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Original Research Article

Risk Factors for Breast Cancer in Sokoto, Nigeria

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Abstract

Most recently published works from across Nigeria and Africa point to a rising prevalence of breast cancer in these hitherto low incidence areas. The literature is also replete with studies on risk factors for the development of breast cancer amongst pre and post- menopausal women. Even though our center has also witnessed a rising trend in the incidence of breast cancer, not much work has been done to elucidate the risk factors associated with breast cancer in this sub region. This study is undertaken to determine the risk factors commonly associated with breast cancer in Sokoto, North-western Nigeria and to highlight the predominant receptor status of breast cancer in this region. A three-year retrospective study in which the case note of patients with histologically confirmed diagnosis of breast cancer between 2013 and 2015 were looked at. Parameters studied included demography, risk factors and receptor status. A total of ninety patients were seen in this study. Out of this, 88 were females, while 2 were males giving a female: male ratio of 44:1. The age range was 20 – 80 years. The mean age was 45.10 years. The median age was 43.00 years while modal age was 35.00 years. 70.45% (62) of the women with breast cancer were pre-menopausal while 29.55% (26) were post-menopausal. The mean BMI was 31.18. The main risk factors associated with breast cancer included, physical inactivity, 20.0%(18), high carbohydrate diet, 14.4%(13), high fatty diet, 12.2%(11), high intake of roasted beef (suya), 11.1%(10), hormonal contraceptive and cigarette smoking, 10.0% (9) each, family history, 8.9%(8) and alcohol comsumption,6.7%(6). Nulliparity, previous benign breast diseases and previous uterine cancer accounted for 3.3% (3), 2.2%(2) and 1.1%(1) respectively. Our centre started routine immunohistochemistry to determine receptor status of breast cancer in 2015. Analysis shows that 47.8% (22) of cancers were ER positive, 41.3%(19) PR positive, 39.1%(18) ER/PR positive, while 43.5%(20) were HER 2/neu positive. Immunohistochemical classification based on ER, PR and HER2 gene expression showed that 24%(11) were Luminal A(ER+, PR+,HER2-), 22%(10) Luminal B(ER+,PR+,HER2+), 26%(12) HER2 type(ER-,PR-,HER2+) while 28%(13) were Basal-like(Triple negative) tumours. Physical inactivity with high calorie (carbohydrate and fat), high protein diet appeared to be important risk factors for development of breast cancer in Sokoto, Nigeria. Majority, 28% (13) of the tumours were triple negative (basal like).

Keywords: Breast cancer, Diet, Risk factors, (Add 2 or more keywords)

INTRODUCTION

Breast cancer is the most common female malignancy in Nigeria and globally (Otu et al., 1989; Adelusola et al., 1996; Abimiku and Mukhtar, 2002; Hoffman et al., 2000; Forbes, 1997). The incidence of breast cancer in Nigeria

has risen steadily from 15.3 per 100,000 in 1976 to 33.6 per 100,000 in 1992 (Ihekwaba, 1992). Jedy Agba et al. in a report from population-based cancer registries in 2012 gave an age standardized incidence rate (ASR) of breast cancer of 52.0 per 100,000 women in Ibadan, South-Western, Nigeria and 64.6 per 100,000 women in Abuja, North-Central, Nigeria (Jedy-Agba et al., 2012). However we reported a prevalence of 10.4 per 100 000 women in a retrospective study from our centre in North-Western Nigeria in 2011 (Agbo et al., 2014). Incidence is considered to be low in black Africa and Asia compared to Western Europe and North America where it ranges between 50 to 100 per 100 000 women (Althuis et al., 2005; Bray et al., 2004). The variable incidence of breast cancer in different regions of the world suggests that environmental factors play an important role in its aetio-pathogenesis and therefore identification of these factors may help prevent the disease to a large extent. The observed increased risk of breast cancer among migrants from low to high incidence areas gives the first strong evidence that environmental factors rather than genetic were responsible for most of the reported regional and inter-ethnic variations in breast cancer incidence (Ziegler et al., 1993; Tyczynski et al., 1994).These studies observed that breast cancer risk increases substantially when women migrate from their native low risk area to high risk areas especially if the migration took place when they were young (Ziegler et al., 1993; Tyczynski et al., 1994). The overall lifetime risk for developing invasive breast cancer in the USA is approximately one in nine with use of the 1987-1988 National Cancer Institute's Surveillance, Epidemiology and End-Results (SEER) data (Feuer et al., 1993). The lifetime risk of developing breast cancer is 8.8% for US Black females and 13.0% for US White females (Nazario et al., 2000). While the lifetime risk of developing breast cancer in Nigeria and most black Africa remains largely unknown, in South Africa risks vary from 1 in 81 among black women to 1 in 13 among whites further highlighting the low incidence of the disease among black Africans (Vorobiof et al., 2001). However, most recent studies have shown a rising trend in incidence in hitherto low incidence areas of Africa and Asia due largely to changing dietary lifestyle, increase in the average life expectancy, use of hormone replacement therapy (HRT) in the urban areas, and better reporting of the disease (Adebamowo and Ajayi, 2000; Seo et al., 1996; Wakai et al., 1995; Yip and Taib, 2012).

