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# Lipid Profile and Hormone Sensitive Lipase [HSL] Gene Variant in Nigeria Women with Breast Cancer

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## ABSTRACT

### Background

Worldwide, breast cancer is the most common cancer in women, being one of the leading causes of death among women and men. Emerging evidence suggests the role of lipid in the development of breast cancer. It becomes a great concern for the modern man and medical curiosity to further investigate alteration in lipid profile and hormone sensitive lipases genes among breast cancer patients in Nigeria.

### Aim and Objective

This study was designed to investigate and compare the atherogenic indices and polymorphism of Hormone Sensitive Lipase gene in individuals with Breast cancer and healthy subjects (non-cancerous subject).

### Materials and Methods

A total of 81women were in this study and were divided into two groups. Blood samples were collected from 50 patients with breast cancer and 31 normal controls for lipid profiles (T-CHOL, TG, HDL-C and LDL-C). The atherogenic indices (Lipid profile) were estimated spectrophotometrically and the Hormone Sensitive Lipase alleles were determined using polymerase chain reaction and Restriction Fragment length polymorphism methods.

### Results

The results of Total cholesterol, Triglyceride and Low Density Lipoprotein in the breast cancer group were statistically significantly increased as compared with normal controls group ($p<0.05$) whereas no significant difference was seen statistically in the mean values of HDL,BMI,AGE($p>0.05$) when test was compared with control group. In the comparison of the frequency of Hormone Sensitive Lipase gene in both Breast cancer and Non-breast cancer subjects, the result shows a higher frequency of mutant HSL in breast cancer cases compared with controls although the difference between the frequency in cases and control was not statistically significant.

### Conclusion

With the result of this research, it may be concluded that LDL, TG and TC might actually have some role in the etiology of breast cancer. This study confirms the association between lipid profile, and increased breast cancer risk. Therefore, early detection and control of these factors may help in reducing the incidence of breast cancer and coronary heart disease and ultimately its social and economic burden on society.

**Keywords:** Lipid Profile, Hormone Sensitive Lipase, Gene, Variant, Nigeria, Women, Breast Cancer.

## INTRODUCTION

Despite tremendous scientific achievements, cancer remains a major global burden of disease. Globally, cancer is one of the common non-communicable diseases [1]. Breast cancer belongs to the group of cancer that are potentially curable if diagnosed early, unfortunately in Nigeria, most cases presented during the late stage of the disease [2].

With increasing industrialization and westernization of dietary and other socio - behavioral attitudes in most developing countries, it is estimated that the burden of cancer will increase to epidemic proportions in twenty-first century [3]. Deaths from cancer in the world are projected to continue to rise, with an estimated nine million people expected to die from cancer in 2015 and 11.4 million in 2030 [4]. The Cancer epidemiological report in Africa showed 667,000 incident cases and 518,000 deaths in 2008 [5].

Cancer of the breast was the most common cancer in women with an estimated 1.05million new cases in the year 2000; and when both sexes were combined, was second to lung cancer [6] [7]. Breast cancer in African continent was characterized by regional variation as the incidence was 27% of cancers in North African countries (Algeria and Egypt) compared with 15% in sub-Sahara Africa [7]. In the North-Western geopolitical zone of Nigeria, cancer of the breast was second to cancer of the cervix, while at University College Hospital (UCH), Ibadan (situated in the South-Western geopolitical zone of Nigeria) it was the leading malignancy among women [9] [10]. In the North central geopolitical zone, breast cancer constituted 22.41% of new cancer cases registered in 5 years and accounted for 35.41% of all cancers in women [11].

Lipolysis has also been shown to be elevated in multiple human cancers [12]. It is conceivable that cancer cells require reservoirs for lipids, namely lipid droplets (LDs), to store newly synthesized lipids on one hand and provide lipids for hydrolysis on the other hand. As early as the 1970s, LDs were reported in clinical studies of mammary carcinoma [13]. Since then, lipid accumulation has been described in many types of human cancers, including breast, brain, colon, and others [13] [14] [15]. Thus, it is conceivable that an equally remarkable attenuation in cancer progression might be achieved with such a reduction in lipid accumulation. [16].

