Prostate cancer perspective: Africa versus the world

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Prostate cancer (PCa) is one of the most commonly diagnosed cancers among men, with a rising global incidence. Currently, the PCa landscape is vastly different between developed countries and Africa. Of note, owing to various biological, socioeconomic and institutional factors, black African men often present with more advanced disease and suffer greater mortality. This review will focus on the burden of PCa globally and in Africa, compare the state of the disease in Africa with that in more developed regions of the world, and answer the question why it can sometimes look like a 'different' disease compared with developed regions. In addition, we address the racial disparities of PCa.

Prostate cancer (PCa) is one of the most commonly diagnosed cancers among men. It is frequently cited as the most common cancer diagnosed in men and is the fifth leading cause of death globally.[1] Similarly, PCa is the most commonly diagnosed cancer among South African (SA) men across all population groups.[1] Black African men have been found to present later with a more advanced stage and higher histological grade at presentation than their non-black counterparts.[2] The incidence of PCa in southern Africa has increased by an estimated 60% in the past decade and a half[3] and could lead to an increase in mortality rates in black African men if the disease is not adequately and timeously managed.

Another concern is the disparity in resources for diagnosing and treating PCa at any stage in developing countries, especially African countries, when compared with the developed world. Although Northern and Western Europe have some of the highest PCa incidence rates globally, at the same time they also have very low mortality rates.[1] This situation, of course, creates a scenario where meticulously compiled guidelines and treatment strategies, usually based on data from the developed world, remain mostly theoretical and are often not applicable or even beneficial to patients in developing countries.

This review will focus on the state of PCa in Africa by comparing it with developed global regions in terms of early detection and diagnosis to ascertain why, at times, it almost looks like two different diseases between different global regions.

Methods

A literature search of PubMed and Google Scholar databases was performed. Keywords were 'prostate cancer', 'presentation', 'clinical presentation', 'pathological stage', 'South Africa' and 'Africa'. These were combined with various Boolean operators to obtain the relevant and applicable results. A search period of 10 years was used, and relevant English language abstracts were assessed. Full-text articles were accessed from the abstracts. Articles older than 10 years were included if no recent data were available on the subject or if they were found to be significant.

Review

Epidemiology

According to the World Health Organization (WHO), PCa was the second most common cancer diagnosed among men of all ages globally in 2020, accounting for 14.1% of all cancers diagnosed in men that year. When considering both sexes, PCa represented 7.3% of all cancers diagnosed in 2020, ranking fourth, behind breast, lung and colorectal cancers. In 2020 alone, there were 1 414 259 new cases of PCa diagnosed across the globe.[1]

In terms of mortality, PCa is the fifth leading cause of cancer-related deaths among men of all ages, worldwide. In 2020, PCa was responsible for 375 304 deaths globally, translating to 6.8% of all deaths among men worldwide.[1]

PCa is the most commonly diagnosed cancer among men of all ages in 112 out of 185 countries, making it the most commonly diagnosed cancer among men in more than half of the world. It is the leading cause of cancer-related deaths among men in approximately a quarter of the world (48 out of 185 countries). When age-standardised incidence rates (ASIRs) are considered, the highest rates are seen in Northern and Western Europe, North and South America, Australia and New Zealand, the Caribbean, and southern Africa.[4]

Africa

According to the WHO, PCa was the most common cancer diagnosed among African men in 2020, as well as the leading cause of cancer-related death among African men.[5] Incidence rates in Africa have been rising.[1] This rise is thought to be largely due to better awareness, improvements in healthcare systems, and wider use of prostate-specific antigen (PSA) testing.[1] More of a concern is that Africa carries one of the highest PCa mortality rates. Despite the declining mortality rates in most high-income countries since the mid-1990s,[1] the mortality rate in Africa continues to increase. According to the 2020 GLOBOCAN report, the incidence and mortality rate of PCa in Africa were 36.8 and 18.3 per 100 000, respectively,[1] compared with 23.2 and 17.0 per 100 000 in 2012.[6] The highest incidence was found in southern Africa (65.1 per 100 000), while the lowest was in North

Africa (16.6 per 100 000). Middle/Central Africa has the highest mortality rate (24.8 per 100 000), which is the second highest globally. North Africa has the lowest mortality rate (8.2 per 100 000).[1]

