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Age Specific Incidence of Breast Cancer in Calabar, Nigeria

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Authors' contributions

This work was carried out by the Calabar Breast Study Group in collaboration with the Calabar Cancer Registry. Author GAE collated the data and wrote the work. Author OEO analysed the results. Author IAE is the director of the Calabar cancer registry and provided the data, carried out the editing work. All the other co-authors provided the patients or pathology reports and read the manuscripts and effected corrections and fine tuned the work. All authors read and approved the final manuscript.

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ABSTRACT

Aim: To determine the incidence of breast cancer in our uncharted population with a view to determining the disease burden so as to aid planning and intervention.
Study Design: A trend analysis of breast cancers in Calabar between 1st January 2004 to 31st December 2013.
Place and Duration of Study: Calabar Cancer Registry, May to June 2015.
Methodology: Data obtained from record of registered cases of breast cancer seen within 2004 to 2013 from Calabar registry area, was entered and analyzed using SPSS version 21.0. The information sought for includes sex of patients, age, place domiciled in the last one year, rural or urban dwelling as well as topography and morphology of the breast cancers. The population of

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females domiciled in Calabar was determined using the 2006 national population census data and 3.0 % population growth as specified by the national population commission.
Results: Three hundred and sixty nine cases of breast cancers, comprising 11 males and 358 females were seen during this period. Male breast cancer cases were excluded from further analysis. The mean (SD) age of female cases was 44.9 (11.9) years, ranging from 23 to 85 years. Approximately half of the cases (176 or 49.2%) were seen in the 34 to 50 years age group with commonest age group at diagnosis being 40 - 44 years age group. There was a fairly steady increase in annual frequency of cases seen within study period, with 2011 yielding the highest proportion of cases (54 or 14.5%), and about two-thirds of cases (227 or 63.4%) were seen in the latter half of the 10-year study period. Adjusted incidence rate was highest in 2010 (61.3 per 100,000), and high incidence rates was found among subjects in 65-69 year age group in 2009 (179 per 100,000), and 55-59 year age group in 2010 (192 per 100,000).The age specific incidence rate of breast cancer in Calabar is 37.4 per 100,000.
Conclusion: This study has shown that breast cancer is common in Calabar, and it occurs at a relatively early age.

Keywords: Calabar; breast cancer; incidence; females.

1. INTRODUCTION

Breast cancer incidence is rising in Nigeria [1-3], although no national population based cancer registry is available. Data from Ibadan and Abuja registries which are population - based cancer registries operating in the cities of Ibadan and Abuja, as well as reviews from many institution based registries around the country, seem to suggest this [4-6]. To date, the true incidence of breast cancer in the country is not known. Estimates from Ibadan and Abuja cancer registries with limited coverage, estimated at 2.5% of the National population, show that the age standardized incidence rates (ASR) of breast cancer in females stood at 52.0 and 64.4 per 100,000 respectively [1]. This rate appears to be intermediate between the low incidence areas of the world such as Mongolia, 8.0 per 100,000 [7], Inuit population [8], Shenzhen-China (21.1 per 100,000) [9] and the high incidence areas for example, 94 per 100,000 in Aachen Germany [10], 97 per 100,000 among white American women [11] and 109.9 per 100,000 women in Manitoba Canada [12].

