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Original Research Article

Contributory roles of lipids, adiposity and the underlying effect of antioxidant levels in the aetiology of breast cancer in Nigerian women

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Abstract

The susceptibility of lipids to oxidation has been suggested as a mechanism that can contribute to the burden of breast cancer. To further elucidate this relationship, this study sought to know if a direct relationship exists between lipid levels, adiposity and oxidative stress in individuals with breast cancer. A total of 100 (100) female participants (50 patients and 50 age-matched apparently healthy individuals as control) were recruited. Blood samples were analyzed for Total cholesterol, Triglyceride (TG), High density lipoprotein cholesterol (HDL), Total antioxidant status (TAS), Calcium and Albumin spectrophotometrically. There was a significant decrease ($p<0.05$) in HDL cholesterol of the patients compared to the control group while the total antioxidant status was found to be higher in the control group than in the case (1.08 ± 0.33 versus 0.76 ± 0.21; $p<0.05$). There was also a strong positive correlation between TAS and HDL levels ($P = 0.001$) in this study. This study has shown a role for lipids especially reduced levels of high density lipoprotein in the aetiology of breast cancer. This role has been suggested to probably be through the antioxidative effect of the HDL molecule.

Keywords: Lipids, oxidative stress, breast cancer.

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1. Introduction

Breast cancer ranks second in global cancer incidence and is the most common cancer diagnosis among Nigerian women [1]. It is currently the most common malignancy in Nigerian women and the incidence seems to be on the increase. It has overtaken carcinoma of the cervix and if the present trend is maintained it will become, for Nigeria, and other developing countries, the most important non-communicable disease of the new millennium [2]. Well-established risk factors for breast cancer includes early age at menarche, late age of menopause, late age at first pregnancy, obesity, use of oral contraceptives and hormone replacement therapy, diet, family history, lactation, and prior history of benign breast disease [3]. The effect of adiposity on the prognosis of both pre- and post-menopausal breast cancer has aroused increasing interest in recent years, and has immense public health implications [4].

In the same vein, the relationship of lipids and breast cancer is not yet fully understood either in playing a role in initiating, promoting or perhaps in protecting against this malignant disease; although it has been found that one of the clinical manifestation of adiposopathy is low HDL-cholesterol levels in all cases of cancer and that fat distribution has been proposed as more predictive of breast cancer risk than body mass [5]. Until recently, conflicting results have been reported on the association of dietary fat and increasing breast cancer risk [6]. Park *et al.,* 2012[7] in a study involving data collected from developed countries during the past few decades on population aggregates with elevated lipid intakes reported an elevated breast cancer incidence and morbidity. Some studies also reported that women with relative androgen excess (such as polycystic ovary syndrome) have lower levels of serum HDL-C which has been suggested as a marker of androgen status when compared with those having normal ovarian function. Low

HDL-C is further related to increased levels of several other hormones including estrogens, insulin, and IGF-I, all of which may stimulate cancer development [8]. Furthermore, studies have found that the turnover of triglycerides (TG) was faster in breast cancer tissue than in the adjacent normal tissue, indicating a significant difference in TG metabolism between the mammary tissues [9,10].

At the same time, the susceptibility of lipids to oxidation has been suggested as a mechanism that can contribute to the burden of breast cancer [11]. The oxidative damage of lipids, DNA and proteins has been shown to ultimately lead to outcomes such as disorganization, dysfunction, and destruction of membranes, enzymes and proteins [12]. Specifically, peroxidation of membrane lipids may cause impairment of membrane function, decreased fluidity, inactivation of membrane bound receptors and enzymes, increased permeability to ions and possibly eventually membrane rupture. Free radical damages can accumulate over time and may thereby contribute to cell injury and development of human diseases including atherosclerosis, diabetes, cancer, chronic inflammatory diseases and neurodegenerative diseases as well as in the process of aging [13]. Accumulation of lipid peroxidation products in these individuals depletes body antioxidants thereby leading to oxidative stress which has also been shown to be an aetiological factor in breast cancers [11].

We have pointed out this pattern of influence in other forms of cancer such as prostate cancer in earlier studies [14]. To further elucidate this relationship in breast cancer, we sought to know if a direct relationship exists between lipid levels, adiposity and oxidative stress in individuals with breast cancer. Knowledge of these modifiable factors could potentially reduce the risk of breast cancer in Nigerian women.

