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Breast Density as a Risk Factor for Breast Cancer amongst a Cohort of Women in Uganda.

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Background: The incidence of breast cancer in Uganda has nearly tripled in three decades, the reasons not wholly understood. Country specific evidence is needed to better understand associated risk factors. Breast density is a strong predictor of breast cancer risk in Caucasian populations. The aim of this study was to establish whether increased breast density is a contributory risk factor for breast cancer amongst black African women.
Methods: A case control study carried out at the National Referral and teaching Hospital, Mulago in Kampala Uganda over a 6 months period. All patients who presented for breast cancer screening and underwent a mammography breast examination during the study period had their breast densities measured using the BI-RADS classification were eligible. Those diagnosed with breast cancer during the period formed the cases and those who had a normal breast examination formed the controls. Mulago receives patients from all over the country but more so from the central part, owing to its location (proximity). Prevalence of high breast density between the two groups was compared using cross tabulations and an association between high breast density and breast cancer was defined. Prior ethical approval was obtained.
Results: The prevalence of high breast density (Grade III & IV) among this cohort of East African women was 39% (52/135) overall; with a distribution of 51% (26/46) among the cases and 29% (26/89) among the controls There was a positive association between HBD and breast cancer with odds ratio of 3.15.
Conclusion: High breast density seems to be associated with breast cancer among this group of East African black women. Although prevalence of high breast density was comparable to some of the studies done in Caucasian populations, there was an unexpected inverse relationship between HBD, high parity and early age of first pregnancy.

Introduction

Breast cancer is the most common type of cancer diagnosed among women, excluding skin cancer[1]. The incidence of breast cancer in Uganda has nearly tripled from 11:100,000 in 1961 to 31:100,000 in 2006[2]. The reason for this apparent surge is mostly speculative; presumed change in lifestyle to a 'western' kind of diet being one reason. What is also apparent is nearly half of the women with breast cancer today in Uganda are 40years and below. Whether all the well established risk factors in other populations apply to this East African women population remains to be confirmed. What is known in Caucasian women population is that those with very dense breasts have a 4 to 6-fold greater risk for breast cancer compared to women with little or no dense breast tissue (Grades I and II)[3]. Mammographic breast density referred to in this study is the proportion of stromal and epithelial tissue relative to fat in breast tissue as seen on a mammogram. Fat attenuates x-rays least and appears dark on a mammogram, whereas stroma and epithelium attenuate x-rays more and appear white. The purpose of this study therefore was to explore the risk association of high breast density (HBD) and breast cancer among a cohort of black Ugandan women who presented for screening.

Patients and Methods

A case control study carried out between October 2009 and March 2010 at the national referral hospital a large public tertiary facility, that received patients from all over the country but especially the central part whose make up is mostly representative of all ethnic groupings in the country. Ethical approval was obtained before starting the study. The study recruited consenting female patients aged

30 years and above. Breast density for all study participants were measured as part of the routine mammogram examination using the BI-RADS (Breast Imaging Reporting and Data System) classification method. The Ugandan cancer treatment guidelines suggest 30-35years as the cut off age for mammography in this population[4]. This system has four categories: category 1; almost entirely fatty <25% dense, category 2; scattered fibroglandular densities approximately 25-50% dense, category 3; heterogeneously dense 51-75% dense and category 4; extremely dense. Standard x ray films were used. Patients whose mammography breast examination had been done elsewhere, or who did not have their mammo-films with them and declined a repeat mammogram were excluded from the study. This was to ensure uniformity of classification of Breast density using BI-RADS by the attending radiologists. The BIRADS scores were assigned by more than one radiologist experienced in BIRADS scoring to minimize scoring bias.

In this study, high or increased density referred to both categories (grades) 3 and 4. Presence of cancer was confirmed using fine needle aspiration cytology (FNAC), or and core biopsy histology The patients were then divided into those with invasive breast cancer and those with normal breasts findings.. Sample size was calculated using the chi square statistic to compare proportions of dichotomous variables, using $P_1 = 0.28$, $P_2 = 0.05$ hence $P_1 - P_2 = 0.23$. The minimum number of patients required was 70, so as to detect a significant association between invasive breast cancer and normal subjects; with category 3 and 4 breast density as compared with those with category 1 and 2 on standard film mammography. The data was then entered into the computer using Epi Info and analyzed using SPSS v12. Using the bivariate analysis the prevalence and patterns of breast density were analyzed. The structure and strength of the relationship of high breast density (HBD) and invasive breast cancer (BC) was measured using cross tabulations analysis.

