

**EVALUATION OF THE RELATIONSHIP BETWEEN THE  
INCIDENCE OF BREAST CANCER AND SOME  
ANTHROPOMETRIC VARIABLES IN WOMEN IN ZARIA,  
NIGERIA**

**BY**

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**DECEMBER, 2014.**

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CANCER AND SOME ANTHROPOMETRIC VARIABLES IN WOMEN IN ZARIA,  
NIGERIA

BY

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(M.Sc/MED/4721/2010/2011)

A RESEARCH THESIS SUBMITTED TO THE SCHOOL OF POSTGRADUATE  
STUDIES, AHMADU BELLO UNIVERISTY, ZARIA.  
IN PARTIAL FULFILLMENT FOR THE AWARD OF MASTER OF SCIENCE IN  
HUMAN ANATOMY

DEPARTMENT OF HUMAN ANATOMY,  
FACULTY OF MEDICINE,  
AHMADU BELLO UNIVERSITY,  
ZARIA, NIGERIA.

DECEMBER, 2014.

## DECLARATION

I hereby declare that the research work reported in this thesis entitled “**Evaluation Of The Relationship Between The Incidence Of Breast Cancer And some Anthropometric Variables In Women In Zaria, Nigeria**” was carried by me in the Department of Human Anatomy, Faculty of Medicine, A.B.U, Zaria, under the supervision of Dr. S.S. Adebisi, Dr. S.B. Danborno and Dr. D.A. Dawotola. The information derived from the literature has been duly acknowledged in the text and a list of references provided. No part of this work has been presented for another degree in any institution.

.....  
Hadiza Alhassan Rilwan

.....  
Date

## CERTIFICATION

This thesis entitled “**Evaluation Of The Relationship Between The Incidence Of Breast Cancer And some Anthropometric Variables In Women In Zaria, Nigeria**” by Hadiza Alhassan Rilwan meet the regulation governing the award of Master of Science (M.Sc.) degree in Department of Human Anatomy, Faculty of Medicine, Ahmadu Bello University, Zaria, under the supervision of Dr. S.S. Adebisi, Dr. S.B. Danborno and Dr. D.A. Dawotola. It is therefore approved for its contribution to knowledge and literary presentation.

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## **DEDICATION**

This thesis work is dedicated to Almighty Allah for giving me the grace to complete the academic programme successfully. And to my late Father Alhaji Rilwan Alhassan may his soul rest in peace.

## **ACKNOWLEDGEMENTS**

I am most grateful to Allah who has kept me all through my stay in A.B.U, Zaria. I return all praises to him for his faithfulness, mercy and grace all through my academic career. I wish to express my profound gratitude to my Supervisors, Dr S.S. Adebisi (the Head of Department), Dr S.B. Danborno and Dr D.A. Dawotola whose supervision, guidance and suggestions contributed to the success of this thesis.

I wish to acknowledge the encouragements and contributions of Mr Timbuak, Dr Alawa, Dr Dahiru, Dr Umana, Dr Austine and all the lecturers in the Department of Human Anatomy, Faculty of Medicine, ABU, Zaria and the following Post Graduate Students Progress Victor, Rukayat Salaudeen, Ganiyu Mujidat, Abubakar Sadiq, Abel Agbon, Jibrin Danladi, M.M. Kona, and Sani Sabdat for the encouragement and support they gave me throughout the course and completion of this work.

My sincere regards to my beloved husband Eng. Bello and my little angels Maryam and Ahmad may Almighty Allah bless you all.

My sincere regards to my Mother Hajiya Lauratu for her prayers all through, my big brothers Yaya Abdullahi, Yaya Ibrahim, Yaya isyaku and Yaya Musa for their encouragement which made this work a reality. And to my lovely sisters, Yaya Habiba, Yaya Fa'iza, Yaya Murja and Anty Beebeee (Bilkisu) for giving me moral support.

I wish to thank all the participants that allowed me to take their anthropometric parameters and my research assistants: Progress Victor and Rukayyah Salaudeen.

## TABLE OF CONTENT

Contents	Pages
Cover page - - - - -	i
Title Page - - - - -	ii
Fly Page - - - - -	iii
Decalration - - - - -	iv
Certification - - - - -	v
Dedicationon - - - - -	vi
Acknowledgements - - - - -	vii
Table of contents - - - - -	viii
List of Tables - - - - -	xi
List of figures- - - - -	xii
Abstract - - - - -	xiii

### CHAPTER ONE

1.0 Introduction - - - - -	1
1.1 Background - - - - -	1
1.2 Justification of the research - - - - -	7
1.3 Statement of research problem - - - - -	7
1.4 Hypothesis - - - - -	7
1.5 Significance of the study- - - - -	8
1.6 Aim - - - - -	8
1.7 Objectives- - - - -	8

### CHAPTER TWO

2.0 Literature review - - - - -	10
2.1 The breast - - - - -	10

2.1.1 Anatomy-	-	-	-	-	-	-	-	-	10
2.1.2 The embryology of the breast	-	-	-	-	-	-	-	-	11
2.1.3 Structure of the breast	-	-	-	-	-	-	-	-	13
2.1.4 Blood and Nerve Supply	-	-	-	-	-	-	-	-	14
2.1.5 Applied anatomy	-	-	-	-	-	-	-	-	16
<b>2.2 Body mass index and breast cancer</b>	-	-	-	-	-	-	-	-	<b>19</b>
<b>2.3 Waist hip ratio and breast cancer</b>	-	-	-	-	-	-	-	-	<b>21</b>
<b>2.4 Age of menarche and breast cancer</b>	-	-	-	-	-	-	-	-	<b>23</b>
<b>2.5 Parity and breast cancer</b>	-	-	-	-	-	-	-	-	<b>25</b>
<b>2.6 Order of birth and breast cancer</b>	-	-	-	-	-	-	-	-	<b>26</b>
<b>2.7 Ethnic background and Breast cancer</b>	-	-	-	-	-	-	-	-	<b>28</b>
<b>2.8 Educational level and breast cancer incidence-</b>	-	-	-	-	-	-	-	-	<b>31</b>
<b>2.9 Family history of breast cancer and breast cancer incidence-</b>	-	-	-	-	-	-	-	-	<b>32</b>

### CHAPTER THREE

<b>3.0 Materials and method</b>	-	-	-	-	-	-	-	-	<b>34</b>
<b>3.1 Study location</b>	-	-	-	-	-	-	-	-	<b>34</b>
<b>3.2 Sample size determination</b>	-	-	-	-	-	-	-	-	<b>34</b>
<b>3.3 Study Design</b>	-	-	-	-	-	-	-	-	<b>35</b>
3.3.1 Inclusion criteria for breast cancer subjects	-	-	-	-	-	-	-	-	37
3.3.2 Exclusion criteria for breast cancer subject	-	-	-	-	-	-	-	-	37
3.3.3 Inclusion criteria for control subject	-	-	-	-	-	-	-	-	37
3.3.4 Exclusion criteria for control subject	-	-	-	-	-	-	-	-	37
3.3.5 Problems encountered/ Limitations	-	-	-	-	-	-	-	-	37
<b>3.4 Ethical Considerations</b>	-	-	-	-	-	-	-	-	<b>37</b>
<b>3.5 Statistical analysis</b>	-	-	-	-	-	-	-	-	<b>37</b>

## CHAPTER FOUR

<b>4.0 Results</b>	-	-	-	-	-	-	-	-	<b>39</b>
<b>4.1 Descriptive statistics</b>	-	-	-	-	-	-	-	-	<b>39</b>
<b>4.2 Anthropometric variables according to ethnicity in breast cancer</b>									
<b>cases and control</b>	-	-	-	-	-	-	-	-	<b>43</b>
<b>4.3 Anthropometric variables according to age in breast cancer</b>									
<b>cases and control</b>	-	-	-	-	-	-	-	-	<b>43</b>
<b>4.4 Correlation between anthropometric variable in breast cancer</b>									
<b>cases and control</b>	-	-	-	-	-	-	-	-	<b>43</b>
<b>4.5 Association between parity and incidence of breast cancer</b>	-	-							<b>49</b>
<b>4.6 Association between Parity and incidence of breast cancer-</b>	-	-							<b>49</b>
<b>4.7 Association between order of birth and incidence of breast cancer</b>	-								<b>49</b>
<b>4.8 Association between age at menarche and incidence of breast cancer</b>									<b>54</b>
<b>4.9 Association between educational level and breast cancer incidence</b>	-								<b>54</b>
<b>4.10 Association between family history of breast cancer and breast</b>									
<b>cancer incidence</b>	-	-	-	-	-	-	-	-	<b>54</b>
<b>4.11 Association between ethnicity and incidence of breast cancer</b>	-								<b>57</b>

## CHAPTER FIVE

<b>5.0 Discussion</b>	-	-	-	-	-	-	-	-	<b>59</b>
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## CHAPTER SIX

<b>6.0 Summary and Conclusion</b>	-	-	-	-	-	-	-	-	<b>63</b>
<b>6.1 Conclusion</b>	-	-	-	-	-	-	-	-	<b>63</b>
<b>6.2 Recommendations</b>	-	-	-	-	-	-	-	-	<b>64</b>
<b>References</b>	-	-	-	-	-	-	-	-	<b>65</b>

## LIST OF TABLES

Table 4.1: Overall descriptive statistics (n = 718)	-	-	-	-	40
Table 4.2: Comparison Anthropometric variables of breast cancer cases group and control group	-	-	-	-	41
Table 4.3: Student T- Test and CI of Anthropometric Variables for Breast Cancer Cases Group and Control Group	-	-	-	-	42
Table 4.4: Anthropometric variables according to ethnicity in breast cancer cases group and control group	-	-	-	-	45
Table 4.5: Anthropometric variables according to age in breast cancer cases and control	-	-	-	-	46
Table 4.6a: Correlation matrix of anthropometric variables in breast cancer cases					47
Table 4.6b: Correlation matrix of anthropometric variables in control group					48

## LIST OF FIGURES

<b>Figure 4.1</b> Association between breast cancer demographics and BMI	-	50
<b>Figure 4.2:</b> Association parity and incidence of breast cancer	- - -	51
<b>Figure 4.3:</b> Association between order of birth and incidence of breast cancer		52
<b>Figure 4.4:</b> Association Age at menarche and incidence of breast cancer	-	53
<b>Figure 4.5:</b> Association Educational level and incidence of breast cancer	-	55
<b>Figure 4.6:</b> Association between Family history of breast cancer and incidence of breast cancer	- - - - - - -	56
<b>Figure 4.7:</b> Association between ethnicity and incidence of breast cancer	-	58

## ABSTRACT

Breast cancer is one of the most common types of malignant diseases, affecting millions of women around the world, with a high fatality rate (Ghafoor *et al.*, 2001). The prevalence rate of breast cancer, particularly in Nigerian females, has shown a spike in recent years and accounts for 20% to 25% of malignant tumors in women with an annual incidence of about 800 to 1000 cases (Adebamowo and Ajayi, 2000). The “Evaluation of the Relationship between the Incidence of breast cancer and some anthropometric variables in women in Zaria, Nigeria” was undertaken using 718 subjects: 352 breast cancer patients attending clinic in the department of radiotherapy and oncology Ahmadu Bello University Teaching Hospital Zaria. And 366 randomly selected control females from among student and staff of Ahmadu Bello University Zaria from different ethnic background, aged 17 to 75 years. A structural questionnaire was used to collect detailed information from participants regarding age, menarcheal age, parity, order of birth of participants, educational level, and ethnic background. The following anthropometric variables were measured: Weight (Kg), height (cm), Body mass index ( $\text{kg}/\text{m}^2$ ), waist circumference (cm), hip circumference (cm) and Waist hip ratio (cm). The result showed that majority of the study participants are overweight (mean Body mass index  $26.842 \pm 21.392$ ). It was also observed that mean age, weight, Body mass index and Waist hip ratio were higher in the breast cancer group compared to the control group. The breast cancer frequency was seen to be more in multiparous women compared to those with one child and no child. In the association with order of birth breast cancer incidence was higher in first born women when compared to women born of other ranks. Breast cancer incidence was higher in women with early age at menarche compared to women with late menarche. Also women with higher educational level showed higher incidence of breast cancer. Family history of breast cancer had no protective effect on breast cancer incidence

because women with no family history of breast cancer had higher breast cancer incidence compared to women with family history of breast cancer. The incidence of breast cancer was higher among the Hausa and the ethnic group classified as others compared to the Igbo and the Yoruba groups. All the anthropometric variables studied in this work were statistically significant ( $p \leq 0.001$ ) except for the age at menarche ( $p = 0.413$ ) and height ( $p = 0.724$ ). From the present study neither family history of breast cancer nor parity but rather body mass index and waist hip ratio affects breast cancer incidence independently from the anthropometric variables, as found in many other populations (Friedenreich, 2001).

# CHAPTER ONE

## INTRODUCTION

### 1.1 BACKGROUND

Breast cancer is one of the most common types of malignant diseases, affecting millions of women around the world, with a high rate of morbidity and mortality. The prevalence rate of breast cancer, particularly in Nigerian females, has shown a spike in recent years and accounts for 20% to 25% of malignant tumours in women with an annual incidence of about 800 to 1000 cases (Adebamowo and Ajayi, 2000). The availability of such documented records serves as useful tools for further studies, research and other applications (Adebisi, 2008).

Generally, African breast cancer patients tend to present at a younger age, with large tumour and multiple nodal involvements, and have poorer clinical and pathological prognostic factors compared with Caucasian patients (Amin *et al.*, 1993). These characteristics are somewhat similar to that of African-Americans but are in contrast with those of non-Hispanic Whites in the USA, thus heightening the interest in the role of genetic factors in the aetiology of breast cancer in general, and in people of African origin in particular (Ajayi 2001; Ganiyu and Ganiyu, 2012).

One of the often cited reasons for the difference in breast cancer incidence in Africa compared with Western countries is the difference in environmental risk factors such as diet and physical activity both contributing to obesity, use of hormones, other medications, obstetric and gynaecological practices (Friedenreich, 2001, Timothy *et al.*, 2003). The body mass index has emerged as an important parameter of association

between central adiposity and many obesity-related diseases. Recent data from the National Cancer Institute's Surveillance, Epidemiology, and End Results program indicate that the age-adjusted breast cancer incidence rates for women of ethnic minority groups are substantially lower than those for white women, with 141 cases per 100 000 in white women, 122 in African-Americans, 97 in Asian/Pacific Islanders, 90 in Hispanics, and 58 in American Indians/Alaskan Native (Jamal *et al.*, 2003; Ghafoor *et al.*, 2003). In addition, African- American women are likely to be diagnosed at a more advanced stage (Ghafoor *et al.*, 2003) and to have larger tumours that are more commonly estrogen receptor negative than their white counterpart (Joslyn, 2002; Li Ci *et al.*, 2003) and high grade (Li Ci *et al.*, 2003; Middleton *et al.*, 2003) than those in white women. African-American women also have higher breast cancer mortality than white women (Newman and Manson 2002) though all these differences remain largely unexplained (Weirhk *et al.*, 2003).

