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Hypovitaminosis C Among Women of African Descent with Breast Cancer in Sokoto, North-Western Nigeria: Case for Ascorbic Acid Supplementation

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Abstract: In women, cancer of the breast is the most common neoplasm and cause of cancer-related death. An increasing number of women in Nigeria are affected with breast cancer. There is however paucity of data on the ascorbic acid levels among women of African descent with breast cancer. This study was a hospital-based case-control study to examine the levels of vitamin C among women of African descent with breast cancer in Sokoto, North Western Nigeria. The study included a total of 46 breast cancer patients aged 18-70 years and mean age 42.91±5.83 years visiting the Specialist Hospital, Sokoto. Forty –six age-matched apparently healthy women were monitored as controls. Venous blood was collected from the subjects and controls for estimation of vitamin C by a standard chemical method. Data were analyzed using SPSS 22.0 statistical package. Linear regression analysis was carried out to calculate correlation coefficient. A p-value ≤0.05 was considered significant in all comparisons. The results of the present study indicate a strong association of vitamin C with breast cancer among women with breast cancer in Nigeria. The mean value of ascorbic acid was significantly lower among breast cancer patients (0.44±0.02 mg/dl) compared to controls (1.98±0.21 mg/dl) (p=0.000). There was no statistically significant difference in the Vit C levels of subjects based on whether subjects were on treatment or naïve (0.43±0.04 vs 0.45±0.03) p=0.65. There was a statistically significant difference in the Vit C levels of subjects based on stage of the disease (p=0.05). Findings from this study have shown that breast cancer patients have a significantly lower ascorbic acid levels compared to controls. Determination of ascorbic acid level should be taken as an essential tool in the investigation and management of breast cancer. Active breast cancer awareness campaign should be carried out on the need for early diagnosis. This study may be a justification to routinely offer ascorbic acid supplementation to women of African descent with breast cancer as a prophylactic measure.

Keywords: Hypovitaminosis C, Women, African Descent, Breast Cancer, Sokoto, Nigeria, Supplementation

1. Introduction

Breast cancer is a commonest form of cancer among women worldwide. It is the fifth leading cause of death with an average of 522,000 cases per year [1, 2]. In developing countries, it is the first leading cause of death among women [3]. In 2012, the number of new cases of breast cancer among women was 1.7 million (25% of all cancers), with majority of cases observed in the developed regions (883,000 cases against 794,000 in developing countries) [4].

Breast cancer is disproportionately responsible for mortality among women in developing countries compared to

those in developed countries. There are several challenges militating against the effective management of breast cancer in Nigeria; financial barriers limit women's access to screening and treatment services, late-stage presentation, high incidence of triple negative breast cancers and failure in stewardship by government in their inability to provide the best possible cancer-related care like their counterparts in the West.

The mortality rate associated with breast cancer varies proportionally with age. It also depends on the stage of disease at diagnosis, the speed of management, type and extent of the tumour, complacency and response to initial treatment. The main risk factors associated with breast cancer include; hormonal factors related to pre-menopausal estrogenic impregnation, genetic predispositions-related factors, behaviors and environmental factors [5].

In the North-Western geopolitical zone of Nigeria, cancer of the breast is second to cancer of the cervix, while at University College Hospital (UCH), Ibadan (situated in the South-Western geopolitical zone of Nigeria) it is the leading malignancy among women [6, 7]. In the North- central geopolitical zone, breast cancer constituted 22.41% of new cancer cases registered in 5 years and accounted for 35.41% of all cancers in women [7]. In developing or low-income countries, breast cancer was characterized by late clinical presentation and in advance stage of the disease, when only option available is chemotherapy and palliative care and therefore associated with high mortality [7-10].

