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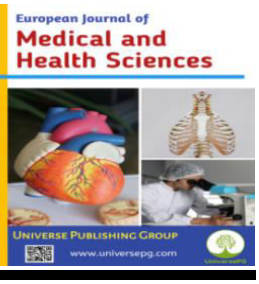

Evaluation of Serum Hormones and Biochemical Tumor Markers among Breast Cancer Patients in the South-South Region, Nigeria

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ABSTRACT

Breast cancer remains one of the most frequent malignancies in women and the primary cause of cancer-related death in women all over the world. Hormones and tumor biomarkers have been implicated as possible causes and prognostic biomarkers of breast cancer. The present study investigated the use of serum hormonal levels and tumor biomarkers; Carcinoembrvonic antigen (CEA), and cancer antigen (CA 15-3) for the diagnosis of Breast Cancer, and generation of different subtypes using Estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2). This study is a cross-sectional study comprising 120 subjects; sixty breast cancer patients, and sixty apparently healthy women who served as control. One hundred and twenty blood samples were collected and analyzed for estrogen, progesterone, Carcinoembrvonic antigen and cancer antigen. The results showed that the peak age of incidence of breast cancer was 40-49 years. Majority (56.7%) of the cases were menopausal women, while 43.3% were in their premenopausal period. Serum estrogen, cancer antigen, and Carcinoembrvonic antigen concentrations were elevated significantly ($p<0.05$) in the breast cancer patients than the control group. Premenopausal patients have higher progesterone, estradiol, Carcinoembrvonic antigen and cancer antigen levels than those during the postmenopausal period. HER2 negative subtype (50.0%) is the most prevalent subtype of breast cancer. 8.4% were triple negative (ER–/PR–/HER2–) cases, while 1.7% were triple positive (ER+/PR+/HER2+) cases. Breast cancer is strongly associated with hormonal changes especially estrogen and progesterone during premenopausal and postmenopausal periods in women. Thus, determination of the concentration of estrogen, progesterone, Carcinoembrvonic antigen, cancer antigen, and human epidermal growth factor receptor 2 statuses could help in the prognosis of breast cancer.

Keywords: Breast cancer, Menopause, Sex hormones, Cancer patients, and Tumor markers.

INTRODUCTION:

Breast Cancer (BC) is heterogeneous disease that is considered to be the commonest malignancy in woman-hood and the principal cause of cancer mortality in women worldwide (Siegel *et al*., 2012). It develops from the lobules of the mammary gland or the inner lining of milk ducts (Sharma *et al*., 2010). After lung cancer, breast cancer ranks second globally on cancer-related deaths among women (American Cancer Society, 2013). Approximately 35% of all malignancies in Western women are caused by breast cancer, with 50% of predominance in women less than 55 years old

(Rafael *et al.,* 2005). The prevalence, mortality and survival rates of breast cancer patients vary between countries and regions based on the variances in the disease's burden (Coughlin and Ekwueme, 2009).

Epidemiological studies have documented that approximately 55% of the global burden is currently felt in high-income countries, while incidence rates in low-income countries are fast growing (Farley, 2008). Nigeria ranked fourth globally for breast cancer-related mortality, with 0.70% death cases recorded for breast cancer in all deaths (Ojewusi *et al.,* 2016). Breast cancer (BC) is reported to be associated with a number of risk factors namely; socioeconomic factors, reproductive factors (Lambertini *et al.,* 2016), hormonal factors (Bhupathiraju *et al*., 2016), alcohol consumption, obesity, cigaratte smoking, family history, dietary factors, and exposure to ionizing radiation (Fortner *et al*., 2016; Shield *et al*., 2016). The mechanism by which these factors raised risk of the disease is not well understood. Only 5percent cases of breast cancer can be explained by uncommon, highly penetrant mutations in genes like Breast Cancer gene 1 (BRCA1) and Breast Cancer gene 2 (BRCA2), despite the fact that 10-15percent had some family history of the disease (Shah *et al*., 2020, Erhabor *et al*., 2018).

