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Risk Factors Associated with Aggressive Breast Cancer Forms Seen in Young Women of Western Kenya

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ABSTRACT

Today in Africa, breast cancer cases are on the rise, seen in a much younger age, more aggressive and likely to kill compared to North America. It is not clear if risk factors associated with development of these forms of breast cancer in African women are similar to those recorded elsewhere.

We determine established risk factors in histologically confirm breast cancer cases and suspected breast lumps in Western Kenya. Study questionnaires were used to obtain personal details, family history, reproductive factors, lifestyle behaviors and environmental factors associated with developing breast cancer. Data entry was done in excel spreadsheet and exported to Statistical package for social sciences (SPSS V.20) for analysis Results were considered significant at p=0.05. Multiple binary logistic regression indicated that use of alcohol was a significant risk factors for breast cancer (p=0.029). Those not using alcohol were less likely to be cases (OR; 95%CI: 0.052(0.004-0.736). The Kalenjin were more likely to be cases compared to other tribes though not statistically significant. Similarly, those using injection for contraceptive are more likely to be cases. We report that tribe, place of residence, reproductive and lifestyle habits are associated with development of this disease suggesting that genetics, lifestyle and environmental risk factors could be responsible with the early onset of breast cancer in African women therefore screening for these risk factors should be done at an earlier age with the aim of early detection and treatment and thus increase chances of survival. Further research on the effects of already known and the unknown risk factors on the tumor suppressor genes need to be ascertained.

Key Words: *Risk Factors, Aggressive breast cancer, young women, Western Kenya*

Introduction

Breast cancer is among the fastest rising non communicable disease in low and middle income countries, Kenya included. The age frequency distributions have revealed that African women were younger at diagnosis compared to Europeans (Kadhel et al. 2014). Though breast cancer in Africans appears in low prevalence rate, it is more aggressive than in women from European origin (Fregene & Newman 2005, Easton, 2005) and is likely to kill by the age of 40 years (Easton, 2005). It is not clear if risk factors associated with development of the aggressive forms of breast cancer in African women are similar to those recorded in breast cancer patients from outside Africa. Risk factors accounting for differences in prevalence rates include non-modifiable (gender, age, genetic susceptibility, history of breast cancer, ethnicity, and menstrual history) and modifiable (socio- demographic profiles, lifestyle behaviors, and reproductive factors) risk factors (Kluttig& Schmidt- Pokrzywiniak, 2009).

Women breast cells are constantly exposed to growth–promoting effect of estrogen and progesterone this alone predisposes women to this disease more than men. Age increases the risk of breast cancer in women (Fregene and Newmasn, 2005). Family history of both first and second degree relatives increases the risk of developing breast cancer (Chen et al, 1999). Early menarche (<12 years) and late menopause (>55 years) increases the duration of oestradiol and progesterone that increases the risk of cancer (Grant 2008) while late menarche leads to lower endogenous estrogen levels thereby reducing breast cancer risk (Fregene and Newman, 2005). Long term use of oral contraceptive use may have an increased risk of breast cancer (Fox 2006). Multiparity in Africans has a protective role for it lowers endogenous estrogen levels over a life time therefore reduces the risk of breast cancer (Fregene and Newman, 2005). Similarly prolonged lactation among African women decreases cumulative number of ovulation menstrual cycles this would in turn reduce the risk of breast cancer (Fregene and Newman, 2005).

This study will identify risk factors associated with development of aggressive breast cancer in young Kenyan women with the intension of providing information that will help prevent this upcoming pandemic.

Materials and Methods

Study Population.

Eligible participants from the general population residing in Western Kenya who had histological proven breast cancer were taken as cases while those with non-malignant breast lumps were the controls. Ethical approval was obtained from the Institutional Ethics and Review committee (IREC) of Moi teaching and Referral Hospital (MTRH). Those who consented were given a questionnaire to fill, for those who could not read and write an interpreter assisted them to fill the questionnaire.

Data collection

Study questionnaires were used to obtain personal details, family history (presence of breast and other types of cancer in the family), and age at menarche, use of hormone replacement therapy and a number of lifestyle factors including,

alcohol consumption, smoking and environment factors.

