ETHNICITY AND BREAST CANCER CHARACTERISTICS IN KENYA

Dr. Shahin Sayed [Principal Investigator/Consultant Pathologist],
Department of Pathology, Aga Khan University Hospital, Nairobi

Dr. Zahir Moloo [Chair],
Department of Pathology, Aga Khan University Hospital, Nairobi

Prof. Ronald Wasike [Consultant Surgeon],
Department of Surgery, Aga Khan University Hospital, Nairobi

Dr. Peter Bird [Head of Surgery],
Department of Surgery, AIC Kijabe Hospital

Dr. Raymond Oigara [Surgeon],
Department of Surgery, St. Mary's Mission Hospital/Kisii Referral Hospital

Dr. Faith Wambui Njoroge [Surgeon],
Department of Surgery, Nyeri Provincial General Hospital

Dr. Asim Jamal [Consultant Oncologist],
Department of Medical Oncology, Aga Khan University Hospital, Nairobi

Dr. Satya Vara Prasad [Resident Pathologist],
Department of Pathology, Aga Khan Hospital, Kisumu

Dr. Sudhir Vinayak [Chair/Radiologist],
Department of Radiology, Aga Khan University Hospital, Nairobi

Gretchen L. Gierach [Senior investigator],
Division of Cancer Epidemiology and Genetics, National Cancer Institute, Bethesda, MD, USA

Sanford M. Dawsey [Senior investigator],
Division of Cancer Epidemiology and Genetic, National Cancer Institute, Bethesda, MD, USA

Maya Palakal [Research fellow],

Corresponding Author: Shahin Sayed, Department of Pathology, Faculty of Health Sciences - East Africa Aga Khan University, Nairobi, Kenya, Shaheen.sayed@aku.edu.

COMPETING INTERESTS

Authors have no competing interests to declare

AUTHORS' CONTRIBUTIONS

SS, ZM and MS conceived and carried out the study; SS, ZM, PO, SG carried out the centralized laboratory work; IA, CK, TH,SM performed data management; TH, SM, CK, GLG, SF, MM, MP, analyzed data; RW, PB, RO, FWN, AJ, SVP, SV, RC, AZ, MM, BB, CM, OAS, AM, AG, JG, JK, RN, RN, IM, JOO, DOR, EBM, IA contributed to data collection and/or data management. All authors were involved in writing/reviewing the manuscript. All authors gave final approval of the submitted version of the manuscript

ETHICAL STANDARDS

Aga Khan University Hospital, Nairobi Research and Ethics Committee (REF: 2011/25) and the institutional review boards of all participating health facilities approved the study. Written informed consent was obtained from all study participants.

Division of Cancer Epidemiology and Genetics, National Cancer Institute, Bethesda, MD, USA

Shaoqi Fan [Research fellow],
Division of Cancer Epidemiology and Genetics, National Cancer Institute, Bethesda, MD, USA

Maeve Mullooly [Research Fellow],
Division of Cancer Epidemiology and Genetics, National Cancer Institute, Bethesda, MD, USA

Dr. Rajendra Chauhan [Consultant Surgeon & Oncologist],
Department of Surgery, Aga Khan University Hospital, Nairobi

Dr. Patricia Okiro [Consultant Pathologist],
Department of Pathology, Aga Khan University Hospital, Nairobi

Dr. Samuel Gakinya [Consultant Pathologist],
Department of Pathology, Aga Khan University Hospital, Nairobi

Dr. Ancent Nzioka [Anatomic Pathologist],
Department of Pathology, AIC Kijabe Hospital

Dr. Catherine Kyobutungi [Director of Research],
Epidemiology, African Population And Health Research Centre (APHRC)

Shukri Mohamed [Senior Research Officer],
Epidemiology, African Population And Health Research Centre (APHRC)

Dr. Tilahun Haregu [Associate research scientist],
Epidemiology, African Population And Health Research Centre (APHRC)

Dr. Mustafa Mussajee [Surgeon],
Division of Surgery, Kenyatta National Hospital

Dr. Betty Bonass [Radiologist],
Department of Radiology, Kenyatta National Hospital

Dr. Costa Mariwa [General Surgeon],
Department of Surgery, Aga Khan Hospital, Kisumu

Dr. Omar Ali Sherman [Anatomic Pathologist],
Department of Pathology, Aga Khan Hospital, Mombasa

Dr. Abdihakim Mohammed [Surgeon],
Department of Surgery, Aga Khan Hospital, Mombasa

Dr. Andrew Gachii [Pathologist/Senior. Medical Specialist],
Department of Human pathology, Kenyatta National Hospital

Dr. Joseph Githaiga [Consultant Surgeon],
Division of Surgery, Kenyatta National Hospital

Dr. Joseph Karanu [Surgeon],
Department of Surgery, St. Mary's Mission Hospital

Dr. Robert Nyagah [Surgeon],
Department of Surgery, St. Mary's Mission Hospital

Dr. Richard Njoroge [Pathologist],
Department of Pathology, Garissa Provincial General Hospital

Dr. Irene Muramba [Pathologist],
Department of Pathology, Coast Provincial General Hospital

Dr. James Obondi Otieno [Surgeon/Head of Surgery],
Department of Surgery, New Nyanza Provincial General Hospital

Dr. Dan Omondi Raburu [Consultant Surgeon],
Department of Surgery, New Nyanza Hospital Provincial General

Elizabeth B. Mwachiro [Consultant Surgeon],
Department of Surgery, Tenwek Hospital

Innocent Abayo [CME Coordinator], and
Department of Pathology, Aga Khan University Hospital, Nairobi

Mansoor Saleh [Oncologist]
Division of Haematology& Oncology, University of Alabama at Birmingham

Abstract

Purpose—There are no published data from specific regions of sub-Saharan Africa describing the clinical and pathological characteristics and molecular subtypes of invasive breast cancer by ethnic group. The purpose of this study was to investigate these characteristics among the three major ethno-cultural groupings in Kenya.

Methods—The study included women with pathologically-confirmed breast cancer seen between March 2012 and May 2015 at 11 hospitals throughout Kenya. Socio-demographic, clinical, and reproductive data were collected by questionnaire, and pathology review and immunohistochemistry were performed centrally.

