Prostate Cancer in Sub Saharan Africa

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Abstract: Prostate cancer is the leading male cancer worldwide. While there are abundant data on the epidemiology, natural history, treatment and outcomes of the disease in the US and many developed countries, prostate cancer is a good example of cancer disparity in that a little is known about the disease in Sub Saharan Africa. Because of the dominant black race in this region and the fact that black men suffer the higher burden of the disease, it is important to understand that cancer in this population. The purpose of this review is to describe the literature of prostate cancer in Sub Saharan Africa. The authors reviewed the published studies on prostate cancer in Sub Saharan Africa available on PubMed. In addition any other accessible study on the topic was included.

Keywords: Prostate Cancer, Cancer disparities, black male, Africa, Epidemiology.

INTRODUCTION

Prostate cancer is the leading non-cutaneous male cancer in the US with an estimated incidence of 238,590 and a disease related deaths reaching 29,720 in 2013 [1]. A high incidence and age specific mortality have been observed since the approval of Prostate Specific (PSA) by the food and drug administration of the United States and the wide use of this test in prostate cancer screening [2]. Such screening has led to the diagnosis of considerable proportion of localized prostate cancer with excellent long-term survival [1]. In this setting, most men with prostate cancer die of other causes rather than prostate cancer [3]. A large number of patients underwent an active treatment [4] therefore exposing them to the risks of treatment related morbidity and quality of life impact [5]. In fact, many prostate cancers would never cause any impairment to quality or quantity of life if they remained undetected and are thus said to be over-diagnosed [6, 7]. That is why for the larger number of men diagnosed with low-risk tumors, a growing consensus supports deferring immediate treatment in favor of active surveillance (AS) [8].

While prostate cancer natural history and clinical aspects have considerably been studied in developed countries, a little is known about the disease in the developing world especially Sub-Saharan Africa. Sub-Saharan Africa involves all African Countries to the exception of the 6 Northern African countries that are Morocco, Algeria, Tunisia, Libya, Egypt and Western Sahara. Based on the world health organization (WHO) regions, in 2011 Africa had the lowest Growth National Income (GNI) of 2513 and the lowest Per capita government expenditure on health with 49.2 US Dollars compared to 1695.7 US Dollars in America and 1786.3 US Dollars in Europe [9]. The large majority of health spending are dedicated to prevent and treat tropical disease such as infections and malnutrition. Therefore non communicable diseases including cancers mobilize a relatively small part of health expenditure.

Studies conducted in the US and the Caribbean show that prostate cancer has a highest incidence and poorer prognosis in black male [10, 11]. Given the SSA origin of black men, a better understanding of prostate cancer in this region may help explain the characteristics of prostate cancer in black men.

In this context of resource-poor settings, the purpose of this review is to describe the knowledge on prostate cancer in men of SSA based on the published studies.

PROSTATE CANCER INCIDENCE IN SUB-SAHARAN AFRICA (SSA)

According to the International Agency for research on Cancer (IARC), in 2008 worldwide prostate cancer was the leading male cancer after lung cancer with an age standardized rate of 28.5/100 000 [12]. However GLOBOCAN estimates have important limitations related mostly to the facts that the data were often derived from registries covering Hospitals, small subnational areas or only major cities specially in the developing countries [13]. In SSA, estimates were mostly extrapolated from results of Ibadan (Nigeria) and Kampala (Uganda). In fact in 2006 only 26% of the world population was covered by tumor registries and this figure was even smaller in Africa (11%) and Asia

