Prostate Cancer in Southern Africa: Does Africa Hold Untapped Potential to Add Value to the Current Understanding of a Common Disease?

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Prostate cancer (PCa) is the most common cancer diagnosis in men from economically stable countries and is a leading cause of cancer-related death.[1] However, the population with the highest reported incidence and mortality rates globally are African Americans. Although the lifetime risk of a cancer diagnosis (one in two) or cancer-associated mortality (one in four) is no different for American men of African or European heritage, the figures are dramatically skewed for PCa.[2] Incidence and mortality rates are 1.6- and 2.4-fold greater for African Americans than for European Americans, respectively.[3] Additional clinical parameters exasperated in African Americans are higher serum prostate-specific antigen (PSA) levels population wide and at diagnosis, younger age at diagnosis, shorter PSA doubling before surgery, higher tumor grade and volume at surgery, higher incidence of anteriorally located tumors (more challenging to obtain a biopsy sample), and faster growing tumors (greater potential for metastasis).[4-10] Although African American men have the greatest PCa burden globally, the relationship to men from Africa is less clear. We present the challenges and largely overlooked potential to address the impact of PCa within Africa. We provide commentary from our experiences as the clinical (M.S.R.B.) and scientific (V.M.H.) directors of the Southern African Prostate Cancer Study (SAPCS).

Suggested explanations for observed African-associated PCa disparity include socioeconomic factors and genetics. A recent literature review found that African American men were less likely than European American men to seek treatment as a direct or indirect consequence of financial barriers, lack of health insurance, and/or poor health-seeking behavior.[11] Although genome-wide association studies have identified > 100 PCa susceptibility loci, discovery studies have been biased toward non-African cohorts and have identified common alleles estimated to explain approximately 33% of the familial risk in men of European ancestry.[12,13] Risk prediction for known alleles declines for African Americans,[14] which leaves a substantial proportion of the estimated 57% (95% CI, 52% to 63%) PCa heritability[15] unexplained. In 2009, Odedina et al[16,17] suggested that the roots of the significant African American PCa burden can be explained (at least in part) by enhanced genetic susceptibility traced back to the approximately 360,000 predominantly West/West-Central African transatlantic slaves. Like these authors, we argue that to truly understand the etiology behind African-associated PCa risk, we must turn our attention to Africa.

Africa is the world's second largest and second most populated continent. It is home to 54 countries, nine territories, and two sovereign states, with a population of 1.2 billion.[18] Ethnolinguistic groups within Africa are numerous, unique, and defined by extreme diversity in culture, language, and genetics not only between, but also within countries. Determining the burden of PCa within the continent has been problematic and compounded by a lack of unified systems of monitoring and reporting.[19] A recent meta-analysis of the literature on PCa incidence in Africa over the past 35 years (ending June 2015) identified only 40 studies that met inclusion criteria across 16 countries (Fig 1).[20] The estimated pooled incidence rate across the study was 22.0 (95% CI, 19.93 to 23.97) per 100,000, whereas regional incidence rates varied dramatically. West and West-Central African countries were the largest contributors that reported incidence rates as low as 0.38 and as high as 182.5 per 100,000. As the predominant source of African ancestry to the Americas, genetic studies have further defined ancestral fractions as 82% West/West-Central African, specifically non-Bantu (68%), Bantu (14%), and Southwest Bantu (18%).[21] The deciphering of a direct genetic link to

