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Relationship between central adiposity and breast cancer tumor grade in females with breast cancer in south east Nigeria

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Abstract

Background: Breast cancer is the most common cancer in women worldwide and the second most common cause of cancer-related death. Breast cancer is commonly graded using the Modified Scarff-Bloom-Richardson (SBR) system because it is simple and effective with less inter-observer variability.

Obesity: Obesity is a growing public health concern and has been associated with the evolution of many cancers including breast cancer. There are conflicting studies on the relationship between waist circumference which can be a measure of central obesity and breast cancer aggressiveness, as measured by the Modified Scarff-Bloom-Richardson score. These studies are few in Nigeria

Methodology: This was a prospective, hospital-based, cross-sectional study that involved females with breast cancer. The waist circumference of the patients was measured on presentation. Patients underwent Core Needle biopsy. Those with histologically diagnosed carcinoma were enrolled in the study.

Result: The mean age (SD) of the subjects was 49(13) years; all the participants were women. The mean (SD) waist circumference (WC) was 94.46(11.80) The mean (SD) WC for premenopausal and postmenopausal women was 94.11cm and 94.76cm respectively, thus both older and younger individuals have similar central adiposity. There is a moderate correlation between waist circumference and grades of breast cancer.

The study findings show the importance of weight reduction in women of all age groups.

Keywords: Breast cancer; Central adiposity; Obesity; Scarff-Bloom-Richardson Grading system; Waist circumference

1. Introduction

Breast cancer is the most common cancer in women worldwide. [1]In 2018 there were 2.1 million newly diagnosed cases, accounting for 25.0% of cancer cases in women worldwide.[2] The incidence varies greatly worldwide from 37.3 per 100,000 in West Africa to 92.6 per 100,000 in Western Europe. Though lower incidence rates are found in Africa these rates are gradually increasing.[2] It is the second most common cause of death in women worldwide. There were 626,679 deaths worldwide from breast cancer in 2018 of which 58.0% occurred in less developed parts of the world.[2]

Obesity is related to increased breast cancer incidence, more aggressive tumors, and poorer prognosis.[3] Evidence suggests that women of all ages who develop breast cancer are likely to have higher mortality if they are obese.[4] Some studies[5][6] have linked obesity with higher cancer-related death. studies[7][8] have found a positive correlation between

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obesity and the aggressiveness of breast cancer through some proposed mechanisms such as the role of insulin. Insulin and insulin-like growth factors bind to the insulin receptors expressed on breast cancer cells and activate signalling through P13K/Akt and Ras/Mapk pathways. This finally leads to increased tumor proliferation.[9]

Some studies have demonstrated a positive association between obesity and advanced tumor grade and stage at diagnosis. Ayoub et al[5] in Jordan in their evaluation of the impact of obesity on clinicopathology of breast tumor found that obesity was significantly associated with a higher grade of breast carcinoma. This he suggested maybe because obese patients have more biologically aggressive tumors as indicated by higher expression of cellular proliferation markers.[10] One of the most common methods of assessing this grade is the Modified Scarff-Bloom-Richardson (SBR) grading system. It uses 3 parameters: tumor tubule formation, mitotic index, and nuclear pleomorphism.[11] This system has been endorsed by the College of American Pathologists and the World Health Organisation.[12] The basic principle is the summation of scores for the three variables, each of which is assigned from one to three points according to the degree of departure from the normal epithelium. The value ranges from SBR grade 1, which has the best differentiation, to SBR grade 3, which has the worst differentiation.

There is paucity of published study in Nigeria on adiposity and tumor grade. This study aimed to determine the relationship between central adiposity and the aggressiveness of breast cancer in adult Nigerian females

2. Patients and methods

This was a hospital-based, cross-sectional, prospective done at the General surgery clinic of Nnamdi Azikiwe University Teaching Hospital, Nnewi from March 2021 to February 2022 following approval from the hospital ethical committee.

All new adult female patients, aged between 18 and 75yrs that attended the breast clinic in NAUTH, who met the inclusion criteria, and who voluntarily gave their consent for the study, were enlisted in the study. Patients with eventual histologic confirmation of breast cancer were included. Exclusion criteria were patients who refused to give consent, patients on active weight reduction programme, patients with co-morbidities such as AIDS or Tuberculosis, Stage IV breast cancer and Patients whose histological result turns out to be negative.

