-82 mg/dl

1.4.3.3 Causes of low results:

Genetic, uremia, DM, liver disease, hypertiglyceridemia, heavy smoker, obesity and some drugs ⁽⁴⁾.

1.4.3.4 Causes of high results:

Moderate alcohol intake, some drugs, regular exercise and weight loss ⁽⁴⁾.

1.4.4 Low Density Lipoprotein (LDL-cholesterol):

Normally, IDL delipidated by hepatic LPL to form LDL. Some IDL is taken up by the liver. The remaining IDL then lose more TG and proteins in the liver by lipase becoming LDL.

LDL cholesterol carries mostly fat and only a small of proteins from the liver to other parts of the body. A high level of LDL cholesterol may increase chances of developing heart disease. LDL provides cholesterol to the tissues. For that LDL is called bad cholesterol. In the liver, LDL is taken up by receptor that recognizes apo-B100 of LDL. These receptors are located in cell membrane in regions called "coated pits". By these receptors LDL internalizes into cells ⁽⁴⁾.

1.4.4.1 Normal level:

Optimal :< 100 mg/dl

Near optimal: 100-129 mg/dl

Border line: 130-159 mg/dl

High: 160-189 mg/dl

Very high: 190 mg/dl or higher.

1.4.4.2 Measurement of LDL-cholesterol:

Several methods have been used to measure LDL-C. The first reference laboratory procedure, involve ultracentrifugation to separate LDL from other lipoproteins, followed by analysis as cholesterol.

Finally, more recently developed homogeneous methods for measuring LDL-C are now used. A much more common second method uses the friedewald formula to calculate LDL-C ⁽⁴⁾.

Friedewald's equation: $LDL = T.\text{cholesterol} - (HDL + TG/5)$

1.4.4.3 Causes of high results:

Primary hyperlipoproteinemia, high intake, hypothyroidism, acute MI, some drugs, nephrotic syndrome and obstructive liver disease ⁽⁴⁾.

1.4.4.4 Causes of low results:

A betalipoproteinemia, malnutrition, malabsorption and liver disease ⁽⁴⁾.

Rationale:

Breast cancer is one of the most serious problems worldwide, and there is strong association between prolactin and lipid profile and breast cancer which is give a reason to be a target for researchers to find out a new ways for early diagnosis, prevention, treatment and follow up. Many studies had conducted to determine the effect of prolactin in breast cancer in different parts of the world, but there are no such studies in Sudan. Therefore this is the first study to determine the levels of prolactin and lipid profile in Sudanese women with breast cancer in order to develop future prevention strategies for breast cancer in this country.

Objectives:**General objective:**

-To evaluate serum prolactin and lipid profile levels in breast cancer women - Khartoum State.

Specific objectives:

- To estimate serum prolactin level in study groups.
- To estimate serum cholesterol level in study groups.
- To estimate serum TG level in study groups.
- To estimate serum HDL-cholesterol level in study groups.
- To estimate serum LDL-cholesterol level in study groups.
- To find association of serum prolactin and lipid profile levels with body mass index (BMI) and menopausal status.

CHAPTER TWO

MATERIALS AND METHODS

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2. Materials and methods:

2.1 Study Design:

Descriptive cross-sectional hospital base study, to estimate serum lipid profiles and prolactin levels in Sudanese women with breast cancer.

2.2 Study area:

This study will be carried in Khartoum state during the period from February to July 2014, in Radio and Isotope Centre Khartoum.

2.3 Study Population:

The targeting group in this study is Sudanese women who have breast cancer.

2.4 Sample size:

The size included 110 samples, 60 samples from women patients with breast cancer and 50 samples from healthy non cancerous women (control group).

2.5 Inclusion and exclusion criteria:

Samples were collected from breast cancer women who have not metastasis of cancer to other part of the body, and also they were collected from control group who have not any diseases that effect in lipid profiles.

2.6 Collection of samples:

Early morning samples were collected by using sterile dry, plastic syringes, tourniquet was used to make the veins more prominent, Puncture sites was cleaned with 70% ethanol and blood sample (5ml) was collected in plane containers from each volunteer. All blood samples were allowed to clot at room temperature. Then they were centrifuged at 4000 rpm to obtain the serum, and stored in -20° until the analysis.

