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Thyroid hormones and obesity in Nigerian women with breast cancer

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Abstract

Background: Africans have breast cancer expressions different from Caucasians. Interactions between oestradiol (E_2), adiposity and thyroid hormones in breast cancer development have been reported but controversial. The study was designed to investigate the relationships among thyroid hormones, E_2 and adiposity in Nigerian pre and postmenopausal women with breast cancer (pre cases and post cases respectively).

Methods: One hundred and sixty nine non-pregnant women aged 48.3±1.3 years were recruited for this study. They comprised of 85 histologically confirmed breast cancer patients (pre-therapy) matched with 84 apparently healthy women without breast cancer (controls) according to age and menstrual phase. Anthropometry was obtained by standard methods. Blood (10ml) was obtained from participants for determination of free thyroxine (fT_4), free triiodothyronine and thyroid stimulating hormone (TSH) by enzyme immunoassay (EIA). Data analysed by chi-square, student's t-test and multiple regression were significant at $p < 0.05$.

Results: 16 (29.63%), 18 (33.96%); 12 (22.22%), 4 (7.55%) pre cases and controls were overweight and obese respectively. 12 (38.71%), 15(48.39%); 8 (25.81%), 4 (12.90%) post cases and controls were overweight and obese respectively. The fT_4 was significantly higher in pre and postmenopausal cases than controls ($p<0.05$). Only waist circumference had inverse relationships with TSH in both pre cases and post cases (â=-8.790, $p=0.005$). E_2 was elevated in post cases only ($p<0.05$) but had no relationship with any of the thyroid hormones in all groups.

Conclusion: Altered adiposity and subclinical hyperthyroidism may be associated with breast cancer. Weight control and thyroid hormone testing may improve associated morbidity and mortality.

Keywords: *Thyroid hormones, oestrogen, adiposity, breast cancer, anthropometry, menstrual status.*

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Résumé

Contexte: Les Africains ont des expressions de cancer du sein différentes des Caucasiens. Des interactions entre l'œstradiol (E_2), l'adiposité et les hormones thyroïdiennes dans le développement du cancer du sein ont été rapportées mais controversées. L'étude a été conçue pour étudier les relations entre les hormones thyroïdiennes, l'E_2 et l'adiposité chez les femmes nigérianes pré et post-ménopausées atteintes d'un cancer du sein (pré-cas et post-cas respectivement).

Méthodes: Cent soixante-neuf femmes non enceintes âgées de 48,3 ± 1,3 ans ont été recrutés pour cette étude. Ils comprenaient 85 patientes atteintes d'un cancer du sein confirmées histologiquement (pré-thérapie) assorties avec 84 femmes apparemment en bonne santé sans cancer du sein (témoins) en fonction de l'âge et de la phase menstruelle. L'anthropométrie a été obtenue par des méthodes standard. Du sang (10 ml) a été prélevé sur les participants pour la détermination de la thyroxine libre (fT_4), de la triiodothyronine libre et de la thyréostimuline (TSH) par immunodosage enzymatique (EIA). Les données analysées par le chi-carré, le test t d'élève et la régression multiple étaient significatives à $p < 0,05$.

Résultats: 16 (29,63%), 18 (33,96%); 12 (22,22%), 4 (7,55%) pré-cas et les contrôles étaient en surpoids et obèses respectivement, 12 (38,71%), 15 (48,39%); 8 (25,81%), 4 (12,90%) post-cas et les contrôles étaient en surpoids et obèses respectivement. Le fT4 était significativement plus élevé dans les cas pré et post ménopausiques que chez les témoins ($p < 0,05$). Seul la circonférence de la taille avait des relations inverses avec la TSH dans les deux cas pré-cas et post-cas (β = -8,790, p = 0,005). L'E_2 était élevée dans les post-cas seulement ($p < 0,05$) mais n'avait aucun lien avec les hormones thyroïdiennes dans tous les groupes.

Conclusion: Une altération de l'adiposité et une hyperthyroïdie sub-clinique peuvent être associées au cancer du sein. Le contrôle du poids et le test des hormones thyroïdiennes peuvent améliorer la morbidité et la mortalité associées.

