Breast Disease

Incidence of male breast carcinoma in North Uganda A survey at Lacor Hospital, Gulu, during 2009-2016

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Abstract:	BACKGROUND Little information is available on male breast cancer (MBC) incidence from sub-Saharan Africa. OBJECTIVE This is a retrospective study on MBC in rural North Uganda, based on the pathology records of a private, non-profit, missionary hospital. METHODS All male patients that had histological diagnosis of breast carcinoma from January 2009 to December 2016 were included in this study. RESULTS In time span of 8 years, there were 337 consecutive breast cancer presentations, including 21 MBC (6.2%). The latter patients showed advanced disease (mean symptom duration: 20.3 months; mean tumour size: 5 cm;) skin ulceration and ipsilateral lymph node metastasis: 60%). The mean age was 60.52 years (from 30 to 85 yrs). Ductal infiltrating carcinoma was the prevalent histological type in our series (65%), followed by an unusually high rate of papillary carcinomas (15%). There appeared to be a prevalence for left breasts (11 LT vs 6 RT; 64.7%), a finding also observed in the majority of MBC. CONCLUSIONS This study is representative of the scenario in Northern Uganda, where MBC accounts for 6.2% of breast cancers, More information on the occurrence and risk factors of this

	unusual neoplasm in African countries may prompt prevention of chronic liver disease and early recognition and treatment of MBC
Suggested Reviewers:	
Response to Reviewers:	Reviewer #1: 1.2. 4. Lack of important data, including risk factors, survival etc in the interpretation despite author already explained in discussion. Association with alcohol consumption and viral hepatitis leading to chronic liver disease difficult to ascertain as no history, risk factors or data collected to even make an association. It would be important to make it as comprehensive as possible with good data such as family history, important risk factors, survival and adjuvant treatment As stated by the reviewer and explained in the paper “we would have preferred to obtain more information regarding the individual risk factors of breast cancer from our patients, but hospital pathology records do not routinely have such data”. The clinical records are given to the patients and not filed in the hospital. We used the little information present in the pathology request sheet, mostly concerning tumour presentation and clinical impression. Our study certainly cannot answer to many interesting questions, and the cancers were not adequately investigated (molecular prognostic factors, etc), but this is true for most of African series reviews, due to local habits and lack of resources. I worked as a volunteer Pathologist in this missionary district hospital, set in a rural area, for just a month/yearly and had little way on the daily routine. However, interesting data on rare diseases where there, and I believe they are worth sharing, despite limitations of the study. At least, the diagnosis of breast cancer was verified histologically in our survey, differently from other studies where breast cancer cases had only an assigned diagnosis entered by the surgeon in the theatre registry (see 10.1371/journal.pone.0219601) 3.There was error labelling locally advanced disease as stage IV as it is advanced disease or metastatic This is true when referred to clinical stage, but the paper deals with pathological results and the TNM staging classification considers T4 a tumour that has grown into the chest wall (a), or into the skin (b), or both (c), which was the case for some of our patients. Table 1 clearly indicates that the stage was referred to TNM classification. At any rate, to avoid misunderstandings, pTNM stage is now used in the text Nevertheless, Stage IV (metastatic) disease is also a tumour that has spread to chest wall, according to the AJCC Cancer Staging Manual, Eighth Edition (2017) Reviewer #2 1.2. Author quote old studies. Kindly quote the recent data or WHO classification of Breast Tumors 2019. WHO classification of Breast Tumors 2019 gives different incidence rates. Done. However, we failed at identifying different incidence rates for male breast cancer in WHO classification of Breast Tumors 2019. Under the “epidemiology” paragraph of WHO book it reads: Male breast cancer accounts for <1% of all breast cancers and for <0.5% of all cancer deaths in men in the USA. Our paper states: In developed countries, male breast carcinoma (MBC) is a rare cancer (0.6% of all breast carcinoma and <1% of all cancers in men) 3.Too old data. The author should give reference to recent studies. Unfortunately, it is not clear to which old data the reviewer is referring, as there was no indication of the paragraph line to help recognising the sentence to be mended. 4. 10.1371/journal.pone.0219601 is also available for Author`s country We thank the reviewer for suggesting this interesting paper concerning the rate of breast cancer surgery in Uganda. The incidence of male breast cancers quoted by the authors has been added in Table 2. 5. What would you like to expect to achieve at the end of the study, and How it may be useful for the medical literature and your country The following sentence was added to Introduction: We also compared our results with those of other African authors to evaluate whether geographical differences exist among African countries. Additionally, more published data on male breast cancer may help shed some light and increase awareness on this rare disease.