2.7 Ethical Considerations:

Before the study conducted the proposal of the study were ethically approved by ethical committee of the Sudan University of Science and Technology. Then the verbal informed consent was agreed by the general managers of the hospital in which the study was performed.

2.8 Methods:

2.8.1 Estimation of Prolactin hormone:

By sandwich ELISA method.

2.8.2 Estimation of cholesterol, TG and HDL-cholesterol:

By enzymatic method.

2.8.3 Estimation of LDL-cholesterol:

By friedewald equation; $LDL = T.\text{cholesterol} - (HDL + TG/5)$

2.9 Statistical analysis:

The data was analyzed using statistical package for social sciences (SPSS) computer program version 11.5. Data were expressed as frequency, means, standard deviation (SD), following analyzes using student T-test, which was performed for comparison between control and patient groups. A value of $P < 0.05$ was considered significant.

CHAPTER THREE

THE RESULTS

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3 Results:

In this study found that the levels of prolactin hormone, total cholesterol, triglyceride and LDL-cholesterol elevated in breast cancer group more than control group, but the level of HDL-cholesterol is less affected.

Figure (3-1): showed frequencies of breast cancer in different age group, expressed as percentage (%):

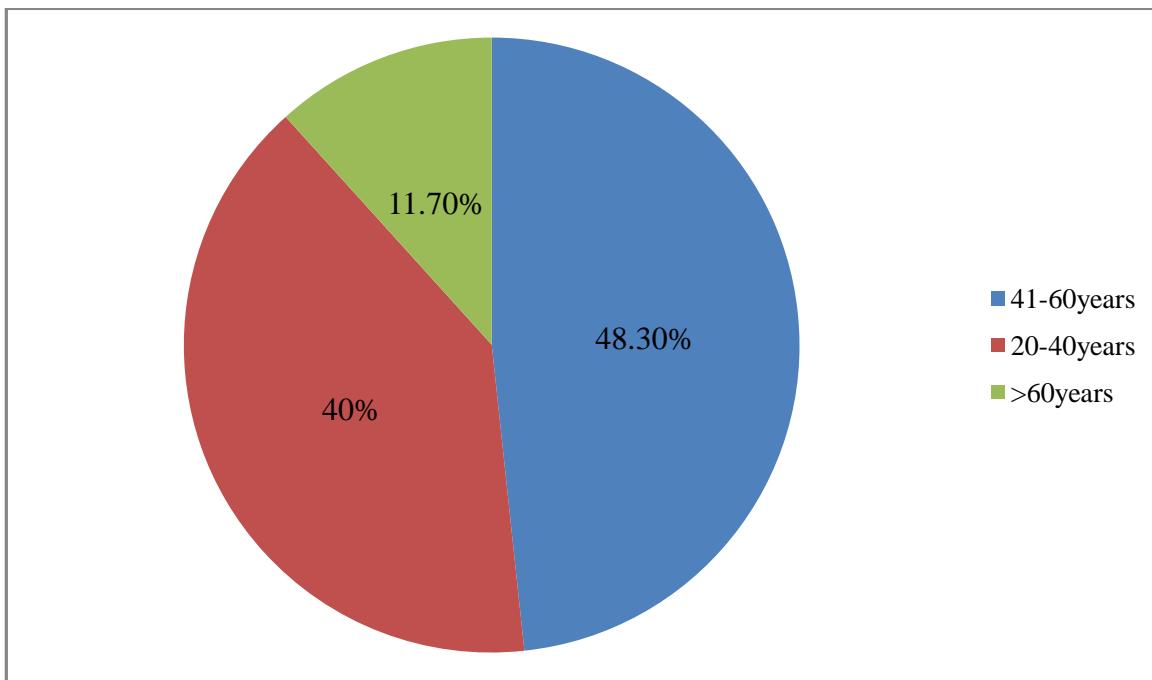
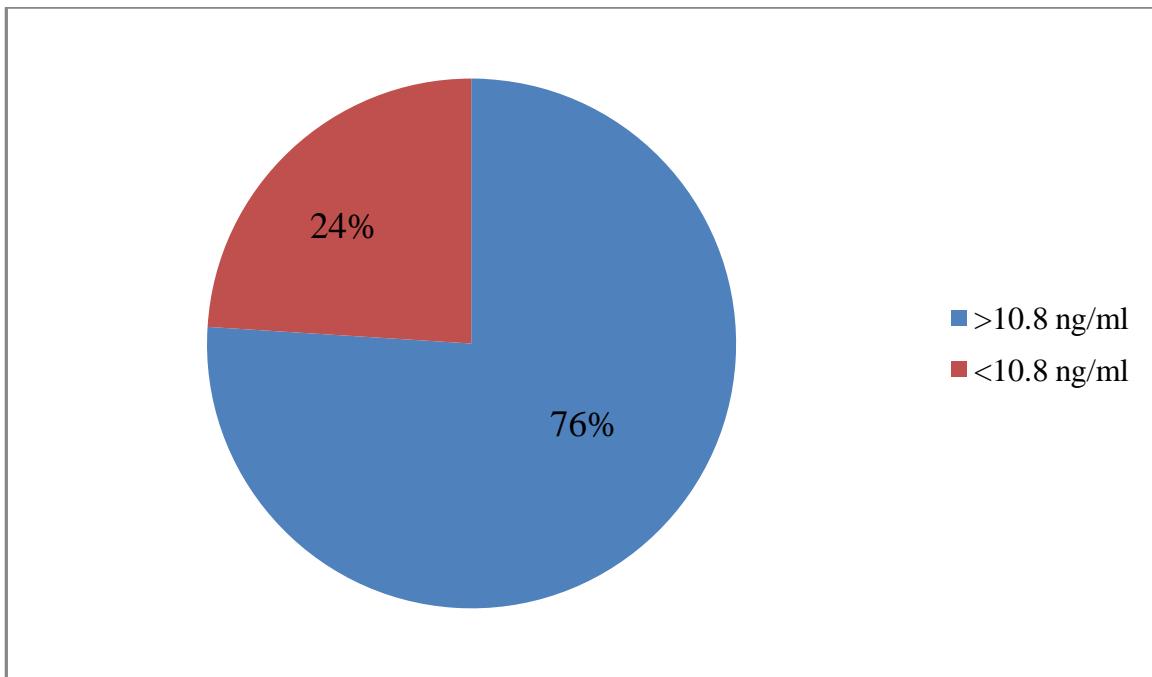