According to the National Cancer Registry (NCR), PCa was the most diagnosed cancer among SA men of all ages in 2020.[7] Local data have shown that the incidence of PCa increased by ~41% between 2007 and 2017.[8] The latest available data from the NCR report an ASIR of 39.46 per 100 000 in 2020 among SA men,[7] representing a total of 8 070 new cases in 2020. These figures are in contrast with the WHO's GLOBOCAN database,[1] which reported a total of 13 152 new PCa cases among SA men for the same period, with an ASIR of 68.3 per 100 000. This discrepancy is probably due to under-reporting by the NCR, which is only a database of histologically confirmed cancers. Another shortcoming of the NCR is that private laboratory data are at times withheld, which may further contribute to under-reporting.[9] From the WHO's GLOBOCAN database, the SA PCa mortality rate in 2020 was reported as 22.1 per 100 000.[5] These discrepancies highlight the issue of unreliable cancer registries in Africa, which is a point raised by other researchers.[10,11]

Financial burden of disease

PCa places a significant financial burden on healthcare systems worldwide. England and Wales spent an estimated GBP94 240 004 (ZAR1 064 714 141) on PCa adjusted for 2010.[12] It has been reported that a large portion of the costs will be incurred in the first year after diagnosis.[13] Fourcade et al.[14] found that the 2010 adjusted first-year costs after diagnosis per patient in the UK, Germany, France, Italy and Spain were EUR3 705 (ZAR35 934), EUR4 741 (ZAR45 982), EUR6 837 (ZAR66 311), EUR6 107 (ZAR59 231) and EUR3 805 (ZAR36 904), respectively. The 5-year cost of PCa in the UK was estimated to be ~EUR269 million (ZAR2.6 billion), and the 5-year cost per patient varied by stage and ranged between EUR7 040 (ZAR68 280) and EUR8 580 (ZAR83 216).[12]

In the USA, Trogdon et al.[15] reviewed data from the Medicare programme and found that the median per-patient cost within 3 years of PCa diagnosis amounted to USD14 453 (ZAR208 701), of which the treatment costs alone were USD10 558 (ZAR152 458). Another study from the USA found that the cost of therapy for PCa patients was ~USD2 800 (ZAR40 432) per month and USD34 739 (ZAR501 631) annually.[16]

Africa

Good-quality data assessing the cost of PCa across Africa are scarce. Makau-Barasa et al.[17] analysed the costs in seven sub-Saharan African countries (Ethiopia, Ghana, Kenya, Nigeria, Senegal, Tanzania and Zimbabwe). The mean costs of screening and diagnosis in US dollars were USD61.14 (ZAR882.86) and USD136.15 (ZAR1 966), respectively. Radical surgical treatment had a mean cost of USD1 427.87 (ZAR20 618.44), and radiation treatment amounted to USD2 276.18 (ZAR32 868.03). Medical castration cost USD823.57 (ZAR11 892.35), while surgical castration cost USD511.98 (ZAR7 393). The mean cost of chemotherapy was USD1 168.61 (ZAR16 874.73).[17]

In 2018, the total financial burden of PCa in Eswatini was USD6.2 million (ZAR82.1 million).[18] Higher disease stages incurred higher costs. Costs associated with stage I and II disease totalled USD1.3 million (ZAR17.2 million), while the cost for stage III and IV disease was USD3.3 million (ZAR43.7 million). These figures must be interpreted with caution, considering that the majority of the authors' cohort had either stage III (25.5 %) or stage IV (44.4 %) disease. The increasing cost associated with higher PCa stage is very significant in

the context of Africa, where patients often present with more advanced disease than in developed nations.[18]

Unfortunately, there are very few recent robust data in peer-reviewed journals regarding the financial burden of PCa in SA. The published figures are obtained from medical aid/insurance reports. In 2018, the average cost for a member within 12 months after PCa diagnosis was estimated to be ZAR123 334, according to the Discovery Health Medical Scheme oncology claims tracker.[19] It seems that there is definitely a need for a study to assess the financial burden of this disease in SA.

Gabela et al.[20] evaluated the cost of managing and treating patients with metastatic castrate-resistant PCa over a period of almost 3 years in SA, and found a total cost of ZAR10 338 558. This worked out to ZAR161 540 per patient.

PCa adds a sizeable financial burden to any healthcare system, and this effect is even greater in severely constrained and resource-limited healthcare systems, which is often the case in developing or low-income African countries.[18,20]

Screening

Screening for PCa is an area of frequent debate. Screening practices and guidelines aim to balance the early detection of clinically significant cancers against the risk of potential overdiagnosis and resulting overtreatment of clinically insignificant PCa.