The Calabar cancer registry has been in operation for slightly more than three decades. It is Located in Calabar the capital city of Cross River State in the Niger Delta region of Nigeria. It covers the capital city, Calabar and Akpabuyo fully; this comprises three local government councils with population just above 700,000. Data from the rest of the state comprising fifteen local government councils are aggressively being refined. Previously issues of funding, lack of institutional support, lack of acceptable national population data militated against it being truly population based in the first two decades (1978-2008). With the last population census conducted in 2006, the registry quickly took advantage to become truly population based, covering the three Local government areas fully and striving to improve the remaining fifteen Local Government areas. Temporal trends from the registry, although unpublished suggest that breast cancer incidence progressively increased in the first two decades to become the dominant cancer in females over cervical cancer which used to be the commonest. The area adequately covered by the registry includes both urban and rural settlements, however the boundary between both is not so clear cut. Consequently the incidence of breast cancer in both population groups shall be calculated as a homogeneous group. Many studies albeit, show variations in incidence rates among residents within the same geopolitical areas, for example, the urbanized areas of Philippines have incidence rates three times the rates in the rural municipalities [3]. In the same vain Shenzhen China, has 5 breast cancer zones with age standardized incidence rate ranging from 20.0 per 100,000 to 54.1 per 100,00 [9]. A study in Wales also highlighted this regional variations [13]. A gridded incidence was also reported for Connecticut [14]. Among some of the factors implicated in accounting for this variation in incidence in populations living in the same area, are life style factors [15,16], race [11,17], recent immigration [18,19], age [3,20-22] and diet [8]. Environmental pollution, the plague of many urban centres is strongly suspected to cause breast cancers. Rudel et al. in a 2003 review found out that few occupational studies have found association between breast cancer and exposure to polycyclic aromatic compounds

[23]. They found out that population based studies have been few and limited to organochlorines and the results tended to be negative [23]. They therefore encouraged prioritization of investigation of hormonally active agents in commercial products and pollutants some of which are known to induce mammary tumours in animal models [23]. More definitively however Perry Hystad 2015, in a case controlled study carried out in eight Canadian provinces, determined the risk of developing breast cancer from traffic related air pollution. The pollutant in question was Nitrogen dioxide (NO2). By employing three models of measurements, [1] satellite-derived observations; [2] satellite-derived observations scaled with historical fixed-site measurements of NO2; and [3] a national land-use regression (LUR); they concluded that traffic related air pollution may be associated with breast cancer especially in premenopausal women [24].

The cause of breast cancer is unknown, but several risk factors documented elsewhere have been verified through case controlled and systematic reviews. Kaminska et al. in their study of risk factors of breast cancer in Poland conveniently grouped them into two groups [1] inherent factors such as age, sex, race and genetic makeup promoting the familial occurrence of neoplastic disease or benign proliferative disease of the breast. The second comprising extrinsic factors conditioned by lifestyle, diet or long term medical intervention such as the use of oral contraceptives or hormone replacement therapy [25]. They averred that the first group of factors may not be easily modifiable in the course of the patients lifetime while the second group of factors may be modifiable. They concluded that identification of such modifiable risk factors will contribute to the development prevention strategies that will lead to decreased breast cancer incidence [25]. Among the few Nigerian studies documenting the risk factors of breast cancer among Nigerian cohorts are a studies on Hip waist ratio and obesity and height by Adebamowo et al. Both study results supported previous studies that reported positive association with breast cancer [26,27]. In another study Huo et al. found that increased parity and prolonged breast feeding were protective against breast cancer [28]. Perhaps one of the most informative studies in this area is the discovery of high prevalence of BRCA1 and BRCA 2 mutations amongst 434 breast cancer patients in Ibadan, South West Nigeria. In that study they found a high prevalence of BRCA 1 and BRCA 2 mutation of 7.1% and 3.9% respectively. That study reported sixteen BRCA1 mutations seven of which had not been previously reported and thirteen BRCA2 mutations, six of these have not been previously reported [29]. More research needs to be conducted in nearly every aspect of breast cancer in Nigeria because the field is still virgin and appears to hold good prospect of helping to unravel the factors responsible for early breast cancer in our environment.

To date most breast cancer patients in Nigeria present late to hospitals [30], due to preference for alternative practitioners, quacks [31] and poor breast cancer awareness [32-34]. Other socio-demographic factors such as; being single, educational level at primary level, ignorance of illness type, belief in herbal and spiritual intervention, were found by a Lagos group to be responsible for late presentation [35]. A study amongst rural dwellers in South- West Nigeria found that respondents attributed breast cancer to be caused by putting money in brassiere and attacks from enemies [36]. None of this women identified early presentation as an advantage in breast cancer treatment [36]. Whilst the lay communities could be accused of ignorance of breast cancer, several studies have shown unpardonable ignorance of breast cancer among medical personnel of all cadre ranging from trainees, nurses and doctors in Nigeria, as is in many third world countries [32-34,37,38]. There is no age standardized breast cancer incidence reported for Calabar. The data analyzed is involves Calabar and Akpabuyo, and involves cases resident in Calabar and Akpabuyo one year prior to the cancer incidence. The registry is fed primarily from Department of Pathology, Surgical clinics, Department of Haematology, all in the University of Calabar Teaching hospital. Additional information is obtained from General hospital Calabar, St. Joseph's Hospital Ikot Ene Akpabuyo and seven private hospitals which are visited by the Registry's team every two weeks. Because of the paucity of information available on breast cancer in this environment, the need for this study cannot therefore be over emphasized.