Figure (3-2): Showed frequencies of hyperprolactinemia in breast cancer women expressed as percentage (%):



The result of frequencies revealed, appearance of hyperprolactinemia in 76% of breast cancer women.

Table (3-1): Showed (Mean \pm SD) of cholesterol, TG, HDL and LDL levels in patients and control group:

	Patient N=60	Control N=50	P value
	Mean \pm SD	Mean \pm SD	
Cholesterol(mg/dl)	172.33 \pm 35.28	128.82 \pm 40.87	
TG(mg/dl)	132.15 \pm 68.45	91.78 \pm 49.48	0.001
HDL(mg/dl)	63.81 \pm 22.85	68.36 \pm 22.11	0.294
LDL(mg/dl)	81.42 \pm 35.96	42.10 \pm 29.83	0.000

The study noted significant increase of cholesterol level in breast cancer women (172.33 \pm 35.28) compared to controls group (128.82 \pm 40.87), with (p-value 0.000). Also this study noted significant increase of TG level in breast cancer women (132.15 \pm 68.45) compared to controls group (91.78 \pm 49.48), with (p-value 0.001).

The results of the present study revealed that, there is insignificant decrease in the mean of HDL-cholesterol level in patients group (63.81 ± 22.85) when compared to controls group (68.36 ± 22.11), with (P -value 0.294).

The study also noted significant increase of LDL- cholesterol level in breast cancer women (81.42 ± 35.96) compared to control groups (42.10 ± 29.83), with (p -value 0.000).

Table (3-2): Showed (Mean \pm SD) of PRL level in patients group classified as <45 years and >45 years:

	Age groups(years)	No.	Mean \pm SD	P value
Prolactin(ng/ml)	<45years	33	20.84 ± 8.66	0.003
	>45years	27	9.85 ± 7.24	

The study noted significant increase of prolactin level in breast cancer women in group one (age less than 45 years), compared to group two (age more than 45 years), (20.84 ± 18.66), (9.85 ± 7.24), respectively with (P -value 0.003).