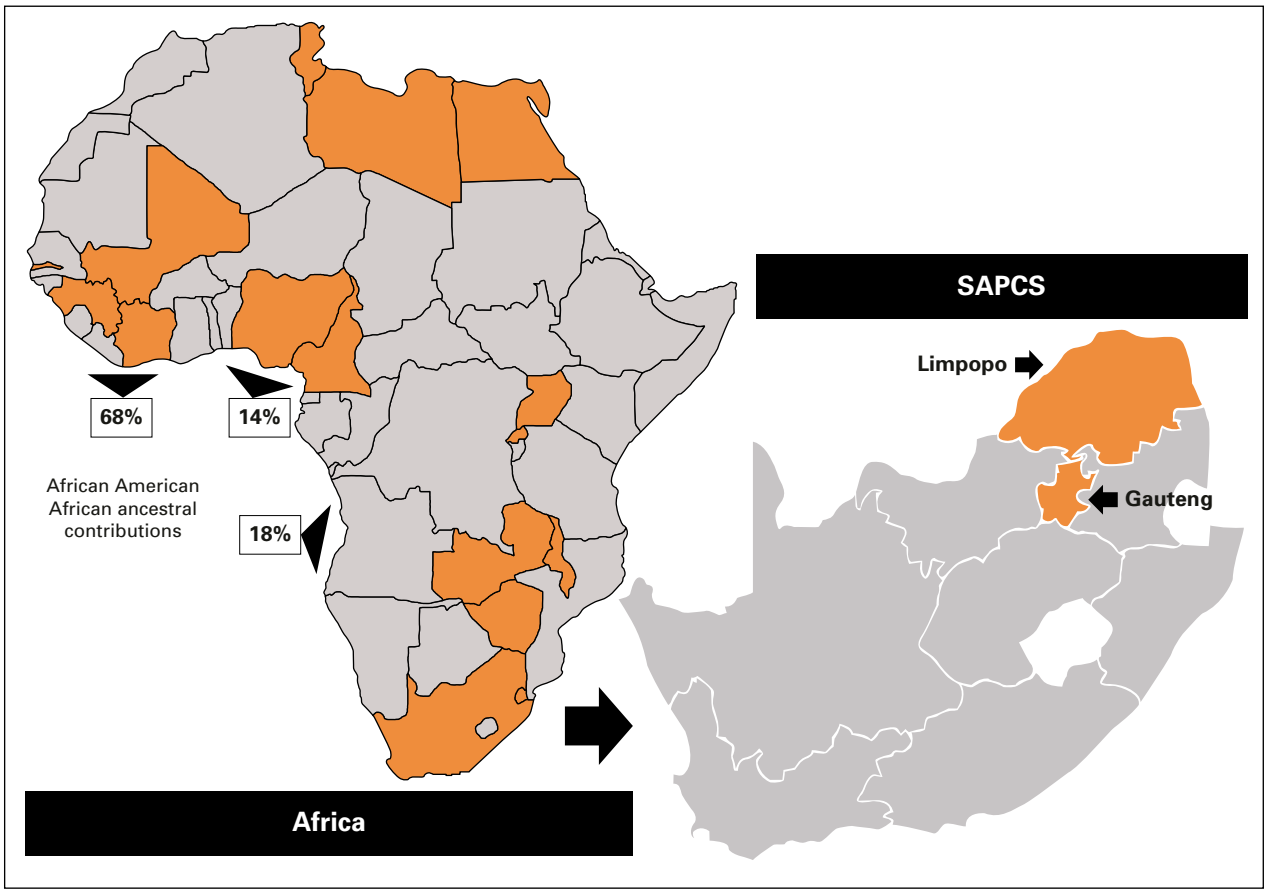

Fig 1. Map of Africa depicting the current contribution of knowledge on prostate cancer burden across 16 countries (gold) as described by Adeloye et al[20] and the provincial South African contribution to the Southern African Prostate Cancer Study (SAPCS, gold inset). Within Africa, countries are further classified geographically as North African (including Tunisia, Libya, and Egypt), West African (including The Gambia, Guinea, Mali, and Côte d'Ivoire), West-Central African (or West Bantu, including Cameroon and Nigeria), East African (including Uganda and Rwanda), and Southern African (including Zambia, Malawi, Zimbabwe, and South Africa [including Swaziland]). The published estimated African ancestral contributions to the African American population is further presented.[21]

the African ancestral PCa burden will require extensive analyses across Africa, including environmental contributions.