Mots-clés: *Hormones thyroïdiennes, œstrogène, adiposité, cancer du sein, anthropométrie, état menstruel.*

Introduction

Breast cancer is the most common type of cancer among women worldwide with a noticeable fatality rate [1]. The genetic predisposition of African women, particularly younger women to triple negative breast cancer expressions has been suggested as a reason for the aggressiveness of the disease. These women present late in the clinic with advanced breast cancer in stages 3 and 4 [2]. Despite these associations, the pathophysiology of breast cancer is inconclusive.

The growing and developing breasts require the coordinated action of several hormones such as oestrogen, progesterone, and thyroid hormones [3]. Oestrogen, progesterone, gonadotrophins, adiposity and their probable interactions with endocrine disruptors resulting in epigenetic changes have been reported as possible mechanisms in breast cancer development [4]. Oestradiol is a potent mitogen for normal mammary gland while thyroid hormones appear to stimulate lobular development, contributing to the differentiation of normal breast tissue [5]. It is postulated that the thyroid gland interacts with the breast tissues based on the common property of the mammary and thyroid epithelial cells to concentrate iodine by a membrane active transport mechanism. Additionally, TSH receptors in fatty tissues which are abundant in mammary gland have been reported to be a possible reason for this interaction [6, 7].

Thyroid hormones are the only iodine-containing substances of physiologic significance in vertebrates [8]. Thyrotropin releasing hormone (TRH) acts on the pituitary thyrotropes to stimulate both the synthesis and release of TSH. Thyroid stimulating hormone controls the size and number of thyroid follicular cells. It stimulates the thyroid gland to produce thyroxine (T_4). Thyroxine, a pro-hormone is converted to triiodothyronine (T_3), the active form of thyroid hormone in the peripheral tissues by 5'-deiodination [8, 9].

The relationship between breast cancer and thyroid hormone is controversial [10]. Many studies show that thyroid diseases are common in women with breast cancer while others observed no association between thyroid diseases and breast cancer [6, 11]. Many forms of thyroid diseases including hyperthyroidism have been identified in association with breast cancer [12-14]. The contribution of subclinical hyperthyroidism to breast tumour growth has been speculated in postmenopausal patients [10]. The importance of fT_3 in the physiology of fibrocystic breast disease [15] has also been suggested.

Interactions between E_2 and thyroid hormones in the development of breast cancer have been reported. Physiological concentrations of T_3, the more active form of thyroid hormone, significantly enhance E_2 growth stimulation of a number of human breast carcinoma cell lines [16]. In T47D breast cancer cells, E_2 and T_3 similarly regulate cell cycle progression and proliferation raising the p53 level and causing hyperphosphorylation of pRb [17]. The mimicking of E_2 by T_3 at supra-physiologic concentrations and in the absence of E_2 possibly through the ER in breast cancer cell line has been demonstrated [18].

Obesity, a global epidemic with an increasing prevalence, is associated with increased risk of metabolic diseases including cancer [19]. Central obesity has been linked with thyroid dysfunction [20]. Triiodothyronine regulates metabolic processes and thermogenesis [21]. Impaired thyroid function might be associated with dyslipidemia and insulin resistance which have been implicated in breast carcinogenesis [22, 23]. Reports showed that subclinical and overt hypothyroidism are frequently associated with weight gain, decreased thermogenesis and metabolic rate [24, 25]. Emerging evidence suggests that slight variations in thyroid function, even as indicated by tests that are within laboratory reference ranges could contribute to the development of regional obesity and the tendency to gain weight [26, 27].

The menstrual status of women may be an important determinant of breast cancer as differences were observed in the pattern of hormones and some hormone receptor expressions in pre and post menopause. Oestradiol was associated with postmenopausal breast cancer while triple negative receptor expressions (Oestrogen, progesterone and human epithelial receptor 2 receptor expressions) were more prominent in premenopausal breast cancer [4].

Although, several studies on breast cancer have been conducted in Nigeria to identify its aetiology and possible mechanisms to improve patient management, there is paucity of information on the association of thyroid hormones with breast cancer. We therefore investigated the role of thyroid hormones and their interaction with oestrogen and

adiposity in Nigerian pre and postmenopausal women with breast cancer.