Table (3-3): Showed (Mean \pm SD) of cholesterol, TG, HDL and LDL levels in patients group classified as <45 years and >45 years:

	Age groups(years)	No.	Mean \pm SD	P value
Cholesterol(mg/dl)	<45 years	33	175.00 ± 34.07	0.522
	>45 years	27	169.07 ± 37.08	
TG(mg/dl)	<45 years	33	139.12 ± 73.22	0.388
	>45 years	27	123.63 ± 62.42	
HDL(mg/dl)	<45 years	33	68.818 ± 21.08	0.060
	>45 years	27	57.704 ± 21.08	
LDL(mg/dl)	<45 years	33	78.358 ± 37.05	0.471
	>45 years	27	85.163 ± 34.92	

This study noted insignificant increase of cholesterol, TG and HDL-cholesterol levels in breast cancer women in group one (age less than 45 years), compared to group two (age more than 45 years), (175.00 ± 34.07), (169.07 ± 37.08), (139.12 ± 73.22), (123.63 ± 62.42), (68.81 ± 21.08), (57.70 ± 23.81), respectively with (P-value 0.522, 0.388 and 0.060 also respectively).

Also this study noted insignificant decrease of LDL-cholesterol level in breast cancer women in group one (age less than 45 years), compared to group two (age more than 45 years), (78.35 ± 37.05), (85.16 ± 34.92), respectively with (P-value 0.471).

Table (3-4): Showed (Mean \pm SD) of PRL level in patients group classified as <28.6 (kg/m^2) and >28.6 (kg/m^2):

	BMI(kg/m^2)	No.	Mean \pm SD	P value
Prolactin(ng/ml)	<28.6	45	16.25 ± 13.43	0.768
	>28.6	15	14.86 ± 12.27	

Body mass index (BMI) results showed insignificant increase of prolactin levels in women with breast cancer who have BMI less than 28.6 Kg/m^2 (16.25 ± 13.43) and others who have BMI more than 28.6 Kg/m^2 (14.86 ± 12.27), with (P-value 0.768).

Table (3-5): Showed (Mean \pm SD) of cholesterol, TG, HDL and LDL levels in patients group classified as <28.6 (kg/m^2) and >28.6 (kg/m^2):

	BMI(kg/m^2)	No.	Mean \pm SD	P value
Cholesterol(mg/dl)	<28.6	45	170.22 ± 35.97	0.427
	>28.6	15	178.67 ± 33.47	
TG(mg/dl)	<28.6	45	136.44 ± 70.76	0.405
	>28.6	15	119.27 ± 61.43	
HDL(mg/dl)	<28.6	45	62.15 ± 24.39	0.334
	>28.6	15	68.80 ± 17.17	
LDL(mg/dl)	<28.6	45	79.88 ± 38.53	0.572
	>28.6	15	86.01 ± 27.49	

The present results revealed that, there is insignificant decrease of cholesterol levels in women with breast cancer who have BMI less than 28.6 Kg/m^2 (170.22 ± 35.97) compared to others who have BMI more than 28.6 Kg/m^2 (178.67 ± 33.47), with (P-value 0.427).

The present results also revealed that, there is insignificant increase of TG levels in women with breast cancer who have BMI less than 28.6 Kg/m^2 (136.44 ± 70.76) compared to others who have BMI more than 28.6 Kg/m^2 (119.27 ± 61.43), with (P-value 0.405).

The present results also revealed that, there is insignificant decrease of HDL-cholesterol levels in women with breast cancer who have BMI less than 28.6

Kg/m^2 (62.15 ± 24.39) compared to others who have BMI more than 28.6 Kg/m^2 (68.80 ± 17.17), with (P-value 0.334).

Finally, the present results revealed that, there is insignificant decrease of LDL-cholesterol levels in women with breast cancer who have BMI less than 28.6 Kg/m^2 (79.88 ± 38.53) compared to others who have BMI more than 28.6 Kg/m^2 (86.01 ± 27.49), with (P-value 0.572).

CHAPTER FOUR

DISCUSSION

CHAPTER FOUR

4.1 Discussion:

Malignant proliferation of breast tissue in women has been associated with change in plasma lipids and lipoproteins⁽⁴³⁾.