Emerging evidence suggests the role of lipid in the development of breast cancer; Hormone sensitive lipase represents a key enzyme involved in the metabolism of lipids. Hormone-sensitive lipase (HSL) activity was first identified as an epinephrine-sensitive lipolytic activity in adipose tissue. Its name was coined to reflect the ability of hormones such as catecholamine, ACTH, and glucagon to stimulate the activity of this intracellular neutral lipase [17]. Hormonal activation of HSL occurs via cyclic AMP dependent protein kinase (PKA), which phosphorylates HSL as the enzyme responsible for the release of free fatty acids (FFA) from adipose tissue. Obesity on the other hand is a risk factor for breast cancer and is associated with increased plasma concentrations of free fatty acids (FFAs) [18]. Cholesterol levels, including high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), and triglycerides have been reported to be associated with breast cancer risk [19]. Cholesterol, an important factor in the etiology of coronary heart disease has recently become the focus of attention in the etiology of cancer. A number of epidemiological studies have shown the increased risk of death from cancer with hypocholesterolaemia, although several studies proposed the low levels of cholesterol is a predisposing factor for carcinogenesis [16]. More recently there has been a growing acceptance for a link between obesity and cancer. However, the nature of this relationship remains to be fully elucidated. On one hand, obesity increases the risk of many types of cancer, including esophageal, endometrial, thyroid, colon, renal, liver, and breast. The other aspect is that obesity is also associated with changes in the progression of many cancers. These include higher grade disease in prostate and breast cancer and poorer outcomes in endometrial, kidney, pancreas, esophageal, and thyroid cancers [20]. Of interest is the emerging role of hormone sensitive lipase (HSL) in the development of obesity, decreased HSL expression has been implicated in the development of obesity. Since both obesity and lipid profile are both risk factors in the development breast cancer the study was designed to study the relationship between HSL gene polymorphism and lipid abnormality in obese

and non-obese subject with breast cancer and controls without breast cancer.

## RATIONALE

Worldwide, breast cancer is the most common cancer in women, being one of the leading causes of death among women and men. It is not known whether Hormone sensitive Lipase gene polymorphism is associated with Breast cancer.

This study will further help to further investigate alteration in the lipid profile and hormone sensitive lipases genes among breast cancer patients in Nigeria

## AIM AND OBJECTIVE OF THE STUDY

The aim of this study is to investigate and compare the atherogenic indices and polymorphism of Hormone Sensitive Lipase gene in obese and n individuals with Breast cancer and healthy matched control subjects.

### Research Question

Are there differences in the frequency of occurrence of hormone sensitive lipases gene polymorphism in breast cancer patients compared with apparently healthy subjects?

### Research Hypothesis

Null hypothesis (HO)

1. There is no percentage difference in hormone sensitive lipases gene allele breast cancer subjects when compared with apparently healthy subjects (non –cancerous)
2. There is no difference in the atherogenic indices in individuals with breast cancer and non-breast cancer subjects.

### The Specific Objectives of Study

1. To determine the allelic frequency of occurrence of Hormone sensitive Lipase gene in breast cancer patient compared with apparently healthy subjects
2. To determine the atherogenic indices (Lipid profile) in individuals with breast cancer.

## MATERIAL AND METHODS

**Study design:** A case control study

The study was approved by the Hospital's Ethical Committee (permission grant No. FMC/OWO/380/VOL.XXII/94)

### Duration of research

Three months (June 2015 to September 2015)

## MATERIALS

- Needle and syringe; was used for withdrawing blood from the suitable venipuncture site.
- Tourniquet; was used to increase the distension of veins when a blood sample is being collected.
- Swab; was used to clean the vein puncture site and allow for free flow of blood.
- Lithium heparin bottle; was used to collect the blood withdrawn from the vein puncture site for lipid profile estimation
- Plain specimen container; was used to collect the plasma that was spun for lipid profiles estimation
- Scale; was used to take the subjects weights.
- Tape rule was used to take the subject waist circumference

## STUDY AREA

The study was conducted in Owo, Owo local government. Owo is a town in Ondo State, situated in the Southern-Western Nigeria, latitude 7.19620 and longitude 5.586810 at an elevation/altitude of meters. It is at the southern edge of the Yoruba hills, and at the intersection of roads from Akure, Kabba and Benin City. The people are farmer, traders and Civil service worker. The study protocol was approved by an ethical board committee of the Federal Medical Center Owo, Ondo State, Nigeria.