	6. They should write clear about institute policy regarding retrospective study involving human body organs for histopathology. The hospital has no ethics committee and the Medical Superintendent approved data collection from the Pathology files for this retrospective study. The latter sentence has been added to “Material and Methods” 7.What is the trend of MBC between 1998 to 2020? This was added to the text: The peak of incidence was observed in 2000, when an age-standardized incidence rate for men of 1.24 per 100,000 was recorded by SEER program in the USA [Anderson]. The age-adjusted incidence rate for USA male breast cancer between 2010 and 2015 was 1.2 per 100,000 individuals per year, which is slightly higher than the rate during the 10 years preceding period (1.1 per 100,000 per year) [khoury]. 8. Indian study: Old study. The author may use the data from the national cancer registry program. The old study was removed from the text and reference list Conclusion: Association of alcohol consumption habit and male breast cancer was not the objective of the study, and no association was proved. The sentence was deleted Reviewer #3: Add images in manuscript. We are grateful to Reviewer 3 for the kind appreciations. We chose not to add microphotographs as none of the MBC we describe can be considered rare, generally speaking. Only, some histotypes are less common in men compared to women. Therefore, the histology features are already well recognised by pathologists.
Additional Information:	
Question	**Response**
Is this work funded by the National Institutes of Health (NIH) or any of the NIH related PMC-participating or Europe PMC funders?	No
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Incidence of male breast carcinoma in North Uganda A survey at Lacor Hospital, Gulu, during 2009-2016

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ABSTRACT

BACKGROUND: Little information is available on male breast cancer (MBC) incidence from sub-Saharan Africa. **OBJECTIVE:** This is a retrospective study on MBC in rural North Uganda, based on the pathology records of a private, non-profit, missionary hospital. **METHODS:** All male patients that had histological diagnosis of breast carcinoma from January 2009 to December 2016 were included in this study. **RESULTS:** In time span of 8 years, there were 337 consecutive breast cancer presentations, including 21 MBC (6.2%). The latter patients showed advanced disease (mean symptom duration: 20.3 months; mean tumour size: 5 cm;) skin ulceration and ipsilateral lymph node metastasis: 60%). The mean age was 60.52 years (from 30 to 85 yrs). Ductal infiltrating carcinoma was the prevalent histological type in our series (65%), followed by an unusually high rate of papillary carcinomas (15%). There appeared to be a prevalence for left breasts (11 LT vs 6 RT; 64.7%), a finding also observed in the majority of MBC. **CONCLUSIONS:** This study is representative of the scenario in Northern Uganda, where MBC accounts for 6.2% of breast cancers,

More information on the occurrence and risk factors of this unusual neoplasm in African countries may prompt prevention of chronic liver disease and early recognition and treatment of MBC

Key words: male breast cancer, Uganda, pathology, epidemiology

INTRODUCTION

In developed countries, male breast carcinoma (MBC) is a rare cancer (0.6% of all breast carcinoma and <1% of all cancers in men) [13,26], typically occurring at 0.5-2.4% the frequency of female breast cancer [3]. On the other hand, in sub-Saharan Africa, the incidence of male breast cancer is relatively high, up to 15% and 16% of all breast cancers, respectively, in Ethiopia [21] and Zambia [6].

As a literature search revealed scarce [15] or old data relative to MBC in Southern Uganda [22], we decided to present our experience in a large missionary hospital of North Uganda. We also compared our results with those of other African authors to evaluate whether geographical differences exist among African countries. Additionally, more published data on male breast cancer may help shed some light and increase awareness on this rare disease.