The impact of breast cancer risk factors on the differences in incidence and clinical characteristics associated with ethnicity or race has received limited attention (Vastag 1998; Rowan *et al.*, 2005). Consequently, the relationships were explored in a cohort of patients from the ethnically diverse Women's Health Initiative (WHI) study (JAMA, 2002). The primary aim was to examine whether known and or presumptive breast cancer risk factors would explain the difference in breast cancer incidence between white women and women of minority groups. Recent epidemiologic studies have examined the possibility as a result of early life exposures to hormone that increase cancer risk in adult (Nichols *et al.*, 2008). Trichopoulos (1990) postulated that a highly estrogenic intrauterine environment would create a 'fertile soil' for carcinogenesis in breast tissue and lead to higher risk for breast cancer later in life. Because retrospective prenatal hormone measurements cannot be obtained for large numbers of people, Trichopoulos and others

(1990), proposed that birth and maternal characteristics be investigated as surrogates for a highly estrogenic intrauterine environment. These birth characteristics include high birth weight, maternal age 20–24 years at birth, and low birth rank. Much work in the past decade has been done on birth weight in particular, and there seems to be a modest positive association between high birth weight and breast cancer that is stronger in younger women, which is consistent with the estrogen hypothesis (Hall and Newman, 2000). Up to 10% of breast cancer in Western countries is due to genetic predisposition (Elizabeth *et al.*, 2004).

Positive correlations have been seen with coronary heart disease, adult-onset diabetes mellitus and stroke (Swerdlow, 2002). However, the result with breast cancer has been inconsistent (Stoll, 2002). Abdominal obesity may be related to breast cancer through aberrant insulin signaling leading to increased endogenous androgen and oestrogen levels (Rose and Royak, 2001). If modifiable risk factors were corrected, the situation would probably improve. High body weight measured in terms of body mass index, (BMI) has been recognized as an important risk factor for breast cancer among postmenopausal women in many previous epidemiological studies in Western countries (Cold and Hansen, 1998). After menopause, epidemiological evidence found a substantial positive association between BMI and breast cancer risk (Lahmann *et al.*, 2004). One of the most plausible and classical biological explanations is a female hormone-related mechanism because adipose tissue may be a major source of oestrogens (Siiteri, 1987), which are critical mitogens for mammary epithelial cells (Pike *et al.*, 1993; Anderson and Clarke, 2004). Previous studies have provided explanations for an increased risk of breast cancer in relation to excess post-menopausal body weight, as follows: increased levels of estrogen production due to aromatization of androgens in peripheral fat tissue (Siiteri, 1987; Key *et al.*, 2003) and decreased production of sex hormone binding globulin due to

obesity (Enriori *et al.*, 1986). These hormone-related mechanisms could increase the supply of free bioavailable estrogen to breast tissues. In fact, the observed increased risk of breast cancer with increasing post-menopausal BMI was apparently attenuated after adjustment for bioavailable serum estrogen concentration (Key *et al.*, 2003; Beral *et al.*, 1997). A meta-analysis showed that the substantial positive association between post-menopausal BMI and breast cancer risk was confined to oestrogen receptor positive (ER+) and progesterone positive (PR+) tumours (Suzuki *et al.*, 2009). Furthermore, it is well known that the observed positive association between post-menopausal BMI and increased risk of breast cancer was attenuated among ever-users of post-menopausal exogenous hormones (Suzuki *et al.*, 2009). These results strongly support the estrogen-related hypothesis that the substantially increased risk of breast cancer with an increase in post-menopausal BMI is mainly as a result of the associated increase in bioavailable oestrogens. A mid-life increase in body mass index may substantially increase postmenopausal breast cancer risk, according to research by investigators from NCI and Columbia University's Mailman School of Public Health (Suzuki *et al.*, 2009). In a recent analysis, women who reported a gain in BMI of five points ( $5 \text{ kg/m}^2$ ) or more between age 20 and postmenopausal age (ages 55-74) had nearly twice the risk of developing postmenopausal breast cancer compared to women who maintained their BMI during the same time period (Ben Ahmed *et al.*, 2002). In the early-adult stage (i.e., pre-menopausal) an inverse association between BMI and breast cancer risk is noted particularly in western population (Lahmann *et al.*, 2004) and Japanese women (Kawai *et al.*, 2010; Suzuki *et al.*, 2011). The observed inverse (i.e., protective) association could be attributed to obese-related preventive mechanisms, such as frequent anovulatory cycles (Key and Pike, 1988) and faster clearance rate of oestrogens in the liver (Siiteri *et al.*, 1982) due to pre-menopausal obesity. These obese-related preventive mechanisms, however, cannot

explain the epidemiological results findings reported by Key and Pike, (1988) which revealed a lower prevalence of obesity among the Asian population compared to Western populations (Murakami *et al.*, 2009). For example, in the Japanese population, a substantial inverse association between level of BMI at age 20 and breast cancer risk has been reported in two prospective cohort studies (Kawai *et al.*, 2010; Suzuki *et al.*, 2011). This may suggest the presence of other favorable biological mechanisms (not obesity-related, but body mass-related) in the early adult life.

After puberty, secondary sexual development generally causes the ovaries to grow. A subsequent increase in the secretion of oestrogens and progesterone, leads to the normal development of the mammary gland. Oestrogens generally act in the development of the breast duct. Progesterone, in addition to estrogen, may also play an important role in the development of mammary gland lobes. Animal studies had shown (Sakakura *et al.*, 1979) that fat tissue within the breast mass may play a critical role in the normal development of mammary gland lobes during the early adult life, and this process may occur synergistically with oestrogen and progesterone (Sakakura *et al.*, 1979, Shyamala, 1999). For young adult women, insubstantial levels of fat tissue and low levels of oestrogen and progesterone within the breast bud may provide an obstacle to the maturity of mammary glands during the early adult life.

In early adult life, a low BMI may indicate a lack of mammary fat pad or deficiency of progesterone, which may promote an accumulation of excessive body fat (Kalkhoff, 1982). For a normal differentiation of the mammary gland, sufficient levels of mammary fat pads, progesterone, or both, may be required during early adulthood (Sakakura *et al.*, 1979; Russo *et al.*, 2001).

Furthermore animal studies have shown that mammary fat pad plays a number of vital roles in normal growth, differentiation in mammary gland morphogenesis and epithelial–mesenchymal interaction. It has been suggested that body fat might play an important role in differentiation of a normal mammary development. Recently, Prat and Perou (2009) have proposed that a distinct link exists between the human mammary epithelial differentiation hierarchy and tumour subtype. They suggested that within the human breast, the process of mammary epithelial differentiation hierarchy might start with an undifferentiated oestrogen receptor negative (-) mammary stem cells that differentiate into progenitors. Through the process of differentiation, which form mature cells that are derived from differentiated luminal epithelial cells.

Similar studies had also reported a significant association between leanness at age 20 and an increased risk of breast cancer with oestrogen receptor negative (-) progesterone receptor negative (-) tumours (Visvader and Lindeman 2006). This result could be explained by immature differentiation due to lack of body fat. A low BMI resulted in a lack of breast fat and a low level of ovarian hormones in the early adult life, which lead to the hypothesis that a low BMI is associated with an increased risk of breast cancer.

The increased risk in overweight postmenopausal women is chiefly due to higher levels of free oestrogen produced by excess aromatase activity in peripheral adipose tissue (Peacock *et al.*, 1999). Conversely, the protective mechanism among premenopausal women is not well understood.

## **1.2 STATEMENT OF THE RESEACH PROBLEM**

The prevalence of breast cancer in Nigerian women has shown a spike in recent years and accounts for 20% to 25% of malignant tumours in women with an annual incidence of 800 to 1000 cases and the body mass index has emerged as an important parameter of association between central adiposity and many obesity-related diseases. It is therefore necessary to investigate the relationship between different anthropometric variables and incidence of breast cancer in Nigerian women, where it seems that many women have a relatively high body mass index.

## **1.3 JUSTIFICATION OF THE RESEARCH**

There is an increasing incidence of breast cancer among Nigerian women, it is therefore necessary to establish a relationship between BMI and incidence of breast cancer in Nigerian women. There is also need to establish a relationship between waist – hip ratio, parity, order of birth and breast cancer incidence in Nigerian women.

## **1.4 HYPOTHESES**

The following hypothesis will be considered

- i. There will be association between BMI and breast cancer incidence in Nigerian women.
- ii. High waist – hip ratio will be associated with breast cancer incidence in Nigerian women.
- iii. There will be association between parity and incidence of breast cancer in Nigerian women.
- iv. Order of birth will be associated with breast cancer incidence in Nigerian women.

- v. Menarcheal age will be associated with breast cancer in Nigerian women.
- vi. Ethnic background and educational level will be associated with breast cancer risk in Nigerian women.

## **1.5 SIGNIFICANCE OF THE STUDY**

This study will establish a reference data for the association between different anthropometric variables and breast cancer incidence in Nigerian women. This study will also create awareness to the general public on the importance of weight control and general lifestyle which can be an effective measure of breast cancer prevention in women at risk.

## **1.6 AIM**

This study seeks to investigate the relationship between anthropometric variables such as body weight, height, waist circumference, hip circumference , parity, order of birth and incidence of breast cancer in Nigerian women in Zaria Nigeria.

## **1.7 OBJECTIVES**

The objectives of the study are to investigate:

- i. The relationship between body mass index and breast cancer incidence in Nigerian women.
- ii. The relationship between waist – hip ratio and breast cancer incidence in Nigerian women
- iii. The relationship between parity and breast cancer incidence in Nigerian women

- iv. The relationship between order of birth and breast cancer incidence in Nigerian women
- v. The relationship between age and breast cancer incidence in Nigerian women
- vi. Possible association of age at menarche and breast cancer incidence in Nigerian women.
- vii. Relationship between ethnicity and breast cancer incidence in Nigerian women
- viii. The association between educational level and the incidence of breast cancer in Nigerian women.

## **CHAPTER TWO**

### **LITERATURE REVIEW**

#### **2.1 THE BREAST**

The breast (mammary gland) is the most important structure in the pectoral region. It is rudimentary in men and becomes fully developed in the females after puberty. It is a modified sweat gland which forms an important accessory organ of the female reproductive system providing nutrition to the new born in the form of milk (Moore and Dalley, 1999).

##### **2.1.1 Anatomy**

**Situation:** It lies in the superficial fascia of the pectoral region. The axillary tail of Spence pierces the deep fascia and lies in the axilla. This may enlarge during lactation in some women and may be mistaken for lump or enlarged lymph nodes (Gray's Anatomy, 2004).

**Extent:** Vertically, it extends from the second or third to the sixth rib. Horizontally, it extends from the lateral border of the sternum to the mid-axillary line (Gray's Anatomy, 2004).

**Deep relations:** The breast lies on the pectoral fascia covering the pectoralis major. Still deeper are the parts of three muscles, namely the pectoralis major, the serratus anterior, and the external oblique muscle of the abdomen. The breast is separated from the pectoral fascia by the loose areolar tissue sometimes called the retromammary space or bursa. Because of the presence of this loose areolar tissue the normal breast can be moved over the pectoralis major (Gray's Anatomy, 2004).

### **2.1.2 The Embryology of the Breast**

Embryologic development of the mammary gland consists of a series of highly ordered events involving interactions among a number of distinct cell types. These interactions are regulated by an array of systemic and local factors such as growth factors and hormones. Development is initially identical among males and females of the same species (Singh, 2003).

During the fourth week of gestation, paired ectodermal thickenings termed mammary ridges or milk lines develop on the ventral surface of the embryo and extend in a curvilinear convex fashion towards the midline from the axillae to the medial thigh. This is the first morphologic evidence of mammary gland development. In normal human development, these ridges disappear except at the level of the fourth intercostal space on the anterior thorax, where the mammary gland subsequently develops (Gray's Anatomy, 2004; Singh, 2003). In other species, such as cats and dogs, multiple paired mammary glands develop along the mammary ridges in the chest, abdominal, and groin regions. The number of paired glands varies greatly among mammalian species and is related to the number of offspring in each litter (Montagna, 1964).

During the fifth week of gestation, the remnant of the mammary ridge ectoderm begins to proliferate and is termed the primary mammary bud. This primary bud subsequently begins growth downward as a solid diverticulum into the underlying dermis during the seventh week. By the 10th week, the primary bud begins to branch, yielding secondary buds by the 12th week, which eventually develop into the mammary lobules of the adult breast (Gray's Anatomy, 2004).

This initial downward growth and subsequent branching have been shown to occur as a result of an inductive influence of the extracellular matrix of the mesoderm on the

primary mammary bud. This epithelial-mesenchymal signaling is probably through paracrine and juxtacrine mechanisms where the underlying mesoderm produces growth factors and hormones that interact with receptors on the overlying ectodermal cells of the primary mammary bud. The adipose tissue in the underlying mesoderm represents a significant store of lipids for the production of hormones and growth factors, which are then available to promote and regulate growth of the developing mammary gland (Singh, 2003).

During the remainder of gestation, these buds continue lengthening and branching. By the 20th week, small lumina develop within the buds that coalesce and elongate to form the lactiferous ducts. The canalization of the mammary buds with formation of the lactiferous ducts is induced by placental hormones entering the foetal circulation. These hormones include progesterone, growth hormone, insulinlike growth factor, oestrogen, prolactin, adrenal corticoids, and triiodothyronine. At term, approximately 15-20 lobes of glandular tissue have formed, each containing a lactiferous duct. Support for the breast comes from both the skin envelope and the fibrous suspensory ligaments of Astley Cooper that anchor the breast to the pectoralis major fascia (Singh, 2003).

The lactiferous ducts drain into retroareolar ampullae that converge into a depressed pit in the overlying skin. Each of the 15-20 lobes of the mammary gland has ampulla with an orifice opening into this mammary pit. Stimulated by the inward growth of the ectoderm, the mesoderm surrounding this area proliferates, creating the nipple with circular and longitudinally oriented smooth muscle fibers. The surrounding areola is formed by the ectoderm during the fifth month of gestation. The areola also contains other epidermal glands, including glands of Montgomery which are sebaceous glands that serve to lubricate the areola (Singh, 2003).

### 2.1.3 Structure of the Breast

The structure of the breast can be studied by dividing the breast into the skin, the parenchyma, and the stroma.

The skin: It covers the gland and presents the following features:

- i. A conical projection called the nipple is present just below the centre of the breast at the level of the fourth intercostals space. However the position varies in multiparous women and therefore is not a reliable guide to fourth intercostal space in adult females. The nipple is pierced by 15-20 lactiferous ducts. It contains circular and longitudinal smooth muscle fibres which can make the nipple stiff or flatten it. It has few modified sweat and sebaceous glands. It is rich in nerve supply and has many sensory end organs at the terminations of nerve fibres (Moore and Dalley, 1999)
- ii. The skin surrounding the base of the nipple is pigmented and forms a circular area called areola. This region is rich in modified sebaceous glands, particularly in its outer margin. These become enlarged during pregnancy and lactation to form raised tubercles of Montgomery. Oily secretions of these glands lubricate the nipple and prevent them from cracking during lactation. Apart from sebaceous glands the areola also contains some sweat glands and accessory mammary glands. The skin of areola and nipple is devoid of hair, and there is no fat subjacent to it (Moore and Daley, 1999).