Both Adeloye et al[20] and the WHO 2012 GLOBOCAN report[22] have suggested that incidence rates are highest in sub-Saharan Africa. Thus, we turn our attention to the Southern Bantu populations of South Africa, which present with the highest within- and between-population genetic diversity globally.[23,24] We have defined the ancestral genetic contributions to the Southern Bantu peoples as uniquely African, specifically ancient Bantu (approximately 72%) and indigenous KhoeSan (approximately 28%), while excluding non-African fractions. The SAPCS collects clinical, epidemiologic, and genetic data from men self-identified as Southern Bantu either with or without PCa.[25,26] Compared with African Americans, Southern Bantus present with significantly more aggressive disease defined by a histopathologically derived Gleason score > 7 (17% and 36%, respectively), with additional PSA levels at diagnosis ≥ 20 μg/L (17.2% and 83.2%, respectively). Our experiences have been gathered over an 8-year period from predominantly two localities that represent a typical rural and urban African setting (Fig 1, inset). Slightly larger than the state of Mississippi, rural Limpopo is home to approximately 5.6 million predominantly African village residents faced with significant financial constraints.[27] In contrast, Gauteng, smaller than the state of New Jersey, has the largest population of approximately 13.2 million of whom roughly 74% are African. Gauteng is culturally diverse and home to the largest South African city, Johannesburg, with more than one third of the population living in informal settlements known as townships. Although we report exaggerated aggressive PCa presentation in men from rural versus urban South African localities, PSA levels at diagnosis are notably not proportionally increased.[24] Black South African men will present, on average, 5 years later than Americans, and within South Africa, 3 years earlier within an urban versus a rural locality. Factors associated with later PCa presentation are likely to resonate throughout Africa, which confounds accurate assessment of disease burden and stratification of data across the region and globally. From our experiences, these variables broadly include education, culture, and economics.

In stark contrast to non-African PCa studies, $< 2\%$ of the SAPCS cases were eligible for surgical treatment

as a result of advanced disease presentation.[26] Contributing factors are discussed further. More than 42% of the study participants reported the use of traditional health practitioners as primary care.[26] Traditional medicine plays a vital role throughout Africa,[28] including South Africa.[29,30] Traditional health practitioners also represent various specialties, such as the mungome (divine healer), maine (faith healer), and tshigomamutanda (herbalist) so named among the VhaVenda of South Africa. Although traditional health practitioners play a significant role in palliative care for PCa patients,[31] with no earlier symptoms, preventing advanced disease becomes limited within a traditional health system.

Underrepresentation of male-related diseases within health care systems and the media has been noted. Although South Africa has national registries for breast and cervical cancer, none exists for PCa. The bias toward female-related cancers is further reflected in the national funding schemes and awareness programs, such as the Cancer Association of South Africa Mobile Health Clinics to reach women in remote areas.[32] The status of men, particularly elderly men within tribal communities usually is one of leadership and high esteem. The cultural association of male superiority, the importance placed on virile masculinity, and the linking of sickness with a supernatural encounter (ancestor, evil spirit, or deity) all contribute negatively to male attitude with regard to health and foster a reluctance to seek medical care. In turn, the predominance of females within health care roles, particularly female nurses as the most common primary first contact, further conflicts with the largely patriarchal values associated with gender roles.

Within the SAPCS, Tshilidzini Hospital, the public hospital at Thohoyandou, which services approximately 1.2 million rurally located people, requires patients with urinary complications to be referred to Polokwane Hospital in Limpopo's capital approximately 185 km away. A single part-time urologist, understaffing, overcrowding, and major financial constraints bias clinical care toward reactive management (emergency) over preventive management, which is further overshadowed by the significant impact of HIV/AIDS, tuberculosis, and malaria. Lack of provincial priority is further exasperated by an average male life expectancy of 57.3 years.[27] Although a June 2013 report by the Prostate Cancer Foundation of South Africa recommended that men of African ancestry older than 40 years of age undergo routine PSA testing, $< 3\%$ of the SAPCS participants had received a previous PSA test.[26]

Along with cultural differences, language barriers and local colloquialisms have potential for study biases. South Africa is home to 11 official languages, with additional sublanguages and dialects. Although questionnaires are language sensitive in the SAPCS, an important lesson learned during the early phase was the misinterpretation of the word aspirin, which locally refers to any common pain-relief drug and not exclusively acetylsalicylate.[26] Use of pictures instead of words and extensive local involvement in both study design and interpretation have gone a long way to reduce translational errors.