2. Method

2.1 Participants

A total of one hundred (100) female participants between 24 – 70 years, from the Oncology clinic of the University College Hospital, Ibadan were recruited for this study. Fifty (50) participants newly diagnosed at different stages of breast cancer were recruited. The control group consisted of fifty (50) apparently healthy women that have been controlled for adiposity without any history of breast disease

2.2 Inclusion criteria

1) Women with breast cancer who voluntarily wished to participate in the study.
2) Women who consented to take part in this study.

2.3 Exclusion Criteria

1) Women who have undergone any form of treatment for the disease
2) Women with diabetes mellitus, cardiac disease, pregnancy and thyroid disorders
3) Women who do not give their consent.
4) Women at extremes of age i.e. below 18 and over 75 years of age

2.4 Consent/Ethical considerations

Participants were fully briefed on the research protocols and a written consent obtained. Detailed gynecological, including obstetrical, endocrinological, and general medical histories, the use of alcohol, and smoking habits as well as their dietary habits were determined by paramedical assistants, using a standard structured questionnaire. This study was approved by the University of Ibadan /University College Hospital Joint Ethical Review Committee with approval number UI/EC/14/0073.

2.4 Biochemical assays

2.4.1 Determination of Total Cholesterol

Total Cholesterol was determined by spectrophotometric method based on CHOD-PAP methodology [15].

2.4.2 Determination of Triglycerides

Triglyceride was determined by spectrophotometric method, based on GPO-PAP methodology [16].

2.4.3 Determination of HDL-Cholesterol

Direct determination of HDL-Cholesterol method was used to determine HDL-cholesterol based on enzyme selective protection method.

2.4.4 Determination of Albumin

Albumin was determined by spectrophotometric method, which is based on bromocresol green (BCG) methodology [17].

2.4.5 Determination of Total Calcium

Calcium was determined by spectrophotometric method, which is based on modified Ortho-cresolphtalein complex methodology [18].

2.4.6 Total Protein (TP) Assay

This was done by the Biuret Method, using kits from Randox laboratories limited, (Randox laboratories limited, 55 Diamond Road, Crumlin, county Antrim, BT29 4QY, United Kingdom. lot number 750TP), and following the manufacturer's instructions.

2.4.7 Determination of Serum Total Antioxidant Status (TAS)

Plasma total antioxidant status was determined by the method described by Koracevic *et al.,* 2001[18].

2.5 Statistical analysis

All data was analyzed using the Statistical Package for Social Sciences (SPSS) software computer program version 15.0 (SPSS, Chicago, IL). Data were expressed as mean and standard deviation following analysis using student *t*-test, which was performed to evaluate differences by case-control status. Analysis of variance (ANOVA) was used to compare the difference between the means of the three groups of BMI studied Pearson's correlation studies were used to investigate the relationship between

anthropometric measures and other biochemical parameters studied. A value of $p < 0.05$ from two-sided tests was considered statistically significant.

3. Results

A total of one hundred (100) female participants were recruited, consisting of 50 women with breast cancer with mean age ± SD of 45.60 ± 11.71 and fifty (50) apparently healthy controls with mean age of 41.46 ± 10.06. The breast cancer group consisted of 47% of premenopausal women and 53% postmenopausal women and the control group consisted of 69% and 31% pre- and post-menopausal women respectively.

The statistical analysis of anthropometric measurements is shown on Table 1. There was no significant difference between the age, height, weight, waist circumference and hip circumference between the case and the control. There was no significant difference observed in the two measures of adiposity employed in this study between the cases and the control i.e. percentage body fat (PBF) (35.61 ± 7.91 versus 37.45 ± 6.32) and body mass index (BMI) (25. 70 ± 3.28 versus 26.99 ± 5.10). There was however a significant difference in the waist hip ratio (WHR) (0.90 ± 0.08 versus 0.85 ± 0.09; p<0.05).

Table 2 shows the lipid profile and other biochemical parameters measured in the study participants i.e. breast cancer patients compared with the control group. The analysis for the lipid profile (total cholesterol, triglycerides, HDL cholesterol and LDL cholesterol) showed that there was no significant difference (P >0.05) in the total cholesterol, LDL cholesterol and triglyceride levels, but there was a significant decrease (p<0.05) in HDL cholesterol of the patients compared to control group. The total antioxidant status was found to be higher in the control group than in the case (1.08 ± 0.33 versus 0.76 ± 0.21; p<0.05). There were no significant differences in the mean levels of albumin, calcium and total protein between the controls and participants with breast cancer.