## SAMPLE SIZE

The sample size was determined by the formula

$N = 4pq/1^2$

Where, N is sample size,

Q is 1-p, and 1 is permissible error (5% of p)

P is the prevalence of breast cancer in Nigeria = 11.2 %= 0.112 [21].

Sample size = $4pq/1^2$

P= 11.2

q =1-p, 1-0.112= 0.888

1 is constant

$N = 4 \times 11.2 \times 0.888 /1^2$

N= 40

## STUDY POPULATION

A total number of 81 individuals participated in this study. Their age bracket was 22-68 years. A written consent form was signed by each participant after full explanation of the procedure of the study. All participants had the right to withdraw at any time during the study without any explanation. They were told that all the data were confidential and were only for research purposes.

## DATA COLLECTION PROCEDURE

Data collection took place in two steps. The first step was to fill out the questionnaire and the second step involved the use of anthropometric measurements for the determination of Body Mass Index (BMI). The questionnaire included socio-demographic data, present, past and family history of any medical condition, data about physical activity and dietary habits. At the end of the session, anthropometric measurements were taken. Height was measured using a meter rule and weight also measured using a weighing scale, both were used to derive BMI. Waist circumference measurements were determined using a tape rule at the narrowest part of the waist. Blood pressure and pulse rate were taken simultaneously using a sphygmomanometer.

## METHODS

### Sample collection

All participants were asked not to eat after 10pm, the evening before the test. The following day, 5mls venous blood sample was collected from each participant for laboratory analysis. Venous blood was collected into Lithium heparin tubes for lipid profile estimation, and also into an EDTA (ethylene diamine tetra acetic acid) tubes (bottles) for genetic analysis.

### Processing of specimen

100ul of blood was collected from the sample in the EDTA tubes for genetic analysis. Plasma was separated from the red cells by centrifuging the blood samples at 1500rpm for 15mins. The plasma was then stored in refrigerator at 2 - 4˚C prior to analysis.

### Sample size

Total sample size of 81 subjects was used and divided into two groups, A and B. Group A include 50 subjects with breast cancer while Group B 31 apparently healthy subjects, age, sex and socio economically matched as a control

**Group A** (50 subjects with Breast cancer)

**Group B** (31 apparently healthy subjects as control).

### Methodology

- DNA EXTRACTION
- POLYMERASE CHAIN REACTION
- LIPID PROFILE.

### Biochemical analysis

Venous blood was drawn for biochemical examination, which included fasting lipid profile. TC, (HDL-C and TG were estimated directly while LDL-C was calculated using Friedewald formula (Callaway et al., 1988). The initial venous blood sample was collected into a Lithium heparin tube (blue cap tube) for serum lipid and EDTA sample bottle for DNA extraction.

## ANTHROPOMETRICS MEASUREMENT

### Weight

Weight of each participant was determined with each of them wearing minimal clothing in kilograms (Kg).

### Height

Height was measured in meter using an appropriate ruler with the participants standing erect, bare-footed and looking straight ahead.

### Waist Circumference (WC)

Was measured in inches with a flexible but non elastic measuring tape. Waist circumference was measured at the level of the natural waist.

### Body mass index (BMI)

Was calculated by dividing the body weight (in kilograms) by the height (in meters squared). Body mass index was calculated as follows:

$$\text{Body mass index} = \frac{\text{Weight (kg)}}{\text{Height}(m)^2} = kg/m^2$$

Participants were grouped as;

Normal weight: BMI is between 18.5 kg/m$^2$ - 24.9 kg/m$^2$

Overweight: BMI is between 25 kg/$m^2$ – 29.9 kg/$m^2$
Obese: BMI is greater than 30 kg/m2

### Method of DNA extraction

The blood samples used for this investigation were collected, identified authenticated and properly mixed and was kept at $4^0$c together with the plasma, which was separated while the extracted DNA was kept at room temperature. All this was done on the very day of sample collection.