Evidence of the impact of screening on overall survival and cancer-specific survival is conflicting.[21,22] Screening practices combine both digital rectal examination (DRE) and PSA testing, as it has been shown that DRE alone, especially in the primary care environment, has a sensitivity and specificity <60%.[23,24]

Currently, the European Association of Urology (EAU) guidelines suggest that PSA testing cannot be performed without counselling. An individualised risk-adapted approach for PSA-based screening has been suggested. Men with an increased risk of PCa include those >50 years of age, men of black African descent aged >45 years, men aged >45 years with a family history of PCa, and men aged >40 years carrying BRCA2 mutations. It is also recommended that men at increased risk be followed up every 2 years, whereas follow-up can be delayed by 8 years in those not in the high-risk group.[21,24] Men with a life expectancy of <15 years are unlikely to benefit from screening and early diagnosis.

Africa

Screening practices and guidelines for PCa and their availability vary across Africa.[17] It is not unreasonable to associate the higher incidence of late or more advanced stage disease in sub-Saharan Africa with a lack of screening, or at least the unavailability of accessible and/or affordable screening programmes.

It has been widely reported that PSA-based screening is more prevalent in higher socioeconomic populations with better access to healthcare.[25] The cost of screening for PCa varies among regions and countries and can be a major barrier to screening. Even though the cost of screening in some areas is relatively low, the higher cost of diagnostic tests and treatment might lead to unwillingness of men to undergo screening.[17]

A lack of knowledge about PCa and screening for the disease may be a significant factor in the high rate of advanced or metastatic disease, even at presentation. Ajape et al.[26] questioned 156 men in northern Nigeria regarding PCa and found that 78.8% had never heard of PCa and only 5.8% had heard about PSA screening. Significantly, 84.6% of men reported that they would be willing to pay for screening. In a questionnaire-based study from Bloemfontein in SA, which included 346 men aged ≥35 years, only 45.7% had

heard of PCa and only 24.7% knew from what age screening for PCa is important.[27] Unemployment and low school education were significant factors for low knowledge of PCa.

According to the Prostate Cancer Foundation of South Africa, screening with PSA testing and DRE is recommended in males with a life expectancy of ≥10 years in the following instances: annually from the age of 40 years in black South Africans and those with a positive family history of PCa or breast cancer in a first-degree relative, and annually from the age of 45 years in all other males.[28]

A survey-based study conducted among urologists from East and West Africa and SA showed interesting differences in screening practices.[29] Although more common in SA, screening for PCa had not been reported as part of routine medical care in East and West Africa. Men with a family history of PCa were less commonly screened in East Africa than in West Africa or SA.

Diagnosis

The foundation of a definitive PCa diagnosis is histopathological confirmation by prostate biopsy. Prostate biopsy is indicated in the setting of abnormal findings on DRE and/or an elevated age-adjusted PSA level.[30,31]

An isolated elevated PSA level (up to 10 ng/ml) should be confirmed after a few weeks with a repeat test.[24] This should be performed under standardised conditions, i.e. no active urinary tract infections, lower urinary tract manipulation, recent ejaculation or urinary retention.[21,28] Multiparametric magnetic resonance imaging (MRI) of the prostate is now recommended by the EAU guidelines in the pre-biopsy setting to avoid unnecessary biopsies.[24]

MRI is also used in the prostate biopsy setting as MRI targeted biopsy (MRI-TBx). It is well reported that MRI-TBx significantly outperforms systematic biopsy (SBx), specifically in patients requiring repeat biopsies. Three landmark studies have shown that MRI-TBx and MRI-TBx combined with SBx increase the detection rate of International Society of Urological Pathology (ISUP) grade ≥2 and ≥3 cancers by 20 - 23% and 21 - 30%, respectively, in biopsy-naive patients. In the repeat biopsy setting, improvements in the detection rates of ISUP grade ≥2 and ≥3 cancers were even more pronounced.[32-34]

Africa

In the African context, resource limitations may preclude urologists from strictly adhering to international guidelines and recommendations. Using a questionnaire, Rebbeck et al.[29] found interesting variability among diagnostic practices in different African regions. While all the urologists who responded utilised prostate biopsy as part of the diagnostic work-up, only 80% of respondents from East Africa and 83% from SA utilised total PSA. Biopsy practices vary between regions. The majority of respondents from both East and West Africa performed 6-core biopsy techniques v. a 12-core biopsy, which was the technique of choice for most SA respondents. 83% of respondents from SA utilised transrectal ultrasound (TRUS) as part of their diagnostic work-up, compared with only 40% of East and West African respondents, and the vast majority of respondents did not employ MRI as part of their diagnostic work-up.[29]

