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Breast Cancer and Food: A Quasi-epidemiological Evidence of a Role for Dietary Phytoestrogens in Northwestern Nigerian Women

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Abstract: The relationship between breast cancer and dietary phytoestrogen intake in northwestern Nigerian women was explored in a case control study involving 189 cases versus 189 matched controls. Cases had significantly earlier menarche than controls and when these were adjusted for, cases significantly consumed more dietary phytoestrogens than controls. Consumption of food items like *Sorghum bicolor, Manihot esculenta* and *Typha domigensis* appear to increase the risk of breast cancer while *Oriza sativa, Mangifera indica* and *Musa sapientum* appear protective.

Key words: Breast cancer, diet, phytoestrogens, case control study

INTRODUCTION

Neoplastic diseases often have disastrous consequences on patients living in a developing economy like Nigeria. Patients typically present with late stage diseases and this may be related to illiteracy, ignorance and financial constraints, which may limit early attempts at treatment to non-orthodox practitioners. The highly limited option in treatment algorithms in developing economies also suggests that even those who present early to orthodox practices might have been missed. Given this scenario, preventive medicine remains the parsimonious option. Even this is difficult to optimize because behavioral modification is often also required and, especially in Africa, this is often restricted by highly conservative cultural values. One option is to identify and optimize beneficial factors within a cultural setting. Diet may be one such factor. Breast cancer is the commonest cancer in women[1] and is probably the commonest cancer in Nigeria. A case control study in Nigeria implicated oral contraceptive use as a risk factor for development of breast cancer[2] while current evidence suggest that daily conjugated equine estrogen (0.625 mg) combined with medroxyprogesterone acetate (2.5 mg) increase the risk of breast cancer in postmenopausal women on replacement therapy[3]. Meanwhile Soybean, rice, beans and yam are common diets in Nigeria but these have been shown to contain significant amount of dietary phytoestrogens. The impact of such diet on the risk of breast cancer in Nigerian women is uncertain. Studies in other communities and races have shown inconsistent results. Epidemiological studies comparing Asian and Western women suggest that phytoestrogens may protect against breast cancer[4] while studies in Chinese women revealed no association between phytoestrogen and breast cancer[5]. However *ex vivo* studies using concentrations equivalent to levels measured in humans consuming 40 mg of phytoestrogens supplement daily, demonstrated a stimulatory effect of phytoestrogens on Estrogen Receptor (ER)-positive breast cancer cell lines with no effect on ER-negative cells[6,7]. Difference in efficacy and potency between different phytoestrogens may be one explanation but the recent findings of lower levels of Estrogen Receptor (ER) alpha gene expression in normal breast tissue in Japanese women compared with white Australian women may be an alternative or additional explanation[8]. Whichever, it appears obvious that a global statement on the interactions between dietary phytoestrogens and breast cancer might be premature. Further studies may be important to expose

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ethnic differences in breast cancer rates and the association with dietary phytoestrogens. This study was carried out in northwestern Nigeria in such context.

MATERIALS AND METHODS

Three urban (Specialist Hospital Sokoto, Nigeria; Karaye Hospital Sokoto, Nigeria and Sir Yahaya Memorial Hospital Birnin Kebbi, Nigeria) and one rural (General Hospital Wurno, Nigeria) northwestern Nigerian hospital settings were selected by convenient sampling and using hospital records 189 patients who reported self as an ethnic Hausa tribe, according to Hospital records, had clinical diagnosis of advanced breast cancer with or without histopathological confirmation and who had partial or radical mastectomies were identified and either introduced to the study at the next follow up clinic or traced, if lost to follow up. Case tracing was particularly emphasized at the rural setting because of poor follow up clinic attendance but easy trace ability due to the close nit of rural communities. Cases versus 189 social level, age and parity matched neighborhood controls were interviewed using an interviewer completed 41-item questionnaire that was designed and validated in a pilot study following the method of Block *et al.*[9]. Briefly, a food list was first developed by interviewing 1329 randomly selected respondent from the community and probing them for a 24 h recall of food intake. Because only 21 food items were listed food codes were considered unnecessary. Portion size estimation was done by simple counts for unitary items (e.g. egg, oranges) and by the use of three-dimensional models for non-unitary items. In this model, abstract 3 dimensional diagrams of 5 different amounts are provided as an aid in estimating usual portion size for each food. The volume and the gram weight of the chosen model, for that particular food is pre-determined and are assigned appropriately post hoc. The questionnaire also comprised questions on demographic data including age at menarche, age at menopause, age at first full-term pregnancy and family medical history of breast cancer. To quantify the phytoestrogen content of each food item on our food list, we first translated the local Hausa name to botanical name using the list of Blench[10] and confirmed the identity by presenting samples to Crop scientists. We then conducted a literature search on Medline, Vivisimo and Agricola first by a simple query-e.g. phytoestrogen content of *Vigna sinensis* or cowpea and/or by using the common and biological names of a food item combined with all of the terms-phytoestrogens, plant estrogens, isoflavones, enterolactone, enterodiol, coumestans, lignans, daidzein, genistein, formononetin, biochanin A, coumestrol, matairesinol and secoisolariciresinol. Arithmetic Mean of published values of phytoestrogen content were determined and converted to mg/100 g food. Values reported as trace were allocated the sensitivity limit of the assay method used in that study, and food items whose values could not be obtained (2 items) were allocated values of the nearest food item determined at genus level. To estimate the average daily consumption of phytoestrogen per study subject, we multiplied the score of each food item by the serving size of the food summed across the 2 weeks food recall list per subject and then determined the arithmetic Mean. Food items may contain other unknown factor that may contribute to its overall influence on breast cancer. To test for the association of a particular food item or combinations of food items with breast cancer, we considered that direct comparison of quantity taken may give a false impression of measurement accuracy and that ranking may be more predictive. Therefore, we first determined the product of portion size and frequency of each item on the food list for each subject, and ranked this value into food-item-specific quartiles. Each subject's consumption was then allocated a quartile ranked placement as 1 (1st quartile), 2 (2nd quartile), 3 (3rd quartile) and 4 (4th quartile) per food item. The food specific modal values for cases versus controls was then determined and compared.