## EXTRACTION PROCEDURE

### Procedure for extraction of DNA

- Using an eppendoff tube, three hundred microliter of red cell lysis was added to one hundred microliter of the whole blood cell and mixed thoroughly.
- The set up was left on the bench for thirty minutes and then spun at 5000rpm for five minutes.
- It was shaken to decant the mixture.
- One hundred microliter of cell lysis was added together with one hundred and fifty microliter of protein precipitate. It was left at room temperature for fifteen minutes.
- The mixture was spun 5000rpm for 5minutes.
- The supernatant of the centrifuged mixture was taken into another eppendoff tube containing two hundred and fifty microliter of isopropanol.
- A strand of DNA was seen and centrifuged down to decant the supernatant in order to add 70% of alcohol.

## PREPARATION OF POLYMERASE CHAIN REACTION (PCR) MIX

- 0.5ul of 1.25uM of each of the three primers was added into a 0.2 ml thin walled PCR tube containing 12.5ul of 2x dream Taq green master mix
- The mixture was made up to 24ul with nuclease free water
- 1ul of template DNA was then added to the mixture

The primers used in this amplification process are

- COMMON FORWARD PRIMER- 5' – GAGGGAGGAGGGGCTATGGGT-3'
- COMMON REVERSE PRIMER- 5'-TCCCTGGGCTGGGACTACGG – 3'

- The 0.2 ml thin walled PCR tubes were covered with their respective caps and then placed into the thermal cycler. The lid was firmly fixed on the thermal cycler in order to start the program
- The PCR was conducted under the cycling conditions below.
- $95^0$C - 2min
- $95^0$C - 30sec
- $71^0$C - 30sec
- $72^0$C - 1min
- $72^0$C - 7min
- $4^0$C - forever.

These primers generate a product of 565bp which was cut into fragments of 380 and 185 bp in the presence of the RsaI cutting site (G-60 allele).

## GEL ELECTROPHORESIS

A total of 15 uL of PCR product was loaded in each well, with 100bp ladder occupying the first well. The gel was allowed to run for 30 minutes at 120V from negative to positive electrode. After the period, the gel was placed on the UV trans illuminator and observed for the bands of DNA. The negative control, lane showed no visible bands. The picture of the visible bands on the gel was finally taken and compared with respect to the ladder.

## PROCESSING OF SPECIMEN

Samples were collected into lithium heparin bottle and centrifuged then plasma was separated from red cell and frozen until the time for analysis.

### Estimation of triglycerides

Estimation of triglycerides was carried out using enzymatic method.

### Principle

The triglycerides are determined after enzymatic hydrolysis with lipases. The indicator is a quinoneimine formed from hydrogen-peroxide, 4-aminophenazone and 40chlorophenol under the catalytic influence of peroxidase.

$$\text{Triglycerides} + H_2O \xrightarrow{\text{lipase}} \text{glycerol} + \text{fatty acids}$$

$$\text{Glycerol} + ATP \xrightarrow{\text{Glycerol Kinase}} \text{glycerol-3-phosphate} + ADP$$

$$\text{Glycerol-3-phosphate} + O_2 \xrightarrow{\text{Peroxidase}} \text{Dihydroxyacetone} + \text{phosphate} + H_2O_2$$

$$2H_2O_2 + \text{4-aminophenazone} + 4\ \text{chlorophenol} \xrightarrow{\text{dismutase}} \text{quinoneimine} + HCl + 4H_2O$$

## Estimation of total cholesterol

Total cholesterol estimation is done using the enzymatic Endpoint method.

## Principle

The cholesterol is determined after hydrolysis and oxidation. The indicator quinoneiminine is formed from hydrogen peroxide and 4-aminoantipyrine in the presence of phenol and peroxidase.

$$\text{Cholesterol ester} + H_2O \xrightarrow{\text{cholesterol esterase}} \text{cholesterol} + \text{fatty acids}$$

$$\text{Cholesterol} + O_2 \xrightarrow{\text{cholesterol oxidase}} \text{cholestene-3-one} + H_2O2$$

$$2H_2O_2 + \text{phenol} + \text{4-Aminoantipyrine} \xrightarrow{\text{peroxidase}} \text{quinoneimine} + 4H_2O_2$$

## Estimation of HDL and LDL

Estimation of serum HDL and LDL is carried out using CHOD-PAP method.