The parenchyma: It is made up of glandular tissue which secretes milk. The gland consists of 15 to 20 lobes. Each lobe is a cluster of alveoli, and is drained by a lactiferous duct. The lactiferous ducts converge towards the nipple and open on it.

Near its termination each duct has a dilatation called a lactiferous sinus (Moore and Daley, 1999).

- iii. The stroma: It forms the supporting framework of the gland. It is partly fibrous and partly fatty. The fibrous stroma forms septa, known as the suspensory ligaments of Cooper, which anchor the skin and gland to the pectoral fascia (Moore and Daley, 1999).
- iv. The fatty stroma forms the main bulk of the gland. It is distributed all over the breasts, except beneath the areola and nipple. During puberty (8-15 years of age), the breasts normally grow because of glandular development and increased fat deposition. The areola and nipples also enlarge. Breast size and shape result from genetic, racial, and dietary factors. In a nursing mother milk accumulates in the lactiferous sinus. As the infant begins to suckle, compression of the areola (and the lactiferous sinus beneath it) expresses the accumulated droplets and encourages the infant to continue nursing as the hormonally mediated 'let down reflex' ensues and the mother's milk is secreted into not sucked from the gland by the baby's mouth (Guyton and Hall, 2000).

#### **2.1.4 Blood and Nerve Supply**

**2.1.4.1 Blood Supply:** The mammary gland is highly vascular. It is supplied by branches of the internal thoracic artery (a branch of sub-clavian artery), the lateral thoracic artery, superior thoracic and thoracoacromial artery branches of the axillary artery and lateral branches of the posterior intercostal artery (Moore and Daley, 1999). Venous drainage: The venous drainage is mainly to the axillary vein but there is some drainage to the internal thoracic vein (Gray's Anatomy, 2004).

**2.1.4.2 Lymphatic Drainage:** The lymphatic drainage of the breast is important because of its role in the metastasis of cancer cells. Lymph passes from the nipple, areola and lobules of the gland to the subareolar lymphatic plexus, and from it, most lymph (more than 75%), especially from the lateral quadrants of the breast, drains to the axillary lymph nodes, initially to the pectoral nodes for the most part, however, some lymph may drain directly to the other axillary nodes or even to the interpectoral, deltopectoral, supraclavicular, or inferior deep cervical nodes (Moore and Dalley, 1999).

Most of the remaining lymph, particularly from the medial quadrants, drains to the parasternal nodes or to the opposite breast, while lymph from the lower quadrants passes deeply to the inferior phrenic (abdominal) nodes.

Lymphatic vessels in the skin of the breast, except the nipple and areola, drain into the axillary, inferior deep cervical, and inferior clavicular nodes, and also into the parasternal nodes of both sides. Lymph from the axillary nodes drains into infraclavicular and supraclavicular nodes and from them into the subclavian lymphatic trunk, which also drains lymph from the upper limb. Lymph from parasternal nodes enters the bronchomediastinal trunk, which drains lymph from the thoracic viscera. These trunks open independently into the junction of the internal jugular and subclavian veins to form the brachiocephalic veins (Moore and Dalley, 1999).

**2.1.4.3 Nerve Supply:** The breast is supplied by the anterior and lateral cutaneous branches of the 4<sup>th</sup> to 6<sup>th</sup> intercostal nerves. The nerves convey sensory fibres to the skin, and autonomic fibres to smooth muscle and to the blood vessels. The nerves do not control the secretion of milk. Secretion is controlled by the hormone prolactin, secreted by the pars anterior of the hypophysis cerebri (Moore and Dalley, 1999).

## **2.1.5 Applied Anatomy**

**2.1.5.1 *Changes In the Breast:*** Changes, such as branching of the lactiferous ducts, occur in the breast tissues during the menstrual cycles and pregnancy. Although mammary glands are prepared for milk secretion by mid pregnancy, they do not produce milk until shortly after the baby is born. Colostrum, a creamy white to yellowish pre-milk fluid, may secrete from the nipples during the last trimester of pregnancy and during initial episodes of nursing. Colostrum is rich in protein, immune agents, and a growth factor affecting the infant's intestines (Moore and Dalley, 1999).

In multiparous women the breasts often become large and pendulous. The breasts in elderly women are small and wrinkled because of the decrease in fat and atrophy of glandular tissue.

**2.1.5.2 *Breast Quadrants:*** For the anatomical location and description of tumours, the surface of the breast is divided into four quadrants, upper outer, lower outer, upper inner and lower inner.

**2.1.5.3 *Incisions:*** Incisions into the breast are usually made radially to avoid cutting the lactiferous ducts.

**2.1.5.4 *Cancer Of The Breast:*** Understanding the lymphatic drainage of the breasts is of practical importance in predicting the metastasis of carcinoma of the breast. Carcinomas of the breast are almost all adenocarcinoma derived from the glandular epithelium of the terminal ducts in the mammary gland lobules. Cancer cells that enter a lymphatic vessel usually pass through two or three group of lymph nodes before entering the venous system (Moore and Dalley, 1999).

Interference with the lymphatic drainage of the breast by cancer cells may cause deviation of the nipple and produce a leatherlike, thickened appearance of the skin with prominent pores that give it an orange peel appearance (peau d'orange), because of the oedema resulting from the blocked lymphatic drainage. The larger dimples result from cancer invasion of the glandular tissue and fibrosis that causes shortening of the suspensory ligaments. Subareolar breast cancer may cause inversion of the nipple by the same mechanism (Moore and Dalley, 1999).

The posterior intercostal veins drain into the azygos/hemiazygos system of veins alongside the bodies of vertebrae, which empties in the superior vena cava. Through this route cancer cells can spread from breast to the vertebrae and from there to the skull and the brain.

When cancer cells invade the retromammary space and attach to or invade the deep pectoral fascia overlying the pectoralis major or metastasize to the interpectoral nodes, the breast elevates when the muscle contracts. This movement is a clinical sign of advanced cancer of the breast. To observe this upward movement, the physician should ask the patient to place her hands on her hips and press to tense her pectoral muscles.

Lymphatic vessels carry cancer cells from the breast to lymph nodes, chiefly those in the axilla. The cells lodge in the nodes, producing nests of tumour cells (metastasis). Abundant communications between lymphatic pathways and between the axillary, cervical, and parasternal nodes may cause metastases from the breast to develop in the supraclavicular lymph nodes, the opposite breast, or the abdomen. Because the axillary lymph nodes are the most common site of metastases from a breast cancer, enlargement of these palpable nodes in a woman suggests the possibility of breast cancer and may be the key to detection (Moore and Daley, 1999).

**2.1.5.5 Mastectomy:** Surgical Excision of the breast is called mastectomy. It is one of the treatment modalities for breast cancer. In simple mastectomy, the breast is removed down to the retromammary space. Radical mastectomy, is a more extensive surgical procedure which involves removal of the breast, pectoral muscles, fat, fascia, and all lymph nodes in the axilla and pectoral region. In current practice, however, only the tumour and surrounding tissues are removed; this is lumpectomy, or a wide local excision (Moore and Dalley, 1999).

**2.1.5.6 Mammography:** It is the radiographic examination of the breasts. It is one of the techniques used to detect breast masses. The carcinoma appears as a large, jagged density in the mammogram. Mammography is also used by the surgeons to guide them when removing breast tumours, cysts, and abscesses (Moore and Dalley, 1999).

Polymastia, polythelia, and amastia: Supramammary breasts (exceeding the normal number) polymastia or polythelia nipples may occur superior or inferior to the normal breasts, occasionally developing in the axilla or anterior abdominal wall along the mammary line (Moore and Dalley, 1999). Usually supramammary breasts consist only of a rudimentary nipple and areola, which may be mistaken for a mole (naevus) until they change pigmentation with the normal nipples during pregnancy. However, glandular tissue may also occur and further develop with lactation. Extra breasts may appear anywhere along the milk line extending from the axilla to the groin, the location of the embryonic mammary ridge (milk line) from which the breasts develop and along which breasts develop in animals with multiple breasts. In either sex, there may be no breast development (amastia) or there may be a nipple but no glandular tissue.

**2.1.5.7 Breast Cancer In Men:** Approximately 1.5% of breast cancer occurs in men. As in women, breast cancer in men usually metastasizes to lymph nodes, bone, pleura, lung,

liver, and skin. A visible and or palpable subareolar mass or secretion from a nipple may indicate a malignant tumour. Although breast cancer is uncommon in males, the consequences are serious because they are frequently not detected until extensive metastases have occurred, as in bones (Moore and Dalley, 1999).

**2.1.5.8 Gynaecomastia:** Enlargement of the breast in males is called gynaecomastia. It commonly occurs at puberty but may also accompany ageing or be drug related following treatment with diethyl stilbestrol for cancer of prostate. It may also result from a change in the metabolism of sex hormones by the liver (Moore and Dalley, 1999).

## **2.2 BODY MASS INDEX AND BREAST CANCER**

BMI is an index that expresses adult weight in relation to height. It is calculated as weight in kilograms divided by height in meter square. It is categorized according to the WHO BMI levels as the following: low weight (BMI < 18.5), appropriate weight (18.5>BMI< 25), over weight (25.1>BMI<29.9), and obese (BMI = 30) (WHO, 1998). >30.00-<34.99 kg/m<sup>2</sup> as obese class I, BMI >35.00-<39.00 kg/m<sup>2</sup> as obese class II “severe obesity,” and BMI > 40 kg/m<sup>2</sup> as obese class III “morbid obesity.”(WHO, 2010). In the surgical literature, people with a BMI > 50 kg/m<sup>2</sup> are classified as “super obese” (Alvir, C, & thy, 2009) and BMI > 60 kg/m<sup>2</sup> are classified as “super-super obese” (Rowland, *et al* 2002). The higher the BMI, the more health threatening problems, such as cardiovascular diseases, high blood pressure, cancer, and gallstone/cholecystectomy (NIH, 1998).

Reducing the levels of body mass index has shown reduction in the risk of certain conditions such as high blood pressure, heart disease, diabetes and cancer. Research has shown that even if your weight and body fat remains constant, as you get older the distribution of fat changes and is more likely to shift to the trunk area especially post

menopause. In an international multicenter case-control study multiple logistic regression procedures were used to model data from 3,993 breast cancer cases and 11,783 controls from 7 study centers representing the range of international variation of breast cancer incidence. Height and obesity (measured through the weight/height<sup>2</sup> index) were independent risk factors for breast cancer among post-menopausal but not pre-menopausal women; post-menopausal women taller by 10 cm had a 12% higher risk of breast cancer (95% confidence interval, CI, 3-21%) and post-menopausal women of average height had an 11% higher risk of breast cancer (CI 7-16%) when they were heavier by 10 kg (and, therefore, more obese by 4 kg/m<sup>2</sup>). High body weight (measured in terms of body mass index, BMI) has been recognized as an important risk factor for breast cancer among postmenopausal women in many previous epidemiological studies in Western countries (Cold and Hansen, 1998). After menopause, epidemiological evidence found a substantial positive association between BMI and breast cancer risk (Lahmann *et al.*, 2004). One of the most plausible and classical biological explanations is a female hormone-related mechanism because adipose tissue may be a major source of oestrogens (Siiteri, 1987), which are critical mitogens for mammary epithelial cells (Pike *et al.*, 1993; Anderson and Clarke, 2004). Previous studies have provided several potential hormone-related explanations for an increased risk of breast cancer with excess post-menopausal body weight, as follows: increased levels of oestrogen production due to aromatization of androgens in peripheral fat tissue (Siiteri, 1987; Key *et al.*, 2003), and decreased production of sex hormone binding globulin due to obesity (Enriori *et al.*, 1986). These hormone-related mechanisms could increase the supply of free bioavailable oestrogen to breast tissues. In fact, the observed increased risk of breast cancer with increasing post-menopausal BMI was apparently attenuated after adjustment for bioavailable serum oestrogen concentration (Key *et al.*, 2003). A meta-analysis showed

that the substantial positive association between post-menopausal BMI and breast cancer risk was confined to oestrogen receptor+ and progesterone+ tumours (Suzuki *et al.*, 2009).

### **2.3 WAIST HIP RATIO AND BREAST CANCER**

In most Western cultures, females with low WHR are rated as more sexually attractive (Singh, 1994; Henss, 1995; Furnham *et al.*, 1997). This preference has ecologic validity because higher ratios (e.g. > 0.80) are associated with various adverse factors. Female waist-hip ratio begins to decline during childhood from 1.03 at 4 months of age to 0.78 at the time of menarche (Fredriks *et al.*, 2005), and there is a steep increase in hip circumference just before menarche (Frye, and Silverman 1992). Researchers have shown that, women with high Waist Hip Ratio exhibit decreased fertility ( Whincup *et al.*, 2001), more menstrual irregularities (Hirshaut and Pressman, 2000 ) cancer and cardiovascular disease risk factors ((Hirshaut and Pressman, 2000).

The medical profession argued that low WHR is ideal from the perspective of both health and fertility. Because of the benefits associated with low WHR (0.7) one might expect all women to have a low WHR, these benefits include greater fertility, health and attractiveness (Lassek and Gallin, 2008). Higher fertility was reported in females with low WHR; (Whincup *et al.*, 2001; Wass *et al.*, 1997; Moran, 1999; Jasienska *et al.*, 2004; Kirchengast and Hubes, 2004). It was reported that females with low WHR and large breasts have estradiol levels indicating a threefold increase in the probability of conception and these women are the most fecund quartile in their sample than the rest of the sample. Similarly, Whincup *et al.* (2001) reported that there was a decrease in the probability of conception per cycle by 30% when 0.1 increase in WHR was recorded.

Oestrogen decreases WHR directly by increasing fat storage in the thigh and hip area and increases lipolysis in abdominal fat (Rebuffe-Scrive, 1986), and indirectly by mitigating the effects of androgen through an increase in SHBG, which keeps circulating androgen protein bound and unavailable to tissues. Variation in a female WHR exists between one population to the other. In societies where females get resources through direct productive work rather than through investing males, the females have a higher WHR (Pawlowski and Jasienska, 2008). Testosterone levels in women exposed to chronic marital stress is high when compared with women who experience stable marriages (Powell *et al.*, 2002).

Van Ander *et al* (2005) reported that there is a significant and highly positive correlation with WHR and bioavailable testosterone in healthy post-menopausal women, WHR is a visible biomarker of bioavailable testosterone and there is a positive association between BMI and WHR. It has been observed in other populations (Jones *et al.*, 1997), there were racial differences in a number of anthropometric measures. African-American women with breast cancer in North Carolina population were more likely than White women to be obese, to be severely obese, and to have greater WHR. They also were more likely to be diagnosed with later-stage breast cancer, larger tumours, positive lymph nodes, and distant metastases. Among both African-American women and White women, severely obese women and those with a higher WHR more likely to be diagnosed with later-stage breast cancer.

In an age-adjusted model, inclusion of WHR explained 20 percent of the later stage at diagnosis observed in African-American women (Newman *et al.*, 1995). Together, WHR and severe obesity explained 27 percent of the observed racial difference in stage at diagnosis of breast cancer, which suggests that anthropometric characteristics contribute substantially to this relation (Harvie *et al.*, 2003).