Vitamins are organic substances often found in food and usually required in small amounts. They cannot be synthesized by the body in adequate quantities [11]. Thirteen vitamins have been demonstrated to have clinical effects in human and vitamin C is prime among them. Vitamin C has been shown to enhance the synthesis of immunoglobulins, increases the phagocytic action of leucocytes and acts as an antioxidant and reduces the risk of cancer. It is a water soluble versatile vitamin, and plays an important role in human health and disease [12]. It serves as an antioxidant to protect intracellular and extracellular components from free radical damage. It mops up free radicals and forms the less reactive ascorbyl radical. Vitamin C consumption is important and may help reduce tissue inflammation levels. However, few studies have explored the relationship between vitamin C and breast cancer. There is paucity of data on ascobate level among women with breast cancer in Nigeria. Compared with Caucasian women particularly in sub Saharan Africa experiences a disproportionate burden of aggressive Triple Negative Breast Cancer. There is a high incidence of late stage presentation, low level of public awareness of the disease, suboptimal health infrastructure, poor access to affordable interventions and poor prognosis. The aim of this present study was to investigate the ascorbic acid levels among women of African descent with breast cancer in Sokoto, North Western, Nigeria.

2. Materials and Method

2.1. Study Area

The study was carried out as a collaborative effort between the Department of Haematology of Usmanu Danfodiyo University, Sokoto and the Department of Surgery, Specialist Hospital, Sokoto, Nigeria. Specialist Hospital Sokoto is a tertiary health facility located in Sokoto, the Sokoto State Capital. It serves as a referral center for residents in Sokoto and neighboring Niger in the West African sub-region. The state is located in the extreme Northwest of Nigeria, near the confluence of the Sokoto River and the Rima River. The State is in the dry Sahel, surrounded by sandy savannah and isolated hills, with an annual average temperature of 28.3°C (82.9°F). Sokoto is, on the whole, a very hot area. However, maximum daytime temperatures are for most of the year is generally under 40°C (104.0°F) and the dryness makes the heat unbearable. The warmest months are February to April when day time temperature can exceed 45°C (113.0°F). The rainy season is from June to October during which shower are a daily occurrence. Sokoto city is a major commerce center in leather crafts and agricultural products. As at 2006, the state has a population of 3.6 million [13]. However, based on the population annual growth of 3%, the calculated projected population for Sokoto State is now stands at around 4.9 million.

2.2. Study Population

The participants for this study included 46 female breast cancer patients aged 18-70 years (subjects) and 46 healthy aged-matched females who were monitored as controls.

2.3. Inclusion Criteria

Inclusion criteria included age ($\geq$ 18 years), histologically confirmed breast cancer including those that have started treatment and those who are treatment naive, and willingness to offer a written informed consent to participate in the study.

2.4. Exclusion Criteria

All non-consenting adults, non- adults (<18 years), non-breast cancer patients, pregnant breast cancer patient, those with benign breast tumor and breast cancer subjects who did not offer a written informed consent to participate in the study were excluded.

2.5. Study Design

The research is a case-control study involving 46 breast cancer patients who served as subjects. The control participants consisted of 46 non- breast cancer apparently healthy adults. Qualitative data were elicited using a structured interviewer-administered questionnaire administered to each patient and information on patient's demographic and socioeconomic characteristics including gender, age, marital status, occupation, and education were obtained. Information on the patient nutritional status, stage

of breast cancer and whether they were under therapy or newly diagnosed were also obtained. While quantitative data were gotten by estimating the ascorbic acid levels of subjects and control participants.

2.6. Ethical Consideration

Ethical approval for the study was obtained from the Ethical Committee in Specialist Hospital, Sokoto.

2.7. Informed Written Consent

Written informed consent was obtained from all the participants (subjects and controls).

2.8. Sampling Technique

Subject Selection

All the breast cancer patients who met the inclusion criteria were consecutively selected from the population of breast cancer patients attending the Surgical Clinics of Specialist Hospital, Sokoto.

2.9. Questionnaire

An inter-viewer administered questionnaire was used to collect bio- data and related information from the subjects and control participants.

Estimation of Ascorbic Acid (Vitamin C)

Serum vitamin C (ascorbic acid) was assayed using a standard chemical method [14]. The principle is based on ascorbic acid being oxidized by copper II ion to form dehydroascorbic acid, which reacts with acidic 2, 4-dinitrophenylhydrazine to form a red bis-hydrazone which is measured spectrophotometrically at 520nm.