2. MATERIALS AND METHODS

Database of breast cancer cases between 1st January 2004 and 31st December 2013, stored as Can Reg. 4 format, in the Calabar Cancer registry was accessed. Data obtained from record of registered cases of breast cancer seen

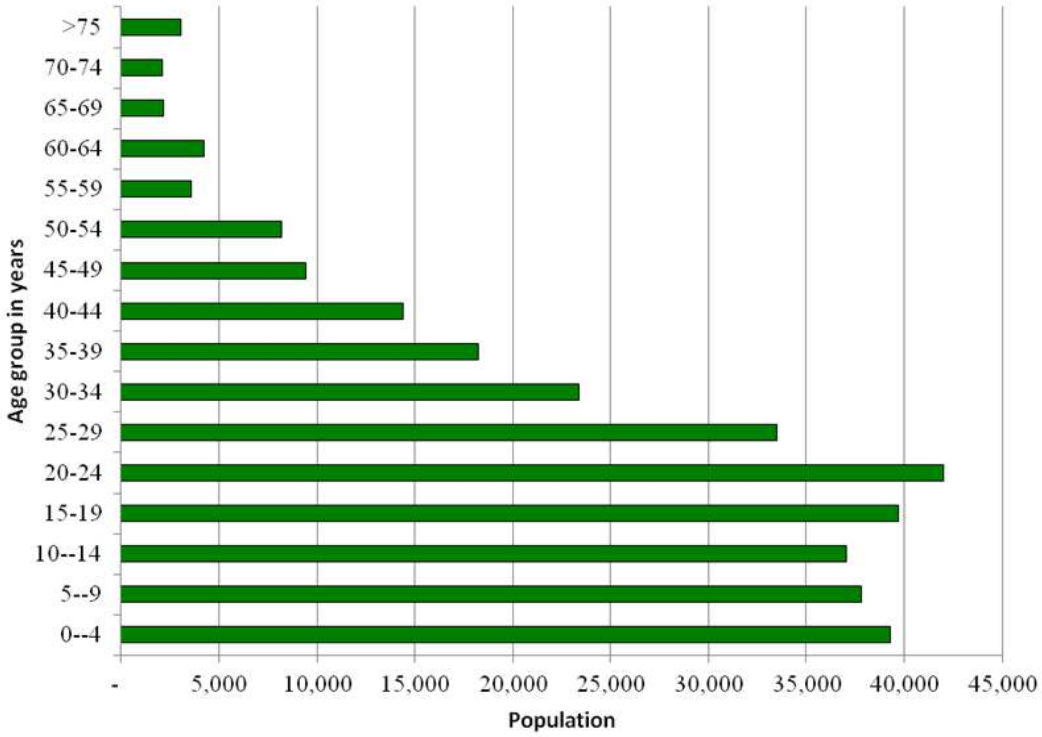

Fig. 1. Female population of Calabar Registry Area (Calabar Municipality, Calabar-South and Akpabuyo), by age group, census of 2006

within 2004 to 2013 from Calabar registry area, was entered and analyzed using SPSS version 21.0. The patients age, sex, date of incidence, area domiciled in the last one year, whether rural or urban and histological diagnosis were the important research questions.

2.1 Population

Age distribution of the population of female residents in the study area was obtained from database of population census conducted in 2006, with intercensal estimations made in collaboration with the National Population Commission, Calabar, Nigeria, using constant annual growth rate of 3.0% (Fig. 1). World standard population was used to calculate the age-standardized or adjusted rates.