The sample size was calculated based on the statistical formula:

$$nf = \frac{n}{1 + \frac{n}{N}}$$

80 patients were the calculated sample size. Detailed clinical assessment including breast examination was done for each patient.

Waist circumference was measured using the WHO guideline. The measurement was made at the midpoint between the lower margin of the last palpable rib and the top of the iliac crest using a stretch-resistant measuring tape. The measuring tape was snug around the body and was not pulled so tight to avoid constricting the body. The tape was oriented parallel and at a level parallel to the floor. The patient stood with the arms at the sides and the feet close together. The patients were relaxed and the measurements were taken at the end of normal expiration. Each measurement was repeated twice; if the measurements were within 1cm of each other, the average was calculated but if the difference between the two measurements exceeded 1cm, the two measurements were repeated.

Patients with suspected breast cancer underwent core needle biopsy. Using size 16G Semi-Automatic Tru-Cut needle (Geotek Semi-Automatic biopsy needle, Ankara Turkey), at least five samples were taken from positions 12, 3, 6, and 9 o'clock and the centre. The samples were inserted into a universal container with 10% formalin and sent to the histopathology laboratory with an accompanying properly filled pathology request form.

The samples for histology were analysed by the same Consultant Histopathologist (with 10 years of experience) and the tissue was graded using the Modified Scarff- Bloom-Richardson (SBR) grading. All data were entered into structured proforma and analysed using the IBM Statistical Package for Social Science (SPSS) Version 25 Chicago Illinois. Data were subjected to Spearman Correlation. A p-value ≤ 0.05 was considered statistically significant. Results were presented in tables and charts where appropriate

3. Result

The total number of patients recruited and analysed were 80 out of 172 patients that were seen during the study period. The mean age of the patients was 49 years and all the patients were females.

Figure 1 showed the age distribution with the age range of 40-49 years having the highest number (42.5%) of patients. Most (76.3%) of the patients were married 80% of the patients had at least a secondary level of education

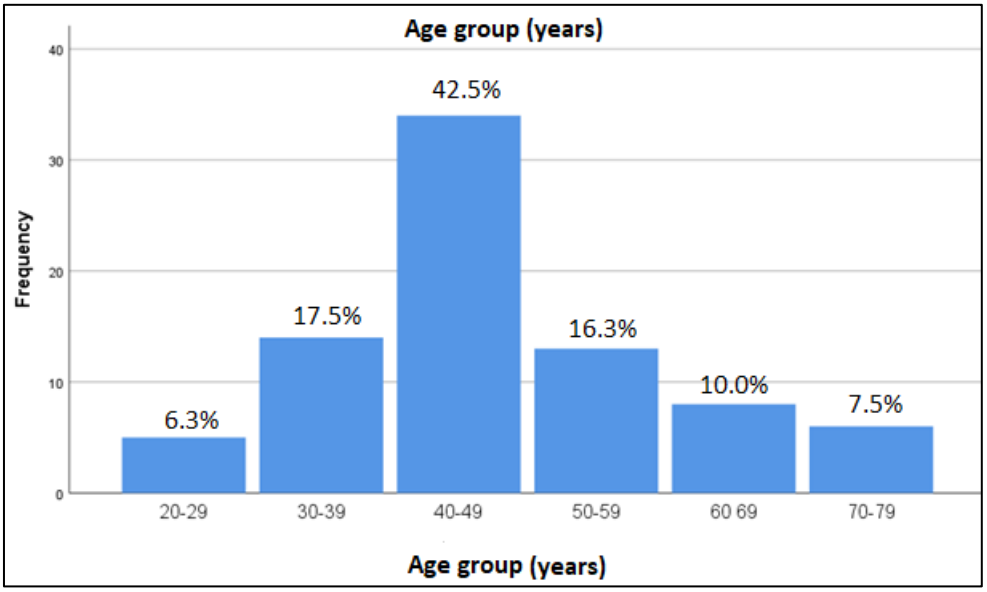

Figure 1 Age distribution

3.1. Anthropometric variables

The mean (SD) waist circumference of the study is 94 cm (11.80) indicating high central fat accumulation (Table 1). Only 10% of the patients had WC < 80cm while most patients (72.5%) had WC equal to or greater than 88 cm (Table 2). When the patients were categorised based on menopausal status, 63.7% (51) were pre-menopausal while 36.3%(29) were postmenopausal. The mean waist circumference for the premenopausal women was 94.11cm while that of postmenopausal women was 94.76cm.