There was a strong positive correlation between TAS and HDL levels (P = 0.001) as shown in the scatter plot represented in Figure 1.

Table 1: Comparison of Anthropometric measurement in study participants and controls (mean ± SD)

Parameter	Control n = 50	Cases n = 50	t-value	*p*-value
Age (years)	41.46 ± 10.06	45.60±11.71	1.822	0.072
Weight (Kg)	72.49± 10.41	69.50±18.05	-0.861	0.392
Height (m)	1.65± 0.07	1.65±0.08	0.174	0.862
BMI (Kg/m2)	25.69± 3.29	26. 99±5.11	1.339	0.185
Waist Cir. (cm)	90.81± 21.33	91.42±15.27	0.147	0.883
Hip Cir. (cm)	100.4± 15.15	102.4±14.91	0.559	0.578
WHR	0.85± 0.09	0.90±0.08	2.017	0.047*
PBF (%)	32.45± 5.28	35.61± 7.91	-1.161	0.231

* Statistically significant at *p* 0.05; PBF= percentage body fat; WHR=waist hip ratio; BMI= body mass index; WC= waist circumference; HC= hip circumference

Table 2: Comparison of biochemical parameters in study participants and controls (Mean ± SD)

Parameter	Control n = 50	Cases n = 50	t-value	*p* –value
Albumin (mg/dl)	4.52±0.40	4.45± 0.47	- 0.733	0.466
TC (mg/dl)	158.5± 35.6	169.9±143.3	0.543	0.588
Triglyceride (mg/dl)	68.36± 25.52	76.5± 36.32	1.288	0.201
LDL-cholesterol (mg/dl)	82.8± 34.6	92.7± 44.6	1.195	0.235
HDL-cholesterol (mg/dl)	63.02± 21.3	42.07± 12.4	-5.941	0.000*
MDA (×10-5U/mg protein)	4.29± 1.02	3.45± 1.78	-1.895	0.620
Total protein (mg/dl)	6.73± 0.73	6.81± 1.05	0.439	0.662
Corrected Ca^{2+} (mg/dl)	8.54± 0.73	8.75± 1.52	0.877	0.383
TAS (mmol/l)	1.08± 0.33	0.76 ± 0.21	-5.593	0.000*

* Statistically significant at *p*<0.05; TAS= total antioxidant status; MDA= malondialdehyde; Ca2+ = Calcium; TC= Total cholesterol

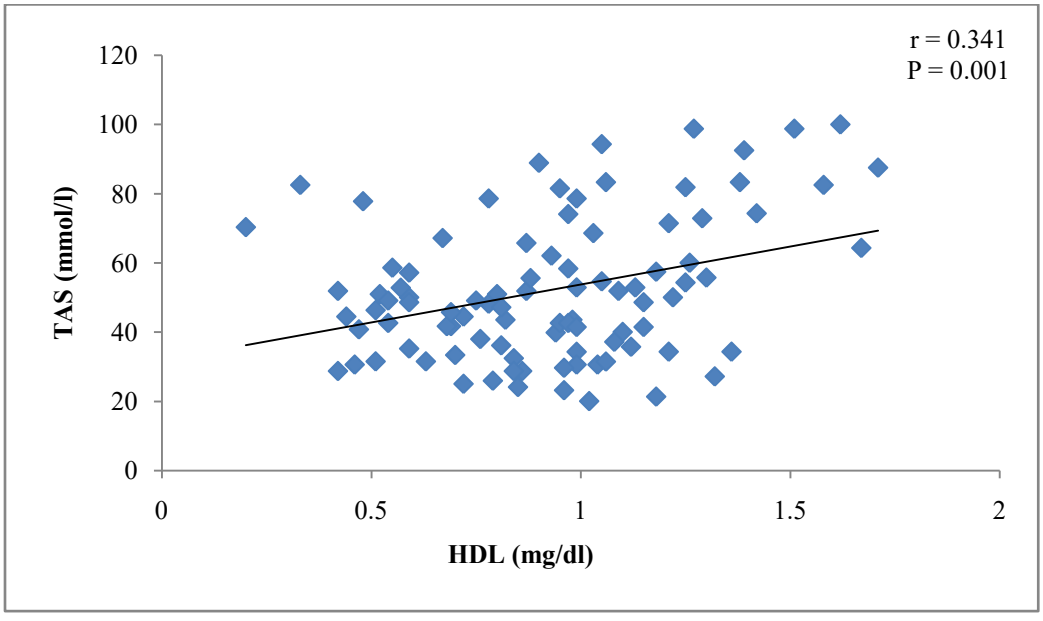

Fig. 1: Scatter plot between Total antioxidant status and High density lipoprotein levels