MATERIAL AND METHODS

This retrospective study was carried out in the Department of Pathology of St. Mary's Lacor Hospital in Gulu, Uganda. This hospital is a referral oncology centre for the population of North Uganda and also for patients seeking medical treatment from the neighbouring South Sudan and Congo. To our knowledge, no data exists for breast cancer in rural North Uganda.

All male patients that had histological diagnosis of breast carcinoma from January 2009 to December 2016 were included in this study. Unfortunately, data were limited solely to pathology records, as clinical records are kept by the patients. Therefore, risk factors, clinical stage, survival outcome, and co-morbidities were often not determined. Data for hormone receptor status were also unavailable because this service is not present at our hospital.

The Medical Superintendent approved data collection from the Pathology files for this retrospective study.

RESULTS

Overall, data from 337 patients with histological diagnosis of breast carcinoma were collected, including 21 (6.2%) males. The characteristics of the MBC are shown in Table 1. The patients had no known history of other cancers and no history of chemotherapy prior to diagnosis. Their mean age was 60.52 years (from 30 to 85 yrs).

Most patients detected themselves a lump, and only few patients experienced local pain. Tumour laterality was not recorded in 4 cases; however, there appeared to be a prevalence for left breasts (11 LT vs 6 RT; 64.7%). None of our patients presented with bilateral disease. Median duration of symptoms was 21.5 months. The large majority of the patients presented with advanced disease, including tumour size > 5cm (min 2,5- max 16 cm; mean 5 cm), skin or chest wall invasion, and/or ipsilateral axillary lymph node metastasis (Table 1). Surgery was the only available treatment. Histologically, all but one (5%) were invasive carcinomas. The ductal phenotype "not otherwise specified" (NOS) was prevalent. Three cases (15,8%) were papillary variants. There were also a mucinous and an apocrine carcinoma (one case each).

DISCUSSION

In general, MBC shows a low incidence, due to both the unlikeliness for cancer to develop in vestigial parts such as male breasts, and the lack of a continuous oestrogen stimulation. However, according to data obtained from the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) program, for unknown reason the incidence rates of MBC have shown marked increase (26%) in the USA over 1973 to 1998, albeit less than the increase observed for women over the same time period (52%) [13]. The peak of incidence was observed in 2000, when an age-standardized incidence rate for men of 1.24 per 100,000 was recorded by SEER program [4]. The age-adjusted incidence rate for USA male breast cancer between 2010 and 2015 was 1.2 per 100,000 individuals per year, which is slightly higher than the rate during the 10 years preceding period (1.1 per 100,000 per year) [16]. Other studies over the years have also shown evidence of

increasing numbers of MBC patients in Western and Asian countries [23]. The same trend was observed in the area of Kampala, Uganda, where the Kampala cancer registry showed a trend toward an increased age standardized incidence of MBC from 1,2/100.000 males in years 1991-1995, to 2.5/100.000 in years 2006-2010 [24]. Notably, this rate of incidence is higher than that recorded in USA in year 2000 (1.24/100.000 men) [4,13]. On the other hand, the past incidence rates in Egypt were 12-times that of the USA, but the current incidence rate (1.4%) is only slightly higher than the USA rate. This has been attributed to the recent decline in Schistosoma parasitic infection and its associated liver fibrosis [9].

The majority of MBC appears to be sporadic in origin, although inherited risk factors such BRCA2, BRCA1, PTEN, p53 and CHEK2 mutations, have being described in 10% [9, 17]. Men with a genetic predisposition to breast cancer are also at higher risk of getting prostate cancer at a younger age than usually diagnosed.

Increased levels of oestrogen or hypoandrogenism are known risk factors for MBC, and are associated with testicular injury, orchitis/epididymitis, undescended testes, Klinefelter syndrome or cirrhosis of the liver [9]. The latter, as well as liver fibrosis secondary to Schistomal infection, seem to play a significant role in the occurrence of African MBC. Liver disease increases peripheral oestrogen conversion from androgens [18], thus predisposing to MBC. Liver cirrhosis is rather frequent in Uganda and is caused by both endemic viral chronic hepatitis and chronic excess alcohol consumption. Differently, obesity and diabetes have been pointed out as a possible cause for a higher risk of MBC in the USA [9]. We would have preferred to obtain more information regarding the individual risk factors of breast cancer from our patients, but hospital pathology records do not routinely have such data. The higher incidence of MBC in African countries (Table 2), as compared to Europe or USA, may also depend from ethnicity, as higher rates are observed in black (1.8/100.000) than white men (1.1/100.000).