Table 1 Anthropometric variables

VARIABLE	MEAN	SD	MEDIAN	MODE	MIN	MAX
WC	94	11.8	98	96	62	120
BMI(Kg/m^2)	27.5	6.1	27	27	16.8	41
WC PREMENOPAUSAL(cm)	94.11	11.99	96	87	62	115
WC POSTMENOPAUSAL(cm)	94.76	12.07	95	85	62	120

Table 2 Waist circumference

Waist Circumference	No of patients	Percentage
<80	8	10
80-87.7	14	17.5
≥88	58	72.5
TOTAL	80	100

3.2. Presenting complaints

All the patients presented with breast lumps with most occurring in the left breast (55%) while right breast lumps occurred in 43.8% of the patients. One patient (1.3%) presented with a bilateral breast lump. Few patients (6.25%) presented with additional symptoms of nipple discharge. The mean duration of symptoms is 1.66years with a range of 0.08 to 15 years.

3.3. Scarf bloom richardson grading

The most common grade found in the study was grade II seeing in 50 (62.5%), followed by grade III 19 (23.8%) while the remaining 11(13.8%) had a grade 1 tumor.

3.4. Anthropometric variables and sbr grade

There was a moderate correlation with statistical significance (P=0.001; r =0.5) between waist circumference and the SBR grades of breast cancer as outlined in table 3. When the patients were stratified into menopausal status, there was a statistical difference in correlation between waist circumference and grades of breast cancer in both premenopausal and postmenopausal women (P=0.0001 vs 0.001) as shown in table 4. There is a low correlation between BMI and grades of breast cancer (r=0.2, P=0.039).

Table 3 Relationship between waist circumference and grades of breast cancer

GRADE	N(%)	NORMAL WC	MODERATE WC	HIGH WC	P-VALU
					0.001
GRADE I	11(13.75)	1	3	7	
GRADE II	50(62.5)	5	9	36	
GRADE III	19(23.75)	1	3	15	
TOTAL	80(100)	7	15	58	

Table 4 Relationship between anthropometric variables and menopausal status.

VARIABLES	CORRELATION COEFFICIENT	P-VALUE
WC FOR PREMENOPAUSAL	0.49	0.0001
WC FOR POSTMENOPAUSAL	0.6	0.001
BMI	0.2	0.039
BMI FOR PREMENOPAUSAL	0.25	0.030
BMI FOR POSTMENOPAUSAL	0.21	0.047

4. Discussion

The mean age of the patients in this study is 49 years. This is similar to studies done by Olaogun et al[13] and Oguntunde et al [14] in Nigeria. The mean age of presentation of breast cancer has not changed much in South East Nigeria from what was seen in early 2000. The study by Anyanwu [15] in the same centre in 2008 showed a mean age of 46.85 years. This contradicts western studies which have higher mean age at presentation. The peak age incidence of breast cancer is between 60-65 years in most Western studies[6] [16]. A study by Bandera et al[8] in New Jersey showed a slightly lower mean age of presentation (54.5 years) compared to other Western values, though the study was among black women.

Most patients in this study were educated, with 80.0% attaining at least a secondary level of education, with only 1.3% of the patient not experiencing formal education. The level of education did not affect positively the presentation as most patients still presented late. Only a few patients 16 (20.0%) presented within 3 months of the onset of symptoms. The pattern of presentation is similar to that of many studies in Africa with most patients presenting with a breast lump. All the patients in the index study presented with breast lumps in addition to some that presented with nipple discharge. The left breast was more commonly affected. The left breast was also commonly affected in the study by Egwuonwu et al [17] in the same centre and by Memon et al[18] in Karachi, Pakistan. However, the study by Adeniji et al[19] in Lagos

showed a slightly more occurrence in the right breast accounting for 50.2% of the study population. The sample size was more in this study. Late presentation is the pattern in developing countries. The mean duration of symptoms before the presentation is 1.7 years (see table 1) with most patients presenting with stage III disease. A study done by Olaogun et al[13] also demonstrated that all the patients presented with lumps with a mean duration of the symptom of 9 months. This late presentation is in contrast to the developed countries where patients present early and some are asymptomatic and the diagnosis is made during routine screening. Over 70.0 % of the patients presented in the early stages in the study done by Nattenmuller et al[16] in Germany. The late presentation in the index study is similar to what is seen in Africa and other developing worlds.