Statistical Analysis

Data entry was done in excel spreadsheet and exported to Statistical package for social sciences (SPSS V.20) for analysis. Normality test was performed on continuous/discrete variables using Shapiro wilk and kolmogorovsmirnov tests. Data was summarized using frequencies for categorical variables and median (IQR) for continuous/ discrete variables. Multiple binary logistic regression was used to identify risk factors of cancer controlling for confounders. Results were considered significant at α=0.05. Results were presented using tables and charts.

Results

There was high prevalence of breast cancer among patients below the age of 30 years (Fig I). Categories of non-modifiable risk factors are shown in Table 1.

Age at Diagnosis

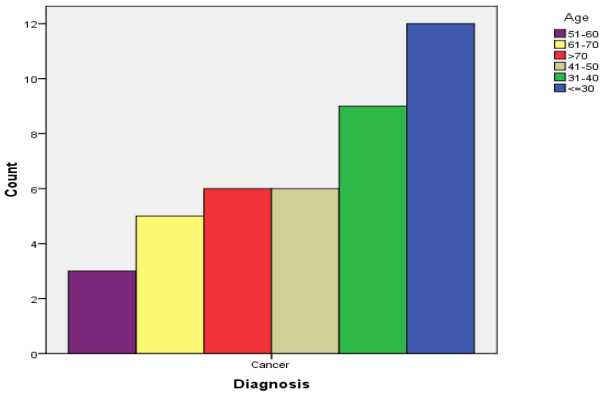

Fig I. Prevalence of breast cancer in different age groups

Table 1: Categories of Non-modifiable Risk factors of Breast cancer in Western Kenya

Factor	Cases	Control	P-value
Median age(IQR)	45.5(37, 65)	46(39.5, 53.3)	0.802
Tribe			
Kalenjin	17(23)	35(51.5)	
Luhya	22(29.7)	18(26.5)	<0.001
Kisii	4(5.4)	7(10.3)	
Luo	7(9.5)	4(5.9)	
Others	24(32.4)	4(5.9)	
History of B/C			
Yes	12(16.2)	20(29.4)	
No	56(75.6)	18(26.5)	<0.001
Other	6(8.1)	30(44.1)	
Menopause			
No (<55)	53(51)	51(49)	0.707*
Yes(≥55)	21(55.3)	17(44.7)	
Tribe			
Kalenjin	17(32.7)	35(67.3)	0.001
Luhya	22(55)	18(45)	
Others	35(70)	15(30)	
Gender			
Male	3(100)	0(0)	0.246*
Female	71(51.1)	68(48.9)	

Test=Chi-square; *Fisher's exact; level of significance p>0.05.

Table2: Level of risk of marital status, lifestyle behavior and environmental factors

Characteristic	Case	Control	Risk Level	p-value
Marital status				
Yes	46(62.2)	53(77.9)	Low	0.041
No	28(37.8)	15(22.1)	High	
Life style behaviour				
Alcohol use				
Yes	2(2.7)	13(19.1)	High	0.001
No	72(97.3)	55(80.9)	Low	
Smoking				
Yes	2(2.7)	6(8.8)	High	0.153*
No	72(97.3)	62(91.2)	Low	
Environmental factors				
Firewood	73(98.6)	68(100)	High	1.000*
Yes	1(1.4)	0(0)	Low	
No				
Live in house with mice	72(97.3)	68(100)	High	0.497*
Yes	2(2.7)	0(0)	Low	
No				

*Test=Chi-square; *Fisher's exact*

Table 3. Level of risk for reproductive factors

Characteristic	Case	Control	Risk level	p-value
Oral Contraceptive use				
Yes	9(12.2)	11(16.2)	High	<0.001
No	26(35.1)	55(80.9)	Low	
Injection Contraceptive use				
Yes	9(12.2)	23(33.8)	High	<0.001
No	53(71.6)	45(66.2)	Low	
Parity	4(16.7)	8(12.1)	High	
0	11(45.8)	27(40)	Medium	0.729
1-5	9(37.5)	31(47)	Low	
≥5				
No. of children breastfed				
None	2(8.7)	8(12.3)	High	
≤4	12(52.2)	27(41.5)	Medium	0.664
≥5	9(39.1)	30(46.2)	Low	
Duration breastfeeding				
<6 months	2(8.7)	7(10.9)	High	
6-11months	1(4.3)	2(3.1)	Medium	0.924
≥12 months	20(87)	55(85.9)	Low	
Miscarriage				
0	26(86.7)	56(86.2)	Low	1.000*
≥1	4(13.3)	9(13.8)	High	