Statistics: Statistical analyses ware performed using Systat 10.2, Minitab 13.1 and Microsoft Excel add-in resampling statistics softwares. Dietary phytoestrogens are of low potency[11] and usually constitute a small percentage of the dietary bulk[12]; therefore we hypothesized that a difference of 30-40% in consumption between cases and control may be required for clinically observed effects. At this effect level, power analysis revealed that 176 sample per group has an 80% power at an alpha 0.05. We resampled data and checked measurements for normality by the Kolmogorov-Smirnov test. Parametrically distributed data were compared by paired t-test and ranked, scored or non-parametrically distributed data were compared by Wilcoxon matched pairs signed ranks test. Trend analyses were done using a linear regression model employing the direct values of phytoestrogen consumed and again by allocating subjects to quartile categories of phytoestrogen intake and inputting modal values of these quartile categories per food item. The association between food item and breast cancer was evaluated by binary logistic regression. We used the Mantel-Haenszel estimator and logistic regression to adjust for socio-economic class (by Tucket's classification[13]), age of menarche, age of regular menstrual cycles, age of marriage and age at first childbirth. Level of significance was $p<0.05$ and as appropriately corrected for multiplicity when co-evaluating hypotheses.

RESULTS

Study participants include 189 cases; age 44.34±13.33 years (range 19-70 year) and 189 controls; age 41.26±17.54 year (range 19-70 year). Cases had significantly earlier age of menarche, regular menstrual cycles, age of marriage and first child birth than controls: 11±1.5 year versus 14.3±2.2 year; 11.3±1.7 year versus 16.2±3.2 year and 9.4±2.4 year versus 14.2±4.1 year, respectively. There was no significant difference between ages at menopause between cases and controls; 47.2±3.6 year versus 45.7±3.9 years, respectively.

In the study population, cases of breast cancer consume significantly more Biochanin A, Coumesterol, Diadzein, Genistein, Secoisolariciresinol than controls ($p<0.05$) (Table 1). However, the intake of Formononetin was not significantly different.

Cases significantly consumed more *Sorghum bicolor* (Sorghum), *Manihot esculenta* (Cassava), *Typha domingensis* (Bulrush), *Pennisetum glaucum* (millet), *Moringa oleifera* (Horseradish), *Hibiscus cannabinus* (Kenaf) and *Vitex doniana* (Black plum) than control ($p<0.05$) (Table 2). Consumption of *Oryza Sativa* (Rice), *Mangifera indica* (Mango) and *Musa Sapeintum* (Banana) had a hazard ratio of 0.5 (95% CI 0.3-0.7), 0.4 (95% CI 0.2-0.6) and 0.6 (95% CI 0.4-0.8) for breast cancer, respectively, while consumption of *Sorgum bicolor* (Sorgum), *Manihot esculenta* (Cassava) and *Typha domingensis* (Bulrush) had a hazard ratio of 1.3 (95%CI 1.2 -∞), 1.5(95%CI 1.3-2.1) and 1.7(95%CI 1.3-2.3) for breast cancer, respectively.