## **2.4 AGE OF MENARCHE AND BREAST CANCER**

A woman's first menstruation is termed menarche and it is an important maturity indicator used to assess the developmental status of a pubertal female (Cameron and Nadgdee, 1996). Menarche inversely correlates with age at onset of puberty with breast development. In girls with early onset of breast development, the interval to menarche is longer (3 years or more) than in girls with later onset (Largo and Prado, 1983; Marti-Henneberg and Vizmanos, 1997; Llop-Vinolas *et al.*, 2004).

Menarche and menopause are markers of onset and cessation, respectively, of ovarian and related endocrine activities which are associated with reproduction. During women's reproductive years the ovary produces steroid hormones that directly affect development and function of the breast. Early menarche and late menopause are known to increase women's risk of developing breast cancer (Dan and Reijo, 1983). Although it is known that early menarche and late menopause increase breast cancer risk, Beral *et al.*, (2011) showed that these effects were not equivalent, in that the excess risk associated with lengthening women's reproductive years by one year at menarche was greater than the excess associated with one year's lengthening at menopause (Beral *et al.*, 2011). They also found that oestrogen receptor-positive and lobular breast cancers are strongly affected by women's menarcheal age, and by their actual age.

The production of steroid hormones by the ovary begins at around the time of menarche and decreases rapidly at around the time of menopause. Most women become menarcheal between the ages of 9 and 15 years (Reeves *et al.*, 2006). By restricting analyses of women with breast cancer in this narrow age range and stratifying by single years of age (and by other potential confounding factors), valid comparisons can be made of the short-term effect of the menarche, and breast cancer risk to about 40% higher in early menarcheal women than in late menarcheal women of the same age (Sherman *et al.*,

1981). The findings indicate a rapid decline in breast cancer risk in women of identical ages with late menarcheal age (EBCTG, 2011). Their finding probably explains the flattening of the age-incidence curve at around age 50 years, the so-called Clemmesen's hook, (EBCTG, 2011). Frequently observed in populations before the widespread use of hormonal therapies and screening. There is accumulating evidence that oestrogen receptor positive and lobular breast cancers are more sensitive to ovarian hormones than are oestrogen receptor-negative and ductal cancers. Not only are oestrogen receptor positive and lobular tumours strongly affected by the menopause, as they have shown, but postmenopausal women who use hormone therapy have a greater increase in oestrogen receptor-positive than oestrogen receptor negative tumours and in lobular than ductal breast cancers. (EHBCCG, 2003) Furthermore, oestrogen-blocking treatments improve survival for oestrogen receptor-positive, but not for oestrogen receptor-negative breast cancer. Women's adiposity was consistently shown to attenuate associations between menopause and breast cancer risk. Circulating oestradiol concentrations increase as postmenopausal women's BMI increases (EHBCCG, 2003). That the relative risk of breast cancer falls more rapidly after the menopause in lean than in overweight and obese women is likely to reflect, at least in part, differences in oestradiol concentrations between such women. Oestradiol concentrations in postmenopausal women are greater the younger they were at menarche, and this might, in part, account for the associations recorded between age at menarche and breast cancer risk (Rannevik *et al.*, 1991). Although a woman's age at menarche does not coincide precisely with the onset of breast development, the two are highly correlated (Clemmesen, 1995). Breast cancer is almost unknown before menarche and extremely rare soon afterwards, making it effectively impossible to study the short-term effects of the hormonal changes associated with menarche by comparing breast cancer risk in women of identical ages before and soon

after menarche. Breast cancer risk increased by a significantly greater factor for every year younger at menarche than for every year older at menopause, indicating that menarche and menopause may not affect breast cancer risk merely by extending women's total reproductive years (Easton *et al.*, 2000). Endogenous ovarian hormones are more relevant for oestrogen receptor-positive disease than for oestrogen receptor-negative disease and for lobular than for ductal tumours. Findings confirm that young age at menarche and old age at menopause increase breast cancer risk. Many factors known to affect breast cancer risk, including childbearing patterns, height, and BMI, are also associated both with women's age at menarche and with their age at menopause (Peto *et al.*, 2002).

## **2.5 PARITY AND BREAST CANCER**

**Gravidity** is defined as the number of times that a woman has been pregnant and **parity** is defined as the number of times that she has given birth to a fetus with a gestational age of 24 weeks or more, regardless of whether the child was born alive or was stillborn (Negri *et al.*, 1988).

Epidemiological studies have provided consistent evidence that reproductive factors are associated with breast cancer risk. Some of these associations vary depending on the hormone-receptor status of the tumour (Antoniou *et al.*, 2003). A recent systematic review and meta analysis reported that parity and young age at first birth decrease the risk of oestrogen receptor-progesterone receptor (ERPR) positive tumours, but do not impact the risk of ERPR-negative tumours (King *et al.*, 2003). The meta-analysis also found that breastfeeding protects against both receptors positive and negative tumours. The risk of developing breast cancer is directly proportional to age at first birth up to the age of 30 years. This protective effect is confined to the first pregnancy and appears to be

life long Speculation that breast cancer may be initiated during the early years of reproductive life is supported by evidence that the breast is most susceptible to radiation-induced carcinogenesis in early adult life (Narrod, 2002). It follows that the latent interval between tumour initiation and clinical presentation may often extend over several decades, during which time tumour growth would be subject to modification by major endocrine events such as pregnancy. Although latency cannot be measured directly, any factor causing appreciable acceleration of tumour growth during the preclinical period would be associated with earlier mean age at presentation (Antoniou, 2002).

Although the relation between parity and the risk of breast cancer has been studied extensively, an effect of parity on age at presentation has not been reported. Also it has been reported that pregnancy can accelerate tumour growth and is compatible with the epidemiological evidence for a protective effect of early first pregnancy provided that a clear distinction is recognized between tumour initiation and development (Frye, *et al.*, 1992). Another study has also proposed that pregnancy influences these two processes by separate mechanisms. In support of this, only the first pregnancy appears to modify risk (Hartge *et al.*, 2002). While another result showed that the effect of parity on tumour development was not confined to the first pregnancy. Although extrapolating observations on animal mammary tumours to the human disease is hazardous, chemically induced tumours of the rat provide an interesting parallel (Narrod, 2002). Prior pregnancy renders the rat mammary gland less susceptible to chemical carcinogenesis, but pregnancy after exposure to the carcinogen shortens the interval between exposure and appearance of tumours (Narrod *et al.*, 2002; CGHFBC, 2002). It is well established that increasing parity and early age at first birth are associated with a lower risk of developing breast cancer in the general population. There is evidence that the protective effect of parity may be restricted to women who are older than 40 years old (Clave- chapelon,

2002). Some studies found evidence that parous women are associated with a lower risk of developing breast cancer and that the protective effect may be limited to women above the age of 40 years (Chang-Claude *et al.*, 1998). There was no suggestion that parity might increase the risk of developing breast cancer in women under the age of 40 years. There was evidence that all levels of parity are associated with a reduced risk of breast cancer among women, but this was statistically significant only for women with two or more live births (king *et al.*, 2003). There was also some suggestion of an increased risk associated with first birth after the age of 30 years, again consistent with the effect seen in the general population. However, this effect seemed to be restricted to parous women. This difference might suggest differences in the development of breast cancer among parous women. Several studies, using a variety of designs, have investigated the effect of parity on breast cancer risk among parous and nulliparous women, but the results have not been consistent. Some studies have not found any significant association with parity (Rebbeck *et al.*, 2002), whereas others have reported that parity may increase the risk of breast cancer. Among these authors, Jernstrom and colleagues (Jernstrom *et al.*, 1999) found an increase in risk of breast cancer among women under the age of 40 years.

## **2.6 ORDER OF BIRTH AND BREAST CANCER**

It has been suggested recently that breast cancer may be influenced by concentrations of maternal oestrogens in utero (Trichopoulos, 1999). Little is known, however, of the correlates of pregnancy oestrogen levels. Bernstein *et al* (1996) reported that the percentage and amount of free estradiol (E2) are significantly higher in the early part of a woman's first pregnancy than at a comparable time- point in her second pregnancy. Panagiotopoulous *et al* (2000) later reported similar results, although their study focused on total, rather than bioavailable E2 and on the late, rather than the early stage of pregnancy, on the basis of these findings, it might be lower in women born of a second

pregnancy than in first born women. If this hypothesis and reported findings are true, women born as their mother second child would be expected to have lower risk for breast cancer than first born women. The association of birth order with breast cancer was examined briefly in the data set of the study by Rothman *et al* (2008). In their investigation of the relation between maternal age at birth and breast cancer risk no association was found for the total group. It has been hypothesized that prenatal exposure to maternal oestrogens may be a risk factor for breast cancer in the offspring (Salber *et al.*, 2006). Maternal estradiol levels in the first pregnancy have been compared to those in the second, and in both studies, levels were higher in the first pregnancy (Breslow, 2008, Nichols *et al.*, 2008). If both the hypothesis and the reported findings were true, women born as their mother's second child would be expected to have lower risk for breast cancer than first-born women. Data from 1,468 cases of breast cancer and 4,175 hospital controls from three previously published studies were modelled through multiple logistic regression to evaluate this possibility (Lowe *et al.*, 2007). The size of the woman's sibship was not related to breast cancer risk. On the other hand, second-born women had, as predicted, lower breast cancer risk than first-born women, although the difference was nominally significant only among premenopausal women (Yuasa *et al.*, 2007).

## **2.7 ETHNIC BACKGROUND AND BREAST CANCER**

The influence of breast cancer risk factor distribution on differences in incidence and clinical characteristics associated with ethnicity/race has received limited attention (Vastag, 2003). Consequently, these relationships were studied in a cohort from the ethnically diverse Women's Health Initiative (WHI) study (WHI, 1998). The primary aim was to examine whether known and/or presumptive breast cancer risk factors would explain the difference in breast cancer incidence between white women and women of

minority groups. In this large cohort of postmenopausal women, it has been found out that all ethnic/racial groups had a lower age-adjusted breast cancer incidence than white women. However, the lower incidence in Hispanic, Asian/Pacific Islander, and American Indian/Native Alaskan women was mostly attenuated after adjustment for the distribution of other breast cancer risk factors. Dietary (Prentice *et al.*, 2001) and/or physical activity factors (Forshee *et al.*, 2003) may account for some of the remaining variability.

Adjustment for breast cancer risk factors also explained some of the difference in breast cancer incidence between African American and white women. However, even in the final model, which adjusted for differential mammography screening rates, the breast cancer incidence was statistically significantly lower in African Americans than whites (HR = 0.75,  $P = .006$ ). A potential factor mediating the lower breast cancer incidence in African American women is their mammographic breast density, which has been reported to be lower than that in white and Hispanic women (Delcarmen *et al.*, 2003).

The lower breast cancer incidence rates in racial/ethnic minority groups than in whites observed in the WHI cohort reflect the pattern previously reported in the general population (Ries *et al.*, 2005). However, a comparison of age-adjusted rates from WHI with those for women in the Surveillance Epidemiology and End Result (SEER) program indicates that breast cancer rates for all racial/ethnic subgroups except African Americans are somewhat higher for women in WHI than for women in the program. The annualized age-adjusted incidence rates (in cases /10 000 per year) for Women Health Initiative (WHI) and Surveillance Epidemiology and End Result (SEER), respectively, are white, 44 versus 41; African American, 29 versus 34; Hispanics, 31 versus 25; American Indians, 28 versus 16; and Asian/Pacific Islanders, 38 versus 25 (Ries *et al.*, 2005). These modest differences may arise from higher educational status and greater access to health care,

including screening mammography, for healthy women volunteering for placebo-controlled clinical prevention studies such as the WHI clinical trials.

Both data and prior observational studies of associations between breast cancer incidence and ethnicity have been limited by the absence of comprehensive information on breast cancer screening. It is known that Hispanics (Thompson *et al.*, 2002; McCarthy *et al.*, 1998) are less likely to undergo breast cancer screening than white women, but accurate assessment of this behaviour in traditional case-control studies is difficult because retrospectively recalled frequency of mammography over long intervals has proven unreliable (Gordon *et al.*, 1993). In this WHI study, by contrast, information on mammography use was collected prospectively and incorporated in the final model. Even though the frequency of mammography was specified in the WHI protocol for the clinical trial participants (representing 58% of the study population), mammogram frequency still differed by ethnicity, with each racial/ethnic group having a somewhat lower rate of mammograms than white women.

The breast cancer risk model of Gail and colleagues is used widely, especially in the United States, to determine clinical prevention trial eligibility and in clinical practice as well (Chlebowski 2003; Armstrong *et al.*, 2000). However, the Gail model was developed in a largely white population of women receiving regular mammograms (Bingham *et al.*, 2003) and has not been validated in other racial/ethnic groups (Armstrong *et al.*, 2000). Indeed, the Gail model was recently adjusted to reflect a lower risk among Hispanic women (Gail and Costantino 2001; NCI, 2001). Few studies have considered ethnicity as an integral component of comprehensive breast cancer risk assessment. In one multiethnic cohort, consideration of seven risk factors (ages at menarche and first birth, parity, age and type of menopause, weight, menopausal hormone therapy, and alcohol use) resulted

in similar breast cancer risk in postmenopausal white, Hispanic, and African American women (Pike *et al.*, 2002). However, that analysis did not incorporate several variables that are strongly related to breast cancer risk and that commonly vary by ethnicity (Bernstein *et al.*, 2003), including breast cancer family history, prior benign breast disease, socioeconomic status, physical activity, and mammogram screening frequency. In the WHI population, a model incorporating only the same seven risk factors resulted in estimates of a slightly lower risk of breast cancer for African Americans than for whites (HR = 0.84, 95% CI = 0.73 to 0.98). That HR moved further away from unity in the final model, which included the full range of breast cancer risk factors and covariates (HR = 0.75, 95% CI = 0.61 to 0.92). It remains to be determined whether differences in unidentified environmental exposures, genetic makeup, or other factors lead to the higher frequency of high-grade, ER-negative cancers in African Americans. The gradient in frequency of high-grade, ER-negative breast cancers seen comparing native Africans in Nigeria (who have the highest frequency) to African Americans (who have an intermediate frequency) to whites (who have the lowest frequency) (Ikpatt *et al.*, 2004) is consistent with involvement of either environmental or genetic differences in this process. Gene expression assay studies have identified breast cancer subtypes representing biologically distinct disease entities (Sorlie *et al.*, 2003). Comparative analyses of gene expression in breast cancers by race/ethnicity are needed to evaluate the possibility that basal-like breast tumours are more common in African American than in women of other racial/ethnic groups.

## **2.8 EDUCATIONAL LEVEL AND BREAST CANCER INCIDENCE**

A positive relationship between level of education and female breast cancer risk is well supported by scientific evidence, but few previous studies could adjust for all relevant potential confounding factors (Lund, 2004). This relationship was studied in a cohort and

the aim was to examine how risk for breast cancer varies with level of education and factors that explain this variation, using data from these prospective cohort studies including 102860 women from Norway and Sweden who responded to an extensive questionnaire in 1998/2003; 1090 incident primary invasive breast cancer cases were revealed during follow-up, which ended in December 2003 (Braaten *et al.*, 2004). Women with more than 16 years of education had a 36% increased risk compared to the lowest educated (7-9 years) (Age adjusted RR=1.36, 95% CI: 1.10, 1.68). The relationship between educational and breast cancer was slightly stronger among postmenopausal (RR 1.51) than among premenopausal (RR 1.25) women as reported by Wagener *et al.*, (2008). In both groups, however, the relative risk estimates turned close to unity by adjustment for parity, age at first birth, body mass index (BMI), height, age at menarche, menopausal status, use of oral contraceptives and consumption of alcohol. The overall multivariate relative risk among the highest educated women was 1.04 (95% CI 0.82-1.32). Many studies suggested a clear positive gradient in risk for breast cancer by level of education, which can be fully explained by established breast cancer risk factors (Hussein *et al.*, 2008).

