Age at First Child Birth as a Risk Factor of Breast Cancer among Ugandan Women at a Tertiary Hospital: a Case Control Study

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Background: ***Breast Cancer in Uganda is the third commonest cancer in women after cancer of the cervix and Kaposi's sarcoma.***
The incidence of Breast Cancer in Uganda has nearly tripled from 1961 to 2006. It has been considered a neglected disease but the reasons to why there is an increase in its incidence have not been fully explained.
Studies show that age at first full term child birth has been associated with risk of developing breast cancer in the Caucasian population.
Objective: To establish whether age at first full term child birth is associated with development of breast cancer among Ugandan women.
Method: ***A case control study was conducted over a six months period from November 2011 to April 2012 with patients confirmed with breast cancer as cases and controls without breast cancer. The sampling were convenient and interview questionnaire were administered, and clinical examinations done .The main predictor were age at first full term child birth and the outcome were histologically confirmed breast cancer. Data were analysed using stata 10; using logistic regression models, p-value of less than 0.05 was considered significant.***
Results: ***Over all, 183 women were enrolled, (93 cases and 93 controls). The mean age at first full term child birth was 19.8 years. The histological subtype was ductal carcinoma. No association were found between age at first full term child birth and risk of breast cancer adjusted OR 0.3 (0.1-2.4), p=0.239.***
Conclusion: ***No associations were found between age at first term child birth and risk for breast cancer disease among this group of Ugandan women.***

Key words: Breast Cancer, Age at First Birth, Uganda

Introduction

Breast cancer is the most common diagnosed cancer and the leading cause of cancer death in women worldwide, with an estimated 1.4 million new breast cancer cases and 458,000 deaths in 2008[1]. The incidence and mortality rates vary internationally by more than 5-fold however, the highest incidence rates are found in Switzerland, U.S. whites, Italy, and many other European countries, whereas low rates are found in Africa, Asia, and South America[2,3]. Generally, the incidence of Breast cancer in some high-income countries is stabilizing, and death rates are falling, but both appear to be increasing in developing countries[4]. According to Stewart, the majority of new cases now occur in women from low- and middle-income countries, in which the incidence is increasing by as much as 5% per year and three-fourths of global breast cancer deaths occur[5,6].

The actual cause of breast cancer is unknown however; studies have attributed it to various factors including lifestyle, anthropometric, reproductive and demographic characteristics[7,8]. Several studies have identified a woman's reproductive history as an important determinant of her breast cancer risk. Factors that protect against breast cancer in the general population include a late age of onset of menarche, multiparity, breastfeeding, and an early age at menopause[9]. Conversely, late age at birth of first child has been reported as one of the major determinants of breast cancer incidence[10] and has been attributed to 28% of its incidence[11].

Little is known about the influence of age at first full term child birth on the risk of breast cancer in a Ugandan setting and especially Mulago Hospital. This study was therefore to generate information on whether AFFB is associated with the risk of developing breast cancer among Ugandan women.

Patients and Methods

This study was a matched case control study conducted at the Endocrine and Breast Clinic, 3C surgical ward and at the Uganda Cancer Institute Solid Tumour Centre at Mulago hospital. It was aimed at determining the association between ages at first full-term child birth with development of breast cancer.

The breast clinic receives an average of five cases of incident breast cancer from the screening program per week. The clinic receives referrals from all over the country of both confirmed and suspected cancer of the breast. The target population consisted of women histologically confirmed to have breast cancer who sought treatment from Mulago Hospital. The controls included women without breast disease who attended surgical outpatients' clinic for other medical conditions during the study period. The controls were matched with cases by age and parity status. The cases were identified from the surgical wards and the endocrine/breast clinic. Clinical breast examination was done by the Principal investigator for every control to exclude those with asymptomatic breast cancer.

Women aged 18 years and above with or suspected to have breast cancer were identified. Those who had histologically confirmed diagnosis of breast cancer, able and willing to give relevant information and had ever given birth to a child were included. Convenience sampling method was used to select the cases. Core biopsies were taken using a BARD MAGMUM gun. The controls in the same age category as cases and who had given birth to at least a child were conveniently selected from the general clinic, plastic clinic, endocrine clinic, and orthopaedic clinic. Clinical breast examination was done for every control to exclude those with asymptomatic breast cancer.

Breast cancer subtype namely ductal, lobular, mixed ductal-lobular, mucinous, medullary, tubular and solid and Age at first full term child birth. Age at menarche, Use of oral contraceptives ,Age at menopause ,Breast feeding habits, Breast cancer screening history , Personal and family history of cancer, Lifetime physical activity , Smoking status and Alcohol intake.

Procedure

An informed consent was sought first after explaining the nature and purpose of the study. The patients were divided into 2 groups; women with a histological diagnosis of breast cancer were recruited in the study as cases while those with no breast disease were recruited in the study as controls. Data were collected by the principal investigator and a trained research assistant over a six month study period. All information was recorded in a data collection form.

