Journal of Scientific Research and Studies Vol. 5(1), pp. 21-25, January, 2018
ISSN 2375-8791

http://www.modernrespub.org/jsrs/index.htm

Full Length Research Paper

Assessment of serum insulin and C-peptide levels among breast cancer patients and healthy controls at a tertiary hospital in Sokoto, Nigeria

Agbo S.P.*, Bello B. and Oboirien M.

Department of Surgery, Usmanu Danfodiyo University Teaching Hospital, Sokoto, Nigeria.

*Corresponding author. E-mail: agbostephen@yahoo.com

Accepted 14 January, 2018

Carbohydrate diets have long been known to influence breast cancer risk by increasing the plasma levels of glucose and insulin. 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. The aim of this study is to compare fasting levels of serum insulin and C-peptide in breast cancer patients with healthy control and see if any association exists between hyperinsulinemia and the risk of breast cancer. A cross-sectional study was done in which all consecutive patients aged between 20 and 80 years with confirmed diagnosis of breast cancer at the surgical clinic of the Usmanu Danfodiyo University Teaching Hospital, Sokoto were selected. Healthy women in same age range were selected as control. Serum levels of insulin and C-peptide, a marker of insulin secretion were assayed. Hyperinsulinemia was defined as a fasting insulin level of ≥10 µU/Ml. The results show that a total of 76 patients were seen comprising 38 cases and 38 controls. The mean age of cases and controls were 40.0 and 30.0 years, respectively. All the patients were females. The mean (±standard deviation) serum insulin level for cases and controls were 18.3(±10.2) and 2.6 (±1.2) µlU/mL, respectively while the mean serum C-peptide was 3.8 and 1.2 nG/mL, respectively. There was a significant association of hyperinsulinemia, 18.3 µlU/mL (OR=7.04, Confidence interval= (13.95, 20.67), P-value = 0.021) with breast cancer. In conclusion, the finding shows that hyperinsulinemia is a significant predictor of breast cancer risk in women from Sokoto, Nigeria.

Key words: C-peptide, insulin, hyperinsulinemia, breast cancer.

INTRODUCTION

Carbohydrate diets have long been known to 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 et al., 2006). Chronic hyperinsulinemia may also exert its action on breast tissue via increased ovarian estrogen production and reduced hepatic secretion of estrogen-binding globulin with consequent increase in free estradiol levels in circulation (Poretsky and Kalin, 1987; Pugeat et al., 1991). A case-control study by Bruning et al. (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. Abdominal obesity, which is a consequence of high calorie diet and physical inactivity, is also linked to hyperinsulinaemia and dyslipidaemia in pre and post-menopausal women (Kopelman, 1994). Adebamowo et

Table 1. Age distribution of cases and controls.

Age (years)	Cases			Controls		
	Sex	Frequency	Percentage (%)	Sex	Frequency	Percentage (%)
15 - 24	F	2	5.26	F	7	18.42
25 - 34	F	9	23.68	F	20	52.63
35 - 44	F	14	36.84	F	7	18.42
45 - 54	F	11	28.95	F	3	7.89
55 - 64	F	2	5.26	F	1	2.63
Total		38	100		38	100

al. (2003) in a case-control study from Ibadan, South-Western, Nigeria was able to demonstrate a positive association between obesity and breast cancer risk among postmenopausal women. Several other studies have also shown an association of obesity with breast cancer especially in post-menopausal women (Schapira et al., 1990; Shu et al., 2001; Folsom et al., 1990). However, epidemiological data linking insulin level and the risk of breast cancer are limited in Nigeria. None currently exists after a thorough literature search. We therefore investigated associations between incident breast cancer and fasting levels of insulin and C-peptide in a prospective cohort of pre- and postmenopausal women.

METHODOLOGY

This was a one year cross-sectional study between November 2016 and October 2017 in which all consecutive patients aged between 20 and 80 years with confirmed diagnosis of breast cancer at the surgical clinic of the Usmanu Danfodiyo University Teaching Hospital, Sokoto, north-western Nigeria were recruited and administered questionnaires for demographic and anthropometric information. This was followed by collection of blood samples for fasting insulin, C-peptide and glucose assays, and the results were entered into the questionnaires. Consenting healthy women in same age range visiting the hospital for other reasons were selected as control. Hyperinsulinemia was defined as a fasting insulin level of ≥10 µU/Ml (based on data from the National Health and Nutrition Examination Survey 1999–2010). Continuous variables in cases and controls were assessed for any association using the Pearson correlation coefficient (r). Also, significant variables were further assessed for association with breast cancer risk using the conditional logistic regression model. A P-value of 0.05 was considered significant. Data was analyzed using the IBM SPSS version 20.0.

