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# EDITORIAL

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## **Urologic cancer in Africa—Papers from the African Organization for Research and Training in Cancer (AORTIC) meeting**

**T**he CJU has a strong commitment to bring global and international healthcare awareness to our readers. As attention is focused on emerging healthcare issues in developing nations, many of the challenges involve urological diseases. We are very pleased to publish, in a special section in this issue of CJU, selected papers from the AORTIC meeting held in October 2007, in Cape Town, South Africa. This conference, whose history is provided in the guest editorial by Dr. Christopher Williams, brought together prominent cancer researchers from all over the world to discuss problems and challenges unique to the developing nations of Africa. Among the attendees were prominent representatives from the National Cancer Institute (NCI, USA), the American Cancer Society (ACS), the American Association for Cancer Research (AACR), the American Society of Clinical Oncology (ASCO), the International Union Against Cancer (UICC, France), and the World Health Organization (WHO, Switzerland).

The purpose of this growing organization is to foster scientific interchange, networking, and research to face the challenges and opportunities of treating cancer in Africa. This issue of CJU highlights presentations from the Genitourinary Sessions of AORTIC chaired by Professors Serigne Gueye of Senegal, Chris Heyns of South Africa, and Timothy Rebbeck of the United States.

Several of the presentations dealt with disease epidemiology and genetic variations among differing populations, and unique issues of treatment in a setting challenged by socioeconomic and cultural considerations. The paper by Ruenes et al describes the importance of bringing modern techniques of radical prostatectomy to an African setting. Olapade-Olaopa et al discusses the management of advanced prostate cancer and Ndom challenges our compassion with his description of inherent difficulties in offering state-of-the-art cancer treatment in an environment devoid of many of the resources that are taken for granted in North America and in most developed nations.

The take home message is that genitourinary malignancies are very prevalent among African patients, and in particular, prostate cancer represents a very common disease of emerging significance. Most cancers are diagnosed late and in advanced stages, as efforts for prevention and early diagnosis are in their infancy. Effective treatment modalities are often difficult to come by for most patients, due to issues of access to care, and a basic lack of resources—economic limitations on travel, affordability of treatments, and lack of infrastructure by governments and public health organizations. Information, statistics on specific cancer-related issues are also difficult to gather due to the lack of adequate cancer registries in most African nations.

Despite this rather gloomy assessment of the state of cancer care in Africa, the conference was invigorating due to the enthusiasm and drive of the attendees to achieve change and progress, and a determination to improve the care of the cancer patient. New initiatives for the prevention, detection, treatment, and research on all facets of malignant disease were discussed in a combination of formal didactic sessions and small, intimate, interactive workshops. The delegates left filled with optimism and high expectations for the future of cancer care in Africa.

We sincerely hope that our readers will find this special collection of articles both educational and enjoyable.

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## ACKNOWLEDGEMENT

*The Canadian Journal of Urology (CJU) is honored to publish a special section on urologic cancer in Africa. The following articles are based on talks by selected speakers from the African Organization for Research and Training in Cancer (AORTIC) meeting held October 2007 in Cape Town, South Africa.*

*We wish to especially thank and acknowledge our special section editor Dr. Serigne Gueye from Dakar, Senegal whose leadership, passion and commitment to the African cancer problem has made this section possible.*

*The editorial board and the publisher hope our special AORTIC section will prove to be helpful in raising our readership's awareness of the problems our African colleagues face each and every day.*

*CJU Editorial Board  
and George Georgieff, Publisher*

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## GUEST EDITORIAL

### *Celebrating 25 years of research and training in cancer in Africa: a historical perspective of the African Organization for Research and Training in Cancer (AORTIC)*

Africa has a long tradition of excellence in cancer research. During the “Golden Age” of cancer control in Africa, in the 1950s and the 1960s, the University of Makerere in Uganda and the University of Ibadan in Nigeria shared a common heritage of excellence in biological research. The heroes of the time included Dennis Burkitt as well as R.J.V. and Isobel Pulvertaft in Uganda, and George Edington, Victor Ngu, and Olusiji Oshunkoya in Ibadan. Burkitt’s lymphoma cell lines such Raji and Daudi were created in Kampala and Ibadan, and their studies have helped in the evolution of modern molecular biology.