## Principle

Low density lipoproteins (LDL and VLDL) and chylomicron fraction are precipitated quantitatively by the addition of phosphotungstic acid in the presence of magnesium ions. After centrifugation, the cholesterol concentration in the HDL fraction, which remains in the supernatant, is determined.

## RESULT AND STATISTICAL ANALYSIS

The tables below shows the mean and standard deviation Obtained from the lipoprotein (Total cholesterol, LDL, HDL and Triglyceride) including anthropometric parameters such as Age, Body mass index (BMI) and Charts of both Test (Breast cancer subjects) and Control groups (non-breast cancer subjects). When the mean values of Total Cholesterol for Test was compared with that of control group it was obvious that the TC value for test (5.49±1.04) deviated from that of the healthy state (4.59±0.93) the mean value is statistically significant ($p<0.05$).Also, there was a significantly Higher mean plasma Triglyceride and Low density lipoprotein in the Test group compared with that of the control group ($p<0.05$).

**Table 1:** Comparing mean concentration of TC, TRIG, HDL, LDL, AGE and BMI of breast cancer subjects (Test) and control group

| PARAMETERS | BC MEAN±SD | CONTROL MEAN±SD | P-VALUE |
|---|---|---|---|
| **TC (MMOL/L)** | 5.49±1.04 | 4.59±0.93 | <0.05 |
| **TRIG (MMOL/L)** | 1.77±0.42 | 1.55±0.29 | <0.05 |
| **HDL (MMOL/L)** | 1.81±0.53 | 1.63±0.52 | >0.05 |
| **LDL (MMOL/L)** | 2.89±0.96 | 2.22±0.94 | <0.05 |
| **AGE (YRS)** | 47.3±9.9 | 42.9±10.69 | >0.05 |
| **BMI** | 30.84±4.68 | 28.97±3.81 | >0.05 |

The table 1 above shows a statistical significance difference in the mean values of TC, TRIG and LDL when test was compared with control group. No significance difference was seen statistically in the mean values of HDL AGE and BMI when test was compared with control group.

**Table 4:** Comparing the Mean concentrations of Lipid Profile Parameters in mutant and wild type Hormone Sensitive Lipase gene.

| BC SUBJECTS | TC | TG | HDL | LDL | BMI | AGE |
|---|---|---|---|---|---|---|
| **MUTANT** | 6.36±0.99 | 2.07±0.25 | 1.48±0.49 | 3.85±1.08 | 34.5±3.27 | 44.33±14.57 |
| **WILD TYPE** | 5.42±2.02 | 1.62±0.69 | 1.83±0.77 | 2.81±1.23 | 30.46±17.99 | 47.25±90.43 |
| **P-value** | P<0.05 | P<0.05 | P<0.05 | P<0.05 | P> 0.05 | P>0.05 |
| **CONTROL** | | | | | | |
| **MUTANTS** | 4.21±0.68 | 1.22±0.06 | 1.45±0.26 | 2.22±0.39 | 27±0.71 | 38.5±1.41 |
| **WILD TYPE** | 4.61±0.95 | 1.57±0.29 | 1.69±0.53 | 2.12±0.97 | 29.07±11.01 | 43.24±3.83 |
| | P>0.05 | P>0.05 | P>0.05 | P>0.05 | P>0.05 | P<0.05 |

Table 2 depicts the mean ± SD of biochemical parameters of breast cancer subject and controls. The mean of each parameter was compared using Analysis of variance, result shows a statistically significant difference in Total cholesterol, triglycerides and LDL-cholesterol when cases were compared with controls.

**Table 3:** Table 4.3 compares the frequency of mutant Hormone Sensitive Lipase gene in test and control group.

| | **Test** | **Control** |
|---|---|---|
| **Mutants N (%)** | 6 (85.7%) | 1(`14.3%) |
| **Wild type N (%)** | 44 (59.5%) | 30(40.5%) |

The chi-square statistic is 1.866. The *p*-value is .171939. The result is *not* significant at $p < 0.05$.

The chart below shows the frequency of Hormone Sensitive Lipase gene in both Breast cancer and Non-breast cancer subjects. The result show a higher frequency of mutant HSL in breast cancer cases compared with controls although the difference between the frequency in cases and control was not statistically significant.