The results of frequencies revealed, appearance of breast cancer in menopausal age. Our findings agreed with (Lucille)⁽¹⁶⁾, who reported that, two third of breast cancer cases occur in women over the age 50, after menopause, it does not occur often in women under age of 30, but it increases sharply in the early forties.

The results of the present study provide experimental evidence that, there is hyperprolactinemia in breast cancer patients. This result in accordance to (Baniet *al.*)⁽⁴⁴⁾.

The study noted significant increase of cholesterol level in breast cancer women compared to controls group. This finding agreed with (Baniet *al.*)⁽⁴⁴⁾, and also agreement with (Hasija and Baga)⁽⁴⁵⁾.

Also this study noted significant increase of TG level in breast cancer women compared to controls group. This finding agreed with (Baniet *al.*)⁽⁴⁴⁾.

The results of the present study revealed that, there is insignificant decrease in the mean of HDL-cholesterol level in patients group compared to controls group. This finding agreed with (Pikulet *al.*)⁽⁴⁶⁾.

The study also noted significant increase of LDL- cholesterol level in breast cancer women compared to controls group. This finding agreed with (Elkhdrawyet *al.*)⁽⁴⁷⁾.

The increased TG, LDL-C and VLDL-C and decreased HDL-C value increases the risk of coronary heart disease⁽⁴⁸⁾, and high body fat with increased serum lipid profiles were important risks for breast cancer. Researchers have reported association of plasma/serum lipids and lipoproteins with different cancers⁽⁴⁹⁾.

The study noted significant increase of prolactin level in breast cancer women in group one (age less than 45 years), compared to group two (age more than 45 years). This finding agreed with (Baniet *al.*) ⁽⁴⁴⁾ who stated that, Plasma prolactin concentrations were found to be higher in cancer compared with non-cancer patients, this effect being more marked in premenopausal than in postmenopausal patients.

Also this study noted insignificant increase of cholesterol, TG and HDL-cholesterol levels in breast cancer women in group one (age less than 45 years), compared to group two (age more than 45 years). This finding disagreed with (Baniet *al.*) ⁽⁴⁴⁾. Thus we suggest that further studies to group important factors including, cancer stages, type of cancer and parity that may affect to lipid profiles in breast cancer patients along with an investigation of new lipid profiles to clarify most lipid factors that may involve in breast cancer are needed.

Also this study noted insignificant decrease of LDL-cholesterol level in breast cancer women in group one (age less than 45 years), compared to group two (age more than 45 years). This finding agreed with ((Baniet *al.*) ⁽⁴⁴⁾).

Body mass index (BMI) results showed insignificant increase of prolactin levels in women with breast cancer who have BMI less than 28.6 Kg/m² compared to others who have BMI more than 28.6 Kg/m². This finding agreed with (Kwa *et al.*) ⁽⁵¹⁾.

The present results revealed that, there is insignificant decrease of cholesterol levels in women with breast cancer who have BMI less than 28.6 Kg/m² compared to others who have BMI more than 28.6 Kg/m². This finding agreed with (Owireduet *al.*) ⁽⁵²⁾.

The present results also revealed that, there is insignificant increase of TG levels in women with breast cancer who have BMI less than 28.6 Kg/m² compared to others who have BMI more than 28.6 Kg/m². This finding agreed with (Kimet *al.*) ⁽⁵³⁾.

The present results also revealed that, there is insignificant decrease of HDL-cholesterol levels in women with breast cancer who have BMI less than 28.6 Kg/m² compared to others who have BMI more than 28.6 Kg/m².This finding agreed with (Padmanabh and Garima) ⁽⁵⁰⁾.

Finally, the present results revealed that, there is insignificant decrease of LDL-cholesterol levels in women with breast cancer who have BMI less than 28.6 Kg/m² compared to others who have BMI more than 28.6 Kg/m².This finding agreed with (Owireduet *al.*) ⁽⁵²⁾.

4.2 Conclusion:

The study concluded that, prolactin hormone level increases in women with breast cancer, and its level inversely correlate with age, but there is no correlation with BMI.

There is significant increase of lipid profiles level in patients group compared to control group except HDL-cholesterol.

Further investigation is needed to determine the association between prolactin hormone and lipid profiles level versus parity, duration of breast cancer, breast cancer stage and metastasis.