The coordinated action of multiple hormones, including prolactin, estrogen, progesterone, adrenal steroids, insulin, growth and thyroid hormones, is necessary for the growth of the breasts (Faupel-Badger *et al*., 2010). While thyroid hormones tend to encourage lobular development, contributing to the differentiation of normal breast tissue, estrogen is thought to be a powerful mitogen for the normal mammary gland (Macias and Hinck, 2012). (Asselin-Labat *et al.,* 2010; Joshi *et al.,* 2010) reported that estrogen and progesterone plays sequential role in breast development during pubertal age mainly via a paracrine mechanism in which ligand binding to receptor-positive cells induces secretion of factors that stimulate cell division. Studies have implicated estrogen and progesterone in the pathophysiology and growth of BC (Faupel-Badger *et al*., 2010; Adam *et al*., 2022; Macias and Hinck, 2012).

Biochemical markers can provide extra information into a patient's diagnosis and disease treatment. Currently, a small number of biomarkers are employed in the management of BC, mainly the tissue expression of the estrogen receptor, progesterone receptor, and HER2. Members of the MUC-1 family of mucin glycoproteins (CA 15-3, BR 27-29), carcinoembryonic antigen, oncoproteins (HER-2/c-erbB-2) and cytokeratins have all been identified as tumor markers for BC (Massacesi *et al*., 2003). Carcinoembryonic Antigen is a glycoprotein that aids in cell adhesion and can be elevated in several malignancies (Grunnet and Sorensen, 2012). Cancer antigens are high molecular weight mucin, carbohydrate-containing protein antigens of the transmembrane glycoprotein MUC-1, which is responsible for the prevention of tumor cell lysis and reduction of cell-cell interaction (David *et al*., 2016). Numerous studies have confirmed that elevated CEA values at diagnosis signify a negative prognosis in primary BC (Wu *et al.,* 2012; Uehara *et al.,* 2008). Also, studies by Shao *et al*. (2015) and Di Gioia *et al.* (2015) have established that elevated serum CA15-3 values at diagnosis are related to higher tumor size and stage. In recent time, the prognostic value of preoperative CEA and CA15-3 concentration in breast cancer patients has gained much attention and has increased overtime. (Pedersen *et al*., 2013; Wu *et al*., 2014) in their separate studies established that serum CEA and CA15-3 values may provide useful understanding for breast cancer detection and treatment. Consequently, the European Group on Tumor Markers has suggested the use of CEA, CA15-3 and others tumor markers for evaluating prognosis, the early detection of disease progression, and treatment monitoring in breast cancer (Shao *et al*., 2015).

Though, there are been conflicting reports on the prognostic value of serum tumor bio-markers in BC recently as reported by Maric *et al*. (2011). Therefore, the present study investigated the use of serum hormonal levels (Estrsogen and progesterone) and CEA and CA15-3 for the early detection of Breast Cancer.

MATERIALS AND METHODS:

Study Population

This research was carried out in Bayelsa State, South-South Region, Nigeria. The hospitals involved include; Federal Medical Centre Yenagoa, and Niger Delta University Teaching Hospital, Okolobiri, Bayelsa State, Nigeria. The participants in the study were split into

two groups. Sixty Breast Cancer patients served as the test group, while sixty apparently healthy subjects served as the controls group. The study comprised of only female subjects who have been reported for evaluation and treatment of BC. All consented subjects were 18 years and above. Subjects who are BC patients without a known endocrine and metabolic disorders, and who consented to the study were included for the study. While, subjects with a known endocrine and metabolic disorder, and who does not give their consent were excluded from the study.

Study Design

This study is a cross sectional study comprising of sixty BC patients who served as subjects, and sixty (60) normal apparently healthy women which served as control subjects. Some information obtained from participant include; age, and if they were under any therapy or they were newly diagnosed case. Quantitative data were gotten by determining the serum concentration of some hormonal (Estrogen and progesterone) and Tumor markers, and Generation of subtypes using Estrogen Receptor, Progesterone Receptor and HER2. The study was carried out for a period of one year between September, 2020 and August, 2021. Ethical approval was gotten from the Health Research and Ethics committee responsible for human research in the two hospitals. Consent of gotten orally from all the subjects (Control and subjects) before sample collection.