Results

The study enrolled 142 subjects, of which 135 were analyzed (46 cases and 89 as controls) majority of whom were black Ugandan women, mainly from the Ganda ethnic tribe. A large proportion of the sample was made up of women aged 30 to 39 years as shown in Figures 1. The mode age was 32years, the mean and median were both 48 years. Figure 2 compares the age distribution of cases with controls.

Table 1. Comparison of Cases and Controls

Variable	Cases (SD)	Controls (SD)	P-value
Mean age	44.9 (10.1)	43.7 (10.6)	0.527
BMI	26.8 (4.9)	27.4 (5.2	0.549
Age at menarche			0.269
Parity	5.93 (3.8)	4.86 (3.0)	0.082
Age at first preganancy	18.63 (4.3)	19.08 (7.4)	0.723
Breast feeding duration	9.41 (7.14)	6.25 (5.39)	0.013
Years of contraceptive use	2.05 (3.2)	2.52(10.2)	0.772
Number with family history	4.26 (15)	3.0 (10)	0.570
Number with Benign disease	6.5 (20.9)	7.2 (22.2)	0.864
Smokers	4.32 (14)	3.05 (10)	0.572
Alcohol takers	1.62 (.49)	1.67 (.47)	0.567

Prevalence of HBD among the cases was 51% (26/46) as compared to 28.6% (26/89) in the controls (Figures 3 and 4). The odds ratio (odds of exposure in those with the condition/odds of exposure in those without the condition (26*63)/20*26) = 63/20) was 3.15, since the odds ratio is greater than 1 (OR>1), there is a positive association between HBD and Breast cancer. There was a general decline in the prevalence of HBD with increase in age and a further decrease after menopause seen in both groups.

Among the cases 51% had HBD as compared 28.6% (LBD = Grades 1&2, HBD Grades 3 & 4) in the controls. There was a general decline in the prevalence of HBD with increase in age. There was an increase of breast density with increases parity among the cases and controls. There was a general decrease in breast density in both groups with an increase in BMI.
Though majority of the participants did not smoke the few that did had both HBD and breast cancer.