3. Result

A total of 46 histologically confirmed breast cancer female patients with mean age of 42.91±5.83 years and 46 age and gender- matched apparently healthy controls with mean age 42.83±5.80 years were enrolled for the study. The results are presented as mean ± standard error of mean. Table 1 shows the socio-economic and demographic characteristics of the subjects and controls and reveals that majority of the patients; 20 (43.5%) and control group; 23 (50%) were in the age range of 40-49 years. Figure 1 shows the age distribution of the Breast Cancer subjects. The distribution of patients and control group based on ethnicity shows that majority of subjects and controls were Hausa/Fulani; 42 (91.3%) and 29 (63%) respectively. The distribution of the subjects based on educational status shows that 6 (13%) had tertiary education, 11 (23.9%) had secondary, 12 (26.1%) had primary education and 17 (37%) had no formal education as compared with control where 6 (13%) had tertiary education, 14 (30.4%) had secondary education, 19 (41.3%) had primary education and 17 (37.0%) had no formal education. Occupational distribution of the subjects indicated that 6 (13%) were employed while the remaining 40 (87%) where either unemployed/full time housewives as compared to control where 22 (47.8%) were employed, 17 (36.9%) were unemployed/full time housewives and 7 (15.20) were students. Most of the subjects and controls were married, 44 (95.7%) and 42 (91.3%) respectively. The classification of the patients based on cancer staging shows that 2 (4.3%) were in stage 1, 17 (37%) were in stage 2, 22 (%) were in stage 3 and 5 (10.9%) were in stage 4. Figure 2 shows the age distribution of the Breast Cancer subjects based on the stage of breast cancer. Table 2 shows the mean comparison of Vitamin C levels among the subjects and controls. The ascorbic acid levels was significantly lower among subjects compared to controls (p= 0.000). The effect of breast cancer treatment on the level of vitamin C-levels was not significant (p=0.65). Table 3 shows the vitamin C levels of subjects based on the presence or absence of therapy. Vitamin C levels were compared among subjects based on the stage of the breast cancer. The ascorbic acid level where higher among patients in stages 1 and 2 compared to the advanced stages 3 and 4 (p=0.05). Table 4 shows the vitamin C levels among subjects based on disease staging.
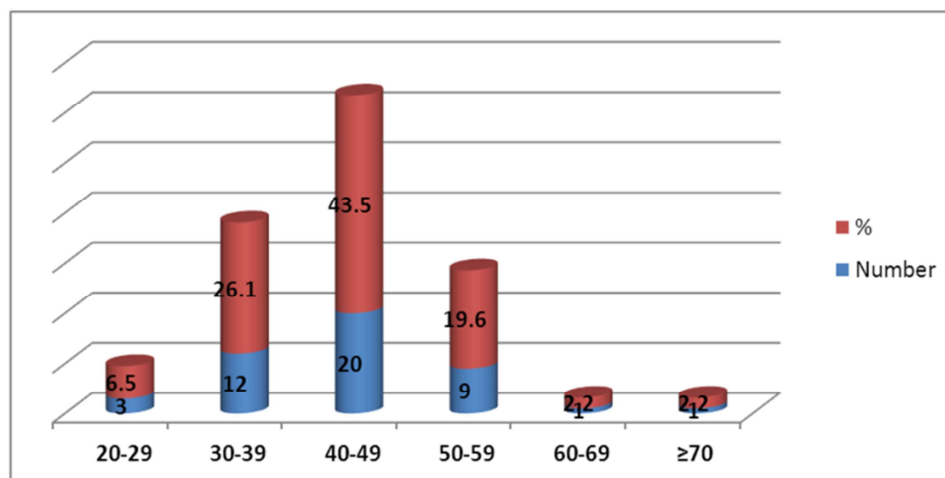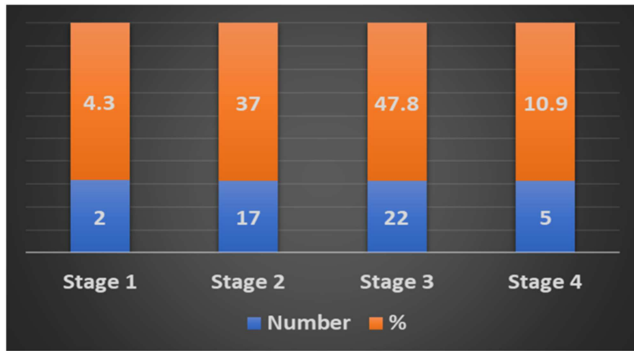

Figure 1. Age distribution of Breast Cancer Subjects.