## **2.9 FAMILY HISTORY OF BREAST CANCER AND BREAST CANCER INCIDENCE**

Breast cancer susceptibility is generally inherited in an autosomal dominant pattern with limited penetrance (Isaacs *et al.*, 2000). This means that it can be transmitted through either sex and that some family members may transmit the abnormal gene without developing cancer themselves. It is not yet known how many breast cancer genes there may be (Jordan *et al.*, 2000). Two breast cancer genes, BRCA1 and BRCA2, which are located on the long arms of chromosomes 17 and 13 respectively, have been identified and account for a substantial proportion of very high risk families those with four or

more breast cancers among close relatives. Both genes are very large and mutations can occur at almost any position, so that molecular screening to detect mutation for the first time in an affected individual or family is technically demanding. Certain mutations occur at high frequency in defined populations. For instance, some 2% of Ashkenazi Jewish women carry either BRCA1 185 del AG, BRCA1 5382 ins C or BRCA 6174 del T, while BRCA2 999 del 5 (deletion of five base pairs at position 999) accounts for about half of all familial breast cancer in Iceland. Inherited mutations in two other genes, p53 and PTEN, are associated with familial syndromes (Antoniou *et al* 2002) that include a high risk of breast cancer but both are rare. These are almost certainly other (as yet unidentified) genes that increase the risk of disease by only a moderate degree perhaps three or four-fold above the general population level. These are unlikely to generate florid multi-case families but they are probably rather common and therefore account for a substantial part of the overall genetic contribution to breast cancer (Willett *et al.*, 2000).

## **CHAPTER THREE**

### **MATERIALS AND METHODS**

#### **3.1 STUDY LOCATION**

Zaria is a heterogeneous city whose 406990 population (NPC, 2006) comes from different parts of the world. It is second in size only to the State capital, Kaduna. Zaria is located on the high plain of Northern Nigeria 652.6 meters above the sea level, and 950 km away from the coast (Latitude  $11^{\circ} 07' 51''$ N; Longitude  $7^{\circ} 43' 43''$  E). The town is characterized by gentle rolling plains dotted with groups of rocky residual hills developed on granite bedrock and possesses a tropical continental climate with a pronounced dry season, lasting up to seven months (October- May). Zaria experiences a brief period of hot but dry weather in March and April, followed by a progressive incursion of tropical maritime air mass from the Atlantic Ocean which displaces the (harmattan) winds. During this short period, the mean daily maximum temperatures are fairly stable, and it range from  $38^{\circ}$  to  $42.2^{\circ}$  (ABU Portal). Data was collected from the cancer patients undergoing treatment in the Department of Radiotherapy and Oncology, Ahmadu Bello University Teaching Hospital Shika, Zaria. Control group was randomly selected from student and staff of Ahmadu Bello University Zaria.

#### **3.2 SAMPLE SIZE DETERMINATION AND SUBJECT**

The sample size was determined using the formula below; (Naing, 2006)

$$n = \frac{Z^2 pq}{d^2}$$

Where n=desired sample size

Z=standard deviation, usually set at 1.96

P=prevalence =0.25 (25%)

Q=1-p

$d$  = degree of accuracy desired, usually set at 0.05.

Therefore  $n = (1.96)^2 (0.25) (0.75) / (0.05)^2 = 288.12$ .

This study involved 718 subjects aged 17 to 75 years consisting of 352 breast cancer patients attending clinic in the department of Radiotherapy and Oncology Ahmadu Bello University Teaching Hospital Shika, Zaria, and 366 randomly selected females also aged 17 to 75 years among students and Staff of Ahmadu Bello University Zaria.

### **3.3 STUDY DESIGN**

This is a prospective study, and data was obtained from the Department of Radiotherapy and Oncology, Ahmadu Bello University Teaching Hospital, Zaria from February 2013 to January 2014.

Demographic information such as age, body weight, height, waist circumference, hip circumference, menarcheal age, menopausal age, parity, order of birth, educational level, and ethnic background were obtained from participants through questionnaires (see appendix 1).

While control for comparison and data were randomly selected from among students and staff of Ahmadu Bello University, Zaria, a structured questionnaire was used to collect detailed information. The following Anthropometric variables were measured.

- i. Weight (kg): an overall measure of body size that does not distinguish between fat and muscle. Weight was measured to the nearest 0.1 kg when the subject was standing and putting on light indoor clothes excluding shoes, belt and sweater using a weighing scale. Heavy jewellery if any were removed and pockets emptied.

- ii. Height (cm): standing height is the measurement of the maximum distance from the floor to the vertex, when the subject is facing forward. Shoes were removed, feet together, and arms by the sides. Heels, buttocks and upper back was also in contact with the wall when the measurement was made. This measurement was carried out using a stadiometer.
- iii. The BMI also known as “Quetelet’s index” is an index that uses the variables of weight and height to measure body fat and protein stores, usually in adults rather than children. It was calculated as the ratio of weight in kilogram by square of height in meters (m<sup>2</sup>). i.e.:  $BMI (kg/m^2) = \text{weight (kg)}/\text{height (m}^2)$  It is a measure of body mass corrected for height which is used to assess the extent of weight deficit or excess. BMI also provides a practical indicator of adiposity and hence overweight or obesity.
- iv. Waist circumference (cm): the tape was used to circle the waist (like a belt would circle the waist) at the natural waistline, which is midpoint between the lowest rib and the iliac crest. The subject was asked to stand erect while measurements were taken. The measurement was taken at the midpoint between the lowest rib and the iliac crest. The measuring tape was placed perpendicular to the long axis of the body and horizontal to the floor, with sufficient tension to avoid slipping off but without compressing the skin. The measurement was made at the end of a normal expiration to the nearest 0.1 cm.
- v. Hip circumference (cm): The measurement was taken with the pants/skirt on. The subject stood erect, the weight evenly distributed on both feet. The tape was placed at the maximum extension of the buttocks, horizontal to the floor, with sufficient tension to avoid slipping off. The tape was held a bit tighter but without

compressing the buttocks. The zero end of the tape was held under the measurement value recorded to the nearest 0.1 cm.

### **3.3.1 Inclusion Criteria For Breast Cancer Subjects**

The following was used as inclusion criteria:

- i. Histologically confirmed breast cancer cases
- ii. Only female subjects

### **3.3.2 Exclusion Criteria For Breast Cancer Subject**

- i. Subjects who have had a documented malignancy in other sites
- ii. Male subjects

### **3.3.3 Inclusion Criteria For Control Subject**

- i. Non cancer patients
- ii. Only female subject

### **3.3.4 Exclusion Criteria For Control Subject**

- i. Subjects who have had a documented malignancy in other sites
- ii. Male subjects.

## **3.4 ETHICAL CONSIDERATIONS**

Ethical approval was obtained from Ahmadu Bello University Research Ethics subcommittee and the Ahmadu Bello University Teaching Hospital Research Ethics committee. Informed consent was obtained from all respondents prior to data collection.

## **3.5 STATISTICAL ANALYSIS**

Data was reported using descriptive statistics. Quartile distribution was used to categorize BMI to facilitate comparisons. Student *t-test* was used to compare between all variables among breast cancer cases and control. Pearson chi square was used to measure the association between breast cancer incidence and parity, family history of breast cancer,

order of birth, age at menarche, ethnicity and educational level. Values were considered statistically significant if P-value was less than 0.05 ( $P < 0.05$ ). Minitab 16 and EZ analyse 3.0 (Poynton, T.A 2007) was used for the analyses.

## CHAPTER FOUR

### RESULTS

#### 4.1 DESCRIPTIVE STATISTICS

Seven hundred and eighteen (718) females of different ethnicity and age range of 17- 75 years participated in this study. The study involved extraction of demographic information and anthropometric parameters. The following anthropometric parameters were taken: weight, height, body mass index, waist circumference, hip circumference, and waist- hip ratio. The demographic information taken were: age, menarcheal age, menopausal age, parity, order of birth, educational level, family history of breast cancer and ethnicity. Histologically confirmed breast cancer cases (n=352) (mean age  $45.699 \pm 12.363$ ) and control female subjects (n=366) (mean age  $26.836 \pm 9.536$ ).

The result showed that majority of the study participants were overweight (mean BMI  $26.847 \pm 21.392$ ), and had high waist- hip ratio (mean WHR  $0.879 \pm 0.135$ ) (Table 4.1). It was observed that the mean value for age, weight, BMI and WHR were higher in the breast cancer group compared to the control group (Table 4.2). Regarding age at menarche, it was found that a number of respondents had a normal age at menarche (Table 4.3) , All the anthropometric variables studied in Table 4.3 were statistically significant ( $P < 0.001$ ) except for the age at menarche ( $P = 0.413$ ) and height ( $P = 0.724$ ) (Table 4.3).

**Table 4.1: Overall descriptive statistics (n = 718)**

<b>Parameters</b>	<b>Mean <math>\pm</math> SD</b>	<b>Minimum</b>	<b>Maximum</b>
<b>Age (year)</b>	36.084 $\pm$ 14.497	17.00	75.00
<b>Menarcheal age (years)</b>	13.678 $\pm$ 2.170	9.00	19.00
<b>Height (cm)</b>	159.280 $\pm$ 9.620	155.00	188.00
<b>Weight (kg)</b>	65.711 $\pm$ 16.881	32.00	165.00
<b>Body mass index</b>	26.847 $\pm$ 21.392	14.15	50.00
<b>Hip Circumference(cm)</b>	98.669 $\pm$ 16.372	33.00	144.00
<b>Waist Circumference(cm)</b>	86.821 $\pm$ 21.434	32.00	193.00
<b>Waist Hip Ratio</b>	0.879 $\pm$ 0.135	0.38	1.581

**Table 4.2: Comparison of Anthropometric variables of breast cancer case group and control group**

Variables	Control (n=366)		Cancer group(n=352)			
	Mean $\pm$ SD	Minimum	Maximum	Mean $\pm$ SD	Minimum	Maximum
Age (years)	45.69 $\pm$ 12.36	17.00	75.00	26.83 $\pm$ 9.53	17.00	59.00
AFM (years)	13.77 $\pm$ 2.633	9.00	19.00	13.57 $\pm$ 1.55	9.00	19.00
HT (cm)	159.15 $\pm$ 10.37	75.00	181.00	159.40 $\pm$ 8.85	55.00	188.00
WT (kg)	72.31 $\pm$ 17.84	32.00	165.00	59.35 $\pm$ 13.07	37.00	165.00
BMI	29.13 $\pm$ 11.16	14.00	41.00	24.64 $\pm$ 27.75	14.15	50.00
HC (cm)	101.42 $\pm$ 20.29	33.00	144.00	96.005 $\pm$ 10.74	38.00	143.00
WC (cm)	97.35 $\pm$ 24.51	32.00	193.00	76.663 $\pm$ 10.65	36.00	124.00
WHR	0.95 $\pm$ 0.12	0.380	1.581	0.81 $\pm$ 0.09	0.53	1.56

AFM= Age at menarche, HT = Height, WT = Weight, BMI = Body mass index, HC = Hip circumference  
WC = Waist circumference, WHR = Waist hip ratio

**Table 4.3: Student T- Test and CI of Anthropometric Variables for Breast Cancer Case Group and Control Group**

<b>Variables</b>	<b>Mean <math>\pm</math> SD (Breast cancer cases group)</b>	<b>Mean <math>\pm</math> SD (Control group)</b>	<b>T- Value</b>	<b>P - Value</b>
Age (years)	45.70 $\pm$ 12.40	26.84 $\pm$ 9.54	- 22.83	0.001
AFM (years)	13.68 $\pm$ 1.72	13.57 $\pm$ 1.55	- 0.82	0.413
HT (cm)	159.20 $\pm$ 10.40	159.40 $\pm$ 8.85	- 0.35	0.724
WT (kg)	72.30 $\pm$ 17.80	59.40 $\pm$ 13.10	-11.07	0.001
BMI	29.10 $\pm$ 11.20	24. 60 $\pm$ 27.70	-2.87	0.004
HC (cm)	101.40 $\pm$ 20.30	96.00 $\pm$ 10.70	- 4.44	0.001
WC (cm)	97.40 $\pm$ 24.50	76.70 $\pm$ 10.70	- 14.57	0.001
WHR	0.95 $\pm$ 0.12	0.80 $\pm$ 0.09	- 19.05	0.001

AFM= Age at menarche, HT = Height, WT = Weight, BMI = Body mass index, HC = Hip circumference  
WC = Waist circumference, WHR = Waist hip ratio

Student T- test of anthropometric variables for breast cancer group and control group is presented in Table 4.3 showing that all the anthropometric variables studied were statistically significant at (  $P \leq 0.001$ ) except for the age at menarche (  $P= 0.413$  ) height ( $P= 0.724$ ) and BMI ( $P= 0.004$ )

#### **4.2 ANTHROPOMETRIC VARIABLES ACCORDING TO ETHNICITY IN BREAST CANCER CASE AND CONTROL GROUPS**

The mean values of variables are presented in Table 4.4. The mean of all anthropometric parameters (weight, body mass index, hip circumference, waist circumference and waist hip ratio) is statistically significant ( $P < 0.01$ ) except for mean height (with  $P = 0.057$ ) and menarcheal age ( $P = 2.218$ ).

#### **4.3 ANTHROPOMETRIC VARIABLES ACCORDING TO AGE IN BREAST CANCER CASE AND CONTROL GROUPS**

The age groups of 17 to 75 years for both groups as shown in Table 4.5 for respective means of height, weight and body mass index were statistically significant at  $P = 0.002$ ,  $0.003$ , and  $0.011$  respectively. Except the mean of hip circumference with  $P = 0.524$  waist circumference ( $P = 0.508$ ) and WHR ( $P = 0.34$ ).

#### **4.4 CORRELATION BETWEEN ANTHROPOMETRIC VARIABLES IN BREAST CANCER CASE AND CONTROL GROUPS**

Table 4.6a shows that age correlates negatively with menopausal age and height but positively with weight which is statistically significant at  $P < 0.01$  while Table 4.6b shows that age correlates positively with menopausal age, parity, weight, waist circumference, BMI, and WHR at a significant level  $P < 0.01$ .

Menopausal age correlates positively with parity and BMI but negatively with educational levels in both groups at a significant level of  $P < 0.05$  as shown in Table 4.6a and 4.6b. Parity correlates negatively with family history of breast cancer ( $P < 0.05$ ).

Height correlates positively with weight and BMI ( $P < 0.01$ ) as shown in Table 4.6a.

Waist circumference correlates positively with weight, BMI, hip circumference and WHR at  $P < 0.01$  as shown in Table 4.6a and 4.6b respectively.