Results—The 846 cases included 661 Bantus (78.1%), 143 Nilotes (16.9%), 19 Cushites (2.3%), and 23 patients of mixed ethnicity (2.7%). In analyses comparing the two major ethnic groups, Bantus were more educated, more overweight, had an older age at first birth and had a younger age at menopause than Nilotes (p<0.05 for all comparisons). In analyses restricted to definitive surgery specimens, there were no statistically significant differences in tumour characteristics or molecular subtypes, although the Nilote tumours tended to be larger (OR for   5 cm vs. < 2 cm: 3.86, 95%CI: 0.77, 19.30) and were somewhat more likely to be HER2-enriched (OR for HER2-enriched vs. Luminal A/B: 1.41, 95%CI: 0.79, 2.49).

Conclusion—This case series showed no significant differences in breast cancer tumour characteristics or molecular subtypes, but significant differences in socio-demographic characteristics and reproductive factors, among the three major ethnic groups in Kenya. We suggest further evaluation of ethnic differences in breast cancer throughout the genetically and culturally diverse populations of sub-Saharan Africa.

Keywords

BACKGROUND

Breast cancer (BC) is the most common female malignancy worldwide, accounting for 1.7 million new cases and 521,900 deaths in 2012.[1] According to the Nairobi Population-based Cancer Registry, breast cancer is the most common malignancy in Kenyan women, accounting for 23% of all incident cases.[2]

The effect of race and ethnicity on breast cancer (BC) stage of presentation, tumor biology and treatment response has been the subject of much investigation and controversy, with numerous studies reporting that the distribution of BC molecular subtypes differs among various races and ethnic groups.

A qualitative systematic review of breast cancer demographics, size, stage, grade, histological type, extra-mammary involvement, and hormone receptor status in patients from Africa, the Middle East, Eastern Europe, Mexico, the Caribbean and South America reported that women with BC in these regions present with large aggressive tumors, and that distant metastases are frequently present at the time of diagnosis.[3] Compared with White American women, Black African women have also been reported to be younger at diagnosis, [4] to have a higher frequency of triple negative tumors,[5] and to be more likely to present with Stage III/IV disease.[6] A review of the histopathological differences between BC in African American (AA) and White Americans also reports that the former tend to have a higher nuclear grade, a higher proportion of lymph node positive tumors, and a younger age-specific incidence of triple negative tumors as compared to White Americans.[7]

Furthermore, a recent registry data review from South Africa reported that similar to the Western populations, the age distribution for breast cancer is bimodal in both Black and White South African women, however Black South African women had a younger age distribution of early onset breast cancer than all other groups studied.[8]

In Kenya, there are approximately 40–50 tribes which can be divided into 3 main ethno-cultural groupings: the Bantus who originated from West Africa after 400 AD, the Nilotic tribes who migrated from regions of the present day Sudan and Egypt around 400 AD, and the Cushitic tribes who came from northern Africa around 2000 BC (Fig 1a).

The largest ethnic groups in Kenya, the Kikuyus, are of Bantu ancestry, while the Luos residing in the western part of Kenya are of Nilotic descent. The populations that inhabit the northern parts of Kenya belong to the Cushitic lineage.

The objective of this study was to investigate the differences in-patient, clinical and pathological characteristics of breast cancer in the three major ethno-cultural groupings in Kenya, given their distinct ancestral origin.

METHODS

Study design and setting

This was a Kenya-wide study involving a total of 11 health institutions (Supplementary Table 1) that recruited patients with pathologically confirmed breast cancer between March

2012 and May 2015. The study was coordinated by Aga Khan University Hospital, Nairobi, which is a 300-bed private not-for-profit hospital that provides tertiary level health care services in Kenya. The collaborating hospitals in this study are located in various parts of Kenya and their patient catchment area reflects the distribution of the total population and the three major ethnic groups (Fig. 1b).

Data collection

Relevant socio-demographic, reproductive, and clinical data were collected from all consenting patients using structured questionnaires and clinical data abstraction case report forms.

The ethnicity of patients was determined through self-reporting by respondents of their parents' and maternal and paternal grandparents' tribal affiliations. The tribes were assigned to the corresponding three major ethnic groups; Bantu, Nilotes and Cushites[9] If all maternal and paternal grandparents and parents did not belong to the same tribe, that patient's ethnicity was categorized as mixed. Due to sparse numbers, patients reporting "mixed" ethnicity (N=23, 2.7%) were excluded from the analytic population.

All breast cancer tissues blocks were submitted to Aga Khan University Hospital, Nairobi to undergo central pathology review and immunohistochemistry. Tumor size, tumor grade, presence of lympho-vascular invasion, lymph node metastases and extra nodal extension were documented. ER/PR/HER2 status was analyzed on the Dako Automated platform as previously reported,[10] and tumors were assigned into 3 major breast cancer molecular subtypes based on immunohistochemistry: ER and/or PR positive and HER2 positive or negative (Luminal A/B), ER/PR negative and HER2 positive (HER2 enriched), and ER/PR and HER2 negative (Triple Negative).

Data entry and verification

All data were double entered. If data were missing, or needed clarification, an additional secondary review of the patient files was carried out by the data collection team. Finally, SQL scripts were prepared to facilitate data extraction.

Data Analysis

Distributions of socio-demographic and reproductive risk factors, tumor pathology characteristics, and tumor hormone receptor status were examined across the three ethnic groups (Bantu, Nilotes, and Cushite) and evaluated by Chi-square and Fisher exact tests as appropriate. Because of the small numbers of Cushite patients, these statistical tests were also rerun after restricting the analysis to the two largest ethnic groups, Bantus and Nilotes. Logistic regression models were used to estimate odds ratios (ORs) and 95% confidence intervals (95% CIs) for associations between Bantu or Nilote ethnicity and the tumor characteristics (tumor pathology characteristics and hormone receptor status). Risk factors associated with both ethnicity and the tumor characteristics of interest were included in multivariate logistic regression models, and the final models were determined using backwards elimination. In exploratory analyses attempting to better understand observed

risk factor associations with ethnic group, we also evaluated interrelationships between select socio-demographic characteristics with tumor characteristics.