Sample Collection and Preparation

Blood samples were randomly collected from women diagnosed with BC. Blood samples were collected via venipuncture following the standard operating procedure and transferred into a plain container. The collected samples in the plain container were allowed to clot and dislodged carefully from the sides of the tubes to avoid hemolysis. The samples were then centrifuged at 3500rpm for 5minutes. Using an automatic pipette, the serum was carefully aspirated and transferred into another plain container which was properly labelled and stored frozen at -20^{O}C until analysis. The humans: Estrogen, progesterone; follicle stimulating hormone, luteinizing hormone, and biochemical parameters: Carcinoembrvonic antigen (CEA) and Cancer antigen (CA) 15-3were estimated in each sample.

Determination of Hormonal & Tumor Biomarkers

Serum concentration of progesterone, estrogen, follicle stimulating hormone, and luteinizing hormone assays were estimated using AB Diagnostics, Abia hormone ELISA kits from Halomedicals, Germany (Nelson and Chukwuma, 2022). Carcinoembrvonic antigen and Cancer antigen 15-3 levels were measured using VIDAS® CEA(S) (CEAS) kit, reference 30 453-01, and VIDAS® CA 15-3 (153) kit, reference 30429-01, on the Biomérieux® Minividas automated system by Enzyme Linked Fluorescent Assay method (Deliu *et al*., 2018; Abed *et al.,* 2020). The cut-off values of CEA and CA15-3 were 5.0ng/mL and 25 U/mL, respectively, and the value was considered positive or negative for the marker if the concentration was higher or below the cut-off value. Pathology report from which ER, PR and HER2 were obtained came from achieves of the Pathology Department of Niger Delta University Teaching Hospital and Federal medical Centre, Yenagoa. Immunohistochemistry (IHC) was performed on formalin fixed paraffin embedded tissue sections. The ER and PR tests were scored based on an aggregate score of percentage of tumor stained and staining intensity. Aggregate score of more than 2 were considered positive. HER2 was considered positive if an IHC 3+ result was found.

Statistical Analysis

Data obtained from the study were entered in Excel and analyzed using Special Package for Social Sciences (SPSS) version 23.0 software. Student t-test and Analysis of Variance was employed to compare the averages between the test group and control group. Statistical tests were considered statistically significant when $p<0.05$.

RESULTS:

Sixty diagnosed Breast Cancer female patients with the mean age of 46.13±5.09 years and sixty apparently healthy female subjects with a mean age of 41.52 ± 5.00 years were employed for the study. **Table 1** shows that patients within 20-29 years old had an incidence of 6.7%, age group 30-39 years had 20.0%, age group 40-49 years had 36.6%, age group 50-59 years had 30.0% while age group of 60 years and above had 6.7%. The result showed that majority of the patients 22(36.6%) and control 24(40.0%) fails within the age range of 40-49 years. **Table 2** shows

that 34(56.7%) of the patients were postmenopausal women and 13(43.3%) were premenopausal women. Also, majority 38(63.3%) of the participants who served as control were postmenopausal and 22(36.7%) were premenopausal. **Table 3** shows that estrogen (53.18±3.10); cancer antigen (CA15-3) (85.63±6.07) and Carcinoembrvonic antigen (CEA) (19.34±3.54) concentrations were significantly ($p<0.05$) increased in the breast cancer patients compared to the control (28.59±1.32; 14.99±6.09 and 2.74±0.18) respectively. **Table 4** shows that the mean values of progesterone (15.07 ± 2.80), estradiol (44.59 ± 6.05), CA15-3 (95.45 ± 12.03) and CEA (27.17 ± 2.02) concentrations were significantly ($p<0.05$) higher in the breast cancer patients at premenopausal period compared with the postmenopausal women (9.82 ± 2.87; 18.39 ± 3.23; 78.12 ± 10.77 and 12.17 ± 3.08) respectively.