4. Discussion

Breast cancer is a multifocal disease with several risk factors as studied in recent years. Although early diagnosis has contributed to therapeutic success, breast cancer remains a major health issue and a better understanding of the risks involved will allow for a clearer understanding of the aetiology of the disease.

This study showed a significant increase in waist-hip ratio, a measure of central adiposity in the cases and this trend was observed in a study by Wu *et al.,* 2009[20]. A Nigerian Breast Cancer study on body fat distribution and breast cancer risk showed that a positive association exists between waist circumference and WHR in breast cancer [1]. Borugian *et al.* (2003) [21] suggested that increased breast cancer risk and mortality have been associated with upper body obesity as defined by the waist-to-hip ratio, or suprailiac-to-thigh ratio. Other studies have shown that excess adiposity due to overweight included with lower intakes of antioxidants, such as vitamins, may increase the formation of reactive oxygen species in cells [22]. High TAS was observed in the control than in the cases in this study. Longitudinal study on women carried out by Zhang *et al.* (2008) [23] also showed a strong and positive association between WHR and cancer mortality independently of BMI. Adiposity and physical inactivity drives chronic inflammation linked to breast carcinogenesis and prognosis. The fact that this high level of adiposity is associated to poor health, for example cancer, has led to many considering the adipose tissue as a toxic tissue and this perspective is supported by growing evidence of obesity as an inflammatory state [24].

Furthermore, HDL-C level was noted to be significantly decreased in breast cancer patients in this study which is consistent with studies by Am *et al.,* 2000 [25] and Franky *et al.,* 2008[26]. Decreased levels of HDL-C have been reported to be associated with increased levels of cytokines, which have been shown to be related to both obesity and breast cancer [27,28]. High HDL-C may elicit a protective effect since it is responsible for reverse transportation of cholesterol from peripheral tissues to the liver for excretion or reutilization [29].

This study also showed a significantly reduced level of total antioxidant status, which is indicative of increased oxidative stress, among individuals with breast cancer. This is consistent with findings by Mahmood *et al*., 2009[30] who also advocated that measuring total antioxidant activity is better than measuring the individual antioxidant activity because the measurement of all known antioxidant in biological fluid is time consuming apart from the possibility that many antioxidants may be yet undiscovered. The total activity may also be greater than the sum of the individual antioxidants because of cooperative interaction. Decreased TAS reflects residual antioxidant capacity in response to increased generation of reactive oxygen species and free radicals. It measures peroxyl-scavenging capacity of the extracellular antioxidant system, comprised of sulphydryl groups. Increased ROS has been hypothesized to contribute in the initiation of breast cancer through mitochondrial DNA mutations, chronic inflammation, defective DNA repair mechanism and apoptosis etc. All these finally lead to the development of breast cancer [31].

This study also noted a direct relationship between HDL-cholesterol and TAS suggesting an antioxidative property for HDL. Soran *et al*., (2015)[32] in their study suggested that HDL may play its antioxidative role by providing a pathway for the passage of lipid peroxides and lysophospholipids to the liver via hepatic scavenger receptors and by actually metabolizing lipid hydroperoxides thus, preventing their accumulation, consequently impeding

the atherogenic structural modification of LDL. They however noted that this anti-oxidative function of HDL is observed *in vitro* with similar protein concentrations of LDL and HDL; greater suppression of LDL oxidation might be expected when HDL concentrations exceed those of LDL as they do in the interstitial fluid. In fact, the accumulation of oxidized lipids in HDL likely results not only from their transfer from LDL but also from triglyceride-rich remnant particles and endothelial cells.

5. Conclusion

This study has shown a role for lipids especially reduced levels of high density lipoprotein in the aetiology of breast cancer. This role has been suggested to probably be through the antioxidative effect of the HDL molecule.

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