Analyses of socio-demographic, reproductive factors and hormone receptor status included all participants with relevant data. In contrast, the tumor pathology characteristics (tumor size, tumor grade, lympho-vascular invasion, lymph node metastasis, and extranodal extension) were only analyzed in the 396 (48.1%) cases that underwent definitive surgery. All analyses were performed using SAS 9.3 (SAS Institute, Inc., Cary, NC) and statistical significance was defined as p<0.05.

RESULTS

A total of 823 female study patients with invasive breast tumors were included in the analysis, 661 (80.3%) were Bantus, 143 (17.4%) were Nilotes, and 19 (2.3%) were Cushites. Of these 823 study participants, 427 (51.9%) were diagnosed by core biopsy only, and 396 (48.1%) had both a core biopsy and definitive surgery (lumpectomy or mastectomy). 351 (53.1%) of the Bantus, 37 (25.9%) of the Nilotes, and 8 (42.1%) of the Cushites had definitive surgery.

Sociodemographic and Behavioral Characteristics

Overall, the majority (53.9%) of women were younger than age 50 years at breast cancer diagnosis, with a median (interquartile range) age of 48 (40-57) years (Table 1). Whereas median age at diagnosis was similar for Bantus (48 years) and Nilotes (52 years), the median age at diagnosis for Cushites was much younger (36 years) (p=0.03). About half (50.2%) of the women received only primary school or no education. The most common occupations were farmer (30.8%) and employed worker (23.3%), and only 18.5% said they worked as housewives. By body mass index (BMI, kg/m^2), nearly 70% of the women were overweight (39.2%) or obese (29.5%). Nearly half (42.7%) of the women were exposed to smoking, but very few of them (3.3%) reported ever having smoked or used smokeless tobacco themselves, and only 8.5% used alcohol.

When the analytic population was limited to Bantus and Nilotes, Bantu patients were slightly more educated (51.6% vs. 46.2% with secondary education or above) and slightly more overweight or obese (70.1% vs. 63.2%), and they were more likely to work as farmers (34.0% vs. 20.3%). Nilote patients, on the other hand, were more likely to work as employed workers (31.5% vs. 21.9%) or housewives (26.6% vs. 15.6%).

Reproductive Health Factors

In terms of reproductive health factors in the overall study population, nearly all of the participants reported having normal (age 12-14 years) or late (age 15 years) menarche (49.9% and 49.0%, respectively) (Table 2). Most women (67.9%) had at least three children, for most (62.2%) their age at first pregnancy was between the ages of 20 and 29 years, and the vast majority (90.1%) reported at least 15 cumulative months of breastfeeding. A little less than half (48.1%) of participants were postmenopausal at diagnosis, among whom most (57.9%) reported an age at menopause <50 years. The majority (92.2%) of patients reported no family history of breast cancer.

Though based on small numbers, the Cushites seemed to present with a different reproductive profile as compared with the Bantus and Nilotes: a greater proportion of Cushites were <20 years at first pregnancy (52.6% vs. 24% (Bantus) and 35% (Nilotes); p=0.0008) and were premenopausal at diagnosis (73.7% vs. 52.7% (Bantus) and 45.1% (Nilotes); p=0.04). When reproductive health factors in Bantus and Nilotes were compared, Bantus were more likely to report older age at first pregnancy (72.3% vs. 58.8% ≥20 years) and younger age at menopause (62.2 vs. 43.9% <50 years).

Tumor pathology characteristics (among those with definitive surgery)

Overall, 31.4% of the 396 tumors with definitive surgery were ≥5cm, 59.4% were 2-<5cm, and only 9.2% were <2 cm in size at presentation. Lymphovascular invasion (LVI) was identified in 75.3% of cases, lymph node metastases in 58.8%, and extranodal extension of tumor in 39.1% (Table 3a).

In *post hoc* analyses, we found that the most highly educated patients had the smallest tumors (data not shown). Thus, in multivariate models evaluating the relation of ethnicity with tumor size, we adjusted for education level as well as age and ER status; we found that Nilotes tended to be more likely than Bantus to present with larger tumors (≥5cm vs. <2 cm), (OR: 3.86, 95% CI: 0.77, 19.30; p-trend=0.10). Continuing to compare patients from the two major ethnic groups, we additionally found that Nilotes were more likely to present with LVI (OR: 1.70, 95% CI: 0.68, 4.24), and were less likely to show extra nodal extension (OR: 0.92, 95% CI: 0.45, 1.85), although none of these associations was statistically significant (Table 3b).

Hormone receptor status

Overall, 68.8% of the patients were ER positive, 59.4% were PR positive, and 25.6% were HER2 positive (Table 4a). Categorized by molecular subtypes, 70.2% of patients were Luminal A or B (ER and/or PR positive and any HER2 status), 10.6% were HER2 enriched (ER and PR negative and HER2 positive), and 19.2% were triple negative (ER, PR and HER2 negative).

In multivariate analyses evaluating the association between Bantu or Nilote ethnicity with molecular tumor subtype, Nilotes tended to be more likely to be present with ER negative tumours (36.8% versus 29.7%), although this was not statistically significant (p=0.11) and HER2 enriched tumors as compared with Luminal A/B cases, although this difference was also not statistically significant (OR: 1.41, 95% CI: 0.79, 2.49). Ethnicity was not associated with the likelihood of having a triple negative tumor (OR: 1.09, 95% CI: 0.67, 1.76) (Table 4b).

DISCUSSION

This is the largest case series of histologically proven invasive breast cancers from East Africa that has extensive and uniform risk factor information, uniform histology review, and tumor hormone receptor status measured by immunohistochemistry in a single accredited pathology laboratory. More than eight hundred cases were enrolled over a three-year period

from 11 public, faith-based and private institutions that serve a full range of the geography and population centers in Kenya.