With the exception of Kampala region, precise data on the incidence of MBC are not available from the rest of Uganda as cancer is not a notifiable disease in this country [15, 24]. In the present study,

males accounted for 6.2% of all breast cancers, over a period of 8 years, similar to 6.5% reported from Tanzania [5], 7% from Kenya [23], and 8-9% from Nigeria [1,12]. It is however possible that the number of MBC could be much higher in Uganda, as well as in other sub-Saharan countries, because only about 20% of people with cancer seek medical treatment and, rather, resort to use of herbal treatment. The highest incidence rates of MBC are reported in Ethiopia (16%) [21] and Zambia (15%) [6], while the lowest is recorded in Gambia [21] and Libya [12] (1.5% and 1.6, respectively). Table 2 compares the data of MBC patients in published African series.

Often African MBC presents as advanced disease. In this study, clinical stage was poorly defined based solely on review of pathology reports. However, all of our patients showed locally advanced disease, meaning pTNM Stage III-IV. For comparison, in a French study the incidence of pTNM Stage IV presentation for MBC was 7% [10]. Table 2 shows that advanced stage at presentation is invariably observed in African MBC series. The lack of screening programs, lack of expectation among treating physicians and smaller breast tissue may also explain why MBC tend to have more advanced disease, especially in low-income countries.

Despite the prevalence of several risk factors in the Ugandan population, such as liver cirrhosis at young age, the mean age at presentation in our study population was similar to that recorded in Canadian/European studies (60 vs 63-67 yrs) [10,14]. For comparison, MBC patients in the Middle East, China and South Asia and also in some African countries, are more often in their fifties.

Symptom duration before diagnosis are less than 8 months in western countries, while in our series it ranged from 1 months to as much as 7 years (mean 20.3 months). The length of symptom duration in African series is interesting. Ajayi and coll also report Nigerian cases that sought medical attention after as much as 5 years [2]. This shows that MBC is initially not a very aggressive disease. A painless solid lump under the areola of the nipple is the most frequent initial symptom of MBC; however, our Ugandan patients often (60%) presented with skin ulceration and ipsilateral lymph node metastasis. In general, lymph nodes are clinically detected in nearly half of

the patients at primary diagnosis in the literature [8], due to relatively small sizes and small mass and volume of parenchyma of mammary gland in men. In our series, too, lymph node metastases were present in 50% of cases. The absence of a radiation therapy centre and the high cost of chemotherapy compared to incomes of the population made surgery the most affordable treatment in our Hospital, albeit the expected results are poor.

Ductal infiltrating carcinoma was the prevalent histological type in our series (65%), although much less so than in other European MBC series, where this histological type occurs in over 95% of MBC cases [10], or USA series, where it accounted for 74.3% [13]. This study also confirms the rarity of lobular carcinoma in MBC, as there was no such histologic type in our patients' series. The lack of lobular tissue in the normal male breast most probably explains the rarity of the lobular phenotype. We also detected 3 cases (15%) of invasive papillary carcinoma, 2 cases of invasive tubular carcinoma (10%) and one case each (5%) of invasive mucinous carcinoma and invasive apocrine carcinoma. Papillary carcinoma was the next most frequent histologic type variant in USA and Canadian large MBC series, although it accounted for only 2.6% and 1.9% of cases, respectively [13-14]. For comparison, it accounts for up to 1% of breast cancer in women [17]. A Tanzanian MBC series recorded 7.8% of invasive papillary carcinoma out of 76 cases [4]. In our series, the incidence rate is the highest reported so far.

The preponderance of MBC on the left side is invariably reported in the literature: L/R 50.5%/48.1% in the USA [13], 55%/ 44% in a large Canadian series [14] and can be also appreciated in the African series summarized in Table 2. The explanation eludes us.