Figure 1. Age distribution of Women

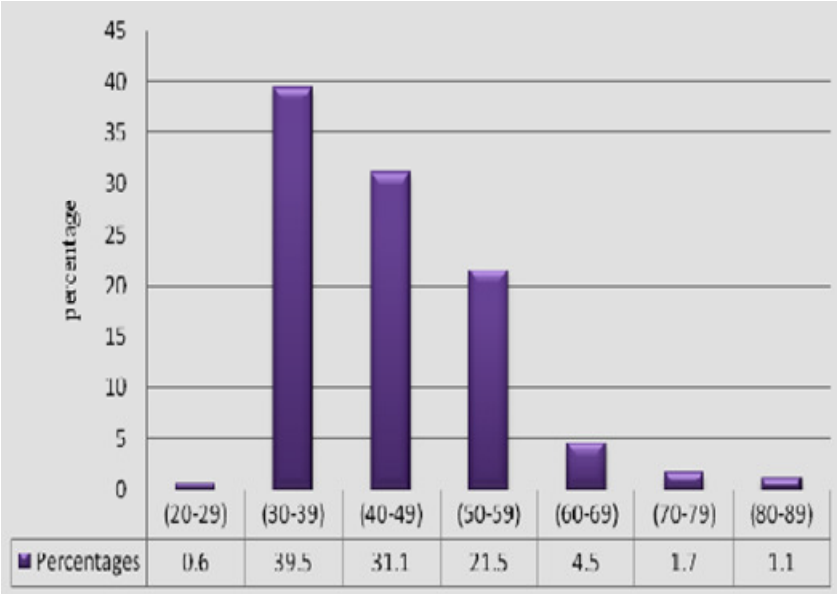


Figure 2. Age Distribution Comparison of Cases and Controls

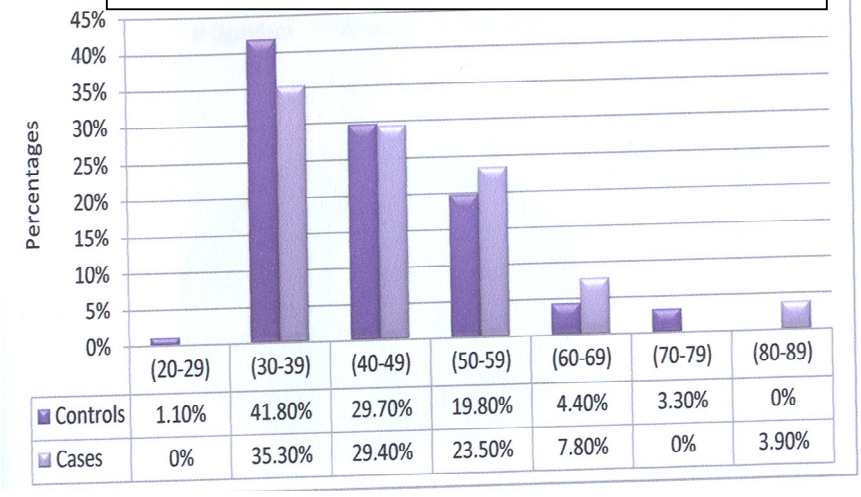


Figure 3. Distribution of High Breast Density

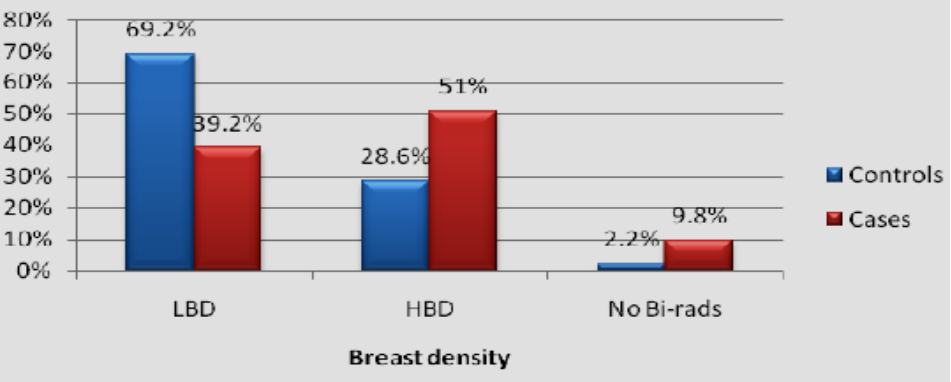


Figure 4. Prevalence of High Breast Density with age

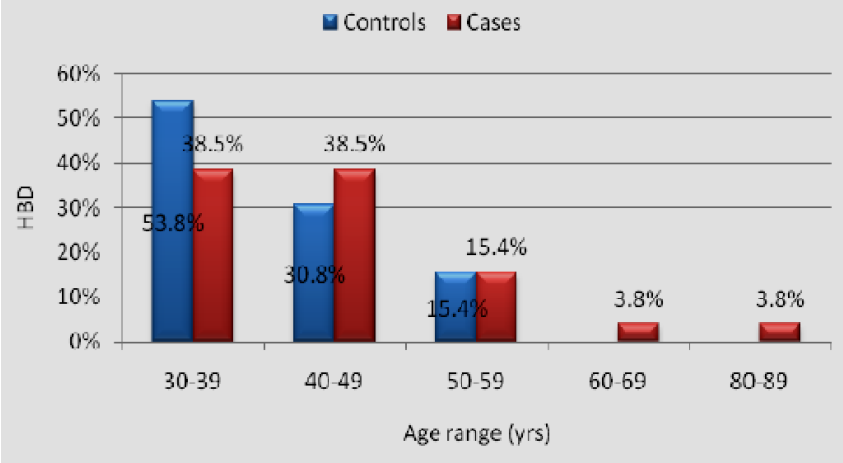
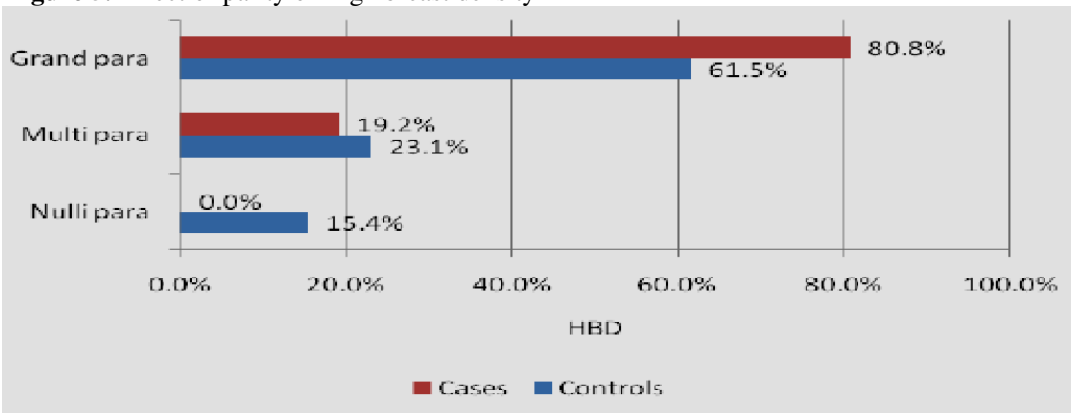


Figure 5. Effect of parity on high breast density



Discussion

High Breast Density was more prevalent among the cases than the controls and this association was found to be significant. The observed general decline in the prevalence of HBD with increase in age, more so after menopause, demonstrates the effect of age and menopause on breast density also

documented in other studies[5,6,7 ,8]. Although previous studies have found high breast density to be lower in parous women and especially those with an early age at first birth[5, 6,7,8,9], this study however found that high parity and an early age at first pregnancy did not result in lower breast densities. There was no clear explanation for this disparity. Perhaps it is part of the several disparities we have seen before between Africans and Caucasians with breast cancer[8]. Further research in this area in imperative to elucidate understanding of this paradoxical relationship.

There are several factors known to be associated with HBD; the use of exogenous hormones whether oestrogen or progesterone alone or a combination of both has been found to be associated with an increase in breast density[9,10,11,12]. Increase in BMI is known to be associated with a decrease in breast density[4,6], this study found similar findings. Looking at only the subjects with HBD, majority did not take alcohol, but among those who did a comparatively higher percentage were among the cases. This association is significant using the Pearson correlation coefficient with a computed value of 0.036 < 0.05 at 95% level of confidence. This is consistent with findings