We observed significant differences in some socio-demographic and reproductive characteristics by ethnicity. For the largest two ethnic groups, the Bantus were significantly more likely to be more educated, more overweight or obese, older at first pregnancy, and younger at menopause in comparison with the Nilotes. We found no statistically significant differences, however, in breast tumor characteristics in women from the two major ethnic groups, although the Nilotes tended to present with somewhat larger tumors and to have a slightly higher proportion of HER2-enriched tumors when compared with the Bantus. These ethnic differences are likely multifactorial in nature, reflecting variations in socioeconomic, environmental and genetic factors.

We used tumor size, tumor grade, LVI, lymph node metastasis, and extranodal extension of the tumor as biologic indicators of tumor aggressiveness. Whether the non-significantly larger tumor sizes seen among the Nilotes reflects more aggressive tumor biology or a consequence of longer delay in presentation and diagnosis is an area worthy of further exploration. In a *post hoc* analysis, we observed an inverse relationship between tumor size and level of education. Lack of or fewer years of education may limit a woman's awareness of breast cancer and her knowledge of breast cancer symptoms and the importance of evaluating breast lumps, may lead to delays in presentation and diagnosis.[11] Differences in traditional beliefs and cultural practices among ethnic groups may also explain differences in time to presentation and tumor size at presentation.[12] Exploring these barriers to late presentation among the various communities warrants further study.

Numerous studies of diverse populations have suggested that socio-demographic factors are likely important for ethnic differences in breast cancer tumor size and stage at diagnosis. For example, Awadelkarim et al reported differences in tumor characteristics between Sudanese and Italian women; Sudanese women tended to present with larger tumors than their Italian counterparts (48 mm vs. 22 mm), they had a higher proportion of aggressive grade 3 tumors (68% vs. 21%), and their tumors were more likely to have nodal involvement (90% vs. 36%).[13] Additionally, a US registry-based study of the 10 largest population groups in the US, including Hispanic, White, Black, Japanese, Filipino, Chinese, Hawaiian, Korean, Vietnamese, and American Indian women diagnosed with breast cancer, reported that among the Japanese and White patients, tumors were smaller in size, had a lower tumor grade (even after adjusting for stage), and were diagnosed at an earlier stage, whereas Black and Hispanic patients were more likely than other groups to have tumors 2 cm in diameter, to have poorly differentiated tumors, and to be diagnosed with metastatic disease.[14] Apart from possible differential exposure to carcinogens and genetic susceptibility, the known disparities in population mammography screening levels and subsequent follow-up care may also be contributory factors.[14] In Kenya, screening for breast cancer is opportunistic and there is currently no national breast cancer-screening program in place.

Although we found suggestive differences in tumor hormone receptor and HER2 status between the Nilotes and Bantus, these differences were not statistically significant. Nilote tumors tended to be more likely to be ER negative and more likely to be HER2 positive,

suggesting biologically more aggressive receptor phenotypes among the Nilotes. There are multiple reports of variation in tumor hormone receptor and HER2 status in different ethnic groups. An NCI study in the SEER registry database which examined 360,933 breast cancer cases diagnosed between 1988-2006 showed that the Asian Indian/Pakistani women had more ER/PR negative breast cancer than Caucasians (30.6% vs. 21.8%, p = 0.0095).[15] Another study reported that relative to non-Hispanic Whites, women of African, Native American, South East Asian, Mexican, South/Central American, and Puerto Rican descent living in the United States had 1.4 to 3.1-fold elevated risks of presenting with ER and PR negative breast cancer.[16] This report concluded that breast cancer tumor characteristics differ by race/ethnicity in the United States and that both biological and lifestyle factors likely contribute to these findings.[16] This hypothesis that the proportions of breast cancer molecular subtypes differ by racial/ethnic groups is also supported by recent reports that East African migrants to the US tend to have less ER negative breast cancer than migrants from West Africa.[17]

The mean and median ages of breast cancer diagnosis (49 and 48 years, respectively) for all ethnicities combined in our study population were not different from those previously reported from Kenya.[10][18] It is noteworthy that there was a markedly earlier age at diagnosis among the Cushites versus the two larger ethnic groups. Although this difference in age at presentation may be suggestive of differences in tumor biology among the ethnic groups, it could also be a chance finding due to the small number of Cushites in our patient population.

Over 60% of the Bantus and Nilotes in this study resided in rural areas, and about half reported menarche at more than 15 years of age, consistent with the findings of a Cameroonian study which reported a higher mean age at menarche for women residing in rural areas (14.3 years) as compared to those residing in urban areas (13.8 years).[19] A significantly greater proportion of Bantus reported age at menopause < 50 years compared to the Nilotes and Cushites. Interestingly, a multiethnic cohort study of non-Latina Whites, Japanese Americans, African-Americans, Native Hawaiians, and Latinas, which investigated factors influencing the timing of natural menopause among 95,704 women, found that race/ethnicity was a significant independent predictor of the timing of natural menopause. While African Americans did not differ significantly from non-Latina Whites, natural menopause occurred earlier among Latinas and later among Japanese Americans, supporting the hypothesis that the timing of natural menopause is driven by a combination of genetic, reproductive, and lifestyle factors.[20] Recently, genome-wide association studies (GWAS) have identified single-nucleotide polymorphism markers that are associated with ages at menarche[21] and menopause[22], which may aid in our understanding of the biology of menarche and menopause.

Differences in body mass were noted between Bantus and Nilotes, with a significantly higher proportion of Bantu patients being overweight or obese (BMI 25 kg/m^2). This may well reflect the dietary habits of the study population. As cited by Christensen et al,[23] a cross-sectional study in Kenya evaluating the prevalence of obesity among rural Luo (representing the Nilotes), who mainly subsist on maize, sorghum and fish, and rural Kamba (representing the Bantus), who subsist on maize, reported higher weights and BMIs in the

latter. In a study of rural and urban Kenyan women, the Kamba (Bantus) had the highest Arm Muscle Area (AMA) and the highest BMI and Arm Fat Area (AFA) as compared with the Luo or the Maasai (both Nilotes), a finding which was marginally significant.[23] Additionally, there were differences related to the location of residence in the prevalence of overweight (BMI 25 kg/m^2) women among all the rural and urban female populations (19.5% and 60.3%, respectively).[23] In our study, there was no difference in Bantu and Nilote cases with respect to rural or urban location of residence, which suggests that location of residence may not contribute to ethnic differences in BMI observed in our patient population.