Data analysis

Descriptive analysis was carried out to characterize the demographic variables of the study participants. For conditional logistic regression, the variables were categorized as: Serum insulin and C-peptide levels, and body mass index (BMI), calculated as weight divided by the square of the height (kg/m^2). Conditional logistic regression model was used to assess the strength of association between each of the hypothesized risk factors and breast cancer risk. Each matched case was paired with the corresponding control to enable differences between the cases and controls to be calculated.

Inclusion/Exclusion criteria

All consenting cases and controls not on steroid or hormone replacement therapy were included in the study. All cases with confirmed histologic diagnosis were also included. All known diabetic and hypertensive patients were excluded from the study.

Ethical consideration

Ethical clearance was obtained from the institution's ethical committee before commencement of this study.

RESULTS

A total of 76 patients were seen comprising 38 cases and 38 controls. The mean (± standard deviation) age of cases and controls were 40.0(±9.53) and 30.0(±5.98) years, respectively, while the median age for cases and controls were 41.0 and 30.5 years, respectively. All the patients were females as shown in Table 1. The mean (±SD) serum insulin level for cases and controls were 18.3(±10.2) and 2.6(±1.2*)* µIU/mL, respectively, while the mean serum C-peptide was 3.8(±2.37) and 1.2 (±0.21) ng/mL, respectively. The mean BMI for cases and controls were 29.76(±4.86) and 28.72(±1.37) kg/m^2, respectively. Pearson correlation coefficient (r) for serum insulin and C-peptide in cases and control were 0.300 and 0.301, respectively (Table 2). There was a significant association of hyperinsulinemia, 18.3 µIU/mL (Odds ratio,

Table 2. Pearson correlation coefficient (r).

Variable	Cases	Controls	r	P-value
Insulin	18.30	2.60	0.300	0.038
C peptide	3.76	1.15	0.301	0.033
BMI	29.76	28.72	0.01	0.100

Table 3. Univariate conditional logistic regression comparing cases and controls.

Variable	Cases	Controls	OR	95% CI	P-value
Insulin	18.30	2.60	7.04	(13.95, 20.67)	0.021
C peptide	3.76	1.15	3.26	(1.84, 3.36)	0.051
BMI	29.76	28.72	1.04	(28.16, 31.36)	0.701

OR=7.04, 95% Confidence interval, CI= (13.95, 20.67), P-value = 0.021) with breast cancer risk (Table 3).

DISCUSSION

The mean age of 40 years in this study shows that breast cancer occurs in younger age group among our patients than in Caucasians (Anyanwu, 2000). Most published works in Nigeria and America revealed 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 breast cancer patients are also more likely to be premenopausal as shown by our study (Anyanwu, 2000; Amir et al., 1994; Hassan et al., 1992). There was a consistent hyperinsulinemia with a mean insulin level of 18.3 µIU/ml among patients with breast cancer compared to a level of 2.6 µIU/mL among controls in this study. C-peptide, a marker of insulin secretion, was also elevated in patients with breast cancer. The association of insulin with breast cancer risk remains largely controversial with some reports supporting a definite link (Bruning et al., 1992; Gunter et al., 2009, 2015; Keinan-Boker et al., 2003; Toniolo et al., 2000; Verheus et al., 2006; Kabat et al., 2009; Debbie et al., 2004; Valentino et al., 2017; Pollak, 2012; Yerushalmi et al., 2012) while others strongly dispute any association (Hernandez et al., 2014; Autier et al., 2013; Mink et al., 2002; Eliassen et al., 2007). There are however increasing experimental and epidemiological body of evidence in support of a possible link between insulin level and breast cancer risk. Gunter et al. (2009), in a prospective case-cohort study among non-diabetic postmenopausal women, examined associations between fasting insulin levels and the risk of breast cancer and concluded that hyperinsulinemia was an independent risk factor for breast cancer. This in their opinion largely explained the association between obesity and the risk of breast cancer in postmenopausal women (Gunter et al., 2009). Abdominal obesity has been directly linked to hyperinsulinaemia and dyslipidaemia in pre and post- menopausal women (Kopelman, 1994). Majority of our patients were premenopausal and obese (Mean BMI = 30 kg/m^2) with normal fasting glucose. We had noted in earlier reports that high calorie diet with physical inactivity were important risk factors for breast cancer among our patients, and it does appear that this is the link between obesity and hyperinsulimia as noted in this study even though the fasting glucose was normal contrary to our expectations (Agbo and Oboirien, 2016). Kabat et al. (2009) also conducted a detailed prospective longitudinal study to assess association of serum glucose and insulin with breast cancer risk among postmenopausal women and concluded that elevated serum insulin levels may be a risk factor for postmenopausal breast cancer. Similar to our study, glucose levels showed no association with breast cancer risk in that report (Kabat et al., 2009). Debbie et al. (2004) however found a positive association between fasting insulin and glucose levels with breast cancer in a similar study they carried out in 2004. Breast cancer cells with mutant p53 gene are known to respond to insulin stimulation by increasing cell proliferation and invasion (Valentino et al., 2017). The mutant gene inhibits the tumor suppressor DAB2IP (DAB2-interacting protein) in the cytoplasm leading to activation of insulin-induced intracellular tyrosine kinase (AKT1), which promotes proliferation, survival, and dissemination of cancer cells (Valentino et al., 2017). This activation is mediated via insulin-like growth factor receptor 1 (IGF1R), which has the capability of signal transduction through the intracellular tyrosine kinase, phosphatidyl-inositol-3 kinase and mammalian target of rapamycin (Akt – PI3K – mTOR) signaling pathway (Pollak, 2012). IGF1R has been shown to be present in all breast cancer subtypes, regardless of the hormone receptor (Yerushalmi et al., 2012). It is therefore possible that the effect of mutant p53 gene acting alone or in association with other factors