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(8%) [14]. In addition to that, the few existing registries in SSA often do not meet the accepted standards for population cancer registries leaving doubt as to the accuracy of calculated incidence [15]. These figures are inconsistent with higher incidence of prostate cancer reported in black men compared to other races. In Cameroon, Angwafo *et al.* [16] found a prostate cancer incidence of 93.8/100000 while in Lagos, Nigeria Osegbe *et al.* [17] found an incidence of 127/100000. These findings are inconsistent with data showing a higher incidence of prostate cancer in black male in Jamaica where the reported incidence was 304/100000 [11] and in the US [18]. The lower reported incidence in SSA is partly explained by the underreporting of cases. And because of the Sub-Saharan origin of the black male studied both in Jamaica and the US and the fact that black race is a risk factor for prostate cancer, it could be hypothesized that the true incidence of prostate cancer in Sub Saharan Africa is close to that in Jamaican and US black males. This is emphasized by the fact that not only do black men of these different geographic areas share the same underlying genetic predisposition to prostate cancer [19], but there are also changes in lifestyle with a trend toward a westernized lifestyle in SSA and an equalization of environmental factors distribution between black men in SSA and black male in the US and west Indies [20]. A recent review shows that in low and middle income countries facing a high prevalence on non-communicable diseases - including cancers - there is no optimal national policy in response to the adverse dietary and physical activity behavior [21].

Unlike in the US, prostate cancer screening in not routine and there are many reasons for that including the lack of resources for cancer management in general and the public health and ethical implications of diagnosing a high number of cases that will ultimately require treatment. In addition to that, there is a lack of awareness about prostate cancer in the general population [22, 23]. In South Africa a screening based on PSA assays and digital rectal examination (DRE) was conducted among 660 men aged 50-70 years attending the clinics. The proportion of black men in that cohort was 60.6%. All patients who had an abnormal DRE and/or a PSA≥4ng/ml were offered a trans rectal ultra sound (TRUS) sextant biopsy. DRE was recorded as clinically suspicious of malignancy in 3.2% of men and PSA was ≥ 4.0 ng/mL in 9.6% of men. Prostate biopsies were taken in 21 patients which represented 3.2% overall and a third of those with a PSA level ≥4.0 ng/mL). Of those who were biopsied, the prostate cancer detection was 43%. But this study failed to evaluate the true value of PSA and DRE because of the lack of compliance to the biopsy and the sextant biopsy schema [24]. A most recent study in Senegal screened 572 men using a PSA cut-off 4 ng/ml and DRE findings [25]. PSA was ≥4 ng/ml in 66 men (21.5%) and DRE was suspicious of cancer in 11 men. In total 72 prostatic biopsies were performed showing a prostate cancer in 22 men (30.6%). However this study is also limited by the absence of TRUS biopsy limiting the interpretation of the value of PSA and DRE. This limitation is due in part to the higher risk of sampling errors at biopsy in the absence of ultra sound guidance. Another study was conducted in Kinshasa among 162 men aged 40 to 70 years with a PSA cut-off 2.5ng/ml, 38 of them underwent a biopsy finding a prostate cancer in 4 men. Again in this study the biopsies were not ultrasound guided [26].

PATHOLOGY DIAGNOSIS OF PROSTATE CANCER

Pathology is the corner stone for the diagnosis of any cancer, treatment decision making and the provision of public health services; however the scarcity of pathologists and pathology infrastructures in SSA is well documented. A survey reported by Adesina *et al.* [15] showed that in 2012 the highest number of pathologists per people were only 1 pathologist/ 226,470 people and 1 pathologist/297.569 people respectively in Botswana and South Africa followed by Ghana, Kenya and Nigeria with 1 pathologist/500,000-1 million. All the other SSA countries had less than 1 pathologist/1 million people. In comparison the figure is 1 pathologist/15,108 people in the UK and 1 pathologist/19,232 people in the US. In addition, only few of the existing pathologists are organ or system specialized and there is inadequate pathology infrastructure.