The most frequently quoted risk factors for breast cancer in literature includes age, sex, reproductive history, diet, previous breast disease and hereditary factors (Okobia and Bunker, 2005; Sally et al., 2010). Others include alcohol, cigarette smoking, hormonal contraceptives, hormone replacement therapy(HRT) and physical activity (Okobia and Bunker, 2005; Sally et al., 2010). In this study we looked at the most commonly observed risk factors associated with breast cancer in our region.

METHOD

This was a three-year retrospective study between 2013 and 2015 in which the case note of patients with histologically confirmed diagnosis of breast cancer were retrieved and reviewed. Parameters studied included demographic characteristics, risk factors and the receptor status of biopsy specimens.

Risk classification

Commonly recurring risk factors were identified and grouped in order of frequencies and presented as absolute values and percentages.

Inclusion/Exclusion criteria

All histologically confirmed malignant breast lesions were included**.** Breast diseases not confirmed by histology were excluded and histologically confirmed non-neoplastic lesions were also excluded from the study.

Data Analysis

Results were analyzed using the windows statistical package for social sciences (SPSS) version 20.

RESULTS

A total of ninety patients were seen in this three-year study. Out of this, 88 were females, while 2 were males giving a female: male ratio of 44:1. The age range was 20 – 80 years. The mean age ±SD was 45.10±13.45 years (95% confidence interval (CI) of 41.925 and 47.400). The median age was 43.00 years while modal age was 35.00 years. (Table 1) 70.45% (62) of the women with breast cancer were pre-menopausal while 29.55% (26) were post-menopausal. The mean body mass index (BMI) ±SD was 31.18±2.17. The main risk factors associated with breast cancer included, physical inactivity, 20.0%(18), high carbohydrate diet, 14.4%(13), high fat diet, 12.2%(11), high intake of roasted beef (suya), 11.1%(10), hormonal contraceptive and cigarette smoking, 10.0% (9) each, family history, 8.9%(8) and alcohol comsumption,6.7%(6). Nulliparity, previous benign breast diseases and previous uterine cancer accounted for 3.3%(3), 2.2%(2) and 1.1%(1) respectively (Table 2). Routine immunohistochemistry to determine receptor status of breast cancer started in our centre in 2015. A total of 46 samples were analysed during this year. Out of this, 47.8% (22) of cancers were ER positive, 41.3% (19) PR positive, 39.1% (18) ER/PR positive, while 43.5% (20) were HER 2/neu positive (Table 3). Immunohistochemical

Table 1. Percentage age distribution of patients with breast cancer

Age group	Frequency	Percentage
20 - 29	4	4.44
30 - 39	31	34.44
40 - 49	29	32.22
50 - 59	8	8.89
60 -69	11	12.2
≥ 70	7	7.78
Total	90	100

Table 2. Risk factors for breast cancer in Sokoto.

Variables	Frequency	Percentage
Physical inactivity	18	20.0
High carbohydrate diet	13	14.4
High fatty diet	11	12.2
Roasted beef(Suya)	10	11.1
Hormonal contraceptive	9	10.0
Cigarette smoking	9	10.0
Family history	8	8.9
Alcohol consumption	6	6.7
Nulliparity	3	3.3
Previous benign breast disease	2	2.2
Previous uterine cancer	1	1.1
Total	90	100

Table 3. Receptor status for breast cancer in Sokoto in 2015.

Status	ER	PR	ER+PR	HER2NEU
N	46	46	46	46
Positive	22 (47.8)	19 (41.3)	18 (39.1)	20 (43.5)
Negative	24(52.2)	27(58.7)	28 (60.9)	26 (56.5)

classification based on ER, PR and HER2 gene expression showed that 24%(11) were Luminal A(ER+, PR+,HER2-), 22%(10) Luminal B(ER+,PR+,HER2+), 26%(12) HER2 type (ER-, PR-, HER2+) while 28%(13) were Basal like (Triple negative) tumours.