In a survey of urologists in Nigeria, 56.9% employed TRUS-guided systematic prostate biopsies, while 43.1% still employed the finger-guided biopsy technique. None of the patients underwent MRI-TBx or transperineal biopsies.[35] In many developing countries in Africa, 'out-of-pocket' healthcare is practised, and something as simple as a TRUS-guided prostate biopsy may be totally unaffordable.[36] It is interesting to note that a study in Cape Town, SA, found that TRUS-guided prostate biopsy only outperformed finger-guided biopsies in

terms of cancer detection when the PSA level was <20 ng/mL, which only became statistically significant when the PSA level was <10 ng/mL, irrespective of the DRE findings.[37] The authors noted that, while far from the gold standard, finger-guided prostate biopsies remain a suitable alternative in resource-limited settings, especially when the prostate is clinically abnormal.

Prostate biopsy, specifically via the transrectal route, is associated with patient risks, with minor complications occurring in ~70% of cases and major complications in 1 - 2%. In developing countries, the cost of prostate biopsy needs to be considered, as well as the cost to the patient, which may include time off work and travel costs. Heyns et al.[38] demonstrated that a reliable clinical diagnosis (without prostate biopsy) of locally advanced or metastatic PCa can be made based on serum PSA, DRE findings and clinical features, thus avoiding the costs and potential complications associated with the biopsy procedure. An earlier study by Heyns et al.[39] demonstrated a 98% positive predictive value (PPV) for detecting PCa with a needle biopsy when the PSA level was >60 ng/mL. A study from Korea reported a PPV for detecting PCa with needle biopsy of 81.2% for PSA >50 ng/mL.[40] The PPV increased to 100% in patients with PSA levels ≥100 ng/mL. Of the patients with a PSA level ≥100 ng/mL, all (100%) had extraprostatic disease, 7% had locally advanced disease, and 93% had metastatic disease. There is therefore sufficient data to suggest that in select patients (elderly with multiple comorbidities), especially in resource-limited settings, a clinical diagnosis (without needle biopsy) of advanced PCa can be made, in order to start androgen deprivation therapy and avoid the associated costs and complications of prostate biopsy. The clinical diagnosis of PCa is also incorporated in the American Urological Association guidelines, which recommend that a prostate biopsy may be omitted in certain patients with PSA levels >50 ng/mL, with no other cause for the increased PSA, as there is a 98.5% estimated likelihood of high-grade PCa at such a PSA level.[41] This recommendation would allow the clinical diagnosis of advanced PCa, to avoid delays in initiation of treatment when urgently required (e.g. spinal cord compression) or when a prostate biopsy is deemed to pose an increased risk (e.g. in a patient on anticoagulation, or a frail patient with significant comorbidities).[41] Imaging studies (radionuclide bone scans or plain film X-rays) could assist with confirming metastatic disease in the setting of a clinical diagnosis.[40]

Stage at presentation

In the USA, especially in the past two decades, screening has led to an increasing number of patients being diagnosed with localised disease. Data from the National Cancer Institute's Surveillance, Epidemiology and End Results (SEER) database demonstrated that the vast majority (80%) of men diagnosed with PCa in the USA presented with localised disease; 12% presented with regional lymph node involvement, and only 4% presented with distant metastases.[42] While 83% of white patients had localised disease at diagnosis between 2004 and 2014, ~80% of African Americans presented with localised disease; 3.8% of white patients and 5.2% of African American patients were diagnosed with metastatic PCa during the same time period.[43]

Africa

The PCa landscape in Africa, and specifically in SA, appears markedly different from that in the developed world. Studies across SA have provided insights into how and at what stage patients with PCa present at the time of diagnosis. Data from Cape Town found no difference in the mean age at presentation (65.7 - 66.4 years) between black and non-black men.[2] The mean PSA level in men

diagnosed with PCa was 66.6 ng/dL. However, in a subgroup analysis, the mean PSA level among black men was 166.8 ng/dL v. 47.5 ng/dL in non-black men. Approximately 10.4% of the men presented with clinically locally advanced disease (T3/T4 on DRE). Findings from a similar study echoed these results.[44] Furthermore, black patients were more likely to present with metastatic disease (53%) than their white and coloured counterparts.[44] A study that included only black men demonstrated that the majority (44.5%) presented with cT4 disease.[45] Only 25% of the patients presented with organ-confined disease, of whom only 6% had low-risk disease; 66% of the men were diagnosed with metastatic disease on presentation, while 43% presented with a Gleason score ≥8. A similar study[11] echoed these results, which clearly show that SA men diagnosed with PCa, particularly black SA men, present late, with a higher PSA level, a higher Gleason score and clinically advanced disease. More advanced disease at presentation would certainly translate into higher mortality and lower cure rates. In this study,[11] <2% of the men were eligible for curative surgery at the time of diagnosis. The higher stage and more advanced disease at presentation among black men could be attributed to poor access to healthcare as well as delayed health-seeking behaviour. However, differences in tumour biology due to underlying genetics are likely to play a major role.