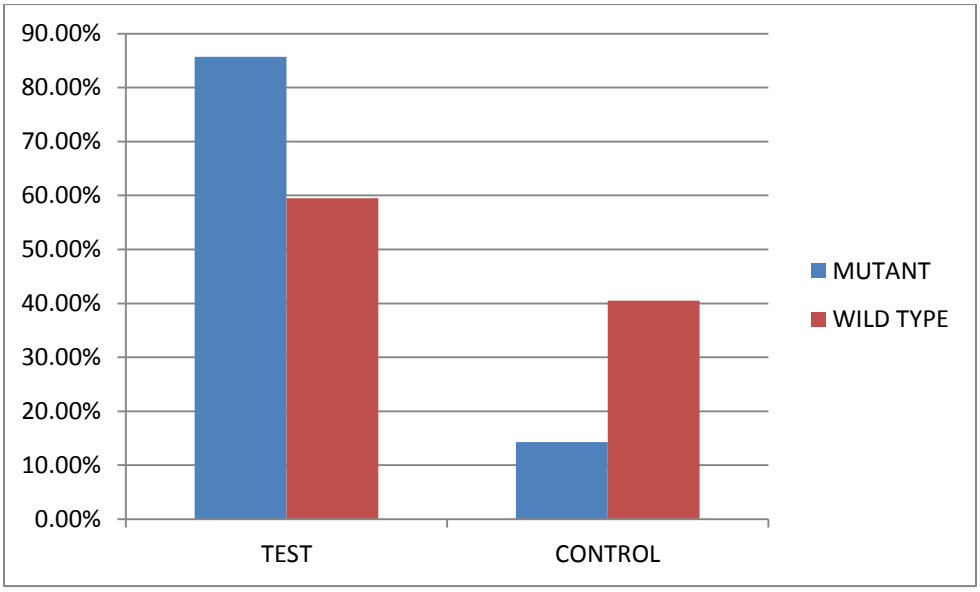
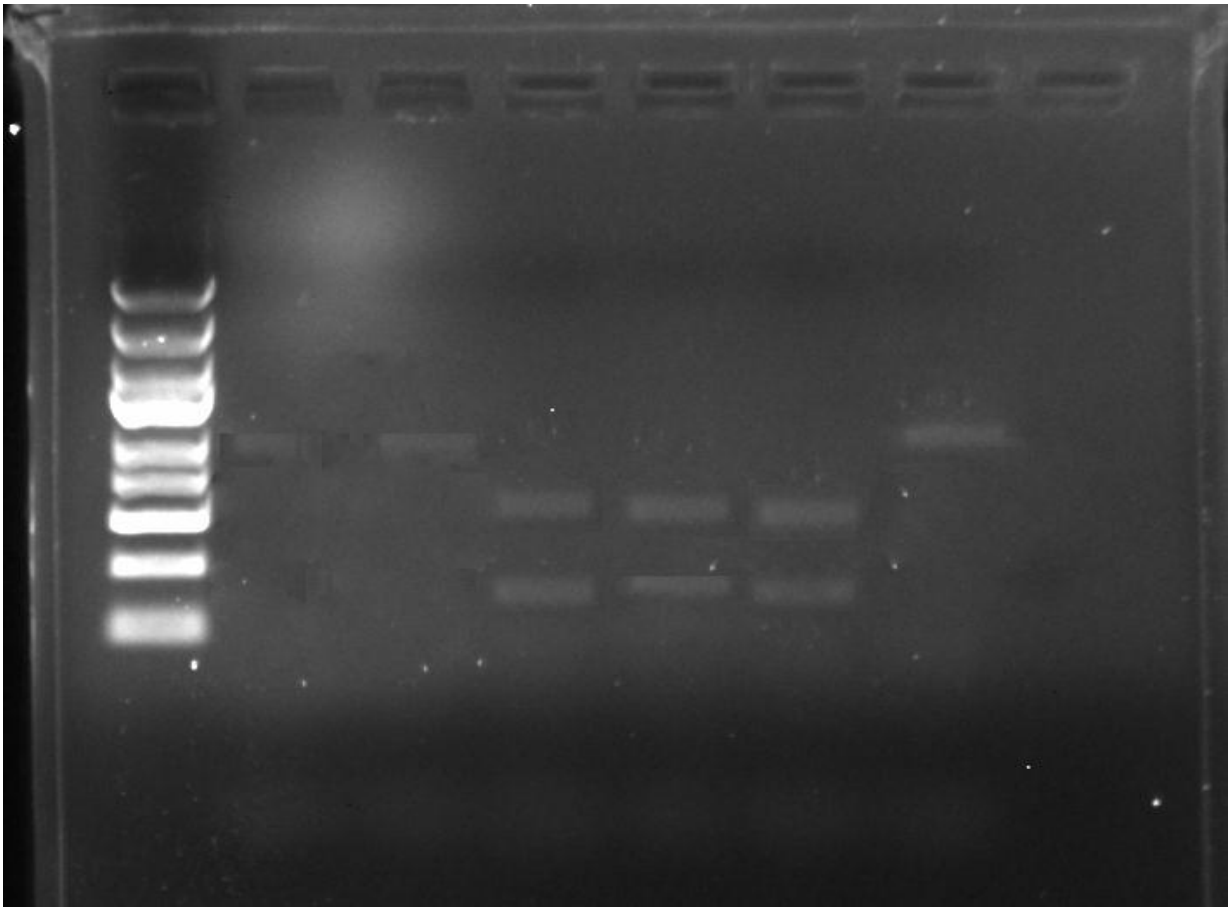