Menopausal status has been associated with grades of breast cancer. Most patients in the index study were premenopausal (63.7%). This is further proof that breast cancer occurs at a much younger age in Africa and is mainly a premenopausal disease. Breast tumors in premenopausal women have been noted to be of a higher grade.[20] A study by Akinyemiju et al[21] in Southwest Nigeria, showed that an almost equal number of the participants were divided into pre- and postmenopausal with the former accounting for 49.4% and later 50.6%. This is in contrast to what is obtainable in Western countries where most patients are postmenopausal.[22] The study by Ayoub et al[5] in Jordan showed that most patients were postmenopausal with premenopausal women making up 44.0% of the population.

Breast cancer grade is a prognostic factor and a representative of the aggressiveness of a tumor. High-grade tumors (grade III) are more aggressive than low grade (grade I), with grade II in between, otherwise regarded as intermediate. Some clinicopathologic factors such as age, ethnicity, hormone receptor status, and menopausal status affect the grade of breast cancer.[20] Grade II was the most common in the index study, accounting for 62.5% of the study population followed by grade III (23.8%), with both accounting for 86.25%. Similar findings were seen in the study by Oluogun et al[23] when they studied the clinical presentation and histological pattern, and survival outcome of breast cancer in Southwestern Nigeria. Another study done by Akinyemiju et al[21] also found grade II to be the most common histological grade. However, a study by Ebughe et al [24] in Calabar to determine the distribution of tumor grades and histologic types of breast cancer showed that grade III tumors are the most common grade accounting for 68.0% of the study population followed by grade II which made up 24.0 %. The grades of the tumor were noted not to be significantly related to different age groups, place of residence, parity family history, menopausal status or histological types; the relationship of the tumor grade to obesity was not assessed in their study. Similarly, Nattenmuller et al[16] also found grade II as the most common SBR grade when they assessed the association between obesity and breast cancer risk in Germany. This is in contrast to a study by Balekouzou et al[25] in the Central African Republic where SBR grade III was the most histologic grade. However, the result of the histologic grade was available only in 28 patients out of the recruited 174 cases. This was therefore, not a true representation of their study population. Also in the study by Ayoub et al[5] in Jordan, the majority (52.3%) of the patients presented with grade III tumors followed by grade II tumours. The disparity may probably be due to the higher sample size in the study. The study by Zheng et al[20] in Western China to assess whether epidemiologic and clinicopathologic features are associated with tumour grade shows that grade I/II tumours are more common accounting for two-thirds of the patients. The study also found that younger patients less or equal to 40 years were more likely to be in grade III whereas older patients more than or equal to 61 years were more likely to be in grade I/II. Premenopausal women were more likely to have increased risk of grade III breast tumor as compared with postmenopausal women (51.16% vs. 45.63%). The mean age of the study population was 50.2 years with age range of 17-95 years. The study by Khalis et al[26] in Morocco found that over 45.0% of the patients have general obesity in contradiction to the index study. However, the study is limited by the fact that most information was self-reported by the participants and central adiposity was not measured. The mean waist circumference of the patients in the index study is 94cm. A systematic review by Adeole et al[27] to estimate the nationwide and zonal prevalence of obesity and overweight in the adult Nigeria population showed that the mean waist circumference and BMI were 86.5cm and 25.2kg/m^2 respectively with over 12 million people aged 15 years or more said to be obese in 2020, however both sexes were used for the study. The mean BMI in the index study is similar to that of Adeola et a[27], though, the waist circumference in the latter is lower probably because both sexes were included in the study.

The negative effect of obesity on the development and progression of breast cancer cannot be overemphasized. Studies have shown that obesity as measured by various methods is associated with higher grades of breast cancer.[28][29] The distribution of body fat is more important to analyse than the overall body weight. Waist circumference is an important parameter used in the measurement and diagnosis of central obesity which many studies have shown to be associated with a worse prognosis of breast cancer in both pre-and postmenopausal women. Tumors associated with obesity are more aggressive and patients usually present in the advanced stage with poorer treatment outcomes. This study noted a statistically significant difference (P=0.001) between central obesity as represented by waist circumference and the grades of breast cancer irrespective of the patient's menopausal status [P=0.0001 for premenopausal and P=0.001 for postmenopausal] (see table 3 and 4). Thus patients with higher waist circumference are more likely to have worse grades of breast cancer and vice versa.