Table 1: Percentage of Age Distribution of the Breast Cancer Patient and Control Subjects under Study.

Age (Years)	**Patients (n=60)**		**Control (n=60)**	
	Frequency (n)	Percentage (%)	Frequency (n)	Percentage (%)
20-29yrs	0	46.7%	06	10.0%
30-39yrs	12	20.0%	06	10.0%
40-49yrs	22	36.6%	24	40.0%
50-59yrs	18	30.0%	18	30.0%
60yrs	04	6.7%	06	10.0%
Total	60	100%	60	100%

Table 2: Percentage Distribution of Breast Cancer Patient and Control Subjects in Premenopausal and Postmenopausal Women under Study.

	Premenopausal (n=60)		**Postmenopausal (n=60)**	
	Frequency (n)	Percentage (%)	Frequency (n)	Percentage (%)
BC patients	26	43.3%	34	56.7%
Control	22	36.7%	38	63.3%

Table 3: Mean Values of Serum Hormones and Tumor Biomarkers of Breast Cancer Patients and Control Group.

Parameters	**Control (n=30)**	**Patients (n=30)**	**t-value**	**P-value**
	(Mean ± SD)	(Mean ± SD)		
Age (years)	41.52 ± 5.00	46.13 ± 5.09	0.082	0.732
Prog. (Pg/ml)	10.30±1.55	10.69±6.37	0.048	0.962
E2 (ng/L)	28.59±1.32	53.18±3.10	7.074	0.000*
CA 15-3 (U/mL)	14.99±6.09	85.63±6.07	10.54	0.000*
CEA (ng/L)	2.74±0.18	19.34±3.54	3.99	0.010*

Key: prog=progesterone; E2: Estrogen; CA15-3= Cancer antigen; CEA= Carcinoembrvonic antigen. Student T- test was used to compare the two group. Values with superscript asterisk* is considered significant ($p<0.05$).

Table 4: Mean Values of Serum Hormones and Tumor Biomarkers of Breast Cancer Patients at Premenopausal and Postmenopausal period.

Parameters	**Premenopausal (n=26)**	**Postmenopausal (n=34)**	**P-value**
Progesterone (ng/ml)	15.07 ± 2.80	9.82 ±2.87	0.024*
Estradiol (ng/L)	44.59± 6.05	18.39±3.23	0.000*
CA15-3(U/mL)	95.45 ± 12.03	78.12 ± 10.77	0.001*
CEA (ng/L)	27.17± 2.02	12.17 ± 3.08	0.001*

Key: CA15-3=Cancer antigen; CEA=Carcinoembrvonic antigen. Student t-test was employed to test the level of significance. Values with superscript asterisk* is considered significant ($p<0.05$).

Table 5: Percentage of various Combined subtypes of Hormone Receptors of Breast Cancer Patients under Studied.

Hormone Receptors	Frequency (n)	Percentage (%)
ER+/PR–/HER2–	02	3.3%
ER–/PR+/HER2+	02	3.3%
ER–/PR+/HER2–	06	10.0%
ER+/PR–/HER2+	02	3.3%
ER–/PR–/HER2+	12	20.0%
ER+/PR+/HER2–	30	50.0%
ER+/PR+/HER2+	01	1.7%
ER–/PR–/HER2–	05	8.4%
Total	n= 60	100%

Key: ER+= Estrogen receptor positive; PR+= Progesterone Receptor positive; ER- = Estrogen receptor negative; PR-= Progesterone Receptor.

Table 5 shows the immunohistochemical pattern of malignant breast lesions studied. Out of sixty (60) malignant cases subjected to immunohistochemical staining, 2(3.3%) cases were estrogen receptor positive (ER+/PR–/HER2–), estrogen receptor negative (ER–/PR+/HER2+) and progesterone receptor negative (ER+/PR–/HER2+), 6(10.0%) cases were progesterone receptor positive (ER–/PR+/HER2–), 12(20.0%) cases were human epidermal growth factor 2 positive, 30(50.0%) cases were human epidermal growth factor 2 negative, 5(8.%) cases were triple negative (ER–/PR–/HER2–), while 1(1.7%) cases were triple positive breast cancer (ER+/PR+/HER2+).