might be responsible for the aggressive nature of breast cancer among African blacks (Gakwaya et al., 2008). On the part of proponents of negative link between insulin and breast cancer risk, Hernandez et al. (2014), who carried out a meta-analysis of the association between insulin resistance and breast cancer using random effects models, reported that higher levels of fasting insulin or non-fasting/fasting C-peptide were not associated with breast cancer in women. Similarly, Autier et al. (2013), in a meta-analysis to examine association of serum concentrations of insulin and C-peptide with breast cancer risk, reported that there was no evidence of an association between serum insulin or C-peptide concentrations and breast cancer risk. Mink et al. (2002) also examined the association of breast cancer incidence with serum levels of insulin and glucose in a large cohort of 7,894 women aged 45–64 years from four US communities and concluded that circulating insulin levels were not predictive of future breast cancer incidence, but that there may be a weak association with type 2 diabetes, modulated via increased adiposity. Irrespective of the arguments however, hyperinsulinemia has been found to be associated with increased risk of death from cancer in both obese and non-obese individuals (Tsujimoto et al., 2017). More prospective studies are therefore needed to explore the complex relationship between insulin level and the risk of breast cancer among women.

Conclusion

The study shows that higher levels of fasting insulin and C-peptide are associated with the risk of breast cancer among our women irrespective of menopausal status. There was however no relationship between glucose level and the risk of breast cancer.

REFERENCES

Adebamowo AC, Ogundiran OT, Adenipekun AA, Oyesegun AR, Campbell BO, Akang EE et al. (2003). Waist–hip ratio and breast cancer risk in urbanized Nigerian women. Breast Cancer Res. 5(2):R18-R24

Adebamowo CA, Adekunle OO (1999). Case-controlled study of the epidemiological risk factors for breast cancer in Nigeria. Br. J. Surg. 86:665-668.

Agbo PS, Oboirien M (2016). Risk factors for breast cancer in Sokoto, Nigeria. Merit Res. J. Med. Med. Sci. 4(11)S:465-471.

Amir H, Kitinya JN, Parkin DM (1994). A comparative study of carcinoma of the breast in an African population. East Afr. Med. J. 71:215-218.

Anyanwu SN (2000). Breast cancer in eastern Nigeria: a ten year review. West Afr. J. Med. 19:120-125.

Autier P, Koechlin A, Boniol M, Mullie P, Bolli G, Rosenstock J, Boyle P (2013).. Serum insulin and C-peptide concentration and breast cancer: a meta-analysis. Cancer Causes Control. 24(5):873-883.

Bruning PF, Bonfrer JMG, van Noord PAH, de Jong Bakker M, Nooijen WJ (1992). Insulin resistance and breast cancer risk. Int. J. Cancer 52:511-516.

Calle EE, Kaaks R (2004). Overweight, obesity and cancer: epidemiological evidence and proposed mechanisms. Nat. Rev. Cancer 4:579-591.

Debbie A, Lawlor AD, George DS, Shah E (2004). Hyperinsulinaemia and increased risk of breast cancer: findings from the British women's heart and health study. Cancer Causes Control 15:267-275.

Eliassen AH, Tworoger SS, Mantzoros CS, Pollak MN, Hankinson SE (2007). Circulating insulin and C-peptide levels and risk of breast cancer among predominately premenopausal women. Cancer Epidemiol. Biomarkers Prev. 16:161-164.

Folsom AR, Kaye SA, Prineas RJ, Potter JD, Gapstur SM, Wallace RB (1990). Increased incidence of carcinoma of the breast associated with abdominal adiposity in postmenopausal women. Am. J. Epidemiol. 131:794-803.

Gakwaya A, Kigula-Mugambe JB, Kavuma A, Luwaga A, Fualal J, Jombwe J, et al. (2008). Cancer of the breast: 5-year survival in a tertiary hospital in Uganda. Br. J. Cancer 99:63-67.