4.3 Recommendations:

- More research should be performed among large sample size to determine the correlation between prolactin hormone and lipid profiles level.
- Further studies to group important factors including, cancer stages, type of cancer and parity that may affect to lipid profiles in breast cancer patients along with an investigation of new lipid profiles to clarify most lipid factors that may involve in breast cancer are needed.
- Efforts to more routinely assess prolactin status and possibly provide supplementation to correct elevation in this at-risk group should be evaluated.

References:

- 1- Judith P. What is breast cancer.Breast cancer perspectives on diseaseand illness,2002; 2: 6-16.
- 2- Bole-Feysot C, Goffin V, Edery M, Binart N, Kelly PA.Prolactin (PRL) and its receptor: actions, signal transduction pathways and phenotypes observed in PRL receptor knockout mice. Endocr. Rev.Journal,June 1998; 19: 225–268.
- 3- Holtkamp W, von Heyden D, Rauschecker H, Nagel GA. Plasma-prolactin concentrations in breast cancer at various stages, in mastopathy and other malignant tumors. Schweiz Med Wochenschr 1983; 113:1513-20.
- 4- Sniderman AD, Blank D, Zakariana R, et al. Triglycerides and small dense LDL: the twin Achilles heels of the Friedewald formula. Clinical Biochemistry, 2003; 36: 499-519.
- 5- Smith D. Epidemiology of dyslipidemia and economic burden on the healthcare system. Am J ManagCare, 2007; 13:68-71.
- 6-Yager JD, Davidson NE. Estrogen carcinogenesis in breast cancer. N Engl J Med,2006;54:270-282.
- 7- Bray F, McCarron P, Parkin DM. The changing global patterns of female breast cancer incidence and mortality. Breast Cancer Res, 2004; 6:229-239.
- 8- Steinhagen-Thiessen E, Bramlage P, Losch C, Hauner H, Schunkert H, Vogt A, Wasem J, Jockel KH, Moebus S: Dyslipidemia in primary care—prevalence, recognition, treatment and control: data from the German Metabolic and Cardiovascular Risk Project (GEMCAS).CardiovascDiabetol, 2008; 7:31.

9- Antalis CJ, Arnold T, Rasool T, Lee B, Buhman KK, Siddiqui RA. High ACAT1 expression in estrogen receptor negative basal-like breast cancer cells is associated with LDL-induced proliferation. *Breast Cancer Res Treat*, 2010; 122:661-670.

10- Nelson ER, Wardell SE, Jasper JS, Park S, Suchindran S, Howe MK, Carver NJ, Pillai RV, Sullivan PM, Sondhi V, Umetani M, Geraerts J, McDonnell DP. 27-Hydroxycholesterol links hypercholesterolemia and breast cancer pathophysiology. *Science J*, 2013; 342:1094-1098.

11- Llaverias G, Danilo C, Mercier I, Daumer K, Capozza F, Williams TM, Sotgia F, Lisanti MP, Frank PG: Role of cholesterol in the development and progression of breast cancer. *Am J Pathol* 2011; 178:402-412.

12- Alikhani N, Ferguson RD, Novosyadlyy R, Gallagher EJ, Scheinman EJ, Yakar S, LeRoith D: Mammary tumor growth and pulmonary metastasis are enhanced in a hyperlipidemic mouse model. *OncogeneJ*, 2013; 32:961-967.

13- Ferlay J, Shin HR, Bray F, Forman D, Mathers D, and Parkin D. Cancer Incidence and Mortality Worldwide. *Globocan Journal*, 2008; 2:19-23.

14- Mayberry RM and Stoddard C. Breast cancer risk factors among black women and white women: Similarities and differences, *American Journal of Epidemiology*, 1993; 136: 1445-1456.

15- Fejerman L, Romieu I, John EM et al. European ancestry is positively associated with breast cancer risk in Mexican women, *Cancer Epidemiology Biomarkers and Prevention*, 1998; 3:128-133.

16- Lucille M. Pederson and Janet M. Risk Factors. Breast cancer family survival guide,2010; 1: 9-10.

17- Susan G. Komen. Breast Cancer Overview. American Cancer Society,2013; 14:460-465.

18- Amy H and Andrea L. Breast cancer: Types and location, Essential Exercises of breast cancer survivors Journal, 2000; 2: 12-13.