3. RESULTS

Data obtained from record of registered cases of breast cancer seen within 2004 to 2013 from Calabar registry area, was entered and analyzed using SPSS version 21.0. Within the study period, three hundred and sixty nine cases of breast cancer were seen, comprising of eleven [11] cases among males (3.0%), and three hundred and fifty eight (358) cases among females (97%). Only female breast cancer cases were further analyzed.

3.1 Female Breast Cancer

The mean (SD) age of female cases was 44.9 (11.9) years, ranging from 23 to 85 years. There appears to be a fairly steady decrease in the mean age at diagnosis, especially in the later years (Fig. 2), but there was no significant difference in mean age comparing the years ($F=0.80$, $p=0.62$). Approximately half of cases seen (176 or 49.2%) were between 34 and 50 years old at time of diagnosis, with the commonest age group being 40-44 years (Table 1). There was a fairly steady increase in annual frequency of cases seen within study period, with 2011 yielding the highest proportion of cases (54 or 14.5%), and about two-thirds of cases (227 or 63.4%) seen in the latter half of the 10-year study period (Table 2).

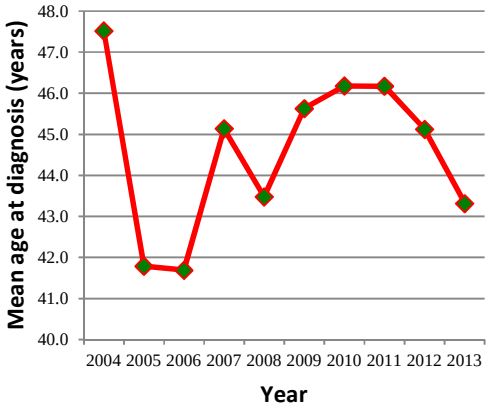

Fig. 2. Mean age at diagnosis of female breast cancer in Calabar, by year (2004-2013)

Table 1. Age-group distribution of breast cancer subjects (N=358)

Age group (years)	Frequency	Percentage
20-24	2	0.6
25-29	20	5.6
30-34	49	13.7
35-39	58	16.2
40-44	63	17.6
45-49	55	15.4
50-54	32	8.9
55-59	30	8.4
60-64	21	5.9
65-69	15	4.2
70-74	7	2.0
≥ 75	6	1.7
Total	358	100.0

Most types of breast cancers (303 or 84.6%) were not otherwise specified (NOS), with about one-tenth (34 or 9.5%) occurring at upper-outer quadrant, and the remaining [21] constituting about 5.9% of cases (Table 3).

Adjusted incidence rate was highest in 2010 (61.3 per 100,000), and high incidence rates were found among subjects in 65-69 year age group in 2009 (179 per 100,000), and 55-59 year age group in 2010 (192 per 100,000) (Table 4). Incidence rates appear to be decreasing, following a peak incidence of 61.3 per 100,000 in 2010 (Table 4, Fig. 3).

Table 2. Annual distribution of female breast cancer cases seen in Calabar (N=358)

Year	Frequency	Percentage
2004	27	7.5
2005	24	6.7
2006	26	7.3
2007	29	8.1
2008	25	7.0
2009	43	12.0
2010	45	12.6
2011	52	14.5
2012	49	13.7
2013	38	10.6
Total	358	100.0

Within the 5-year period from 2004 to 2008, there was an average annual decrease in incidence rate of 3.5% (95% CI: 1.1%-4.9%). However, within the 5-year period from 2009 to 2013, there was an average annual increase in incidence rate of 1.9%% (95% CI: -0.85% to 2.2%).