Gunter MJ, Hoover DR, Yu H, Wassertheil-Smoller S, Rohan TE, Manson JE, Li J, et al. (2009). Insulin, insulin-like growth factor-I, and risk of breast cancer in postmenopausal women. J Natl. Cancer Inst. 101(1):48-60.

Gunter MJ, Xie X, Xue X, Kabat GC, Rohan ET, Wassertheil-Smoller S, et al. (2015). Breast cancer risk in metabolically healthy but overweight postmenopausal women. Cancer Res. 75(2):270-274.

Hassan I, Onukak EE, Mabogunje OA (1992). Breast cancer in Zaria, Nigeria. J. R. Coll. Surg. Edinb. 37:159-161.

Hernandez VA, Guarnizo M, Miranda Y, Pasupuleti V, Deshpande A, Paico S, et al. (2014). Association between insulin resistance and breast carcinoma: A Systematic Review and Meta-Analysis. PLoS One. 9(6):e99317. doi: 10.1371/journal.pone.0099317

Joslyn SA, West MM (2000). Racial differences in breast carcinoma survival. Cancer 88:114-123.

Kabat GC, Kim M, Caan BJ, Chlebowski RT, Gunter MJ, Ho GYF, et al. (2009). Repeated measures of serum glucose and insulin in relation to postmenopausal breast cancer. Int. J. Cancer 125:2704-2710.

Keinan-Boker L, Bueno De Mesquita HB, Kaaks R, Van Gils CH, Van Noord PA, Rinaldi S, et al. (2003). Circulating levels of insulin-like growth factor I, its binding proteins -1,-2, -3, C-peptide and risk of postmenopausal breast cancer. Int. J. Cancer 106(1):90-5.

Kopelman PG (1994). Hormones and obesity. Bailleres Clin. Endocrinol. Metab. 8:549-576.

Michels KB, Mohllajee AP, Roset-Bahmanyar E, Beehler GP, Moysich KB (2007). Diet and breast cancer: a review of the prospective observational studies. Cancer 109: 2712-2749.

Mink JP, Shahar E, Rosamond DW, Alberg JA, Folsom RA (2002). Serum insulin and glucose levels and breast cancer incidence: The atherosclerosis risk in communities study. Am. J. Epidemiol. 156 (4):349-352.

Pollak M (2012). The insulin receptor/insulin-like growth factor receptor family as a therapeutic target in oncology. Clin. Cancer Res. 18(1):40-50.

Poretsky L, Kalin MF (1987). The gonadotropic function of insulin. Endocr. Rev. 8(2):132-141.

Pugeat M, Crave JC, Elmidani M, et al. (1991). Pathophysiology of sex hormone binding globulin (SHBG): relation to insulin. J. Steroid Biochem. Mol. Biol. 40(4-6):841-849.

Schapira DV, Kumar NB, Lyman GH, Cox CE (1990). Abdominal obesity and breast cancer risk. Ann. Intern. Med. 112:182-186.

Shu XO, Jin F, Dai Q, Shi JR, Potter JD, Brinton LA, Hebert JR, Ruan Z, Gao YT, Zheng W (2001). Association of body size and fat distribution with risk of breast cancer among Chinese women. Int. J. Cancer 94:449-455.

Toniolo P, Bruning PF, Akhmedkhanov A, Bonfrer JM, Koenig KL, Lukanova A, et al. (2000). Serum insulin-like growth factor-I and breast cancer. Int. J. Cancer 88(5):828-32.

Tsujimoto T, Kajio H, Sugiyama T (2017). Association between hyperinsulinemia and increased risk of cancer death in non-obese and obese people: A population-based observational study. Int. J. Cancer 141(1):102-111.

Valentino E, Bellazzo A, Di Minin G, Sicari D, Apollonio M, Scognamiglio G, et al. (2017). Mutant p53 potentiates the oncogenic effects of insulin by inhibiting the tumor suppressor DAB2IP. Proc. Natl. Acad. Sci. USA. 114(29):7623-7628.

Verheus M, Peeters PH, Rinaldi S, Dossus L, Biessy C, Olsen A, et al.

(2006). Serum C-peptide levels and breast cancer risk: results from the European Prospective Investigation into Cancer and Nutrition (EPIC). Int. J. Cancer 119(3):659-67.
Yanochko GM, Eckhart W (2006). Type I insulin-like growth factor receptor over-expression induces proliferation and anti-apoptotic signaling in a three-dimensional culture model of breast epithelial cells. Breast Cancer Res. 8:R18.
Yerushalmi R, Gelmon KA, Leung S, Gao D, Cheang M, et al. (2012). Insulin-like growth factor receptor (IGF-1R) in breast cancer subtypes. Breast Cancer Res. Treat. 132(1):131-42.