Figure 2. Distribution of Breast Cancer Subjects Based on Stage of Disease.

Table 1. Socio-demographic Characteristics of Controls and Patients.

Characteristics	Subjects		Controls	
	N=46	Percentage (%)	N=46	Percentage (%)
Marital Status				
Married	36	78.3	37	80.4
Single	3	6.5	5	10.9
Widowed	1	2.2	-	-
Divorced	6	13	4	8.7
Ethnicity				
Hausa/Fulani	42	91.3	29	63
Yoruba	2	4.3	9	19.6
Igbo	1	2.2	7	15.2
Others	1	2.2	1	2.2
Education Level				
Tertiary	6	13	6	13

Characteristics	Subjects		Controls	
	N=46	Percentage (%)	N=46	Percentage (%)
Secondary	11	23.9	14	30.4
Primary	12	26.1	19	41.3
Non-formal	17	37	17	37.0
Occupation				
Employed	6	13	22	47.8
Unemployed / House wives	40	87	17	36.9
Employed	0	0	7	15.2

Key: N= Number, % =Percentage

Table 2. Mean comparison of Vitamin C for subjects and controls.

Parameters	Patients	Controls	t-test	p-value
Vit C (mg/dl)	0.44±0.02	1.98±0.21	-7.16	0.000 (S)

Data are presented as mean ± SD
Key: Vit C = vitamin C (Ascorbic acid), (S) =statistically significant

Table 3. Vitamin C levels of Subjects based on the presence or absence of therapy.

Parameters	Therapy		P- value	Remark
	Yes (N=24)	No (N= 22)		
Vit C (mg/dl)	0.43±0.04	0.45±0.03	0.65	NS

Values are mean ± standard error of mean; Level of significance is considered when p<0.05
Key: N= Number of subjects, Yes= Patients that have started therapy, No= Treatment Naïve patients, Vit C= Vitamin C (Ascorbic acid), (S) = Statistically significant.

Table 4. Vitamin C levels of Subjects based on staging.

Parameters	TNM Classification				p- value	Remark
	Stage I (N=2)	Stage II (N=17)	Stage III (N=22)	Stage IV (N=5)		
Vit C (mg/dl)	0.46±0.05	0.52±0.04	0.39±0.04	0.30±0.04	0.05	S

Values are mean ± standard error of mean, Level of significance is considered when p<0.05
Key: N= Number of subjects; Vit C=Vitamin C, S= Statistically Significant, NS= Not significant.

4. Discussion

Breast Cancer is still one of the leading causes of death and equally prevalent all over the world. Most chemotherapeutic drugs used to kill the neoplastic cells without damaging healthy surrounding tissues [15, 16].

In this study, we observed that the peak age of incidence of breast cancer among our cohort of women of African descent living with breast cancer in North Western Nigeria was 40-49 years (5th decade). Our observation is consistent with previous reports; South Africa and Kenya [17]; Ilorin, Nigeria [18] and Sudan [19] which reported the peak age of incidence of breast cancer to be the 5th decade. Our finding is however in variance with reports from Norway [20] and Philippines [21] which indicated peak age of incidence in the 6th and 8th decade respectively. Similarly, a previous report from Khartoum, Sudan [22] indicated that the peak age was above 50 years. The variation in peak age of incidence of breast cancer may be attributed to the onset of breast cancer aetiopathogenesis which have been found to include, early menarche, late menopause, late age at first birth, and other reproductive factors [23].

It was observed that majority of patients are predominantly Hausa/Fulani (91.3%). Our finding is in agreement with the study carried in Zaria [24]. The reason for this observation may be due to the fact that the Hausa and Fulani are the major ethnic groups in Sokoto, North Western Nigeria.