DISCUSSION

The mean age of 45 years in this study shows that breast cancer occurs in younger age among our patients than in Caucasians (Anyanwu, 2000). Most published works in Nigeria and America reveal that breast cancer in African women occur a decade earlier than the western average (Anyanwu, 2000; Adebamowo and Adekunle, 1999; Joslyn and West, 2000). African-American women also present at significantly younger age than their Caucasian counterparts (Elmore et al., 1998; Gao et al., 1997). Similarly, black British women presented significantly younger (median age of 46 years), than white patients (median age of 67 years) (Bowen et al., 2008). The factors responsible for this are not fully understood although some studies have attributed it to mutations in the breast cancer genes (BRCA 1 and 2) and their variants (Gao et al., 1997; Haffty et al., 2006). African breast cancer patients are also more likely to be premenopausal as our study has shown (Anyanwu, 2000; Amir et al., 1994; Hassan et al., 1992). Most reports from across Africa demonstrates a consistent decline in breast cancer risk following menopause (Adebamowo and Adekunle, 1999; Hassan et al., 1992). This is however in contrast to rising rates seen among postmenopausal women from North America and Western Europe (Adebamowo and Adekunle, 1999; Gao et al., 1997; Hassan et al., 1992). The decline in breast cancer risk at menopause may be attributed to diminishing levels of circulating oestrogen (Henderson et al., 1988) or as some authors have postulated a consequence of demographics, especially population age and overall life expectancy which is lower in Africa compared to developed countries (Adebamowo and Ajayi, 2000).

The most predominant risk factor associated with breast cancer in this study was dietary factor at 37.7% (34) followed closely by physical inactivity at 20.0% (18). These two factors together constituted more than half of the total

risks seen among our patients. Evidence for a role of dietary risk factors in the cause of breast cancer has been conflicting. While most studies found no causal relationship between diet and breast cancer (Adebamowo et al., 2005; Agurs-Collins et al., 2009; Terry et al., 2001; Velie et al., 2005), others have reported strong relationship between diet and breast cancer especially among post-menopausal women (Cottet et al., 2009; Fung et al., 2005; Ronco et al., 2006). Cutsburg et al in a cohort study from USA in 2015 reported that consumption of Western diet characterized by red meat and potatoes was associated with increased risk of breast cancer in postmenopausal women only (Chelsea et al., 2015). Murtaugh et al in a report from the Four Corners Breast Cancer Study in 2008 described the Western diet as a relatively high-fat, high-sugar, and low-fiber diet characterized by the consumption of eggs, high-fat dairy, refined grains, gravies and sauces, fast foods, red and processed meats, potatoes and sugar (Maureen et al., 2008). They found greater risk for breast cancer associated with this diet pattern without respect to menopausal status (Maureen et al., 2008). Our high carbohydrate, high dairy fat and roasted meat pattern of diet was consistent with the Western dietary pattern described above. Nomadic pastoral practice is predominant in this part of our country so consumption of beef and dairy fat is also common. Carbohydrates could influence breast cancer risk by increasing the plasma levels of glucose and insulin (Michels et al., 2007). Raised plasma insulin may cause breast tissue carcinogenesis by directly stimulating insulin receptors leading to increased levels of the insulin-like growth factor-1(IGF-1) which has been found to have strong proliferative and anti-apoptotic effects on breast tissues (Calle and Kaaks, 2004; Yanochko and Eckhart, 2006). A case-control study by Bruning et al in 1992 showed that the serum levels of C peptide, a marker of hyperinsulinaemia was significantly higher among patients with early breast cancer than the controls or other cancer groups (Bruning et al., 1992). Unfortunately, routine insulin levels of our patients were not determined in this retrospective study.

The mean body mass index (BMI) of 31 kg/m^2 in this study agrees with the high rate of physical inactivity among our patients. Abdominal obesity which is a consequence of high calorie diet and physical inactivity is linked to hyperinsulinaemia and dyslipidaemia in pre and post-menopausal women (Kopelman, 1994). Adebawowo et al in a case-control study from Ibadan, South-Western, Nigeria were able to demonstrate a positive association between obesity and breast cancer risk among postmenopausal women (Effiong et al., 2003). Several other studies have also shown association of obesity with breast cancer especially in post-menopausal women (Schapira et al., 1990; Shu et al., 2001; Folsom et al., 1990). It has been postulated that diets high in red meat could promote breast carcinogenesis via its highly bioavailable iron content and the dietary heterocyclic amines and polycyclic aromatic hydrocarbons formed during the cooking and roasting process and which are known to promote mammary gland tumors in animal models (Lauber and Gooderham, 2007). Even though epidemiologic studies to support this theory have yielded conflicting results (Alexander et al., 2010; Mahoney et al., 2008), recent reports have however suggested a possible link between the consumption of red meat and the risk of breast cancer according to specific hormonal receptor status (Cho et al., 2006).