According to Yu and coll, MBC and post-menopausal female breast cancer patients show high oestrogen receptor (ER) expression in the tumour and low oestrogen expression in the body [25]. Over 90% of western MBCs are ER-positive, and 80–96% are progesterone receptor (PR)-positive [20]. Nonetheless, other studies have remarked that breast cancer in black patients lack hormone receptor expression, compared to white men [7,19]. Unfortunately, lack of hormone receptor status

testing in our Pathology Laboratory prevented hormonal therapy (tamoxifen). Anyway, in the light of the low number of hormone sensitive MBC in Africans, tamoxifen should not be adopted as the standard, considering the cost burden of this treatment and the likeliness of lack of effectiveness [7]. For the same reasons, orchiectomy as a palliative treatment for advanced, inoperable MBC, cannot be recommended. Lack of multi-modality therapy for patients with breast cancer is a reality for most in Northern Uganda. Most of our patients only underwent mastectomy, and/or lymphadenectomy. A few had only tumour biopsy to confirm diagnosis, but no surgery, due to late disease presentation. None of them came back at follow-up.

Finally, the reported high association of other primary malignancies with MBC was not confirmed in our series, as none of the patients had such evidence.

In conclusion, this study is representative of the scenario in Northern Uganda, where MBC accounts for 6.2% of breast cancers. More information on the occurrence and risk factors of this unusual neoplasm in African countries may prompt prevention of chronic liver disease and early recognition and treatment of MBC.

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Table 1. Data of our MBC patients

Pt	Age	Side	Skin ulceration	Tumour Ø (cm)	Duration (mo)	Histotype	Grading (G)	pTNM*
1	85	L	Yes	16	24	Tubular	1	T4bNx
2	65	R	No	Nr	3	Ductal, NOS	3	T2Nx
3	78	L	No	2.5	8	Ductal; NOS	3	
4	83	R	No	2.5	84	Papillary		T2Nx
5	36	R	No	3	24	Ductal, NOS	1	T2 N1
6	48	L	No	4	2	Mucinous	3	T2N1
7	82	L	No	3	5	Ductal, NOS	1	T2 Nx
8	68	R	No	Nr	nr	Papillary		
9	47	L	No	4.5	60	Tubular	1	T4bN1
10	77	R	No	Nr	nr	Ductal, NOS	nr	N1
11	40	L	Yes	Nr	nr	Ductal, NOS	nr	T4bN1
12	68	L	No	Nr	24	Ductal, NOS	2	
13	55	R	Nr	Nr	nr	Ductal, NOS		

14	56	L	Yes	2.5	nr	Ductal, NOS	2	T4b
15	60	R	No	3	9	Papillary		T2N1
16	60	L	No	Nr	6	Ductal, NOS	3	
17	46	R	No	Nr	4	Ductal, NOS	2	T4cN1
18	30							
19	67	nr	Yes	3.5	nr	Ductal, NOS	2	T4cN1
20	70	L	Yes	3.5	nr	Ductal, NOS	2	T4bN2
21	50	L	Yes	7	nr	Apocrine	3	T4bN1a

- **Some patients could not be fully staged due to imprecise information regarding T or N status**

Table 2. Comparative data from other male breast cancer studies in African countries

Ref	Country	males/ female (%)	Age (mean)	Diameter (mean, cm)	Laterality (% L/R)	Advanced stage (III/IV or T3/T4)	Mean symptoms duration (mo)
Perkin (IARC, 1986)	Algeria	53/1147 (4.6)	56.1	nr	nr	nr	nr
Forman et al, 2014	Algeria, Setif	19/733 (2.6)	nr	nr	nr	nr	nr
Mrabent et al, 2015	Algeria, Sidi bel Abbes	10/nr	60.2 (42-80	nr	nr	100%	nr
Perkin (IARC, 1986)	Angola	7/52 (13.4)	55.2	nr	nr	nr	nr
Sano D et al, 1997	Burkina Faso, Ouagadougou	5/115 (4.3)	61	5.5-11.5	nr	100%	13
Zongo et al, 2018	Burkina Faso	51/1988 (2.6)	61	2-20	nr	88%	nr