Hysterectomy	71(95.9)	63(92.6)	High	0.48*
Yes	3(4.1)	5(7.4)	Low	
No				
HIV status				
Negative	71(95.9)	64(94.1)	Low	
Positive	3(4.1)	4(5.9)	High	0.710*
Combined Pill and injection				
Yes	2(2.7)	3(4.4)	High	
No	72(97.3)	65(95.6)	Low	0.670*

*Test=Chi-square; *Fisher's exact*

Marital status and several lifestyle behavior such as alcohol use and environmental factors such as exposure to wood smoke are high level risk factors to breast cancer Table 2. While reproductive factors such as parity, breast feeding are protective Table 3. The duration of breast feeding and use of contraceptives are not significantly associated with breast cancer Table 4.

Table 4: Duration of breastfeeding, use of oral pill and use of injection

Time	Case	Normal	P-value
Duration breastfeeding	18(12, 24)	18(12, 24)	0.841
Duration using Pills	2(1, 5)	2(1,5)	0.238
Duration using injection	5(1, 7)	2(0.3, 3.6)	0.179

****median (IQR) test=Mann whitney U-test*

Table5: Multiple Binary logistic regressions of breast cancer cases.

Factor	**Regression coefficient(β)**	**AOR(95%CI)**	**P-value**
Married	-0.604	0.546(0.115-2.595)	0.447
Use pill for contraception	-1.849	0.157(0.009-2.776)	0.207
Use injection for contraception	1.504	4.499(0.735-27.545)	0.104
Tribe (ref=Others)			
Kalenjin	1.161	3.192(0.661-15.404)	**0.148**
Luhya	-0.058	0.944(0.172-5.179)	**0.947**
History of B/C	0.110	1.116(0.267-4.673)	0.880
Alcohol use	-2.954	0.052(0.004-0.736)	**0.029**

Multiple binary logistic regression indicated that use of alcohol was a significant risk factors of breast cancer (p=0.029). Those not usingalcohol were less likely to be cases (OR;95%CI: 0.052(0.004-0.736). The Kalenjin were more likely to be cases compared to other tribes (OR;95%CI: 3.192(0.661-15.404) though not statistically significant. Similarly, those using injection for contraceptive aremore likely to be cases (OR;95%CI: 4.499(0.735-27.545)) Table 5.

Discussion

Non-modifiable risk factors

Non-modifiable risk factors the average median age among the cases in this population was 45.5 (IQR 37, 65). This is comparable with other studies that reported that breast cancer in Africa is common at a young age of 35 and 45 years (Rambau et al., 2011; Akarolo-Anthony et al., 2010). The explanation to the young age at diagnosis is thought to be due to varied reasons. Akarolo-Anthony et al. in their study reported that early onset breast cancer in African women is a demographic phenomenon that is justified by the fact that most African countries have a cone-shaped population pyramid with majority of their citizens being children and young adults with very little elderly population at the top.

In our study we report that demographic pattern alone may not explain this finding, there are other factors that could contribute to early onset of breast cancer in Africans; from our findings some Kenyan tribes seem to have higher incidence of breast cancer certain age group, also there is a general finding that some counties seem to have more cases than others. Genetic and environmental risk factor could be associated with the early onset of breast cancer in African women therefore screening for these risk factors should be done at an earlier age with the aim of early detection and treatment and thus increase chances of survival.

Age at Menarche

The median age at menarche was 14 years (min 12; max 19) this similar to 14.7 years recorded in rural black women of South Africa (Walker et al 2011). Studies have reported that age at which a child's mother attained menarche, racial and ethnic factors may influence the age of menarche. Some environmental factors that have been associated with early puberty are nutrition, pollution, exposure to endocrine disrupting chemicals, stressful life events, family relationships, socioeconomic status, weight, premature birth, and low birth rate (Walvoord, 2010). Researchers have also noted a possible link between environmental contaminants and the obesity epidemic in the United States (Biro, Greenspan, & Galvez, 2012). What is not clear is the link between reduced age at menarche in our population and consumption of animal fat, formula feeding, and inactivity, low income and life stressors such as lack of a father that seem to be part of life in the world today.