Materials and methods

The study was a prospective case-control study conducted in the Surgical Oncology Clinic of the Department of Surgery, University College Hospital, Ibadan. The study protocol was approved by the University of Ibadan and University College Hospital Health Review Committee. Informed consent was obtained from the participants before recruitment into the study. Participants were recruited between April, 2011 and March, 2014 [4].

Study participants

One hundred and sixty nine non pregnant women aged 28-80 years were consecutively recruited for this study. Eighty-five were histologically confirmed breast cancer patients who had not commenced treatment (Cases). They were recruited by the Surgical Oncologist from the Surgical Oncology Clinic of the Department of Surgery, University College Hospital, Ibadan. Eighty-four non-pregnant, apparently healthy women who served as controls were recruited at three Primary Health Clinics (PHC) in Ibadan North Local Government Area of Oyo State namely; PHC, Idi Odundun, Agodi, PHC, Agbowo and Elderly Women/Widows Clinic, Agodi-Gate. Their breasts were examined by trained nurses for the presence of any breast lump. They were asked if they felt any pain or had any discomfort in their breasts. Those that complained of pain, discomfort and/or had lump in their breasts were excluded from the study. One of the controls was excluded from the study due to incomplete data on questionnaire and insufficient blood sample [4].

Each cases was matched for age and menstrual status (follicular phase, luteal phase and pre and postmenopausal) with the controls. Participants were reported as postmenopausal if they had stopped menstruating over the last twelve months [1]. Participants that had bilateral oophorectomy were also considered postmenopausal. Both cases and controls were subdivided into pre and postmenopausal groups (54 premenopausal cases; 31 postmenopausal cases; 53 premenopausal controls; 31 postmenopausal controls respectively).

Exclusion criteria

Pregnant women and those who reported being on hormonal drugs (i.e. contraceptives), had other types of cancers and/or hypertension were excluded from the study. Postmenopausal women on hormone replacement therapy were also excluded [4].

Anthropometric indices

Anthropometric indices: weight, height, body mass index, waist circumference, hip circumference, waist-hip ratio, waist-height ratio were measured by standard methods described and reported elsewhere [28].

Sample collection

Ten ml of venous blood was collected from each woman into plain bottles. For premenopausal participants, blood samples for determination of E_2 were drawn between days 5 and 9 of their menstrual cycle in follicular phase (forward dating) and 5 to 9 days before the anticipated start of their next menstrual cycle in the luteal phase (backward dating) [4]. This was done by applying a tourniquet 10-15 cm above the intended puncture site to obstruct the return of venous blood to the heart and to distend the vein. The site of puncture, the medial cubital vein in the antecubital fossa was cleansed with alcohol swab. The blood was allowed to retract and centrifuged at 3500 rpm for 5 minutes. The resulting serum was aliquoted and stored at -20°C until analysis [4].

Hormonal assay

Serum fT_3, fT_4, TSH and E_2 were determined by enzyme immune assay on TOSOH AIA System Analyzers (Tosoh Corporation, Tokyo 105-8623, Japan). Values for TSH, fT_4 and E_2 have been reported elsewhere [2, 4].

Statistical analysis

Data were analyzed using the statistical package for social scientists (SPSS 18.0) SPP, Inc., Richmond, CA. Chi-square test was used for categorical variables, student's t-test was used for comparison of quantitative variables. Multiple regression analysis was employed to determine relationships between variables. $p<0.05$ was considered statistically significant.

Results

In the premenopausal cases and controls, 26 (48.15%), 31 (58.49%) had normal weight, 16 (29.63%), 18 (33.96%) were overweight and 12 (22.22%), 4 (7.55%) were obese respectively. There was no significant difference in the BMI classes in the premenopausal cases and premenopausal controls ($p<0.05$). In the postmenopausal cases and controls, 11 (35.48 %), 11 (35.48 %) had normal weight, 12 (38.71 %), 15(48.39 %) were overweight, and 8 (25.81 %), 4 (12.90 %) were obese respectively. There was no significant difference in the BMI

Table 1 Thyroid hormones and measures of obesity in premenopausal women with breast cancer and controls