DISCUSSION:

Breast cancers remain one of the most frequent malignancies in women and the principal cause of cancer-related mortality all over the world. Its incidence has gradually increased in the past two decades. However, recent years have seen an enhancement in the survival statistics of patients due to early diagnosis and increased use of more effective systemic chemo-therapy. In the findings of this study, the peak age of prevalence of breast cancer is 40-49 years (5^{th} decade) (**Table 1**). This is concurrence with the previous studies of Afolayan *et al.* (2012), Erhabor *et al.* (2018) and Gabriel *et al.* (2014), which indicated the 5^{th} decade as the peak age of incidence of breast cancer. However, our finding contradicts the reports of Salim and Daoud, (2013) and Radaniel *et al.* (2008) which reported the peak age of incidence of breast cancer in the 6^{th} and 8^{th} decade respectively. The variance in peak age could be associated to several reproductive conditions including early menarche, late menopause, late age at first birth and among others (Sitas *et al*., 2008). Data from this study revealed that majority (56.7%) of the participants were postmenopausal women, and 43.3% were pre-menopausal women (**Table 2**). This confirms the report of Raheem *et al.* (2010) which stated a high prevalence of breast cancer (66%) in menopausal women. Progesterone is a 21-carbon steroid sex hormone that primarily acts biologically by binding to progesterone receptors A and B. This causes specific genes to start to be transcribed, which causes proliferative endometrium in an estrogen-primed uterus to change into secretory endometrium (Britton *et al*., 2020). Progesterone's primary physiological functions are limited to the regulation of the ovulatory stages of the menstrual cycle, the maintenance of pregnancy through stimulation of uterine development and differentiation, and the inhibition of myometrium contractility (Britton *et al*., 2020). Although studies have linked progesterone to breast cancer, there isn't enough epidemiological evidence to support a link between circulating progesterone levels and risk of the disease (Macias and Hinck, 2012; Britton *et al*., 2020). In the current study, the serum concentration of progesterone was slightly higher in the breast cancer patients than the control subject, but not statistically significant ($p>0.05$) as shown in (**Table 2**). Our results are consistent with those of Raheem *et al.* (2010) who found no correlation between circulating progesterone levels and the incidence of breast cancer in pre- and post-menopausal women. However, our finding contradicts Trabert *et al*. (2020) who hypothesized that proges-