Age at Menopause

We report that in Kenya breast cancer is likely to develop early before menopause considering that the median age at presentation was 45.5 years. This age is younger than the age at presentation in Caucasian women, the reason for this is not fully understood but it could be linked to breast cancer genes (BRCA 1 and 2) and their variants (Ghiasvand 2010). Studies have indicated that after the age of 55 years the risk of breast cancer doubles (Sprague et al, 2008) this is because long menstrual history increases life time exposure to sex hormones. In this study 21 cases (28.4 %) were above 55 years while the majority 53(71.6%) was below the age of 55 years. Few studies on

menopausal history and risk of breast cancer in Africans have been documented indicating that more studies on this are needed.

Family History

The majority (75.6%) of the patients in our study reported having no relative diagnosed with any type of cancer which correspond to low risk this is comparable to a study by Lehlasoa (2011) which reported that 77% of their breast cancer patients had no family history. We report that only 16.2 % of our patients had a family history which place them at high risk category this is still comparable to 19.0% of Californian patients (Wrensch et al 2003) and slightly Higher to 13.3% reported for South African patients (Lehlasoa, 2011). These findings indicate that breast cancer seen in Kenya could be as a result of sporadic genetic changes but not hereditary therefore more genetic studies need to be conducted ascertain this.

Modifiable Risk Factors

Socio-demographic Factors

Marital status

Our findings showed higher risk of breast cancer among women who never ever married at the age between 31-40 years followed by those that were ≤ 30 years in the same category. Studies have reported that marital status remains a risk factor for breast cancer development and unmarried, delayed marriage, delayed first child birth are strong cofactors for development of breast cancer (Shaikh et al, 2014). These data suggests that the increased cases of breast cancer seen in our young women could be as a result of psychological and physiological changes associated with life events. Stressful life events could be predisposing young African women to developing breast cancer (Hemminki and Li, 2003), It has been observed that some of these changes affect immunological function by lowering immunosurvillance followed by risk of developing malignancies such as breast cancer (Hemminki and Li, 2003). Furthermore it has been documented that unmarried patients were likely to present with metastatic cancer and have high chances of under treatment resulting to increased mortality rates (Aizer et al, 2013). Most cancer patients in the developing world are trapped by stigma, poverty and misinformation that is why there is late presentation at the hospital when chances of treatment have been lost leading to high rates of deaths. There is an urgent need of intervention in terms of free and efficient counseling and emotional support to the cancer patients and the general public so as to improve the quality of life.

Reproductive Factors

Out of 37 patients who responded to the question whether they use oral contraceptive, 26 (35.1%) had not used OC at the time of interview placing them on low risk for breast cancer (Puri et al. 2009). Of the 9 patients who used OC, the majority 7(77.8%) had used them for a period greater than one year (>1 year) and as a result had high risk for breast cancer (Puri et al, 2009). Majority (71.6%) of the patients had not used hormonal injection for contraceptive as results places them at a low risk for breast cancer. Beaber et al., 2014 reported that high dose estrogen

formulation was linked with increased risk of cancer breast cancer while low dose estrogen pills and injection were the safest, therefore the government should take a lead in ensuring that low estrogen level hormonal contraceptive are prescribe to all so as to protect the uninformed and the illiterate public in our setting.

Parity

There is evidence that giving birth in women confer a long-lasting protection on breast cancer. In this study majority (83.3%) of breast cancer women that were seen had given birth at least once in their lives hence we may not link breast cancer development to parity. Out of these 45.8% of the patients had given birth 1-5 times in life as a result had medium risk for breast cancer while 37.5% had more than five births placing them at low risk for breast cancer. This could be explaining why African women have a lower incidence of developing breast cancer since they have given birth at least once in life. This is supported by several studies that recorded that there was a 7% reduction in the relative risk of breast cancer for each birth independently from other pregnancy related factors (Collaborative Group on Hormone Factors in Breast Cancer, 1996). Yang et al. (2011), in their study estimated that there was 30% decrease in risk of breast cancer in multiparous women of 5 or more births. Only 16.7% were nulliparous in this study thus placing them at high risk of breast cancer. Previously nulliparous have been recorded to have excess 20 to 25 % breast cancer risk as compared in porous (Lehlosoa, 2011).