Variable	Pre Cases (n=54)	Pre Controls (n=53)	t	*P*
Age (years)	40.91±0.65	40.74±0.64	0.187	0.852
Blood Pressure				
SBP (mmHg)	122.96±1.44	119.04±1.24	2.062	0.042*
DBP (mmHg)	82.41±1.12	80.94±1.02	0.967	0.336
Anthropometric Indices				
Waist circumference (cm)	88.54±1.42	78.25±1.31	5.321	<0.001*
Hip circumference (cm)	100.52±1.47	95.98±1.04	2.512	0.014*
Body weight (Kg)	67.99±1.87	60.14±1.30	3.435	0.001*
Height (m)	1.63±0.01	1.57±0.01	4.345	<0.001*
Body mass index (Kg/m^2)	25.70±0.68	24.51±0.51	1.401	0.164
Waist hip ratio	0.88±0.01	0.81±0.01	6.073	<0.001*
Waist height ratio	54.55±0.96	49.97±0.88	3.516	0.001*
Hormones				
E_2 (pmol/L)	452.84±43.34	430.82±46.47	0.347	0.729
fT_3(pmol/L)	3.59±0.39	3.49±0.06	0.249	0.804
fT_4 (pmol/L)	17.83±0.56	14.89±0.33	4.507	<0.001*
TSH (mIU/L)	1.75±0.17	1.48±0.11	1.357	0.178

*n=number of participants, t=Student's t-test, P=probability value, *=significant, mean± SEM (standard error of mean), Pre Controls =apparently healthy premenopausal women without breast cancer, Pre Cases=Premenopausal women with breast cancer, SBP=systolic blood pressure, DBP=diastolic blood pressure, E_2=oestradiol, fT_3=free triiodothyronine, fT_4= free thyroxine, TSH= thyroid stimulating hormone, pmol/L=picomol per litre, mIU/L=milliinternational unit per litre.*

Table 2 Thyroid hormones and measures of obesity in postmenopausal women with breast cancer and controls.

Variable	Post Cases (n=31)	Post Controls (n=31)	t	*P*
Age (years)	61.23±1.50	61.65±1.48	-0.199	0.843
Blood Pressure				
SBP (mmHg)	122.26±1.84	120.00±1.61	0.925	0.360
DBP (mmHg)	80.32±1.27	80.3±1.18	0.000	1.000
Anthropometric Indices				
Waist circumference (cm)	92.16±1.73	89.87±1.46	0.969	0.337
Hip circumference (cm)	103.94±1.70	102.74±1.67	0.500	0.619
Weight (Kg)	71.39±2.18	65.61±1.67	2.103	0.010*
Height (m)	1.63±0.01	1.59±0.01	2.340	0.023*
Body mass index (Kg/m^2)	26.81±0.65	25.85±0.65	1.048	0.217
Waist hip ratio	0.89±0.01	0.88±0.01	0.716	0.477
Waist height ratio	56.63±1.56	56.49±0.91	0.093	0.930
Hormones				
E_2 (pmol/L)	156.48±12.42	90.42±3.59	5.036	0.000*
fT_3(pmol/L)	3.14±0.09	3.34±0.11	-1.372	0.175
fT_4 (pmol/L)	17.65±0.58	14.33±0.39	4.785	<0.001*
TSH (mIU/L)	1.62±0.17	1.33±0.14	1.355	0.181

n=number of participants, t=Student's t-test, *P*=probability value, *=significant, mean± SEM (standard error of mean), Post Controls =apparently healthy postmenopausal women without breast cancer, Post Cases=Postmenopausal women with breast cancer, SBP=systolic blood pressure, DBP=diastolic blood pressure, E_2=oestradiol, fT_3=free triiodothyronine, fT_4= free thyroxine, TSH= thyroid stimulating hormone, pmol/L=picomol per litre, mIU/L=milliinternational unit per litre.

classes in the postmenopausal cases and postmenopausal controls ($p<0.05$).

Table 1 shows comparison of age, reproductive, anthropometry, oestradiol and thyroid

hormones between premenopausal cases and premenopausal controls. The fT_4 levels as well as all anthropometry except BMI were significantly higher in premenopausal cases compared with premenopausal controls ($p<0.05$).