Interestingly, the mean age at first pregnancy was significantly younger for the Cushite patients than for patients from the other ethnic groups. The Somali, Rendile, Oromo and Borana make up the Cushitic ethnic minority, who reside in the semi-arid and arid North Eastern region of Kenya. Traditionally within these communities, girls usually get married before the age of 20 years. As prior studies have suggested, a full-term pregnancy before the age of 20 years may have a transient cancer promoting effect as each pregnancy, including the first one, may increase the risk of early-onset breast cancer [24][25][26], so early marriages and subsequent early pregnancies could contribute to the higher proportion of early onset pre-menopausal breast cancers seen in the Cushites vs. the other two ethnic groups, although the cross-sectional nature of the study design along with the small number of Cushite cases limits our ability to draw conclusions.

The great majority of patients in all three ethnic groups reported lifetime breastfeeding of more than 15 months, and there was no significant difference in the length of cumulative breast feeding by ethnic group. These results are similar to those of a previous report of mean cumulative breast feeding in the major ethnic tribes in Kenya: 12.1 months for the Kamba (Bantus), 15.6 months for the Kikuyu (Bantus), and 17.1 months for the Luo (Nilotes), with no significant differences among these ethnic groups.[27] Based on findings from a large African American cohort study, it has been hypothesized that an early first birth without subsequent breastfeeding is associated with elevated risk of ER negative breast cancer.[28] Hence, the long lifetime duration of breastfeeding in Kenyan women of varying ethnicities may contribute to the observed similarities in the distribution of breast cancer molecular subtypes by ethnicity in our study population.

Strengths of this study include the relatively large size of this African case series; the broad national representation of the major ethnic groups in Kenya, with the majority being of Bantu ancestry (67% versus 30% Nilotes)[29]; the use of uniform questionnaires and case report forms; and the central pathology review and immunohistochemistry. Limitations of the study include the fact that it was a case series, without a control population for comparison, and the smaller representation of the Nilotes and Cushites, compared to Bantus, which limited the interpretive power of our results. Additional studies with a larger representation from each ethnic group and suitable population-based controls are warranted to further our understanding of breast cancer etiology in these populations.