A recent study audited the prostate biopsy practice in centers of sixth SSA countries (Senegal, Ghana, Soudan, Uganda, South Africa, Botswana) [27]. In total 4,672 Black African men underwent prostate biopsy in these centers between 2005 and 2011. There were many practice differences across the centers and a lack of compliance with the European Association of Urology best practice guidelines [28]. Per these Guidelines, Prostate biopsy should be TRUS guided, preferably transrectal and possibly trans perineal. There should be a minimum of 8-12 biopsy cores sampled. The use of an IV or oral antibiotic, especially quinolone, prior to the biopsy is recommended, and

ciprofloxacin is superior to ofloxacin. Peri-prostatic lignocaine block is state of the art for anesthesia. Prostate biopsy cores should be sent in different containers and labeled according to the site of biopsy then processed in different cassettes. For each biopsy site, the proportion of biopsies positive for CaP and Gleason score should be reported. A measure of the extent of cancer involvement (mm or %) should be provided for each core. The microscopic examination should describe all other lesions such as BPH, prostatitis and PIN. Of the cohort of men who underwent a biopsy from these 6 SSA countries, prostate cancer was found in 1241 cases (26,56%) with an advanced mean age at diagnosis (69.9 years). Most of the diagnosed cancers had a Gleason score 6 (3+3) and 7 (3+4 or 4+3) except in Sudan and Uganda where higher Gleason grades tumors (8-10) predominated. The major limitation of that study came from the fact that data were collected from pathology laboratory with limited data about clinical presentation. The predominance of Gleason 6 and 7 was also found in Togo by Amegbor *et al*. [29] Generally the published pathology studies failed to comply with the EAU guidelines [26, 29-35]. The results of the current pathology practice are under diagnosis and a limited help to treatment decision making.

CLINICAL PRESENTATION OF PROSTATE CANCER

The lack of awareness and screening and limited pathologic facilities explains in part the clinical presentation. Table **1** summarized the clinical features at presentation from different studies. In general prostate cancer in diagnosed at an advanced age and this is the case of the reports published before 2013. The average age was between 66.6 and 71.5 years for the reports published before 2013 and 65-65.4 in the Ghanaian report published in 2013 (Table **1**). The lower age in this Ghanaian report can be explained by a selection bias because these patients were referred to the National Radiotherapy center for a potentially curative treatment option suggesting a younger age. At diagnosis patients generally have a high PSA and for this reason qualify mostly for an intermediate or high risk disease status. At the exception of the Ghanaian study by Yamoah *et al.* [36] more than half of the patients have a locally advanced disease with high proportion of metastasis.

The absence of screening programme plays a key role in the advanced clinical presentation of prostate cancer in SSA. In fact a similar trend is expected in populations not using screening. In Denmark, a country where prostate cancer screening is not routinely performed, Boore *et al.* [37] reported that patients presented at the time of diagnosis at an older age with prostate specific or cancer-related symptoms. It that study, the disease was localized (T1-T2) in only 31% of all patients and a metastasis was found at the time of diagnosis in 32% of cases. In comparison, Gueye *et al.* [38] compared the clinical characteristics of prostate cancer between Senegalese, Caucasian American and African American. Their report indicated that Senegalese display the same clinical characteristics as Danish men while in contrast U.S. men both white and black presented at a younger age, with fewer prostate or cancer-related symptoms, more organ-confined disease, and fewer metastases at the time of diagnosis.

Table 1: Clinical Presentation of Prostate Cancer at Diagnosis

Author	Country	Age (years)	PSA (ng/ml)	Stage> T2 (%)	Metastasis M (%)
Osegbe [17]	Nigeria (N=125)	Mean: 68	-	86.4	+++
Gueye [38]	Senegal (N=121)	Mean: 69	Median: 37	50	19 (15.7) *MX: 95 (78.6%)*
Yamoah [36]	Ghana (N=379)	Median: 65	Median: 39	20.3	128 (33.8)
Amégbor K[29]	Togo (N=2002)	Mean: 70 (45-95)	Mean: 88.5 (7.8- 560.4)	-	-
Kabore A [33]	Burkina Faso (N=106)	Mean: 71,5 (52-86)	Mean: 537 (8,41-17850)	78 (73.6)	44 (31.5)
Wasike [39]	Kenya (N=65)	Mean: 67	-	87.5	-
Yarney [53]	Ghana (N=170)	Mean: 65.4 (50–87)	>20: 73.7%	57 (33.5)	-
Ekwere [40]	Nigeria (N=145)	Mean: 66.6 (35-88)	-	118 (81.4)	90 (62)