**Table 4.4: Anthropometric variables according to ethnicity in breast cancer group and control group**

Parameters	Hausa Breast cancer cases	Hausa Control	Yoruba Breast cancer cases	Yoruba Control	Igbo Breast cancer cases	Igbo Control	Other s Breast cancer cases	Others Control	P-values
	Mean ± SD ( N= 128 )	Mean ± SD ( N= 73 )	Mean ± SD ( N= 56 )	Mean ± SD ( N= 53 )	Mean ± SD ( N= 24 )	Mean ± SD ( N= 23 )	Mean ± SD ( N= 145 )	Mean ± SD ( N= 218 )	
<b>AFM(years)</b>	12.29 ± 0.45	12.29 ± 0.455	12.12 ± 0.32	12.12 ± 0.323	12.33± 0.482	12.32 ± 0.476	12.24 V 0.431	12.25 ± 0.433	2.218
<b>HT(cm)</b>	158.30 ± 10.47	159.57 ± 7.28	156.64 ± 17.01	157.82 ± 15.90	161.04 ± 7.32	164.19 ± 7.81	160.52 ± 6.38	159.61 ± 6.16	0.057
<b>WT(kg)</b>	70.45 ± 16.11	58.57 ± 15.02	76.59 ± 20.33	62.20 ± 19.20	77.74 ± 17.02	64.47 ± 10.15	71.48 ± 18.07	59.08 ± 11.27	0.001
<b>BMI(kg/m<sup>2</sup>)</b>	28.56 ± 8.86	23.06 ± 5.86	33.85 ± 21.07	33.42 ± 71.83	29.72 ± 4.81	23.92 ± 3.60	27.72 ± 7.09	23.34 ± 4.85	0.001
<b>WC(cm)</b>	70.45 ± 16.11	74.02 ± 12.07	76.59 ± 20.33	78.32 ± 10.64	77.74 ± 17.02	77.47 ± 7.57	71.48 ± 18.07	77.18 ± 10.48	0.001
<b>HC(cm)</b>	99.66 ± 22.01	93.68 ± 14.22	103.05 ± 18.66	97.79 ± 9.91	103.70 ± 13.19	100.31 ± 7.02	101.57 ± 20.74	96.31 ± 10.57	0.001
<b>WHR</b>	0.95 ± 0.13	0.79 ± 0.10	0.97 ± 0.10	0.80 ± 0.06	0.97 ± 0.13	0.77 ± 0.04	0.95 ± 0.14	0.80 ± 0.09	0.001

AFM= Age at menarche, HT = Height, WT = Weight, BMI = Body mass index, HC = Hip circumference, WC = Waist circumference  
WHR = Waist hip ratio

Table 4.4 is showing the mean values of anthropometric variables according to ethnicity in breast cancer group and control group. The mean values of all the anthropometric parameters are statistically significant at (  $P \leq 0.01$  ) except for mean weight (  $P= 0.057$  ) and menarcheal age (  $P= 2.218$  )

**Table 4.5: Anthropometric variables according to age in breast cancer cases and control**

Parameters	>20 Breast cancer	>20 Control	21-39 Breast cancer	21-39 Control	40-59 Breast cancer	40-59 Control	>60 Breast cancer	>60 Control	P-values
	Mean ± SD (n= 5)	Mean ± SD ( n= 85)	Mean ± SD ( n= 105)	Mean ± SD ( n=227 )	Mean ± SD (n= 192)	Mean ± SD ( n= 54)	Mean ± SD ( n= 50 )	Mean ± SD ( n= 3)	
<b>AFM(years)</b>	12.27 ± 0.452	12.21 ± 0.412	12.67 ± 0.577	12.23 ± 0.420	12.24 ± 0.437	12.34 ± 0.477	12.24 ± 0.427	12.32 ± 0.48	1.013
<b>HT(cm)</b>	158.00 ± 7.64	160.08 ± 6.39	157.06 ± 11.2	159.64 ± 7.50	161.08 ± 5.80	157.16 ± 15.09	156.22 ± 18.20	0.00 ± 0.00	0.002
<b>WT(cm)</b>	47.00 ± 10.93	54.85 ± 8.85	71.09 ± 17.00	59.99 ± 12.15	74.28 ± 19.03	63.57 ± 19.24	69.89 ± 12.42	0.00 ± 0.00	0.003
<b>BMI(kg/m<sup>2</sup>)</b>	18.70 ± 3.58	21.39 ± 3.14	28.61 ± 7.75	23.63 ± 5.05	28.40 ± 6.49	24.32 ± 4.94	27.63 ± 4.32	0.00 ± 0.00	0.011
<b>WC(cm)</b>	80.00 ± 18.64	72.83 ± 7.36	76.76 ± 10.74	77.24 ± 10.61	76.22 ± 10.35	80.27 ± 13.24	78.56 ± 11.33	0.00 ± 0.00	0.508
<b>HC(cm)</b>	103.00 ± 22.76	93.43 ± 7.20	95.61 ± 10.22	96.99 ± 11.20	95.79 ± 10.67	96.00 ± 12.64	96.00 ± 11.09	0.00 ± 0.00	0.524
<b>WHR(cm)</b>	0.77 ± 0.07	0.78 ± 0.07	0.80 ± 0.08	0.79 ± 0.09	0.79 ± 0.08	0.84 ± 0.15	0.82 ± 0.13	0.00 ± 0.00	0.339

AFM= Age at menarche, HT = Height, WT = Weight, BMI = Body mass index, HC = Hip circumference, WC = Waist circumference  
WHR = Waist hip ratio

The mean values of anthropometric variables according to age in breast cancer group and control group is presented in Table 4.5 showing that the mean WT, HT, and BMI are statistically significant at P= 0.002, 0.003, and 0.011 respectively.

**Table 4.6a: Correlation matrix of anthropometric variables in breast cancer cases**

	AGE	AFM	MA	Ethnicity	Edu-Level	Parity	Birth order	FHBC	HT	WT	HC	WC	BMI	WHR
AGE	1	-0.075	-0.112*	0.004	-0.027	-0.026	-0.127*	-0.076	-0.130*	0.212**	0.005	-0.023	0.073	-0.036
AFM		1	0.012	-0.010	-0.043	0.093	-0.082	-0.037	0.041	-0.008	-0.045	-0.030	-0.036	0.021
MA			1	-0.097	-0.124*	0.233**	-0.053	-0.073	-0.132*	0.36	-0.041	0.040	0.135*	0.082
Ethnicity				1	0.065	-0.015	0.043	0.064	0.32	-0.063	0.092	-0.090	-0.075	0.058
Edu-Level					1	-0.020	0.015	0.003	0.102	0.001	0.004	-0.018	-0.0106*	0.058
Parity						1	-0.009	-0.109*	-0.091	-0.090	0.016	0.087	0.017	0.104
Birth order							1	-0.023	0.013	-0.066	0.72	0.021	-0.072	-0.034
FHBC								1	0.21	-0.061	0.057	-0.014	-0.107*	-0.013
HT									1	0.142**	0.043	0.001	-0.629**	0.073
WT										1	-0.012	0.598**	0.000	0.030
HC											1	0.684**	-0.042	-0.252**
WC												1	0.033	0.519**
BMI													1	0.061
WHR														1

AFM= Age at menarche  
WHR = Waist hip ratio  
WT = Weight

WC = Waist circumference  
FHBC = Family history of breast cancer  
BMI = Body mass index

HC= Hip circumference  
HT= Height

\*= 0.05  
\*\*= 0.01  
\*\*\*= 0.001

**Table 4.6b: Correlation matrix of anthropometric variables in control group**

	AGE	AFM	MA	Ethnicity	Edu-Level	Parity	Birth order	FHBC	HT	WT	HC	WC	BMI	WHR
AGE	1	0.084	0.315**	-0.045	-0.025	0.748**	-0.050	-0.145**	-0.090	0.176**	0.059	0.153**	0.120**	0.139**
AFM		1	0.012	-0.000	-0.054	0.092	-0.077	-0.042	0.052	-0.088	-0.052	-0.037	-0.120**	0.139**
MA			1	0.098	-0.118*	0.236**	-0.054	-0.064	-0.057	-0.003	-0.043	-0.043	0.042	-0.089
Ethnicity				1	0.050	-0.023	0.028	0.036	0.074	0.055	0.083	0.081	-0.028	0.025
Edu-Level					1	-0.014	0.003	-0.054	-0.007	0.035	-0.003	-0.009	0.020	-0.008
Parity						1	-0.014	-0.088	-0.051	0.104*	0.008	0.92	0.94	0.110*
Birth ordre							1	-0.023	0.082	-0.006	0.069	0.013	-0.029	-0.054
FHBC								1	0.138**	-0.035	0.026	-0.013	-0.179**	-0.073
HT									1	-0.107*	0.85	0.008	-0.644**	-0.074
WT										1	0.621**	0.668**	0.554**	0.196**
HC											1	0.682**	0.110*	-0.252**
WC												1	0.115*	0.521**
BMI													1	0.029
WHR														1

AFM= Age at menarche  
WHR = Waist hip ratio  
WT = Weight

WC = Waist circumference  
FHBC = Family history of breast cancer  
HC = Hip circumference

HT= Height  
BMI= Body mass index

\*= 0.05  
\*\*= 0.01  
\*\*\*= 0.001

#### **4.5 ASSOCIATION BETWEEN BREAST CANCER DEMOGRAPHICS AND BMI**

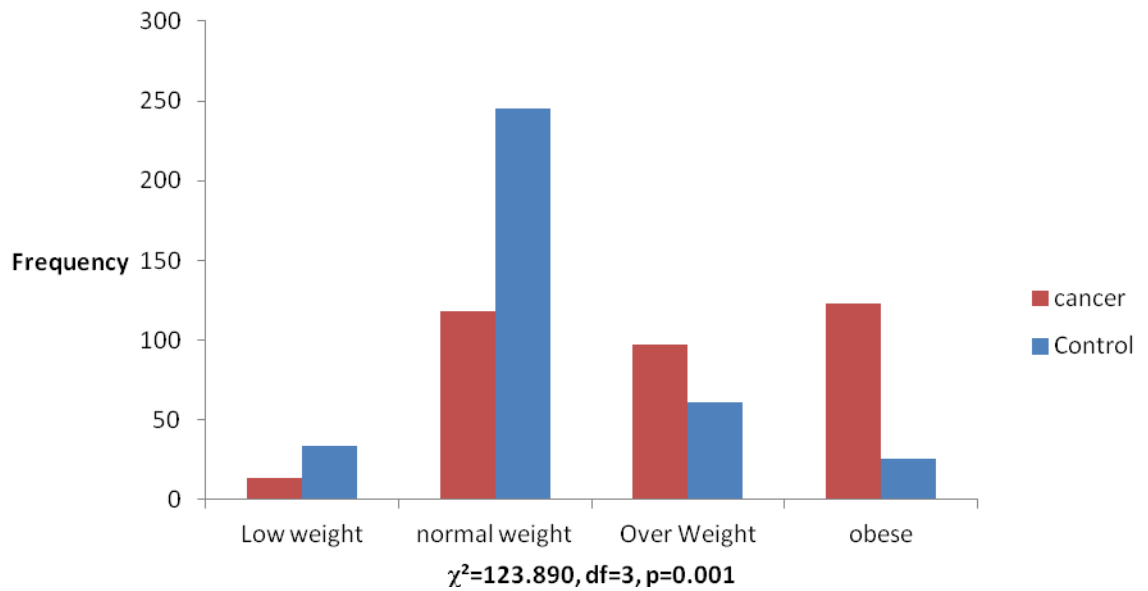
Fig 4.1 shows the association between BMI and breast cancer incidence, from the study the incidence of breast cancer was seen to be more in obese women compared to women with low weight and women with normal weight at a significant level of  $P= 0.001$ .

#### **4.6 ASSOCIATION BETWEEN PARITY AND INCIDENCE OF BREAST CANCER**

Fig 4.2 shows the association between parity and incidence of breast cancer, from the study the incidence of breast cancer was seen to be more in multiparous women compared to women with none or one child at a significant level of  $P < 0.001$

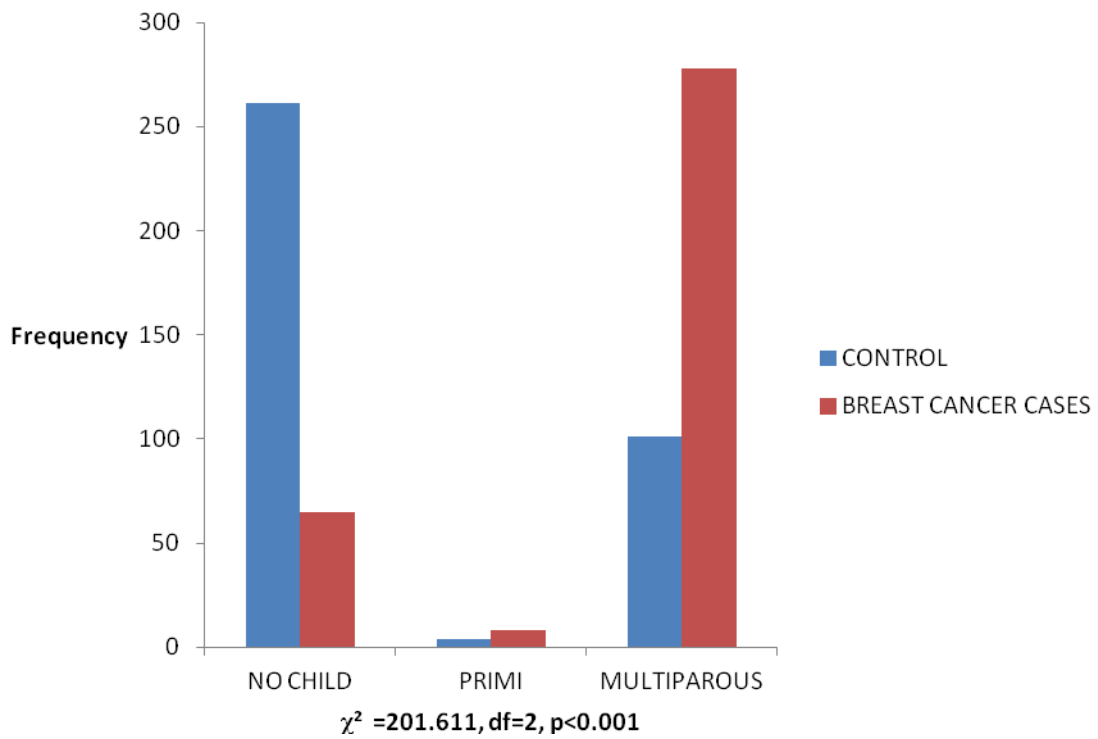
#### **4.7 ASSOCIATION BETWEEN ORDER OF BIRTH AND INCIDENCE OF BREAST CANCER**

The association between order of birth and incidence of breast cancer is presented in Fig 4.3, and shows that breast cancer incidence is more in first born women than in women born of other rank at a significant level of  $P < 0.001$ .