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CONCLUSIONS

This case series showed no significant differences in pathologic features or the molecular subtypes, but significant differences in socio-demographic characteristics and reproductive factors, of breast cancer cases in the three major ethnic groups in Kenya. These differences are probably multifactorial in origin. There were insufficient cases from the Cushite ethnic group to conclude that all three groups were clinicopathologically similar, but the available data suggested that this was the case. This study suggests the need for studying ethnic differences in breast cancer etiology and tumor characteristics throughout the genetically and culturally diverse populations of sub-Saharan Africa. Such studies will clearly enhance our overall understanding of breast cancer etiology and behavior worldwide, and may well help us develop new strategies for prevention and early diagnosis.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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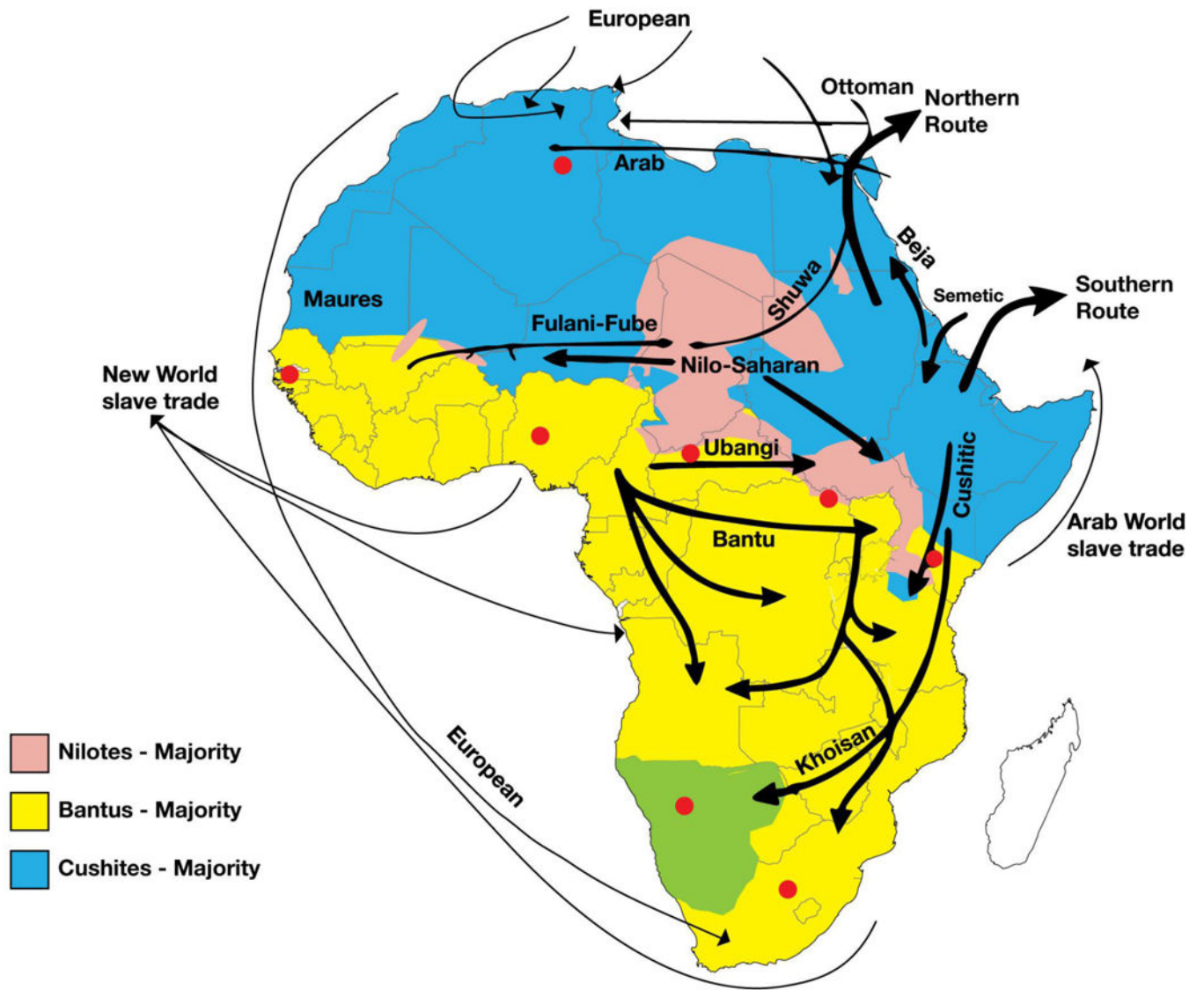
Fig 1a.
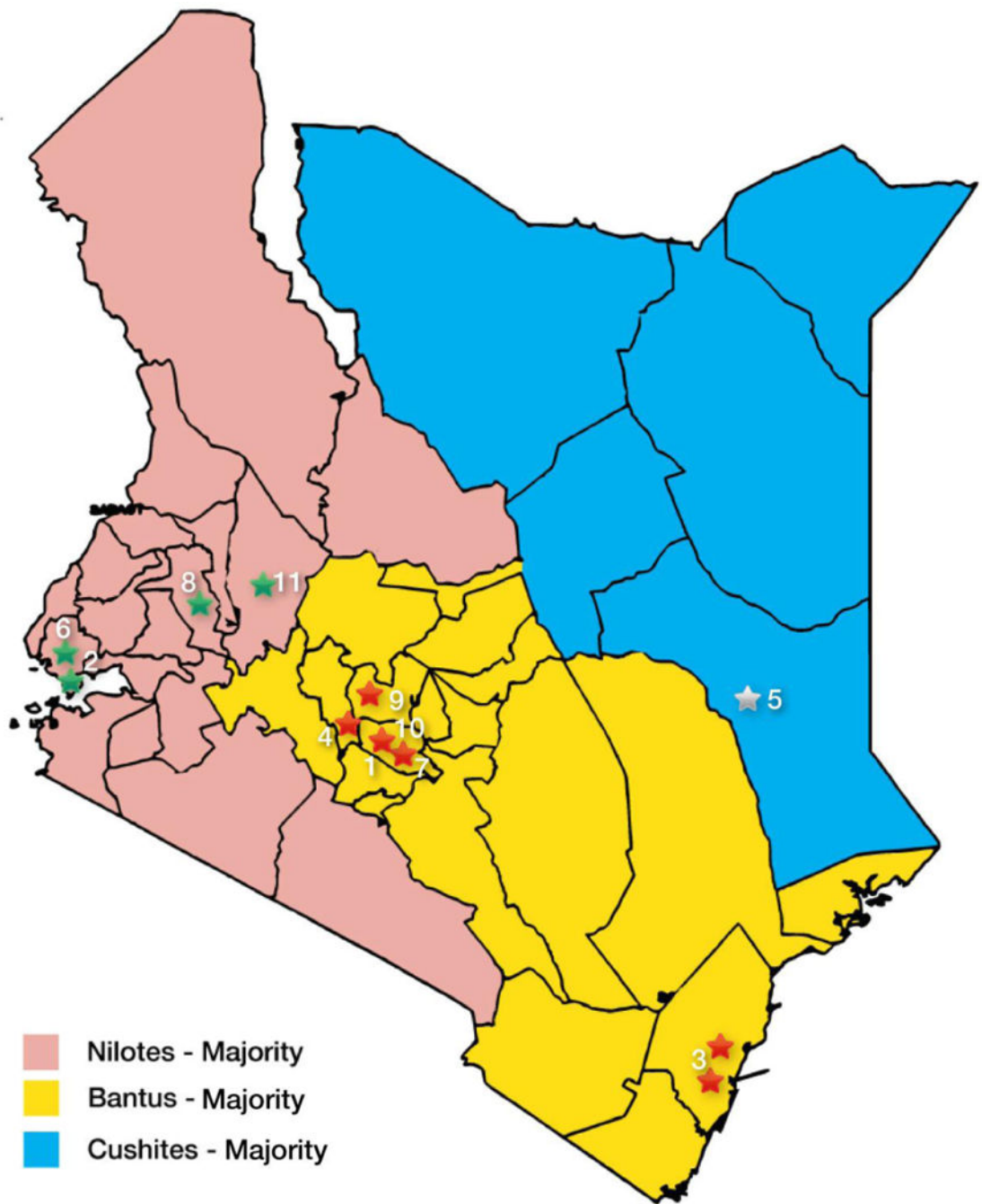Ethinic migration patterns in Africa

Fig 1b.
Distribution of participating study sites

Table 1

Proportions of sociodemographic characteristics with ethnicity: All ethnicities (N=823)