Table 2 shows comparison of age, anthropometry, oestradiol and thyroid hormones between postmenopausal cases and postmenopausal controls. Only body weight, height and fT_4 were significantly higher in postmenopausal cases compared with postmenopausal controls ($p<0.05$).

Table 3 shows multiple regression of thyroid hormones and anthropometric indices in pre and postmenopausal cases as well as pre and postmenopausal controls. Similar relationships were observed in pre and postmenopausal cases. Hip circumference and waist hip ratio were positively related with TSH (β=6.430, p=0.000; β=6.118, p=0.000, respectively) while waist circumference had an inverse relationship with TSH (β=-8.790, p=0.005). In premenopausal controls, only hip circumference and waist hip ratio had positive

Table 3 Multiple regression of thyroid hormones and measures of obesity in women with breast cancer and controls, premenopausal women with breast cancer and controls, postmenopausal women with breast cancer and controls

Groups	Dependent	Predictors	β	t	*P*
Cases					
R^2=0.194,F=2.010,p=0.050	fT_3	TSH	-0.267	-2.309	0.024*
		Height	2.414	2.635	0.010*
R^2=0.252,F=2.815,p=0.007	TSH	fT_3	-0.248	-2.309	0.024*
		Height	1.919	2.143	0.035*
Controls					
R^2=0.219,F=2.308,p=0.024	fT_4	fT_3	0.221	2.016	0.047*
		Waist circumference	8.921	2.722	0.008*
		Waist height ratio	-9.149	-3.358	0.001*
		Height	-1.990	-2.611	0.011*
R^2=0.142,F=1.364,p=0.220	TSH	Hip circumference	3.914	2.708	0.008*
		Waist hip ratio	3.006	2.543	0.013*
Premenopausal cases					
R^2=0.714,F=5.811,p=0.000	TSH	Waist circumference	-8.790	-3.148	0.005*
		Hip circumference	6.430	4.622	0.000*
		Waist hip ratio	6.118	5.232	0.000*
Premenopausal controls					
R^2=0.260,F=1.677,p=0.124	fT_3	Waist circumference	-12.635	-3.119	0.003*
		Hip circumference	3.852	2.212	0.032*
		Height	2.139	2.031	0.048*
		Waist hip ratio	3.264	2.095	0.042*
R^2=0.239,F=1.498,p=0.179	fT_4	Waist height ratio	-8.684	-2.274	0.028*
R^2=0.271,F=1.780,p=0.100	TSH	Hip circumference	5.263	3.214	0.002*
		Waist hip ratio	4.633	3.172	0.003*
Postmenopausal cases					
R^2=0.714,F=5.811,p=0.000	TSH	Waist circumference	-8.790	-3.148	0.005*
		Hip circumference	6.430	4.622	0.000*
		Waist hip ratio	6.118	5.232	0.000*
Postmenopausal controls					
R^2=0.746,F=4.567,p=0.006	fT_3	fT_4	-0.454	-2.153	0.049*
		Body mass index	-0.391	-2.491	0.026*
		Height	-4.677	-2.361	0.033*
		Waist height ratio	-14.308	-2.372	0.033*
	fT_4	fT_3	-0.547	-2.153	0.049*
		Height	-5.772	-2.806	0.014*
		Waist circumference	16.067	2.236	0.042*
		Waist height ratio	-18.627	-3.076	0.008*

*=significant at p<0.05, beta= Standardized coefficient, p=Probability value, fT_3=free triiodothyronine, fT_4=free thyroxine, TSH=Thyroid stimulating hormone

relationships with TSH (β=5.263, p=0.002; β=4.633, p=0.003, respectively). Additionally, hip circumference, height and waist hip ratio had a positive relationship with fT_3 (β=3.852, p=0.032; β=2.139, p=0.048; β=3.264, p=0.042, respectively) while waist circumference was inversely related with fT_3 (β=-12.635, p=0.003). Waist height ratio was inversely related with fT_4 (β=-8.684, p=0.028). In postmenopausal controls, no relationship was observed between anthropometric indices and TSH. However, fT_4, BMI, height and waist height ratio were inversely related with fT_3 (β=-0.454, p=0.049; β=-0.391, p=0.026; β=-4.677, p=0.033; β=-14.308, p=0.033, respectively). Free triiodothyronine, height, waist height ratio were inversely related with fT_4 (β=-0.547, p=0.049; β=-5.772, p=0.014; β=-18.627, p=0.008, respectively). Waist circumference had a positively relationship with fT_4 (β=16.067, p=0.042).