Table 1: Phytoestrogen intake by cases of breast cancer versus control by northwestern Nigerian women

Phytoestrogen	Cases (Arithmetic mean and 95% CI) mg/day	Control (Arithmetic mean and 95% CI) mg/day
Biochanin A	0.13(0.10-0.15)	0.04(0.03-0.44)
Coumesterol	0.39(0.30-0.41)	0.26 (0.19-0.33)
Daidzein	2.31(2.1-2.66)	1.97 (0.99-1.11)
Formononetin	0.09(0.07-0.10)	0.10(0.07-0.12)
Genistein	2.29(1.97-2.41)	1.47(1.37-1.49)
Matairesinol	0.07(0.04-0.91)	0.03(0.02-0.04)
Secoisolariciresinol	0.21(0.17-0.26)	0.11(0.09-0.13)
Total Isoflavones	4.82(4.12-4.99)	3.58(3.14-3.76)
Total lignans	0.28(0.21-0.31)	0.14(0.12-0.16)
Total coumestans	0.39(0.30-0.41)	0.26(0.19-0.33)
Total phytoestrogens	5.42(4.99-5.62)	3.98 (3.11-4.10)

DISCUSSION

The present study revealed a demographic association between duration of exposure to natural estrogen and breast cancer . This is implied by the observation that cases had earlier menarche and regular menstruation compared to controls. The positive association of early marriage and child birth and breast cancer may have different implications in the cultural settings of Africa compared to the Western world because menarche and regular menstruations are cultural indicators of readiness for marriage in the former. Thus the observed relationship between early marriage and breast cancer may just be a surrogate for early menarche. In the African setting, early marriage is also often linked to relative dietary freedom (the women now being limited only by the husbands ability in the choice of diet). Because many African diet have high level of dietary phytoestrogen[12], such dietary freedom may translate to early onset and therefore longer duration of exposure to higher levels of dietary estrogen in cases compared to age matched controls that married latter.

Table 2: Intake of selected food by northwestern Nigerian women by cases of breast cancer versus control

Hausa name	Common name	Biological name	Cases: Modal score (and range)	Control: Modal score (and range)
Shinkafa	Rice	*Oryza sativa*	1 (1-2)	4 (1-4)
Waake	Black-eyed beans or cowpea	*Vigna sinensis*	3 (2-4)	2(1-4)
Dooya	Yam	*Dioscorea praehensilis*	1(1-3)	1(1-4)
Dawa	Sorghum	*Sorghum bicolor*	4(3-4)	1(1-2)
Jedda	Groundnut	*Arachis hypogaea*	2 (1-4)	2(1-4)
Roogo	Cassava	*Manihot esculenta*	4(2-4)	1(1-2)
Maasara	Maize	*Zea mays*	2 (1-4)	2(1-4)
Geero	Bulrush	*Typha domingensis*	4(2-4)	1(1-2)
Maiwaa	Millet	*Pennisetum glaucum*	3(2-4)	1(1-2)
Zoogaale Tomaka	Horseradish	*Moringa oleifera*	4(1-4)	2(1-2)
Ramaa	Kenaf	*Hibiscus cannabinus*	4(2-4)	2(1-2)
Kuuka	Baobab	*Adansonia digitata*	4(3-4)	1(1)
Mangwaro	Mango	*Mangifera indica*	1(1-4)	4(1-2)
Ayaba	Banana	*Musa sapientum*	2(1-4)	4(1-4)
Dunya	Black plum	*Vitex doniana*	4(1-4)	1(1-2)

Score 1-4 represent allocation to 1st, 2nd, 3rd and 4th quartile, respectively, of the consumption of an index food item. Each food item is categorized independently, e.g. category 4 of ,say, *Vitex doniana* (Black plum) is different from and has no relationship with category 4 of , say, *Musa sapientum* (Banana)

The present study also revealed that cases of breast cancer in the study region consume significantly higher amount of dietary phytoestrogen than controls, suggestion that either the type of phytoestrogen, product of intestinal metabolic activation of phytoestrogens or the estrogen receptor expression pattern of breast cancer in the study region may be different from that of in the Western world. In this regard, it may be important to recall that phytoestrogens are essentially inert until they are metabolized[14] and that studies have shown that the preferred pathways of metabolism and/or bioavailability of Isoflavones depend on the colonic microflora[15], which is expected to be richer in the African setting.

It interesting to note that *Oryza sativa* (Rice), *Mangifera indica* (Mango) and *Musa Sapeintum* (Banana), all of which contain significant amount of phytoestrogen[12], appear protective against breast cancer. This further highlights the variable effect of phytoestrogens but may suggest that when taken as part of diet, the overall effect of phytoestrogens probably depend on the overall dietary constituents. Such dietary constituent may contain antiestrogenic factors, directly influence bioavailability and/or modify intestinal microflora.

Sorgum bicolor (Sorgum), *Manihot esculenta* (Cassava) and *Typha domingensis* (Bulrush) appear to increase the risk of breast cancer in the study population. Given that these are the cheaper food item in the study area and are therefore consumed in significant amount, this association could be disturbing. However, a retrospective study is at best hypothesis generating and needs verification in prospective experimental studies. This may be difficult to design in human but *in vitro* carcinogenic studies and *in vivo* studies in animal models may better guide the context which these diet are placed.

This study provides evidence that further support a relationship between phytoestrogen and breast cancer and suggest a complex relationship that may be dictated by factors other than the phytoestrogen. Such factors probably include the contest in which the phytoestrogen is ingested. This may not be surprising considering that the biological effect of native estrogen is also complex[16].

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