However, some studies found contradictory results concerning the relationship between obesity and grades of breast cancer. Chen et al[30] evaluated the prognostic effect of central obesity on triple-negative breast cancer. They found no significant relationship between central obesity and grades of breast cancer among triple-negative breast cancer patients. The study also demonstrated no significant association between general obesity or central obesity and the grade of the tumor, lymphovascular status, and menopausal status. However, obesity was associated with larger tumor mass, and it is an independent prognostic factor of overall and disease-free survival. The difference may be due to the study design and characteristics of the study population which involved only triple-negative breast cancer which is already known to be an aggressive disease. It was a retrospective study and their cut-off point for waist circumference was 80cm against the index study. Also, the method of tumor grading was not stated in the study. Haarkinson et al[6] in USA did not also find any statistical correlation between obesity and grades of breast cancer, tumor markers, or angiolymphatic invasion. However, the study was retrospective and noted that obese patients presented with a larger percentage of large tumors as well as lymph node metastasis. Patients were improperly classified as obese (BMI ≥ 30kg/m^2) which made up 24% of the study population and non-obese (BMI<30kg/m^2) which made up 76% of the study population. The study also demonstrated that the rate of locoregional recurrence is similar in both obese and non-obese groups; however, overall survival was noted to be worse in obese patients. The study found that obesity was more in postmenopausal than in premenopausal women (P=0.002). The findings of the index study is in agreement with the study done by Lopez et al[28] who investigated whether the breast cancer tumor biology in women with larger breast volume, obese women, and women with central adiposity at the moment of diagnosis of breast cancer is more aggressive than in those women without these features. The study found a significant correlation between central adiposity and higher grades of breast tumor both in pre-and postmenopausal women. Central adiposity was assessed with WHR in the study. Similarly, the study by George et al[29] showed that all-cause mortality and breast cancer-specific mortality are worse in women with higher waist circumference. The study revealed that the risk of cancer-related death starts at a WC of >99cm. Of the study population in the index study, 37.5% [30] have a waist circumference higher than this value. Also, Chung et al[31] assessed the prognostic significance of abdominal obesity and its post-diagnosis change and found that there is a reduction of all-cause and breast cancer-specific mortality within 18 months to 2 years for a substantial waist-hip ratio loss of 5% and above compared to stable waist-hip ratio. The study also noted that there is an increased risk of all-cause mortality for an increase in waist-hip-ratio after 2 years of diagnosis with a recommendation of the need for prevention of abdominal obesity and weight gain following a breast cancer diagnosis. The cut-off point at which the waist-hip ratio becomes significant was not stated in the study. Wisse et al[32] in Lund, Sweden assessed the outcome of increasing body size in breast cancer patients concerning its implication for prognosis. They reported a significant increase in the incidence of central obesity between 2002 to 2016, which resulted in the worsening of breast cancer grade and clinical outcome. The patients were followed up for 13 years and patients with WC of more than 80cm and WHR of more than 0.85 had shorter breast cancer-free intervals compared to individuals with smaller waist circumference and WHR.

5. Conclusion

In conclusion, this study showed a significant correlation between obesity and high SBR grade using waist circumference. Obese patients should be educated on the importance of routine self-breast examination, and clinical and radiological breast examination. Assessment of abdominal obesity using waist circumference should be should be considered for incorporation tool in the management of breast cancer patients as there is a less aggressive grade of breast cancer in women with normal adiposity. Hence, more aggressive efforts should be made toward tackling central obesity through lifestyle changes and dietary modifications. Additionally, the predictability of SBR grade is increased when the waist circumference of the patient is known.

Recommendation

The following recommendations are being made from the study

- Integrating waist circumference measurement in the assessment of patients presenting with breast cancer is recommended since high waist circumference is associated with high SBR grade in both premenopausal and postmenopausal women. This will help in prognostication. Ascertaining the Waist Circumference is easy and simple, and will not incur further costs to the patient.
- Women with high central adiposity should be encouraged to get screened for breast cancer earlier than their normal age counterparts.
- There is a need for more public campaign efforts among women in tackling central obesity through lifestyle and dietary modifications to reduce the possible risk of aggressive breast cancer.

Limitations of the study

Some patients were reluctant to expose their trunks for the measurement of their waist circumference, however eventually did after some persuasion

It is a single center study. A multicentre-study with larger sample size maybe more representative

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest.

Statement of ethical approval

Ethical approval. Obtained from Nnamdi Azikiwe University Teaching Hospital Ethics Board with number NAUTH/CS/66/VOL.13/VER.3/18/2021/20.

Statement of informed consent

Written consent was obtained from the patients.

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