PROSTATE CANCER TREATMENT

Prostate cancer treatment is contingent to the clinical presentation and to the available treatment options. Because of the advanced disease at diagnosis observed in the large majority of patients, the commonest treatment option is hormone replacement treatment, mostly orchiectomy [16, 31, 39-41]. Treatment with intent to cure such as radical prostatectomy and radiation therapy are limited by rarity of localized disease at diagnosis. Radical prostatectomy is practiced in some centers owing to oncology fellowship training and continuing training through international collaboration. A report of the first cases of radical prostatectomies in a single center of Dakar, Senegal has shown this procedure is technically doable and safe [42]. In this center, prostate cancer has gained an important focus both in clinical practice and research and apart from oncologic fellowship training of the urologists, it is an important example of the role of in-site continuing medical training in partnership with International colleagues. The collaboration of this center with the Hospital of Doylestown in Philadelphia [43] provided many hands-on training and contributed to improving the practice of radical prostatectomy. A recent report indicates an increase in the number of radical prostatectomies performed in this center [44]. Other reports of radical prostatectomy were published in South Africa [45] and in Ghana where Kyei *et al.* [46] indicate that patients with localized disease can safely undergo radical prostatectomy with limited complications.

Radiation therapy, the second curative treatment option for prostate cancer is not common in SSA. Many efforts are being done to promote Radiation therapy in Ghana. A recent study by Yamoah *et al.* [36] reports radiation therapy in a cohort of patients with organ-confined disease including external beam radiation treatment (EBRT) in 141 patients, Brachytherapy in 13 patients and EBRT + Brachytherapy in 6 patients. Overall The 3 and 5 year actuarial freedom form biochemical failure was 73.8% and 65.1% respectively. These findings are promising and can widen the offer of curative treatment options.

PROSTATE CANCER RESEARCH

Worldwide, men of SSA descent suffer disproportionately from Prostate cancer compared to men of other races or ethnicities [10, 11, 47]. In an effort to investigate such disparities, there is an increasing number of research programme in SSA mostly through international collaboration and funding from the US National Institute of Health. This include the Prostate Genetic Research in Senegal (PROGRES), the Ghana Prostate Health Study (GPHS) [19, 48, 49]. Other funding mechanisms are emerging and that is the case of the Medical Research Council (MRC) of South Africa and the Hayes Fund of Stellenbosch University of South Africa involved in prostate cancer research [50]. Many of these research endeavor are supported by the Men of African Descent Cancer of the prostate (MADCaP) consortium, a large group of researcher from the US and Africa aiming at a better understanding of prostate cancer in black men [49]. The published research from the above mentioned programme focused on the clinical epidemiology of the disease and the genetic susceptibility related mainly to the genes SRD5A2 and CYP3A4 involved in the androgen metabolism pathways [19, 38, 50]. All these studies show an association between black race and the pre-established alleles of susceptibility to prostate cancer. While there is a need for a better understanding of the underlying genetic factors of prostate cancer, it must be emphasized that any research should include a clinical component that may fuel screening and treatment of prostate in order to evaluate outcomes. Translational research is indeed necessary to achieve the double goal of understanding the disease and taking care of the patients. One example is the study of Adam *et al.* [51] on the role of PCA3 in predicting prostatic biopsy outcomes in a cohort of 105 South African men. They found that the higher the PCA3 score the greater the probability of a positive biopsy, however the PSA level (area under the curve=0.844) performed better than the PCA3 score (area under the curve=0.705).

The African Organization for Research and Training in Cancer (AORTIC) has made recommendations on how to have a holistic approach to cancers in the continent with great emphasis on training and education and multidisciplinary cancer research [52].

CONCLUSION

Despite the ongoing clinical and research efforts, there is still a limited understanding of the epidemiology and clinical characteristics of prostate cancer in SSA. Great expectations are toward implementation of health policies that will support the individuals and local and international organizations working on prostate cancer research.

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