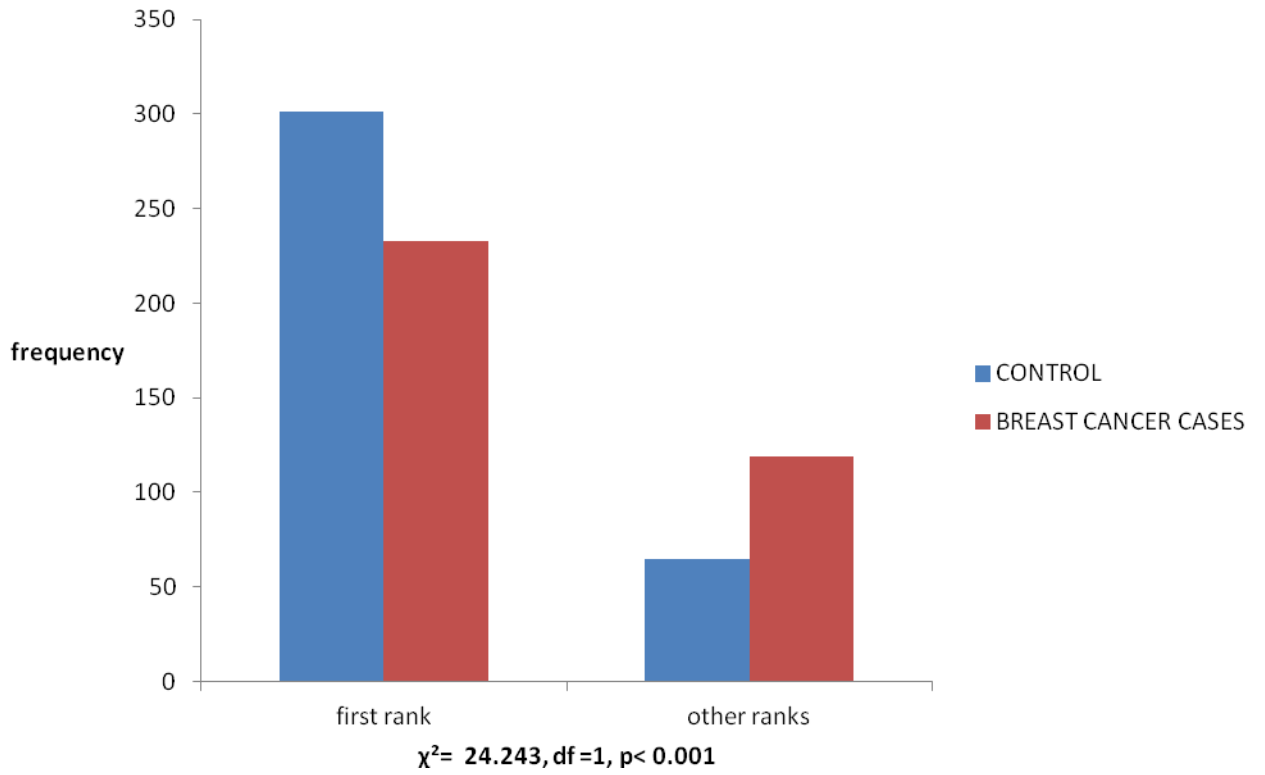
**Figure 4.1** Association between breast cancer demographics and BMI

The study shows that the incidence of breast cancer was seen to be more in obese women compared to women with low weight and women with normal weight at a significant level of  $P= 0.001$ .



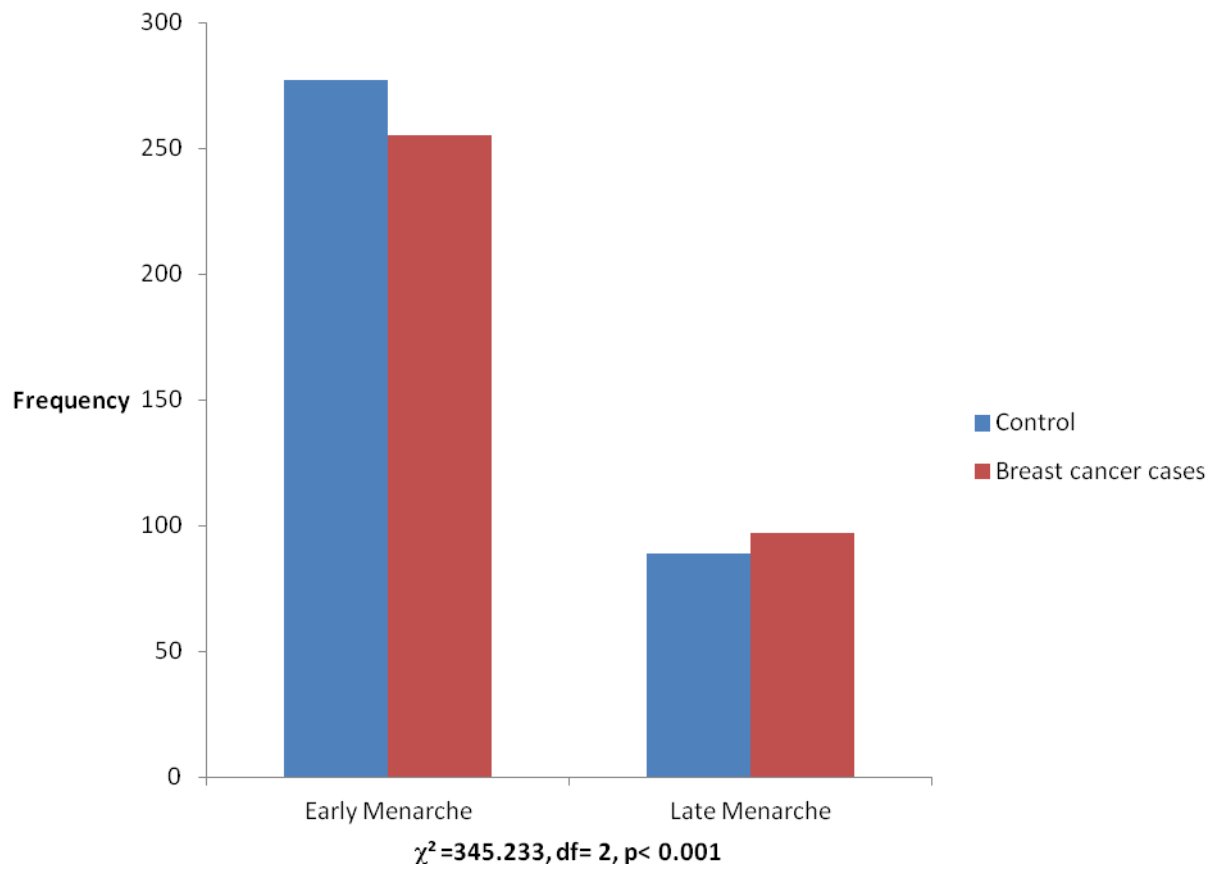
**Figure 4.2:** Association between parity and incidence of breast cancer

This shows the association between parity and incidence of breast cancer. Incidence was higher in multiparous women compared to women with one child and nulliparous women at a significant level of  $P < 0.001$



**Figure 4.3:** Association between order of birth and incidence of breast cancer

Showed that breast cancer incidence was more in first born women than in women born of other rank at a significant level of  $P < 0.001$ .



**Figure 4.4:** Association between Age at menarche and incidence of breast cancer

Showned that breast cancer incidence is higher in women with early age at menarche compared to women with late age at menarche at a significant level of  $P < 0.001$ .

#### **4.8 Association between age at menarche and incidence of breast cancer**

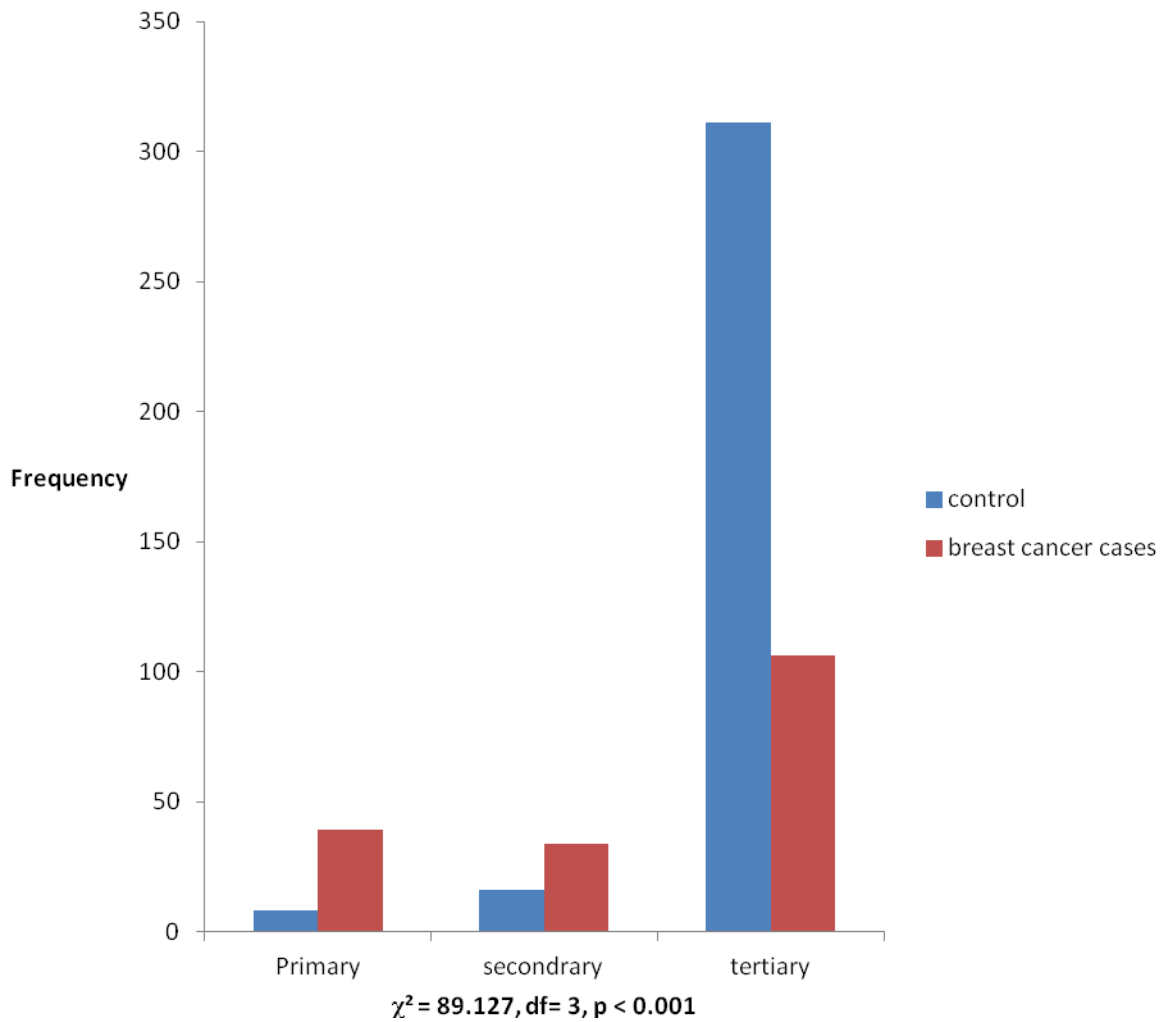
Fig 4.4 shows the association between age at menarche and incidence of breast cancer indicating that breast cancer incidence was higher in women with early age at menarche compared to women with late age at menarche at a significant level of  $P < 0.001$ .

#### **4.9 Association between educational level and breast cancer incidence**

The association between educational level and breast cancer incidence is presented in fig 4.5 showing that there was more of the incidence of breast cancer in women with higher educational level than in women lower educational level at a significant level of  $P < 0.001$

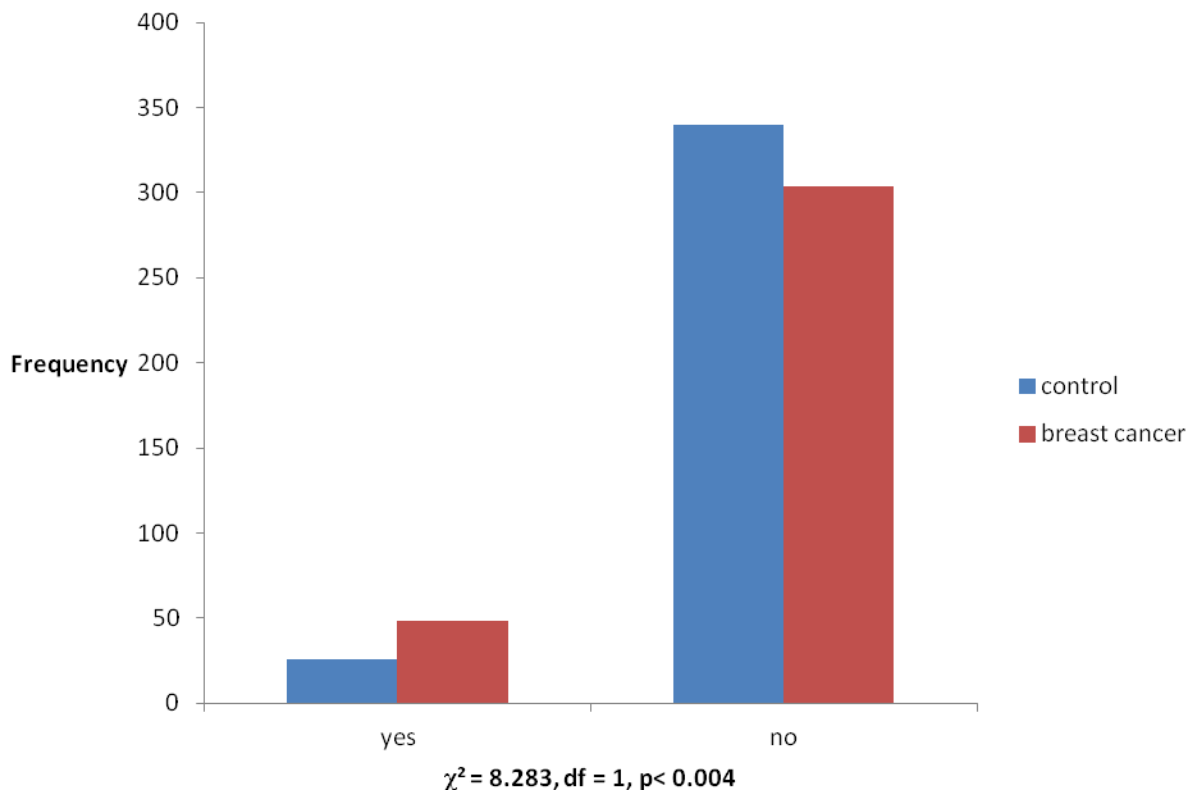
#### **4.10 Association between family history of breast cancer and breast cancer incidence**

Fig 4.6 shows the association between the family history of breast cancer and breast cancer incidence from the study, the incidence of breast cancer was seen to be higher in women with no family history of breast cancer than in women with family history of breast cancer at a significant level of  $P < 0.004$ .