Discussion

Thyroid hormones may be critical in the pathogenesis and progression of diseases due to their regulatory role on cell maturation [29, 30]. Thyroid signalling may be altered in cancer as a result of the activation of growth kinase signalling which may be of physiological relevance [31, 32]. Individuals with thyroid dysfunction have been reported to have an increased occurrence of breast cancer compared with healthy women. However, the potential association between thyroid conditions and breast cancer risk is inconclusive [13, 33-35].

Serum levels of the thyroid hormones in the study participants were within the normal reference interval (fT_3: 3.2-6.0pmol/L, fT_4: 10.6-21.0 pmol/L, TSH: 0.38-4.31mIU/L). However, only serum fT_4 was significantly higher in both pre and postmenopausal women with breast cancer compared with their respective controls (p<0.05). This is consistent with other reports [6, 36]. Emerging evidence shows that changes in thyroid hormone levels within normal range may be associated with proliferative activity of breast tumours in euthyroid patients with breast cancer [37].

The interactions between oestradiol and thyroid hormones in the development of breast cancer have been reported [16]. Physiological concentrations of T_3, have been shown to significantly enhance oestradiol growth stimulation of a number of human breast carcinoma cell lines [16]. The elevation of both E_2 and fT_4 were observed in postmenopausal cases compared with postmenopausal controls in this study. However, there was no significant difference in the premenopausal group in this study. This indicates that they may independently exert their influence in breast cancer development.

The association of increased adiposity with breast cancer as observed in this study has been reported previously [4]. All the indicators of adiposity were similar between pre and postmenopausal cases but not controls in this study. This suggests that the involvement of obesity in breast carcinogenesis is irrespective of menstrual status. The association of regional adiposity with E_2 in postmenopausal women with breast cancer and apparently healthy women with increased adiposity was previously reported [4, 38]. This indicates that obesity alone may not contribute to breast cancer.

Obesity is marked by alteration in the production of adipocytokines-leptin and adiponectin. The promotion of breast carcinogenesis by increased leptin levels and decreased adiponectin levels have been reported [39, 40]. Leptin is strongly angiogenic and may increase tumour angiogenesis by directly acting on the endothelium or by increasing local vascular endothelial growth factor (VEGF) secretion [41, 42]. However, a previous study by Fabian et al reported an association of high leptin levels with increased adiposity in apparently healthy women as a compensatory measure for the maintenance of normal blood pressure [38]. Systolic blood pressure was significantly higher in premenopausal cases than premenopausal controls in this study (p<0.05).

Thyroid hormone receptors expressed on visceral and subcutaneous fat directly influence various functions of the adipocytes [43]. Indicators of various regional fat depots had relationships with TSH, fT_3 and fT_4 in pre and postmenopausal cases and controls in this study (p<0.05) consistent with other studies [44- 47]. However, only waist circumference, an indicator of visceral obesity had significantly inverse relationship with TSH in pre and postmenopausal cases (p<0.05). This suggests that visceral adiposity indicated specifically by elevated waist circumference may be a risk factor for subclinical hyperthyroidism in pre and postmenopausal women with breast cancer, which may have implications in their management. The contribution of subclinical hyperthyroidism to breast tumour growth has been speculated in postmenopausal patients [9].

Conclusion

Free thyroxine and oestradiol may be independent risk factors for breast cancer. Free thyroxine may be important in both pre and postmenopausal breast

cancer. Although, adiposity is associated with breast cancer, only waist circumference had a significantly inverse relationship with thyroid stimulating hormone in pre and postmenopausal subjects implicating subclinical hyperthyroidism in this study. This may be important in the management of these women. Weight control through change in lifestyle is recommended.

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