The controls were recruited from the surgical clinics including the general clinic. The cases were matched by age and parity.

Data collection and management

Case or control status of the patients was concealed to the Interviewers as much as possible. The questionnaires were pretested among five controls and equal number of cases drawn from outpatients department and the wards. The completed questionnaires were evaluated for consistency; accuracy and comments obtained from the RAs and the volunteers were incorporated accordingly. The completed questionnaires were collected on daily basis for data entry as well as safe storage. Data were double entered in Epidata 3.1 and transferred to Stata 10.1 for analysis.

Summary statistics were obtained for each histological subtype identified, clinical features and the independent variables. Bivariate analysis were done for risk factors of BCA including age at first full

term child birth. Variables found to be significantly associated were included in a multivariate logistic regression model. The strength of association were determined using odds ratios and their corresponding confidence intervals.

Results

The study were conducted among 183 female participants of whom 90 were cases of breast cancer with 42 post menopausal and 48 premenopausal. 93 were the study controls of whom 34 were post menopausal and 59 were premenopausal. We administered questionnaires to assess what factors in the cases absent in the controls could have contributed to their risk for breast cancer. Participants were of different nationality, the majority being Ugandans 95.1% from the nearby districts. The mean age of the respondents among cases was 48 and 46 in the controls.

Table 1. General Characteristics of the Study Population and Associated Risk Factors.

Risk factor	Odds (CI)	Crude OR (CI)	Adjusted OR (CI)	P-value
First pregnancy age category				
≤ 25 years	0.98 (0.72-1.32)			
>25 years	0.75 (0.26-2.16)	0.8 (0.3-2.3)	0.3 (0.1-2.43)	0.239
Use of oral contraceptives				
Yes	0.2 (0.1-0.4)	8.2 (3.7-18.3)	16.7 (1.2-226)	0.032
No	1.7 (1.2-2.4)			
Age categories at menopause				
Before 55 years				
After 55 years	1.4 (0.8-2.2)	0.3 (0.1-1.3)	0.16 (0.1-1.5)	0.108
	0.3 (0.1-1.7)			
Months of breastfeeding				
<24	0.5 (0.3-1.0)	Reference	Reference	
24-48	1.1 (0.6-1.9)	2.2 (0.9-5.2)	0.9 (0.1-6.2)	0.945
49-72	1.6 (0.7-3.5)	3.2 (1.1-9.2)	5.6 (0.3-92.4)	0.225
73-96	3.3 (1.1-9.9)	6.5 (1.7-24.3)	1.5 (0.0-24.4)	0.762
>96	0.7 (0.4-1.3)	1. 5 (0.6-3.5)	0.3 (0.1-1.5)	0.136
Breast cancer family history				
Yes	1.1 (0.5-2.6)			
No	0.95 (0.70- 1.30)	0.9 (0.4-2.2)	0.2 (0.1-2.2)	0.193
Alcohol intake				
Yes	1.0 (0.6-1.7)	0.91 (0.5-1.7)	1.6 (0.4-5.6)	0.495
No	0.9 (0.7-1.3)			
Smoking				
Yes	1.5 (0.4-5.3)	0.6 (0.2-2.3)	1.1 (0.1-8.3)	0.958
No	0.9 (0.7-1.3)			
Body mass index				
Normal	1.1 (0.7-1.7)	Reference	Reference	-
Overweight	1.4 (0.8-2.3)	1.2 (0.6-2.4)	1.6 (0.4-6.4)	0.513
Obese	0.3 (0.1-0.7)	0.3 (0.1-0.7)	0.3 (0.1-1.9)	0.178

Risk factors for breast cancer

Table 1 summarizes the distribution of the risk factors between the cases and the controls so that we are able to establish the contribution of age at first child birth to the risk of breast cancer disease.
The distribution of risk factors in both the cases and the controls in almost the same. However significant differences were noted in body mass index, months of breast feeding and oral contraceptive use, age when menstrual period begun. Very few cases than controls were obese. Fewer

cases than controls breastfed for less than 24 months whereas fewer controls than cases breastfed for a period of 73-96 months. Oral contraceptive use was greater in the control group than the cases.

No one was ever diagnosed with breast cancer only. One participant reported to have ever been diagnosed with benign breast disease and this were among the controls p-value of difference in proportions = 0.324.