Racial disparities

It has been reported that black men in the USA have a 1.76 higher chance of being diagnosed with PCa and are 2.14 times more likely to die from the disease than white men.[46] There are also studies hypothesising that PCa may progress and become metastatic at a disproportionately high rate among black men and from a younger age.[47] Reasons for this difference are multifactorial, but may include population genetics, environmental factors and socioeconomic status.[46]

While barriers to accessing healthcare could play a significant role, they may not be the only factors. Hispanic men in the USA, who have barriers to healthcare similar to African American men, have significantly lower PCa incidences and mortality rates than black and white men.[46] Good-quality data from the USA suggest that the disparity in mortality rates may improve somewhat with equal access to healthcare.[48] However, despite equal access to healthcare, black men are still likely to present with higher Gleason scores and PSA levels,[46,47] highlighting a difference in underlying tumour biology across races.

Differences in androgen receptor (AR) signalling may play a role in these disparities. These include higher free testosterone levels, increased AR protein levels, and increased somatic and germline AR hypermutations in black men with PCa.[46] Increased AR expression has also been observed in radical prostatectomy specimens from men of African origin.[49]

Vitamin D deficiency in men of West African ancestry has also been linked to increased PCa aggressiveness owing to the import of androgens via megalin (*LRP2* gene), a cell membrane receptor, rather than protein-bound vitamin D.[50,51] Certain germline mutations in DNA repair genes have also been found to be more common in black men than in white men. Specifically, *BRCA2* gene mutations have been found to be 2.8 times more frequent in black men and are associated with an increased risk of PCa and more aggressive PCa.[52,53]

Numerous susceptibility loci have been identified for PCa. Chromosome 8q24 regions have been extensively studied and have provided evidence of higher PCa heritability in men of African origin than in other populations. Many risk alleles at the 8q24 locus seem to have much higher penetrance among African than among European men. Risk alleles at this locus are also more prevalent in African men. These genetic factors, along with the rarer genetic variation at 8q24, may contribute to the higher risk of PCa observed in African men.[54] Other loci identified among SA black men include 2p11.2, 3p14, 8q23 and 22q13.2, and these are associated with more aggressive disease, a higher PSA level, a worse Gleason score and higher-risk disease at presentation.[55]

Dietary and lifestyle factors that may affect PCa disparities include a high-fat diet, obesity and hypertension, which are said to be more prevalent among black American men than among other races.[47] Obesity and hypertension have been linked to an increased release of inflammatory cytokines and reactive oxygen species, leading to oxidative stress and DNA damage. In addition, activation of nuclear factor kappa-light-chain enhancer of activated B cells (NF-kB) leads to PCa cell proliferation.[47] Southern African data suggest that the same dietary and lifestyle risks are prevalent among black South Africans.[56]

The long-term and ongoing use of dichloro-diphenyl-trichloroethane (DDT) in Limpopo Province, a pesticide banned in most countries, has been linked to increased PCa risk, specifically in SA's Venda population.[3,57]

Finally, the role of traditional medicines in Africa should be noted. A large proportion of SA men report utilising traditional health practitioners for their primary care needs and are influenced by personal and cultural beliefs, accessibility and affordability. While traditional medicine often plays a significant role in palliative care, especially among rural South Africans, it can be argued that relying solely on traditional medicine risks delaying early detection and prevention of PCa.[3,57]

Conclusion

Currently, the landscape of PCa is vastly different between developed countries and Africa. This difference can be attributed to various biological, socioeconomic and institutional factors. These discrepancies, which have serious physical, psychosocial and financial implications for patients, are all targets to be addressed to eliminate the observed disparities. At the ground level, specialists and non-specialists practising in sub-Saharan Africa should aim not only to understand the extent of the PCa burden in their specific regions, but also to gain an understanding of the best possible alternative solutions in situations where resources fall short and gold standards cannot be met, in order to give patients in these regions who suffer from PCa the best possible outcome.

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