		Bantu (N=661) N (%)	Nilote (N=143) N (%)	Cushite (N=19) N (%)	Total (N=823) N (%)	P values-All*	P values - Bantus and Nilotes only*
Mean age at diagnosis		49.2	50.8	42.7	49.3		
Median age at diagnosis (IQR)		48 (40–57)	52 (39–59)	36 (32–56)	48 (40–57)	**0.03** **	0.24 **
Age at diagnosis	20–29	23 (3.5)	5 (3.5)	2 (10.5)	30 (3.7)	**0.005**	**0.02**
	30–39	129 (19.6)	34 (23.8)	8 (42.1)	171 (20.9)		
	40–49	209 (31.8)	27 (18.9)	3 (15.8)	239 (29.2)		
	50+	296 (45.1)	77 (53.9)	6 (31.6)	379 (46.3)		
	Missing	4	0	0	4		
Highest level of education	None	188 (28.4)	53 (37.1)	14 (73.7)	255 (31.0)	**0.0002**	**0.03**
	Primary	132 (20)	24 (16.8)	2 (10.5)	158 (19.2)		
	Secondary	181 (27.4)	25 (17.5)	0 (0)	206 (25.0)		
	Tertiary	160 (24.2)	41 (28.7)	3 (15.8)	204 (24.8)		
	Missing	0	0	0	0		
Place of residence	Rural	414 (62.6)	92 (64.3)	1 (5.3)	507 (61.6)	**<0.0001**	0.70
	Urban	247 (37.4)	51 (35.7)	18 (94.7)	316 (38.4)		
	Missing	0	0	0	0		
Occupation	Farmer	224 (34)	29 (20.3)	0 (0)	253 (30.8)	**<0.0001**	**0.001**
	Employed worker	144 (21.9)	45 (31.5)	2 (10.5)	191 (23.3)		
	Trader	126 (19.1)	20 (14)	5 (26.3)	151 (18.4)		
	Housewife	103 (15.6)	38 (26.6)	11 (57.9)	152 (18.5)		
	Casual worker	25 (3.8)	5 (3.5)	0 (0)	30 (3.7)		
	Other (specify)	37 (5.6)	6 (4.2)	1 (5.3)	44 (5.4)		
	Missing	2	0	0	2		
BMI classification	Normal (<25)	152 (29.9)	49 (36.8)	5 (29.4)	206 (31.3)	0.11	**0.04**
	Overweight (25.00 - 29.99)	213 (41.9)	40 (30.1)	5 (29.4)	258 (39.2)		
	Obese (>=30)	143 (28.2)	44 (33.1)	7 (41.2)	194 (29.5)		
	Missing	153	10	2	165		
Alcohol Use	No	605 (91.5)	131 (91.6)	17 (89.5)	753 (91.5)	0.95	0.98

		Bantu (N=661) N (%)	Nilote (N=143) N (%)	Cushite (N=19) N (%)	Total (N=823) N (%)	P values-All[*]	P values - Bantus and Nilotes only[*]
	Yes	56 (8.5)	12 (8.4)	2 (10.5)	70 (8.5)		
	Missing	0	0	0	0		
Exposure to smoking[a]	Never exposed	371 (56.1)	88 (61.5)	13 (68.4)	472 (57.4)	0.30	0.24
	Exposed	290 (43.9)	55 (38.5)	6 (31.6)	351 (42.7)		
	Missing	0	0	0	0		

[*]
p-values from chi-square test except where noted missing data were excluded from percentage calculations and statistical comparisons.

[**]
p-values from Kruskal-Wallis test.

[a]Only 3.28% (n=27) of study participants reported ever having smoked or used smokeless tobacco. Exposure to smoking is summarized here as exposed/never exposed, where exposed is defined as personal use of tobacco as well as exposure to smoke at the workplace or home during child or adulthood.

Table 2

Reproductive health factors by ethnicity: All ethnicities (N=823)

		Bantu (N=661)	Nilote (N=143)	Cushite (N=19)	Total (N=823)	P values-All*	P values - Bantus and Nilotes only*
		N (%)	N (%)	N (%)	N (%)		
Age at menarche	Early menarche (<12)	9 (1.4)	0 (0)	0 (0)	9 (1.1)		
	Normal menarche (12 - 14)	305 (48.5)	79 (56.0)	9 (50.0)	393 (49.9)	0.40**	0.12
	Late menarche (15)	315 (50.1)	62 (44.0)	9 (50.0)	386 (49.0)		
	Missing	32	2	1	35		
Parity	Nulliparous	28 (4.2)	11 (7.7)	3 (15.8)	42 (5.1)	**0.03**	0.10
	1–2 children	188 (28.4)	32 (22.4)	2 (10.5)	222 (27.0)		
	>= 3 children	445 (67.3)	100 (69.9)	14 (73.7)	559 (67.9)		
	Missing	0	0	0	0		
Age at first pregnancy	Nulligravid	24 (3.7)	9 (6.3)	2 (10.5)	35 (4.4)	**0.0008**	**0.0037**
	<20 years	154 (24.0)	50 (35.0)	10 (52.6)	214 (26.6)		
	20 - 29 years	424 (65.9)	71 (49.7)	6 (31.6)	501 (62.2)		
	>= 30 years	41 (6.4)	13 (9.1)	1 (5.3)	55 (6.8)		
	Missing	18	0	0	18		
Cumulative breastfeeding	never breastfed	28 (4.4)	11 (8.0)	3 (15.8)	42 (5.3)	0.08**	0.15
	<15 months	29 (4.5)	8 (5.8)	0 (0)	37 (4.6)		
	>= 15 months	585 (91.1)	118 (86.1)	16 (84.2)	719 (90.1)		
	Missing	19	6	0	25		
Cumulative hormonal contraception exposure	< 48 months	175 (44.0)	32 (52.5)	1 (33.3)	208 (45.0)	0.44**	0.21
	= 48 months	223 (56.0)	29 (47.5)	2 (66.7)	254 (55.0)		
	Missing	263	82	16	361		
Menopausal status	Premenopausal	348 (52.7)	64 (45.1)	14 (73.7)	426 (51.9)	**0.04**	0.10
	Postmenopausal	312 (47.3)	78 (54.9)	5 (26.3)	395 (48.1)		
	Missing	1	1	0	2		
Age at menopause†	< 50 years	161 (62.2)	29 (43.9)	1 (20.0)	191 (57.9)	**0.004****	**0.007**
	50 years	98 (37.8)	37 (56.1)	4 (80.0)	139 (42.1)		
	Missing	53	12	0	65		
Family history of breast cancer in first degree female relative	No	609 (92.1)	133 (93.0)	17 (89.5)	759 (92.2)	0.85	0.72

	Bantu (N=661)	Nilote (N=143)	Cushite (N=19)	Total (N=823)	P values-All[*]	P values - Bantus and Nilotes only[*]
	N (%)	N (%)	N (%)	N (%)		
Yes	52 (7.9)	10 (7.0)	2 (10.5)	64 (7.8)		
Missing	0	0	0	0		

[*]
p-values from chi-square test except where noted; missing data were excluded from percentage calculations and statistical comparisons.

[**]
p-values from Fisher exact test.

[†]Numbers are calculated for post-menopausal women only.