10.0% (9) of our patients used hormonal contraceptives and 10.0% (9) also smoked cigarette.

Pooled analyses of data from several epidemiological studies on hormonal contraceptives and breast cancer risk have shown that women using the contraceptive pill have a slight increase in breast cancer risk especially among current and recent users (Collaborative Group on Hormonal Factors in Breast Cancer, 1996). Risks were found to decline with increasing time from last use of contraceptive and by10 years after discontinuation, the risk of breast cancer returns to normal (Collaborative Group on Hormonal Factors in Breast Cancer, 1996). Fasal and Paffenbarder in a case-control study in women aged below 50 years found a relative risk of developing breast cancer among "ever-users" of oral contraceptives to be 1.1. The risk among women using oral contraceptives for 2-4 years (recent users) was 1.9. This risk estimate reached 2.5 for the 2- to 4-year users if they were current users of contraceptives (Fasal and Paffenbarger, 1975). In Nigeria, Nwajana and Oboma in a case-control study found a significant increase in breast cancer risk among women in Abuja city who used the oral contraceptive pill compared to control (Nwajana and Oboma, 2016). Majority of the patients in that study were premenopausal (Nwajana and Oboma, 2016).

In South Africa, Urban et al also in a case-control study found that the risk of breast cancer was significantly increased in women who had used either oral or injectable contraceptives within the previous 10 years and did not differ significantly in those ceasing use 10 years or more previously, compared to women who had never used hormonal contraceptives (Urban et al., 2012).

Experimental studies have shown that tobacco smoke contains potential human breast carcinogens like polycyclic aromatic hydrocarbons (eg benzo[a]pyrene), heterocyclic amines (eg 2-amino-1-methyl-6-phenylimidazo[4,5-b] pyridine), aromatic amines (eg 4-aminobiphenyl) and N-nitrosamines (eg 1-nitropyrene and 4-nitropyrene) (Phillips et al., 2001; Hoffmann et al., 2001; IARC, 1986). Case-control studies have also found a high prevalence of smoking-specific DNA adducts and *p53* gene mutations in the breast tissue of smokers compared to nonsmokers (Perera et al., 1995; Li et al., 1999; Conway et al., 2002). Both active and passive smoking have been reported to increase the risk of breast cancer (Morabia et al., 1996). However in Nigeria, a case-control study by Okobia et al did not find any association between cigarette smoking and breast cancer risk (Michael et al., 2006).

They reported that smoking was not a common practice among respondents in that study (Michael et al., 2006). Similarly, Ajayi et al in a case-control study carried out in Warri, South-South Nigeria and Ibadan, South-West Nigeria found that none of the respondents with breast cancer smoked cigarette compared to 1% of control that smoked (Kelechi et al., 2013). They concluded that cigarette smoking was not a significant risk factor for breast cancer in that study (Kelechi et al., 2013). Compared to our study, cigarette smoking was surprisingly high at 10% (9). 8.9% (8) of our patients had positive family history of breast cancer. This figure is not different from figures obtained elsewhere in Nigeria (Ihekwaba, 1992; Kelechi et al., 2013). 6.7% (6) of our patients were regular consumers of alcohol. High alcohol consumption has long been linked to increased risk of breast cancer probably from increased production of oestrogen (Mann et al., 1995). A case-control study conducted across three subsaharan countries by Ojan et al concluded that both past and current drinking were associated with breast cancer risk, with 10-year increase of drinking associated with a 54% increased risk (Qian et al., 2014). Dumitrescu and Cotarla also reported that the risk of breast cancer increases progressively in a dose-dependent manner to alcohol intake of 60 g (2-5 drinks) per day, depending on the strength of the drink (Dumitrescu and Cotarla, 2005). They stated that the risk increases with 9% for every 10 g increment (approximately 0.75-1 L drink) in daily alcohol consumption (Dumitrescu and Cotarla, 2005). Our study showed a preponderance of triple negative (basal like) tumors of 28% (13) compared to other subtypes. Studies from Ife, South-West Nigeria, Uyo, South-South Nigeria and other parts of Africa showed similar pattern (Omoniyi-Esan et al., 2015; Nwafor and Keshinro, 2015; Amanda et al., 2014).

Previous reports have shown that women with luminal A tumors have better recurrence-free and overall survival than women with other molecular subtypes. Luminal tumors also generally have better survival outcomes compared to HER2+ or triple negative tumors (Dawood et al., 2011; Cheang et al., 2008).

CONCLUSION

Physical inactivity with high calorie (carbohydrate and fat), high protein diet appeared to be important risk factors for development of breast cancer in Sokoto, Majority, 28% (13) of the tumours were triple negative (basal like).

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