19- Asmerom T and Roy I. Molecular Biology of BreastCancer in the Horn of Africa: Case Series-A Pilot Study of Breast Cancer from Eritrea, ISRNPathology,2013; 7:487-495.

20- Friesen H and Hardy J.Biosynthesis of Human Growth Hormone and Prolactin.The Journal of Clinical Endocrinology and Metabolism, December 1970; 31: 611–624.

21- Evans AM, Petersen JW, Sekhon GS and Demars R. Mapping of prolactin and tumor necrosis factor-beta genes on human chromosome 6p using lymphoblastoid cell deletion mutants.SomatCell Mol. Genet Journal,May 1989; 15: 203–213.

22- Ben-Jonathan N, Mershon JL, Allen DL, Steinmetz RW.Extrapituitary prolactin: distribution, regulation, functions, and clinical aspects. Endocr. Rev. December 1996; 17: 639–69.

23- Gerlo S, Davis JR, Mager DL, Kooijman R.Prolactin in man: a tale of two promoters.Bioassays, October 2006; 28: 1051–5.

24- Zinger M, McFarland M, Ben-Jonathan N. Prolactin expression and secretion by human breast glandular and adipose tissue explants. *J. Clin. Endocrinol. Metab.*, February 2003; 88: 689–96.

25- Kulick R, Chaiseha Y, Kang S, Rozenboim I, El Halawani M. The relative importance of vasoactive intestinal peptide and peptide histidine isoleucine as physiological regulators of prolactin in the domestic turkey. *Gen Comp Endocrinol*, 2005; 142 : 267–73.

26- Banerjee S, Paul P, Talib V. Serum prolactin in seizure disorders. *Indian Pediatr*, 2004; 41: 827–31.

27-Melmed S, Jameson JL. Disorders of the Anterior Pituitary and Hypothalamus. In: Jameson JN, Kasper DL, Harrison TR, Braunwald E, Fauci AS, Hauser SL, Longo DL. *Harrison's principles of internal medicine* (16th ed.). New York: McGraw-Hill Medical Publishing Division, 2005: 51-68.

28- Kauppila A, Martikainen H, Puistola U, Reinilä M, Rönnberg L. Hypoprolactinemia and ovarian function. *Fertil Steril*, March 1988; 49: 437–41.

29- Corona G, Mannucci E, Jannini EA, Lotti F, Ricca V, Monami M, Boddi V, Bandini E, Balercia G, Forti G, Maggi M. Hypoprolactinemia: a new clinical syndrome in patients with sexual dysfunction. *J Sex Med.*, May 2009; 6: 1457–66.

30- Mancini T, Casanueva F, Giustina A. Hyperprolactinemia and Prolactinomas. *Endocrinology & Metabolism Clinics of North America*, 2008; 3: 67–99.

31- Melmed S and Kleinberg D. Anterior pituitary. In: Kronenberg HM, Melmed S, Polonsky KS, Larsen PR, eds. Williams textbook of endocrinology. 11th ed. Philadelphia: Saunders Elsevier; 2008: 185-261.

32- Gonzales GF, Velasquez G, Garcia-Hjarles M. Hypoprolactinemia as related to seminal quality and serum testosterone. Arch Androl, 1989; 23: 259-65.

33- Ufearo CS, Orisakwe OE. Restoration of normal sperm characteristics in hypoprolactinemic infertile men treated with metoclopramide and exogenous human prolactin. Clin. Pharmacol. Ther, September 1995; 58: 354-9.

34- Holtkamp W, Nagel GA, Wander HE, Rauschecker HF, von Heyden D. Hyperprolactinemia is a indicator of progressive disease and poor prognosis in advanced breast cancer. Int J Cancer, 1984; 34:323-8.

35- Bhatavdekar JM, Patel DD, Vora HH, Ghosh N, Shah NG, Karelia NH. Node-positive breast cancer: prognostic significance of the plasma prolactin compared with steroid receptors and clinicopathological features. Oncology Reports, 1994; 10:841-5.

36- Patel DD, Bhatavdekar JM, Chikhlikar PR, Ghosh N, Suthar TP, Shah NG. Node negative breast carcinoma: hyperprolactinemia and/or overexpression of p53 as an independent predictor of poor prognosis compared to newer and established prognosticators. J SurgOncol, 1996; 62:83-92.