Table 3. Frequency distribution of type of female breast cancer in Calabar (N=358) ICD-10

Site	ICD coding	Frequency	Percentage
Breast – NOS (Mammary gland)	C 50.9	303	84.6
Upper-outer quadrant of breast	C 50.4	34	9.5
Overlapping lesion of breast	C 50.8	8	2.2
Upper -inner quadrant of breast	C 50.2	4	1.1
Lower-outer quadrant of breast	C 50.5	4	1.1
Lower-inner quadrant of breast	C 50.3	3	0.8
Central portion of breast	C 50.1	1	0.3
Nipple	C 50.0	1	0.3
Total	-	358	100

Table 4. Annual crude, adjusted and age-specific incidence rates of female breast cancer in Calabar (2004-2013)

Year	Crude	Adj.	20-24 yr	25-29 yr	30-34 yr	35-39 yr	40-44 yr	45-49 yr	50-54 yr	55-59 yr	60-64 yr	65-69 yr	70-74 yr	≥75 yr
2004	31.7	42.8	0.0	3.0	12.9	16.5	35.0	74.5	0.0	83.9	23.6	46.6	94.9	66.7
2005	27.1	30.0	0.0	3.0	38.6	11.0	20.9	42.4	12.2	0.0	70.7	0.0	47.3	0.0
2006	29.3	32.0	0.0	6.0	21.4	27.4	27.8	52.9	24.4	24.4	23.5	46.3	0.0	0.0
2007	32.5	37.0	0.0	0.0	21.3	43.7	20.8	52.7	0.0	116.2	0.0	46.2	0.0	33.1
2008	28.0	28.7	2.4	3.0	12.7	49.0	13.8	31.5	12.1	82.8	70.1	0.0	0.0	0.0
2009	47.9	56.4	0.0	5.9	8.5	38.0	68.9	104.8	36.3	55.1	23.3	178.6	0.0	32.9
2010	50.0	61.3	0.0	14.8	16.9	21.7	61.8	31.4	72.4	192.2	23.2	91.5	46.2	65.5
2011	57.7	60.1	0.0	11.8	25.3	32.4	41.1	114.6	60.1	27.4	115.8	136.9	46.4	32.7
2012	54.2	56.1	2.3	11.7	29.4	37.7	68.3	31.2	47.9	136.4	92.3	45.5	92.6	0.0
2013	41.9	40.1	0.0	11.7	16.7	32.2	61.3	31.1	95.6	54.4	23.0	45.4	0.0	0.0

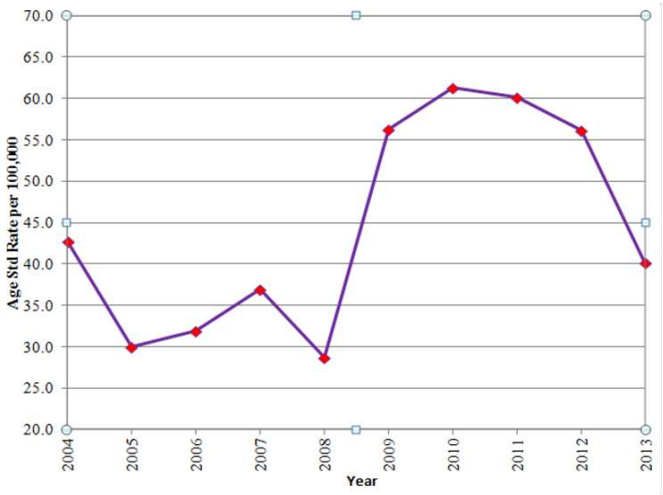

Fig. 3. Trend in age-standardized incidence rate of female breast cancer in Calabar (2004-2013)

4. DISCUSSION

The mean age of breast cancer patients in Calabar is 44.9 (11.9) years; this is similar to several Nigerian institution based studies, Adisa reported 47 years [39], Adebamowo 43 years [40], Ekanem 45.7 years, 42,7 (12.2) years by Ikpatt, Ndoma and Collan [41] and 46 years. The age is similar to some African reports for example, Boder et al. Libya 46 years, [42]. The Calabar mean age is a decade less than reports in some western countries, for example a comparative African and Caucasian study by Ikpatt et al. in their series, compared the age in a Nigerian breast cancer cohort, 42.7 (12.2) years to a Finish Cohort a 58.7 (12.) years. In the same vain Jack et al in south east England reported that black African and Caribbean breast cancer patients were on the average younger than their Caucasian counterparts [43]. What appears to be the emerging difference between countries in the low risk breast cancer belts and the high risk areas is that in the low risk areas, the breast cancer increased incidence is accompanied by a drop in the average age the cancer occurs as many are in the premenopausal age group compared to post menopausal dominance in the high risk areas [15,21,30,42]. There appears to be a fairly steady decrease in the mean age at diagnosis of breast cancer in Calabar, especially in the later years, whether increasing urbanization and change in life style or other factors are at play, needs to be investigated.