**Figure 4.5:** Association between Educational level and incidence of breast cancer

Showed that there is more of the incidence of breast cancer in women with higher educational level than in women lower educational level at a significant level of  $P < 0.001$

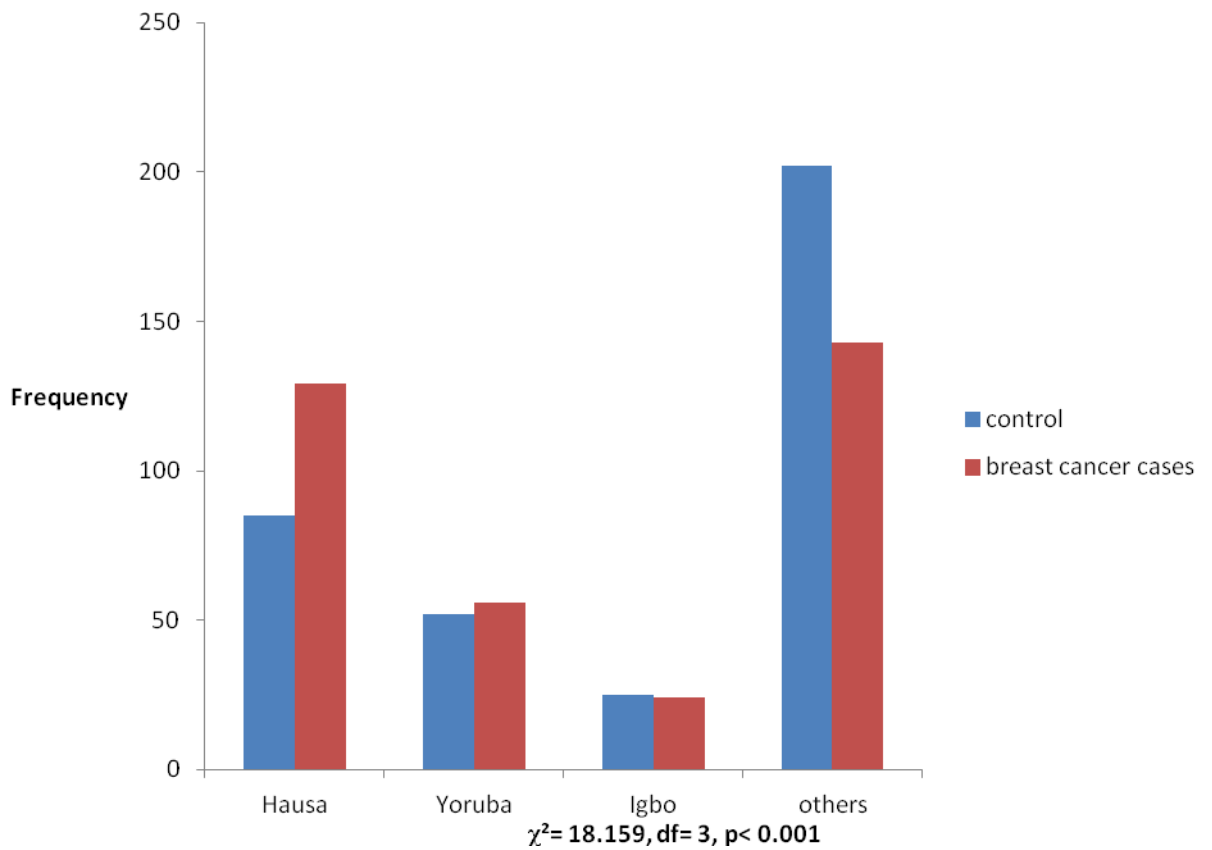


**Figure 4.6:** Association between Family history of breast cancer and incidence of breast cancer

Shows the incidence of breast cancer was seen to be higher in women with no family history of breast cancer at a significant level of  $P < 0.004$ .

#### **4.11 Association between ethnicity and incidence of breast cancer**

Fig 4.7 represents the association between ethnicity and incidence of breast cancer and showed that the incidence of breast cancer was higher in ethnic group classified as others than in the three major ethnic groups although the Hausa ethnic group present more incidence of breast cancer compared to the Igbo and Yoruba groups at a significant level of  $P < 0.001$ .



**Figure 4.7:** Association between ethnicity and incidence of breast cancer

Showed the incidence of breast cancer was higher in ethnic group classified as others and the Hausa ethnic group at a significant level of  $P < 0.001$ .

## CHAPTER FIVE

### DISCUSSION

#### 5.1 DISCUSSIONS

Overweight and obesity are common health conditions and their prevalence is increasing globally. This case control study revealed that the incidence of breast cancer increased with higher BMI throughout the study population. This is in agreement with the work of Ben Ahmed *et al* (2011) and Cold *et al* (2002). Epidemiological evidence found a substantial positive association between BMI and breast cancer risk (Lahmann *et al.*, 2004). One of the most plausible and classical biological explanation is a female hormone-related mechanism because adipose tissue may be a major source of oestrogens (Siiteri, 1987), which are critical mitogens for mammary epithelial cells (Pike *et al.*, 1993; Anderson and Clarke, 2004). Previous studies have provided several potential hormone-related explanations for an increased risk of breast cancer with excess body weight, as follows: increased levels of oestrogen production due to aromatization of androgens in peripheral fat tissue (Siiteri, 1987; Key *et al.*, 2003), and decreased production of sex hormone binding globulin due to obesity (Enriori *et al.*, 1986). These hormone-related mechanisms could increase the supply of free bioavailable oestrogen to breast tissues. In fact, the observed increased risk of breast cancer with increasing BMI was apparently attenuated after adjustment for bioavailable serum oestrogen concentration (Key *et al.*, 2003). Also WHR showed significant association between the breast cancer group and the control group and was seen to be statistically higher in the breast cancer group than in the control group and this is in line with the report of Whincup *et al* (2001).

This finding is in agreement with an age-adjusted model, inclusion of WHR which explained 20 percent of the later stage at diagnosis breast cancer observed in African-American women (Newman *et al.*, 1995). Together, WHR and severe obesity was seen to explain 27 percent of the observed racial difference in stage at diagnosis of breast cancer, which suggested that anthropometric characteristics contribute substantially to this relation (Harvier *et al.*, 2003).

The age at first menstruation did not show any significant difference between the breast cancer group and the control. However the incidence of breast cancer was found to be more in women with early menarcheal age than in women with late. This finding agrees with the report of Beral *et al* (2011) which stated that Breast cancer risk is increased by a significantly greater factor for every year younger at menarche than for every year older at menopause, indicating that menarche and menopause may affect breast cancer risk merely by reducing women's total reproductive years (Easton *et al.*, 2000). Other findings in this study confirmed that young age at menarche and old age at menopause increased breast cancer risk. Many factors known to affect breast cancer risk, including childbearing patterns, height, and BMI, are also associated with women's age at menarche (Peto *et al.*, 2002).

Results from this study disagrees with the effect modification of parity reported by King *et al* (2003) which showed that multiparity and young age at first birth decreased the risk of developing breast cancer and that breast feeding also protected against breast cancer. The result of this study could be due to other risk factors for breast cancer. However, the finding is supported by the work of Jernstrom *et al* (1999) which reported that parity may increase the risk of breast cancer.

The association between birth order and incidence of breast cancer in this study showed that the incidence of breast cancer is more in first born women than in women born of other rank. This is supported by the work of Bernstein et al (1996), which reported that the percentage and amount of free estradiol (E2) are significantly higher in the early part of a woman's first pregnancy than at a comparable time – point in her subsequent pregnancy. Panagiotopoulous *et al* (2000) also reported similar result. It has been hypothesized that prenatal exposure to maternal oestrogens may be a risk factor for breast cancer in the offspring (Salber *et al.*, 2006). In two recent studies, maternal estradiol levels in the first pregnancy have been compared to those in the second, and in both studies the levels were higher in first pregnancy (Breslow, 2008). If both hypothesis and the reported findings are true, women born as their mother's second child would be expected to have lower risk for breast cancer than first-born women.

Women with higher educational level were seen to have higher incidence of breast cancer in this study. High socioeconomic status (SES) which is often defined by income and/ or high educational has been linked to increase risk of breast cancer. This increase risk is not due to high income or educational level itself, but rather to differences in risk factors found in women of different education and income levels (Prentice *et al.*, 2001). Women of higher SES compared to women of lower SES, are more likely to have their first child at a later age, use menopausal hormone therapy, use birth control pills and even drink alcohol. Each of these risk factors increases the risk of breast cancer.

The findings of this study disagree with the work of Hall and Newman (2002) which reported up to 10% of breast cancer to be due to genetic predisposition. In this study it was found that women with family history of breast cancer had lower incidence of breast cancer. This result is supported by a report by Isacc et al which stated that breast cancer

susceptibility is generally inherited in an autosomal dominant pattern with limited penetrance (Isacc *et al.*, 2000). This means that breast cancer can be transmitted through either sex and that some family members may transmit the abnormal gene without developing cancer themselves. This is also supported by the report of the National Institute for Health and Clinical Excellence (2002) which reported that 8 out of 10 women who have close relatives with cancer will never develop breast cancer.

The relationship between ethnicity and breast cancer incidence was shown in a cohort from ethnically diverse women's health initiative (WHI) study in 1998 which examined whether known and/ or presumptive breast cancer risk factors would explain the difference in breast cancer incidence between white women and women of minority groups. In this large cohort of women, it was found that all ethnic/racial groups had a lower age-adjusted breast cancer incidence than white women (Rowan *et al.*, 2005). However, the lower incidence in Hispanic, Asian/Pacific Islander, and American Indian/Native Alaskan women was mostly attenuated after adjustment for the distribution of other breast cancer risk factors. Dietary (Prentice *et al* 2001) and/or physical activity factors (Forshee *et al.*, 2003) may account for some of the remaining variability. The findings of this study showed that other ethnic groups (Yoruba and Igbo) had a lower incidence of breast cancer than the Hausa's. This difference is primarily due to the study location which is mostly dominated by the Hausa's. Women of other minor tribes also showed higher incidence of breast cancer. It remains to be determined whether difference in unidentified environmental exposures, genetic makeup, or other factors may be responsible for the frequency of higher incidence in these groups of women.

## CHAPTER SIX

### SUMMARY AND CONCLUSION

#### 6.1 CONCLUSIONS

In conclusion, neither family history of breast nor parity but BMI and WHR affected breast cancer incidence independently from the anthropometric variables, as found in many other populations similar to a report by Friedenreich, (2001).

This study confirm that early menarche increases breast cancer incidence, to ensure as much comparability as possible between women with breast cancer and control analysis were stratified by these factors; order of birth, ethnic origin and family history of breast cancer.

Family history of breast cancer did not have any effect on breast cancer incidence but rather women with no family history of breast cancer had higher incidence of breast cancer.

First born women had higher incidence of breast cancer than women born of other ranks in the study population.

From this study Hausa women had more incidence of breast cancer compared to Yoruba and Igbo. ( the study location is dominated mainly by the Hausa)

Women with higher educational level were seen to have higher incidence of breast cancer when compared to women with lower educational level throughout the study population.

## **6.2 RECOMMENDATIONS**

- i. Most of the women used for this study are educated thus it is recommended that research should be carried out investigating the association of breast cancer with lactation and breast size.
- ii. More attention to be paid to nutrition and life style habits for improving healthy standards of women in the society by health care providers.
- iii. Teaching women and the populace about the hazardous effect of bad lifestyle habits including diet, alcohol intake, and lack of physical exercise is essential for controlling high risk factors of breast cancer which will contribute significantly to a reduction in the incidence of breast cancer in the society.

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**APPENDIX I**  
**QUESTIONNAIRE**

**Biodata**

Age: \_\_\_\_\_ Date of Birth: \_\_\_\_\_  
Tribe: \_\_\_\_\_ Age at first menstruation: \_\_\_\_\_  
Menopausal age: \_\_\_\_\_  
Educational level (primary, secondary, tertiary): \_\_\_\_\_

**Family**

Birth order (example 2<sup>nd</sup>, 3<sup>rd</sup> etc): \_\_\_\_\_  
Number of siblings: Males: \_\_\_\_\_ Females: \_\_\_\_\_  
Number of Children: \_\_\_\_\_  
Males: \_\_\_\_\_ Females: \_\_\_\_\_


**Health**

Have you ever had any other cancer (circle appropriately) Yes No  
Have you ever been for breast cancer screening? (circle appropriately) Yes No  
If yes, what year: \_\_\_\_\_  
Have you ever had a breast lump removed or any operations on your breast?  
Yes No  
If Yes how old were you: \_\_\_\_\_  
Have any of your family members being diagnose with breast cancer? (circle  
appropriately) Yes No  
If Yes what is your relationship with the person: \_\_\_\_\_

**Anthropometry**

Height (cm): \_\_\_\_\_  
Weight (Kg): \_\_\_\_\_  
Hip circumference (cm): \_\_\_\_\_ Waist circumference (cm): \_\_\_\_\_

APPENDIX II

**HEALTH RESEARCH ETHICS COMMITTEE**  
**AHMADU BELLO UNIVERSITY TEACHING HOSPITAL**  
**SHIKA - ZARIA, NIGERIA.**

E-mail: [abuth@yahoo.com](mailto:abuth@yahoo.com) Website: [www.abuth.org](http://www.abuth.org)

Chairman of Board: Chief. Shuaib Oyedokun Afolabi Fml  
Chief Medical Director: Prof. Lawal Khalid, MBBS, FMCS, FWACS, FRCS(ED) mnl  
Chairman, Medical Advisory Committee: Prof. Abdullahi Mohammed, MBBS, FWACP, FICS  
Director of Administration: Barr. Ishak Bello, LL.B, BL., LL.M, PGDM, AHAN, FCAI

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Our Ref: ABUTH/HREC/TRG /36 17<sup>th</sup> January, 2014  
Your Ref: \_\_\_\_\_ Date: \_\_\_\_\_

**ABUTH HREC FULL ETHICAL CLEARANCE CERTIFICATE**

Re: "Evaluation of the relationship between Breast Cancer and some anthropometric variables in women, in Zaria, Nigeria."

ABUTH Ethics Committee assigned number: ABUTH/HREC/C33/2012

Name of the principal Investigator: - Hadiza Rilwan Alhassan

Address of the Principal Investigator: - Dept. of Human Anatomy  
Faculty of Medicine, ABU, Zaria

Date of receipt of valid application: - 5<sup>th</sup> December, 2013

Date of meeting when final determination on ethical approval was made: - 7<sup>th</sup> January, 2014

This is to inform you that the research described in the submitted protocol, the consent forms, and other participant information materials have been reviewed and *given full approval by the ABUTH Ethics Committee.*

Please note: this approval dates from 17th January, 2014 - 17<sup>th</sup> January, 2015

No participant recruitment into this research may be conducted outside these dates.

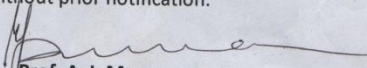
All informed consent forms in this study must carry the ABUTH HREC number assigned to this research and the duration of ABUTH HREC approval of the study.

This HREC expects that you submit your application as well as an annual report for ethical clearance renewal 3 months prior to expiration of study dates. This is to enable you obtain renewal of your approval and avoid interruption of your research.

If there is delay in starting the research, please inform the ABUTH HREC so that starting dates can be adjusted accordingly.

No changes are permitted in the research without prior approval by ABUTH HREC, except in circumstances outlined in national code for Health Research Ethics: <http://www.nhrec.net>.

\*ABUTH HREC reserves the right to conduct compliance assessment visits to your research site without prior notification.

  
Prof. A. I. Mamman  
Chairman, ABUTH HREC