that alcohol intake is associated with increased breast density[14]. Majority of the participants did not smoke but the few that did had both HBD and breast cancer, cigarette smoking is documented to have an anti estrogenic effect on the breast tissue resulting in lower breast density[15], a larger sample size of smokers is required to asses this relationship, as perhaps due to the small numbers the association between HBD and smoking was found not to be statistically significant using the chi square tests.

It has been shown that the odds of developing of breast cancer in dense breasts is much higher in younger women (26%) than in older women (7%)[5]. This study sample clearly shows more cases of breast cancer with HBD and a higher prevalence of HBD in the younger age groups.
An analysis using the risk estimate under the odds ratio at 95%, revealed HBD to be associated with breast cancer, which is similar to studies done among American women that found that 16 – 32% of breast cancers could be attributed to HBD[16] .

This study was not free of limitations; use of standard film instead of digital mammography which with manipulation may pick up more lesions. This is possible when high breast density patients considered taken as controls may have had lesions missed due to increased density introducing a possibility of under estimating the effect. Perhaps this being a hospital based study other than a population based study findings may not be strictly generalizable to the wider population, though the catchment of this hospital is representative of the entire country, it has representation of all ethnic groups, socio economic groupings and ages.

Conclusion

High breast density seems to be associated with breast cancer among black East African women. The inverse relationship between high breast density and high parity revealed by this study warrants further exploration, to uncover the reasons why high parity may not be protective against breast cancer.

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