The crude and adjusted incidence rates of breast cancer in Calabar witnessed progressive increases from 2009 to 2011. While the crude rate peaked at 57.7 per 100,000 in 2011, the adjusted rate peaked at 61.3 per 100,000 in 2010. Both rates progressively declined to 41.9 per 100,00 and 40.1 per 100,000 respectively. Even with the seeming decrease in the last two years, the rates are still higher than that recorded for both values in the first five years from 2004 to 2008, except for 42.8 per 100,000 adjusted incidence rate recorded in 2004. Our analysis did not discriminate between the incidence rate in the largely rural parts of Akpabuyo and the largely urban parts of Calabar like a China cancer registry study did. By analysing the rural and urban cancer registries separately, the Chinese discovered that breast cancer incidence rates were three times as high in the urban than in rural areas [44]. Several other studies reported disparities between rural and urban dwellers [3,7,9,14]. Future reports should strive to further categorize the population better so as to aid analysis and bring out the inherent differences in breast cancer subsets in our cancer registration process. The difficulty in classification also stems from the fact that Akpabuyo has witnessed a massive injection of a middle class population with the construction of housing estates for civil servants in the last 10 years. It is doubtful if the new middle class population injection may be rightly classified as living a rural life. What constitutes rural has to be rigorously defined with regards to Akpabuyo to facilitate thorough analysis.

Approximately half (49.2%) of the breast cancer occurring in females in Calabar was between the ages of 30 and 50 years. This pattern conforms

with reports in many African and Afro Caribbean studies [1,17,30,41-43]. Even though the peak incidence periods were in the 40 to 44 years age bracket, the average age specific incidence rate was highest in the 55 to 59 years (77.3 per 100,000), followed by 57.0 per 100,000 for 45 to 49 years group. There was generally a progressive annual increase in average age specific incidence rate from age 30 to 34 years at 20.4 per 100,000 to its peak at 77.3 per 100,000 at 55-59 years, before a gradual decline from age 65 to 69 years was noted. An unexplainable drop was witnessed in the 50 to 54 years group with an average age specific incidence rate of 36.1 per 100,000. Annual age specific incidence rate also witnessed a progressive increase from age 30 to 43 years, with the highest rates seen in 2009 and 2010, as follows 65 to 69 years (178.6 per 100,00) and peak of 192.2 per 100,000 in the 55 to 59 years group respectively. This is similar to a study in Manila- where the rate started to rise in the 30 to 34 years group and peaked at a higher age of 70 to 74 years [3]. The age specific incidence rate is reported to have doubled in Japan in the 35 to 44 years age group since 1960 [45]. Our observation that the highest yearly age specific incidence of 192.2 per 100,000 occurred in age 55 to 59 years may signal an early change in demographics as was observed in a Singaporean study. The study found that in 30 years the peak age of diagnosis of breast cancer changed from 45 to 49 years to late 50'S [16], perhaps coinciding with a change in their economic fortunes and adoption of a western lifestyle. Whether such a change may occur in Calabar in future, time and an anticipated change in our economic fortunes will tell. Worldwide it has been recorded that breast cancer incidence rose by 30 to 40% between 1970's and 1990's [11]. In Calabar even though our records date back to the late 1970's,records in the first two decades were not refined enough to be reliably extrapolated on the population.