We observed in this study that the majority (37%) of the breast cancer patients had no formal education; the remaining 63% had tertiary, secondary or primary education. This is in consonant to the report of study from Sudan [22] which indicated that 40.9% of their cohort of breast cancer subjects was illiterate. However, the findings in Lagos [25] are at variance with the findings in this present study. The difference may be due to low level of enrollment in primary, secondary and post education level in this study area (Northern Nigeria) than in Lagos (Southern Nigeria).

This study also shows that the most of the patients are full time housewives/ unemployed. This is in agreement with the finding in Sudan [22] and in contrast with the findings in Lagos [25]. This is also related to the low level of education in this study area.

In this study, that majority of the subjects (47.8%) presented with stage 3 disease. Our finding is in agreement with the study carried out in Zaria [24] which indicated that

half of their breast cancer patients presented with stage 3 diseases. Breast cancer, the most prevalent cancer in women worldwide, and the leading cause of cancer death in women [26]. Though treatable in early stages, once metastasis has occurred the survival rate is drastically reduced to a median of 2–3 years and treatment focuses on palliative care [27].

Rath and Pauling [28] in a previous report proposed that the most effective and universal approach to controlling cancer is ensuring optimal synthesis and integrity of collagen, which is dependent upon essential nutrients, such as vitamin C. Ascorbic acid is needed for synthesis and hydroxylation of collagen and is produced by most animals but not by humans [28]. Humans must obtain ascorbate by diet and cancer patients have been shown to have very low reserves of vitamin C [29-30].

Consistent with the findings in this study, numerous clinical studies have noted that cancer patients exhibit abnormally low plasma ascorbate levels secondary to the disease and/or treatment [31-32]. A significant correlation has been demonstrated between deficient plasma ascorbate levels in cancer patients and decreased survival, as well as increased expression of inflammatory factors [33]. Tumour aggressiveness has also been correlated to low ascorbate content and has been implicated in host resistance to neoplasia, at both the stromal and systemic levels. Previous study showed that ascorbate supplementation of gulo KO mice resulted in reduction in the mean tumour weight compared to that in ascorbate-deprived gulo KO mice. Gulo KO mice deprived of ascorbate developed large tumors with dark cores, showing more necrosis, and poorly defined borders. In contrast, gulo KO mice supplemented with ascorbate hosted smaller tumours with smaller, lighter cores, less necrosis and enhanced collagen encapsulation, signifying less metastatic potential [34-36].

This study has shown that there is significant ascorbic acid deficiency among women of African descent with breast cancer. This may be a justification to routinely offer breast cancer patient ascorbic acid as prophylaxis. Previous reports indicate that ascorbate supplementation in cancer patients can potentially reverse their scorbutic symptoms [37-38]. Similarly, Singh and Colleagues [39] observed that the mean vitamin C, vitamin E and selenium levels were lower in patients as compared to the controls and that there was a 84% and 77% lower risk of breast cancer if the levels of vitamin C and vitamin E were increased by 1 unit, respectively. Serum ascorbate levels were significantly lower in patients with benign diseases of the breast and cervix than in controls. In cancer patients, there was a significant trend of lower serum vitamin levels with increasing stage of the disease [40]. Cancer patients have been shown to have very low reserves of ascorbic acid. Previous report shows that ascorbate supplementation has effect on metastasis, tumour growth and tumour immunohistochemistry in mice [41]. Vitamin C has been suggested as having both a preventative and therapeutic role in a number of pathologies when administered at much higher-than-recommended dietary allowance levels. High dose intravenous ascorbate treatments may reduce inflammation in cancer patients [42].

5. Conclusion

This current study has shown that ascorbic acid levels are significantly lower among breast cancer patients compared to controls. There may be need to routinely offer ascorbic acid supplementation to women of African descent with breast cancer as prophylaxis. Determination of ascorbic acid level should be taken as an essential tool in the investigation and management of breast cancer. Active breast cancer awareness campaign should be carried out on the need for early diagnosis. Finding from this study may be a justification to routinely offer ascobate supplementation to women of African descent with breast cancer. Additional epidemiologic studies on the potential role of vitamin C on inhibition or promotion of breast cancer may clarify the nature and practical significance of the relationship between vitamin C supplementation and breast cancer.

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