**Figure 1**

DNA bands of Hormone Sensitive Lipase gene polymorphism in Polymerase chain reaction amplification



## DISCUSSION

The research was specifically designed to ascertain if Hormone Sensitive Lipase (HSL) gene polymorphism with reference to artherogenic indices could be a risk factor in developing breast cancer.

However, from the result obtained, it was evident that the HSL gene polymorphism was not necessarily a risk factor in the breast cancer subjects when the percentage of the different allele in both test and control group were compared. On the other hand, there was significant overall elevated mean plasma Total cholesterol in breast cancer subjects compared with controls as reported by [22]. Our result is in agreement with the previous study reported by Patel *et al*. [23] who also observed increased triglycerides in breast cancer patients. Significant increase in triglycerides is also in accordance with Owiredu *et al*. [24].

No significant difference was observed in HDL-cholesterol levels between the breast cancer patients and controls in this study as reported by Moorman *et al*. [25]. However, LDL -cholesterol levels increased significantly in breast cancer subjects than in the controls. The elevated LDL-cholesterol, which is more susceptible to oxidation, may result in high lipid peroxidation in breast cancer patients. This may be the cause of oxidative stress leading to cellular and molecular damage thereby resulting in cell proliferation and malignant conversions [26].

Body Mass Index was significantly higher in breast cancer subject versus control even though it's not significant statistically. Excess body weight has been linked to an increased risk of postmenopausal breast cancer, and growing evidence also suggests that obesity is associated with poor prognosis in women diagnosed with early-stage breast cancer [27].

Although more data are needed to determine the biological mechanisms for the effect of plasma cholesterol and the HDL and LDL lipoproteins on breast cancer, several reasons as to why there may be an inverse association have been proposed. A biologically plausible explanation for the association between cholesterol and breast cancer is through the production of cholesterol epoxides,

which are present in breast nipple fluid aspirates. This is important because cholesterol epoxides are mutagenic and when exposure to epithelial cells occurs, this may promote breast carcinogenesis. Additionally, there are several other biomarkers that have been shown to associate with cholesterol levels, including sex hormones, which influence the levels of circulating HDL through the regulation of hepatic lipase activity. Levels of HDL are also significantly associated with levels of free, biologically active estradiol, which have long been an established risk factor for breast cancer [19].

## CONCLUSION

Although Hormone Sensitive Lipase gene polymorphism was not associated with breast cancer, Low density lipoproteins, Triglycerides and Total cholesterol were associated with breast cancer. With the result of this research, it may be concluded that LDL, TG and TC may actually have some role in aetiology of breast cancer. Therefore, early detection and control of these factors may help in reducing the incidence of breast cancer and coronary heart disease and ultimately its social and economic burden on society.

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