At an average age specific incidence rate of breast cancer at 37 per 100,000, Calabar boasts an incidence rate like many Eastern European countries [46]. Quite worryingly, the frequency of diagnosis in young women is alarming. In a region still grappling with infectious diseases, a rise in cancer burden as is now experienced will further put a strain on our already low health budget [1], and low sectorial allocation to cancer care. The belief that breast cancer incidence is low in this part of the world may soon be vigorously challenged. If one considers that our population is young and life expectancy is low, were our women to be living as long as their western counterparts the breast cancer picture in Nigeria might be different from what we know today. Time is now to invest on unravelling aetiological factors of breast Cancer in Nigerian women and other women of African ancestry which appear different from their Caucasian breast cancer counterparts [17,20,28,39,40, 47-50].

Within the 5-year period from 2004 to 2008, there was an average annual decrease in incidence rate of 3.5% (95% CI: 1.1%-4.9%). However, within the 5-year period from 2009 to 2013, there was an average annual increase in incidence rate of 1.9%% (95%CI: -0.85% to 2.2%). What might reasonably explain the initial decreased incidence is still farfetched. In the last five years however fine needle aspiration cytology, screening mammography and expansion of surgical services in Calabar may have contributed to the later increases. We do not have credible data on the extent of use of combined oestrogen and progesterone oral contraceptives in Calabar, which are known to increase the relative risk of breast cancer [51]. There are no records on the extent of use of postmenopausal hormone replacement therapy, the reduction of which is reported to cause a decrease in annual incidence in the United states up to 8.6% [52].

The alarming rate of diagnosis of breast cancer in the young in this environment calls for both local and international collaborative research efforts in two major areas (1). There is an urgent need to conduct low cost scans on the genetic polymorphism that determine breast cancer risk in this environment (2). Epigenetic studies should be carried out to determine the DNA methylation pattern and its influence on breast carcinogenesis in this environment. Current understanding of cancer as genetic disease cannot be over stated. Research in this area of medicine nearly outstrip our ability pace with it. More than a decade ago, a systematic review by Allison et al in 1999 on the role of common genetic variants on cancer risk surveyed 46 studies and classified polymorphism in breast allele into high relative risk, moderate and low risk [53]. The same review found out that homozygote's for PR PROGINS allele are thought to be protected of breast cancer, even though the study found the protection of borderline significance [54]. Polymorphisms have even been reported in oestrogen genes which confer increased risk of breast cancer. For

instance a recent study amongst Han Chinese women assayed 32 single nucleotide polymorphism in oestrogen related genes and found out that rs700519 and rs2069522 were associated with breast cancer susceptibility in Han Chinese women [55]. Several methods of epigenetic modification of genes are thought to be in play in the multiple steps in cancer formation. Methylation is thought to be involved in the early stages of carcinogenesis, for instance it was reported that some protective tumour suppressor genes are hypermethylated in their promoter regions and silenced early in the carcinogenic process [56]. Their biological functions include, cell cycle regulation, DNA repair, apoptosis, cellular homeostasis and invasion [56]. Hypermethylation has been explained as the possible cause of oestrogen receptor negativity when Weigel and deConinick found out that ER negative breast cancer cells had no ER mRNA [57] while Ferguson et al could reactivate ER mRNA in those cell lines by inhibition of metthylation [58]. With all these information lacking about African breast cancers chances are that there are genes out there that may explain the early onset of breast cancers as we find in this environment. Better still there may be a primordial gene(s) which may improve our current understanding of the carcinogenic process lurking out there in these patient.

5. CONCLUSION

Breast cancer is a Public Health problem in Calabar-Nigeria with predominance of young women, early detection and treatment of the disease will be the Government desire. It is desirable for government and funding agencies to fund research in genetic polymorphism and epigenetic alteration underlying breast cancer aetiology in this environment.

6. LIMITATION OF STUDY

The sample size is small, effort must be made to extend the cancer registry to cover the entire Cross River State.

7. RECOMMENDATION

To reduce the high incidence of advanced breast cancer, a well coordinated government sponsored intensive breast awareness and mammographic screening programme for high risk groups at designated centres in the six geopolitical zones is recommended. This would contribute to early detection and effective control of breast Cancer in Nigeria.

CONSENT

It is not applicable.

ETHICAL APPROVAL

Ethical permission for this study was granted to the Calabar Breast Study Group by the University of Calabar Teaching Hospital Ethical Review Board.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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