37- Bhatavdekar JM, Patel DD, Shah NG, Vora HH, Suthar TP, Chikhlikar PR, et al. Prognostic significance of immunohistochemically localized biomarkers in stage II and stage III breast cancer: a multivariate analysis. *Ann SurgOncol* 2000; 7:305-11.

38- Bhatavdekar JM, Patel DD, Shah NG, Vora HH, Suthar TP, Ghosh N, et al. Prolactin as a local growth promoter in patients with breast cancer: GCRI experience. *Eur J SurgOncol*, 2000;26:540-7.

39- Mujagić Z, Mujagić H. Diagnostic and prognostic usefulness of prolactin (PRL) in breast cancer (BC). Proceedings of ASCO, San Francisco, 2001; 20:43.

40- Mujagić Z, Mujagić H. Circulating levels of prolactin as an indicator of effectiveness of therapy in breast cancer patients. *Int J Cancer*, 2002; 13: 16.

41- Mujagić Z, Mujagić H. Prognostic significance of circulating levels of prolactin (PRL) in metastatic breast cancer (MBC). Proceedings of ASCO, Chicago, 2003; 22:49.

42- Mujagić Z, Mujagić H. The relationship of circulating prolactin levels to the size of primary tumor in breast cancer patients. *Turk J Bioch*, 2004;29:277-81.

43- Lane D, Boatman K, McCarthy WJ, serum lipids and lipoproteins in women with breast masses. *Breast cancer Res Treat*, 1995; 34:161-9.

44-BaniAetal. Plasma lipids and prolactin in patients with breast cancer. *Br J cancer*, Sep 1986; 54: 439-446.

45-Hasija K and Bagga HK.Alterations of serum cholesterol and serum lipoprotein in breast cancer of women. *Indian J ClinBiochem*, 2005; 20:61-66.

46- Pikul et al. Comparison of serum lipid profiles between Normal Controls and Breast Cancer patients. *J lab physician*, June 2013; 5:38-41.

47- Elkhadrawy TM, Ahsan H, Neugut AI. Serum cholesterol and the risk of ductal carcinoma in situ: A case-control study. *Eur J Cancer Prev*. 1998; 7:393-6.

48- Kannel WB. Status of risk factors and their consideration in antihypertensive therapy. *Am J Cardiol*, 1987;59: 80-90.

49- Schatzkin A, Hoover RN, Taylor PR, Ziegler RG, Carter CL, Albanes D, et al. Site-specific analysis of total serum cholesterol and incident cancer in the national health and nutrition examination survey I epidemiologic follow-up study. *Cancer Res. Journal*, 1988;48:452-8.

50- Padmanabh I and Garima M. Correlation between obesity and High Density Lipoprotein (HDL-C) in Breast Cancer Patients of Southern Rajasthan. *Indian J Surgoncol*. Jun 2011; 2: 118-121.

51- Kwa HG, Cleton F, de Jong-Bakker M, Bulbrook RD, Hayward JL, Wang DY. Plasma prolactin and its relationship to risk factors in human breast cancer. *Int J Cancer*, 1976; 17: 441-447.

52- Owiredu WK et al. Serum lipid profile of breast cancer patients. *Pak J Biol Sci*. Feb 2009;12: 332-8.

53- Kim JS, Kim MH, Lee BK, Rim SJ, Min PK, Yoon SJ, Kim JH, RheeJH, Yoon YW, Hong BK, Kwon HM, Kim C. Effects of Increasing particle size of low-density lipoprotein on rest enosis after coronary stent implantation. *Circ J*,2008; 72:1059-1064.

بِسْمِ اللَّهِ الرَّحْمَنِ الرَّحِيمِ

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College of Graduate Studies

Clinical Chemistry Department

**Evaluation of serum Prolactin hormone and Lipid profiles Levels in Breast
Cancer Patients – Khartoum State**

Questionnaire NO:

Date:

Name:

Age:

Body weight (kg):

Body height (cm):

Body mass index:

Investigations:

Prolactin hormone:ng/ml

Cholesterol:mg/dl

TG:mg/dl

HDL-C:mg/dl

LDL-C:mg/dl