Breastfeeding

Comparable to other studies 87% of breast cancer patients in our study had breastfed for more than 12 months and as a result had low risk of cancer (Lehlasoa, 2011). The median duration of breast feeding was 18 months (min 12; max 24). Only 8.7% had not breastfed and or breastfed for short period (less than 6 months) placing them at high risk of breast cancer. The relative risk of breast cancer decreases by 4.3% for every year of breastfeeding, in addition to 7% for each birth. Although women in low income countries breastfeed for a longer period compared to high income countries, this alone may not protect from breast cancer. There is a possibility that Pressure on women in the developing world to copy western lifestyle including shorter duration of breast feeding, longer spacing of birth, less number of children (Vecchia and Pelucchi, 2012) could be responsible to some extent to the rise of breast and other cancers in the women of low income countries.

We suggest that young women, despite of challenges of work and other stressful events of life should allow their children to breastfeed the longest for this is not only beneficial to the immunity of the baby and bonding between the baby and the mother, but also protects from developing breast cancer.

Lifestyle Factors

Alcohol intake

In the current study, use of alcohol was a significant risk factor of breast cancer (p=0.029; OR; 95%CI: 0.052(0.004-0.736). Among the

drinkers those that were between 41-60 years old were the majority. There is convincing evidence that alcohol consumption increases the risk of cancer of the colorectal, breast, larynx, liver, esophagus, oral cavity and pharynx (Bagnardi et al, 2012). Association between alcohol and breast cancer is linked to increased estrogen and androgen or increased levels of plasma insulin like growth factors that are produced by liver following alcohol consumption (Sarkar et al, 2001). This indicates that a drinker in our setting is likely to develop breast cancer between 41-60 years.

Smoking

Most epidemiological studies associated heavy smoking, smoking of long duration, smoking before a first full term pregnancy (FFTP) and passive smoking with increased risk of breast cancer in women with high levels of estrogen (Catsburg et al 2015). In this study, majority (97.3%) had not smoked tobacco at the time of interview, 2.7% of the breast cancer patients admitted that they have ever smoked tobacco, they were between an ages of 31-60 years. None of the patients smoked at a younger age of below 30 year neither at older age of above 60 years. There were more cases who reported that they have been exposed to side stream smoking. The highest number of side stream smokers was seen in the category of 31-40 years, the age bracket at recorded with the highest number of breast cancer cases indicating that, there could be a link between passive smoking and breast cancer development. Similar to other studies we reported that, there is an increased risk of developing breast cancer in premenopausal women who are passive smokers (Johnson et al, 2009). A shift of tobacco consumption from developed world to the more vulnerable low-resource countries Kenya included, calls for a need of legal restrictions on smoking in public (Sylla and Wild, 2012). This as a critical area that needs urgent attention preferably from the politicians, simple and efficient measures such as increasing taxes and enforcing strict pricing policies as well as restricting cigarrete smoking in public and providing educational information could combat this upcoming pandemic.

Wood smoke exposure

Exposure to wood smoke has previously been reported to increase the risk of developing esophageal cancer (Patel et al., 2013). In a similar study, Kayamba et al. (2015) reported that HIV infection and domestic smoke exposure are risk factors for esophageal squamous cell carcinoma in Zambia. In the current study, almost all (98.6%) the patients were exposed to domestic wood smoke since birth up to the time of interview. There are findings that, exposure to air pollution at birth alters DNA methylation, which will in turn increase levels of E-cadherin, a protein that is known to play a role in maintain a stable cellular environment, they further pointed out that "women with breast cancer who lived in a region with more air pollution were more likely to have the alteration in the DNA in their tumor than those who live in a less-polluted regions". (Science

daily 20 April 2011). Genetic analysis will tell if risk of developing breast cancer in Kenya is as a result of DNA methylation or other effects of air pollution.

In conclusion results from the study indicate the breast cancer risk is positively associated with young age, tribe, alcohol use, passive smoking, exposure to wood smoke and other air pollutants. These results support a role of lifestyle behavior as one of the main predisposing factors to developing aggressive forms of breast cancer in the African population. Although the type of breast cancer in Kenya seems not hereditary, further research on the effects of already known and the unknown risk factors on the tumor suppressor genes need to be ascertained.

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