Ndom et al, 2012	Cameroon	20/585 (3.4)	nr	nr	nr	nr	nr
Ndom et al, 2012	Congo-Brazzaville	11/177 (6.2)	nr	nr	nr	nr	nr
Perkin (IARC 1986)	Egypt	52/635 (8.1)	50.8	nr	nr	nr	nr
Forman et al, IARC 2014	Egypt, Gharbiah	58/3675 (2.1)	nr	nr	nr	nr	nr
Soliman M, Hetnal M, 2016	Egypt, Alessandria	39/nr	59 (33-80)	nr	51.3/48.7	72%	nr
Gebremedhin et al, 1998	Ethiopia	10/62 (16.1)	52.1 (38-75)	nr	nr	nr	nr
Perkin (IARC, 1986)	Gabon	5/76 (6.6)	51.5	nr	nr	nr	nr
Ndom et al, 2014	Gambia	1/66 (1.5)	nr	nr	nr	nr	nr
Sawe RT et al, 2016	Kenya	4/58 (7)	nr	nr	nr	nr	nr
Bird et al, 2008	Kenya	4/125 (3.2)	nr	nr	nr	nr	nr
Alterman	Western Kenya	13/118 (11)	69	nr	nr	nr	nr
Perkin (IARC 1986)	Liberia	4/133 (3)	nr	nr	nr	nr	nr
Forman et al, IARC 2014	Libya, Benghazi	6/364 (1.6)	nr	nr	nr	nr	nr

Perkin (IARC 1986)	Madagascar	4/74 (5.4)	69.5	nr	nr	nr	nr
Forman et al, 2014	Malawi, Blantyre	9/165 (5.4)	nr	nr	nr	nr	nr
Ndom et al, 2014	Mali	8/203 (3.9)	52.6				
Bourhafour et al, 2011	Morocco, Rabat	127/nr (nr)	62	nr	nr	79.3%	28
Alaoui Slimani et al, 2016	Morocco, Rabat	140/nr	61	4 (1-12)	60.5/39.5	26.3%	14.4 (1-48)
Ajayi et al, 1982	Lagos, Nigeria	12/495 (2.4)	56.3 (30-67)	nr	91.6/4	66.6%	43
Ahmed	Zaria, Nigeria	(9)	59	13	54.4/45.6	93%	11
Dogo et al, 2006	Nigeria, North-Eastern	(3.7)	19-80	nr	nr	nr	➢ 12
Rachid et al, 2009	Niger, Niamey	22/361 (6)	52.8 (28-80)	nr	nr	91%	12-84
Perkin (IARC 1986)	Rwanda	2/70 (2.8)	nr	nr	nr	nr	nr
Forman et al, 2014	South Africa	11/175 (6.3)	nr	nr	nr	nr	nr
Perkin (IARC 1986)	Sudan	122	54	nr	nr	nr	nr
From Ndom	Swaziland	2/34					

		(5.8)					
Amir et al, 1992	Tanzania, Dar es Salaam	76/104 (6.5)	50 (16-72)	nr	nr	92.1%	nr
Burson et al, 2010	Tanzania Dar es Salaam	14/474 (2.9)	nr	nr	nr	100%	nr
Beyrouti MI et al, 2003	Tunisia, south	23/nr	68 (40-95)	nr	nr	69.6%	nr
Curado et al, 2007	Tunisia, center, Sousse	8/308 (2.6)	nr	nr	nr	nr	nr
Forman et al, 2014	Tunisia, North	45/2260 (2)	nr	nr	nr	nr	nr
Mourali (IARC 1986)	Tunisia	30	57	nr	nr	nr	nr
Forman et al, 2014	Uganda, Kampala, Kyadondo County	24/498 (4.8)	nr	nr	nr	nr	nr
Hjelm et al, 2019	Uganda, multicentric	10/160 (6.2)	nr	nr	nr	nr	nr
Bhagwandin	Zambia	(15)	50	nr	nr	nr	nr
Forman et al, 2014	Zimbabwe, Harare	13/364 (3.6)	nr	nr	nr	nr	nr