Table 2. Association between Breast Cancer and Chosen Risk Factors

Risk factor	Odds (CI)	Crude OR (CI)	Adjusted OR (CI)	P-value
First pregnancy age category				
≤ 25 years	0.98 (0.7-1.3)	0.8 (0.3-2.3)	0.3 (0.1-2.4)	0.239
25 years	0.75 (0.3-2.2)			
Use of oral contraceptives				
Yes	0.2 (0.1-0.4)	8.2 (3.7-18.3)	13.2 (1.3-138)	0.032
No	1.7 (1.2-2.4)			
Age categories at menopause				
Before 55 years	1.4 (0.8-2.2)	0.3 (0.1-1.3)	0.2 (0.1-1.5)	0.108
After 55 years	0.3 (0.1-1.7)			
Months of breastfeeding				
<24	0.5 (0.3-1.0)	Reference	Reference	
24-48	1.1 (0.6-1.9)	2.2 (0.9-5.2)	0.9 (0.1-6.2)	0.945
49-72	1.6 (0.7-3.5)	3.2 (1.1-9.2)	5.6 (0.3-92.4)	0.225
73-96	3.3 (1.1-9.9)	6.5 (1.7-24.3)	1.5 (0.1-24.4)	0.762
>96	0.7 (0.4-1.3)	1.45 (0.6-3.5)	0.3 (0.0-1.54)	0.136
Breast cancer family history				
Yes	1.1 (0.5-2.6)	0.9 (0.4-2.2)	0.2 (0.1-2.2)	0.193
No	0.9 (0.7- 1.3)			
Alcohol intake				
Yes	1.0 (0.6-1.7)	0.9 (0.5-1.7)	1.6 (0.4-5.6)	0.495
No	0.9 (0.65-1.3)			
Smoking				
Yes	1.5 (0.4-5.3)	0.6 (0.2-2.3)	1.1 (0.1-8.3)	0.958
No	0.9 (0.7-1.3)			

Total number of pregnancies represented as means (SD)
Overall: 5.31(4.53)
Among controls: 5.81(5.64)
Among the cases: 4.8 (2.92)
Mean age at first pregnancy, mean (SD)
Overall: 19.81(3.82)
Among the cases: 19.88 (3.68)

The difference in means between the cases and control was not statistically significant (p=0.8133). The difference in proportions between the cases and controls was statistically significant (p= 0.009). There were more cases that had their menstruation at age 14 years than the controls. The differences in proportions between the cases and controls was statistically significant (p =0.009

Discussion

Contrary to those previous studies, in our study the risk of having breast cancer was 0.20 times less in those who used oral contraceptives compared to a high risk which were 1.65 times in the control group. The reasons which could probably explain this could be smaller sample size which were hospital based compared to larger sample sizes which were population based, the duration when oral contraceptives were used; at what age they were used.

Several studies have identified a woman's reproductive history is an important determinant of her breast cancer risk. Of particular importance is the age at which a woman completes her first full term pregnancy[26]. From the numerous studies of reproductive history and breast cancer risk, there is a consensus that an early first birth is associated with a long term reduction in risk. An early age at first child birth (i.e. before the age of 20) has been reported to reduced a woman's risk of developing breast cancer by up to one half[20], whereas a late age at first child birth (e.g. at age 30 or older) increases her risk. Various studies have shown that the risk associated with a late first term pregnancy may be as great as or higher than the risk associated with nulliparity[12].

In our study it were found out that the risk of breast cancer has 0.98 times higher in woman who gave their first full term child at age 25 years and below compared to those who gave their first full term child at age greater than 25 years (OR 0.75) however this were not statistically significant as shown by the p value of 0.239. A study by LiCI[29], found that age at first full term pregnancy were inversely associated with breast cancer risk. In this study, women who had full term pregnancy at age 19 or younger compared with those who had that first full term pregnancy at age 35 or older had a 2.0 fold (95% C I, 1.1-3.7) increased risk of invasive breast cancer in our case control study done in Mulago national referral hospital, no statistical significance were found between age at first full term child birth with risk of breast cancer. This could be due to genetic, environmental, ethnical and racial variations as far as cancer breast is concerned.

Breast cancer is considered to be associated with various documented risk factors. In our study oral contraceptive use were found to be associated with breast cancer. The risk of breast cancer has been found to be increased with use of oral contraceptives as supported by previous studies which were population based[38]. In these studies, the risk were highest for women who started using oral contraceptives as teenagers, however , 10 or more years after women stopped using oral contraceptives, their risk of developing breast cancer had returned to the same level as if they had never used birth control pills regardless of family history of breast cancer, reproductive history geographic area of residence, ethnic background, differences of family history of breast cancer, and type of hormone (s) used duration of use[39].

Among the different histological types of breast cancer, ductal with productive fibrosis (infiltrating ductal) is the commonest form of cancer of the breast appropriately 80%. A retrospective study done in Bugando medical Center in Tanzania, which looked at 328 case reports of histologically confirmed cancer breast, showed that majority of patients had invasive ductal carcinoma (91.5%) followed by mucinous carcinoma (5.2%), invasive lobular carcinoma (31%) and in situ ductal carcinoma (0.3%). Other studies also showed almost similar findings with percentages of up to 80. In agreement with previous studies, our study also found out that majority of cases had invasive ductal carcinoma (94.4%), invasive lobular 4.4% and papillary 1.1%.

The mean age at first full term pregnancy among the cases was19.9 and among controls, it was 19.8. The difference in means between the cases and controls were not statistically significant.

Conclusion

There was no association between age at first full term child birth and risk of developing breast cancer.

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