Although we present clear challenges to assessing the disease burden and management of PCa within Africa, we argue that the region offers a unique opportunity to identify significant environmental and genetic contributions. In the face of a double burden of disease, chronic noncommunicable diseases, including cancers, are on the increase, with infectious diseases remaining the most significant contributor to mortality, specifically within sub-Saharan Africa. Sub-Saharan Africa also has the highest burden of infection-related cancers, such as human papillomavirus–induced cervical cancer, hepatitis B and C–induced hepatocarcinoma, and human herpes virus 8–induced Kaposi's sarcoma.[33] The potential significance of infectious disease related to PCa was highlighted by a prospective study of 68,675 men from the California Men's Health Study, which showed that prostatitis (inflammation of the prostate) and sexually transmitted infections increase PCa risk.[34] The establishment of a link between pathogenic agents and PCa has been problematic. We propose that Africa provides a unique environment to challenge the pathogenic hypothesis. We have observed a significant association between erectile dysfunction and increased PCa risk, with an inverse relationship associated with sexual activity.[26] This is supported by non-African associations between increased ejaculation history and decreased PCa risk,[35] argued to be explained by pathogenic shedding.

Uniquely African practices and/or environmental exposures provide unparalleled opportunities to leverage new knowledge about PCa risk and biology. Our observations of increased PCa risk within the VhaVenda people[26] could be explained by genetics, whereas the potential carcinogenic impact of dichlorodiphenyltrichloroethane (DDT) cannot be ignored. Banned in most countries, the VhaVenda Vhembe district of Limpopo has been practicing residential DDT spraying for malaria control since 1945.[36] The identification of a link between maternal DDT exposure and urogenital birth defects in newborn VhaVenda boys[37] adds

value to the reported link between pesticide use in the United States and PCa risk and aggressive disease.[38,39]

Although traditional practices provide epidemiologic insights, such as the association between the traditional brewing of maize beer in iron pots and increased incidence of esophageal cancer in South Africa,[40] the more recent shift to urbanization has fostered significant changes in nutrition and physical activity, which provides a unique opportunity to study epidemiologic transition.[41] Within Limpopo, a high prevalence of cancer-associated risk factors has been reported, such as smoking, alcohol use, increased consumption of meat and processed foods, decreased fruit and vegetable consumption, lack of physical activity, hypertension, and increased weight and waist circumference.[42] Recent adaptation from traditional diets has resulted in an increase in diabetes within almost all indigenous communities globally. We have observed a significant association between a diagnosis of diabetes and PCa in South African men.[26]

The replication of largely European-derived genetic risk loci for PCa in African populations ($P < .05$) has been limited to three of 46 tested loci within the SAPCS[25] and 10 of 90 tested loci in a study of men from Ghana.[43] Genome-wide association studies within African populations have been limited by a lack of sufficiently powered resources, non-African–biased genotyping array content, a complex within- and between-populations genetic substructure (which limits pooled analyses), and a lack of associated epidemiologic confounding data. These limitations have recently been overcome by a significant decrease in sequencing costs, which allows for genome-wide interrogation of common to rare risk-associated alleles, whereas smaller study sizes are required for fine mapping African over European sample sources.[44] The latter is a direct consequence of the extent of within-genome diversity (genetic heterogeneity) within African populations, which allows for the construction of more accurate disease-associated haplotypes as a result of low linkage disequilibrium. In contrast, populations outside Africa have undergone a significant historical population decline associated with the out-of-Africa migration (genetic bottleneck) followed by a population explosion that has led to expanded runs of homozygous genotypes shared among individuals.[45]

African ancestry has been particularly relevant for the identification of PCa risk loci in African American studies.[46] The use of ancestry informative markers to measure the probability of inheriting an African over European ancestral chromosomal segment within African American men with PCa, known as admixture mapping, led to the identification of the 8q24 PCa risk locus in 2006.[47] African ancestry has also been used to advance causal variant identification by leveraging differences in linkage disequilibrium among populations through a method known as transethnic fine mapping.[48,49]

Although significant challenges to the study of PCa within Africa exist, we propose that the advantages, if the research is well-designed and conducted in an African-relevant manner, far outweigh the challenges. We propose that Africa holds untapped potential to add significant value to the current understanding of the most common cancer to affect men globally.

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