terone contributes to the development of breast cancer. Estradiol, an 18-carbon steroid sex hormone, contains a hydroxyl group at C3, a phenolic hydroxyl group at C3, and one benzene ring (Samavat and Kurzer, 2015). 17β-estradiol (E_2) and its related compounds mediates the normal physiological growth, proliferation differentiation, development and progression of breast malignancy via binding with estrogen receptor (ER) ERα and ERβ (Yue *et al.,* 2013; Shanle and Xu, 2010). In the current study, the level of estradiol is significantly ($p<0.05$) elevated in the breast cancer female patients in comparison with the control group (**Table 3**). High serum estradiol is considered the most significant breast cancer risk factor because of its important role in the stimulation of breast cancer cell proliferation. Our finding is concurrent with Bernstein *et al.* (1990) and Raheem *et al.* (2010) which demonstrated a higher level of estradiol in breast cancer female patients than control group. Researchers have posited that CA15-3 and CEA are prognostic biomarkers of metastatic breast cancer (Massacesi *et al*., 2003). These bio-markers are overexpressed in greater than 90% of human breast cancers and in their subsequent metastases (Yue *et al.,* 2017). They enhance tumor invasion and metastasis via activation of the mitogen-activated protein kinase signaling pathway (Yue *et al.,* 2017) and downward regulation of E-cadherin (Tanaka *et al.,* 2003) thus making them useful for monitoring the therapeutic response of metastatic breast cancer patients. The current study stated that serum CA 15-3 and CEA concentrations were elevated significantly ($p<0.05$) in the breast cancer patients (**Table 3**). Our result support the findings of (Pedersen *et al*., 2013; Wu *et al*., 2014) which in their separate studies established that serum CEA and CA15-3 values may provide useful understanding for detection and management of Breast Cancer. A similar study by Shao *et al.* (2015) also reported elevated CA 15-3 and CEA in female breast cancer patients compared with normal subjects. This result supported the recommendation of European Group on Tumor Markers on the application of CEA and CA15-3 for breast cancer prognosis, early detection of disease progression and monitoring of patient treatment (Molina *et al*., 2005). A number of studies have documented progesterone, estrogen, CA 15-3 and CEA, and the risk of breast cancer development in women. Data from present study showed that the values of serum progesterone, estradiol, CA15-3 and CEA concentration were significantly ($p<0.05$) increased in the breast cancer patients at premenopausal period when compared with the menopausal period (**Table 4**). This confirms the findings of Raheem *et al.* (2010) which reported that progesterone and estradiol levels in female breast cancer patients during premenopausal period were significantly ($p<0.05$) higher than in menopause. Thomas *et al.* (1997) also posited an elevated mean plasma estradiol concentration in pre-menopausal women than in controls. Receptor status of breast cancer cell is crucial for hormone therapy, because this treatment type reduces the concentration of estrogen/ progesterone or impede their receptors, and therefore making it vital for ER+ or PR+ cancer cells treatment. However, the application of hormone therapy is not helpful forthetreatment of hormone receptor-negative cancers. Thus, hormone receptor-positive cancers have a better prognosis than hormone receptor-negative cancers (Purdie *et al.,* 2014; Davie *et al.,* 2013). Data from the current study showed that immunohistochemical pattern of malignant breast lesions studied were 3.3% cases for both estrogen receptor positive (ER+/PR–/HER2–), estrogen receptor negative (ER–/PR+/HER2+) and progesterone receptor negative (ER+/PR–/HER2+), 10.0% cases were progesterone receptor positive (ER–/PR+/HER2–), 20.0% cases were human epidermal growth factor 2 positive (ER–/PR–/HER2+), 50.0% cases were human epidermal growth factor 2 negative (ER+/PR+/HER2–), 8.4% cases were triple negative (ER–/PR–/HER2), while 1.7% cases were triple positive breast cancer (ER+/PR+/HER2+). This result suggests that ER+/PR+/HER2– subtype (50.0%) is the most prevalent subtypes of breast cancer in the studied patients. This is concurrence with the findings of Poorolajal *et al.* (2016) who reported that ER+/PR+/ HER2– subtype (51.5%) is the most prevalent form of breast cancer. The results from our patients show much lesser receptor positivity as compared with studies done in Asia where positivity for ER and PR ranges from as little as 28% to maximum of 75% (Mudduwa *et al.,* 2009; Shet *et al.,* 2009). Similar studies by (Maeyer *et al.,* 2008; Ng *et al.,* 2012) reported that only 1.5% and 4.6% of the breast cancer cells were ER–/PR+ respectively, while 11.6% were ER+/PR–.

CONCLUSION:

The present study revealed that the peak age of breast cancer incidence in women was 40-49 years. Data from this study also revealed that majority (56.7%) of the patients were menopausal women. Serum estrogen, cancer antigen (CA15-3), and Carcinoembrvonic antigen (CEA) concentrations were significantly elevated in the breast cancer patients in comparison with the control group. Serum progesterone, estradiol, CA15-3and CEA levels were significantly higher in the women at premenopausal age than menopausal period. The study also established that ER+/PR+/HER2– subtype (50.0%) is the most prevalent subtypes of breast cancer in the studied patients.

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CONFLICTS OF INTEREST:

There is no conflict of interest in the publication of this work

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