Table 3a

Tumor pathology characteristics by ethnicity (limited to patients with definitive surgery, N=396)

		Bantu (N=351)	Nilote (N=37)	Cushite (N=8)	Total (N=396)	P values-All[*]	P values - Bantus and Nilotes only[*]
		N (%)	N (%)	N (%)	N (%)		
Tumor size	<2 cm	34 (9.8)	2 (5.4)	0 (0)	36 (9.2)	0.69[**]	0.37
	2–<5 cm	208 (59.9)	20 (54.1)	5 (62.5)	233 (59.4)		
	>5cm	105 (30.3)	15 (40.5)	3 (37.5)	123 (31.4)		
	Missing	4	0	0	4		
Tumor overall grade	Grade 1 (low)	19 (5.6)	2 (5.6)	1 (12.5)	22 (5.8)	0.34[**]	0.82
	Grade 2 (intermediate)	132 (39.1)	16 (44.4)	5 (62.5)	153 (40.1)		
	Grade 3 (high)	187 (55.3)	18 (50.0)	2 (25.0)	207 (54.2)		
	Missing	13	1	0	14		
Lymphovascular invasion	No	90 (25.6)	6 (16.2)	2 (25.0)	98 (24.8)	0.45	0.21
	Yes	261 (74.4)	31 (83.8)	6 (75.0)	298 (75.3)		
	Missing	0	0	0	0		
Lymph nodes with metastasis	No	146 (41.6)	15 (40.5)	2 (25.0)	163 (41.2)	0.73[**]	0.90
	Yes	205 (58.4)	22 (59.5)	6 (75.0)	233 (58.8)		
	Missing	0	0	0	0		
Extranodal extension	No	215 (61.3)	23 (62.2)	3 (37.5)	241 (60.9)	0.44[**]	0.91
	Yes	136 (38.8)	14 (37.8)	5 (62.5)	155 (39.1)		
	Missing	0	0	0	0		

[*] p-values from chi-square test except where noted; missing data were excluded from percentage calculations and statistical comparisons.

[**] p-values from Fisher exact test.

Table 3b

Association between Nilote *vs.* Bantu ethnicity (OR [95% CI]) and tumor pathology characteristics (limited to patients with definitive surgery, N=388)

| | Tumor Size (categories) (N=379)[a] | | | | | | Tumor grade (N=373)[b] | | | Lympho-vascular Invasion (N=385)[c] | | | Lymph nodes w/metastasis (N=385)[c] | | | Extranodal Extension (N=385)[c] | | |
| | <2 cm (N=36) | 2-<5 cm (N=224) | | 5cm (N=119) | | | Grades 1 - 2 (low to intermediate) (N=168) | Grade 3 (high) (N=205) | | No (N=96) | Yes (N=289) | | No (N=160) | Yes (N=225) | | No (N=236) | Yes (N=149) | |
	N	N	OR [95% CI]	N	OR [95% CI]	p-trend	N	N	OR [95% CI]	N	N	OR [95% CI]	N	N	OR [95% CI]	N	N	OR [95% CI]
Bantus (N=351)	34	204	ref	104	ref		150	187	ref	90	258	ref	145	203	ref	213	135	ref
Nilotes (N=37)	2	20	1.92 (0.41, 8.99)	15	3.86 (0.77, 19.30)	0.10	18	18	0.76 (0.38, 1.52)	6	31	1.7 (0.68, 4.24)	15	22	1.01 (0.50, 2.02)	23	14	0.92 (0.45, 1.85)

[a] Adjusted for age, education level, and estrogen receptor status; 9 patients were deleted from the analysis due to missing values for tumor size, age, or estrogen receptor status.

[b] Adjusted for age; 15 patients were deleted from the analysis due to missing values for tumor grade or age.

[c] Adjusted for age; 3 patients were deleted from the analysis due to missing values for age.

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Table 4a

Tumor hormone receptor status by ethnicity[a]

		Bantu (N=622)	Nilote (N=136)	Cushite (N=18)	Total (N=776)	P values- All[*]	P values - Bantus and Nilotes only[*]
		N (%)	N (%)	N (%)	N (%)		
ER Status	Negative	185 (29.7)	50 (36.8)	7 (38.9)	242 (31.2)	0.22	0.11
	Positive	437 (70.3)	86 (64.2)	11 (61.1)	534 (68.8)		
	Missing	0	0	0	0		
PR Status	Negative	246 (39.6)	61 (44.9)	8 (44.4)	315 (40.6)	0.49	0.25
	Positive	376 (60.5)	75 (55.2)	10 (55.6)	461 (59.4)		
	Missing	0	0	0	0		
HER2 Status	Negative	466 (74.9)	99 (72.8)	12 (66.7)	577 (74.4)	0.66	0.61
	Positive	156 (25.1)	37 (27.2)	6 (33.3)	199 (25.6)		
	Missing	0	0	0	0		
Receptor combinations							
ER+ and/or PR+ (Luminal type A/B)		443 (71.2)	90 (66.2)	12 (66.7)	545 (70.2)	0.60[**]	0.32
ER- and PR- and HER2 positive (HER2^{+})		61 (9.8)	19 (14.0)	2 (11.1)	82 (10.6)		
ER- and PR- and HER2 negative (Triple Negative)		118 (19.0)	27 (19.9)	4 (22.2)	149 (19.2)		

[*]
p-values from chi-square test except where noted; missing data were excluded from percentage calculations and statistical comparisons.

[**]
p-values from Fisher exact test.

[a]
47 patients were excluded from analysis due to missing data for hormone receptor status: Bantu 39, Nilote 7, and Cushite 1.

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Table 4b

Association between Nilote *vs.* Bantu ethnicity (OR [95% CI]) and tumor hormone receptor status[a]

	Luminal A/B (comparison)		HER2+			Triple Neg	
	N=519	**N=79**	**OR [95% CI]**	**N=142**		**OR [95% CI]**	
Bantus (N=604)	429	60	ref	115		ref	
Nilotes (N=136)	90	19	1.41 (0.79, 2.49)	27		1.09 (0.67, 1.76)	

[a] Adjusted for age and age at first birth; 64 patients were excluded from the analysis due to missing data for hormone receptor status, age or age at first birth: Bantu 57, Nilote 7.