Several principles of cancer chemotherapy were derived from seminal publications on the curative management of Burkitt’s lymphoma by John Ziegler and his colleagues at the National Cancer Institute of the United States working in collaboration with Makerere University at the Cancer Institute of Mulago Hospital, in Kampala, Uganda. In fact, in the 1960s and early 1970s, many advances in cancer treatment emanated from Uganda.

Through studies of Kaposi’s sarcoma carried out in East and Central Africa in the 1950s and 1960s, the world had considerable awareness about the pathology and treatment of the African endemic form of the disease, which some 30 years later was useful in understanding its epidemic variant that became the first HIV/AIDS-associated disease in the 1980s in the United States.

Then, in the late 1970s and early 1980s, a process of unraveling of the African continent, and with it, African cancer research, began. Data from African cancer registries that used to feature prominently in the publication *Cancer in Five Continents* were no longer considered fit for publication, because of diminished quality and reliability.

Meanwhile, elsewhere in the world, real and significant progress was being made in the understanding of the disease process and the development of methods of prevention and cure of cancer. A major impetus had been given to the process by the declaration of the “War Against Cancer” by United States President Richard Nixon in December of 1971. Cooperative research groups such as the Cancer and Leukemia Group B (CALGB) and the Eastern Cooperative Oncology Group (ECOG) had been created and were making changes in cancer care in North America.

It is against this background that AORTIC was founded. The idea for the creation of the organization was conceived during a lunch break meeting at the 13<sup>th</sup> Congress of the Union Internationale Contre Le Cancer (UICC) meeting in Seattle, Washington, which was held on September 8-15, 1982. Participants at this meeting became the founders of AORTIC. They included Dr. Victor Ngu of Cameroon who became Pro Tem Chairman, Dr. Toriola Solanke of Nigeria (Chairman of the Organizing Committee), Dr. James F. Holland of New York City (Scientific Adviser) and I (Pro Tem Secretary General). The Committee was to identify and contact established African doctors and scientists interested in cancer as well as raise funds for the inaugural meeting of AORTIC. This meeting was held in Lome, Republic of Togo, on July 22-23, 1983. It was attended by 24 doctors from 14 countries, including 12 African and 2 non-African countries.

The period of 1984 to 1990 witnessed concerted activities in organization and research. However, by early 1990s, faced with communication challenges, economic chaos of the African nations, and emigration of principal members of AORTIC, the organization ceased to function.

The process of reactivation of AORTIC was started in April 2000 at an annual meeting of the American Association for Cancer Research (AACR), in San Francisco, California, by a group of people, including the original founders and some energetic newcomers, mainly expatriate African cancer professionals, scientists, and their non-African associates. They formed AORTIC International (later renamed AORTIC North America), which over the following 3 years engaged in a process of deliberation and planning, with the aim of repatriating the organization to Africa. In October 2003, at the 5<sup>th</sup> AORTIC International Conference on Cancer in Africa, held in Accra, Ghana, Africa-based AORTIC leaders were elected, thus, completing the process of repatriation of the organization. AORTIC has since held meetings biennially in Africa, including in Dakar, Senegal, in 2005, and in Cape Town, South Africa, in 2007.

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## GUEST EDITORIAL

AORTIC has many reasons to celebrate its silver jubilee in spite of its inability to influence cancer control effectively in Africa since its inception 25 years ago. The mere fact that cancer researchers assembled in Cape Town, South Africa, in October 2007, is a major reason to celebrate. Following the meeting in Seattle, Washington in 1982, it was my duty as the Pro Tem Secretary General to travel the world to spread the news about the young organization. I visited the World Health Organization (WHO) headquarters in Geneva, Switzerland, and the WHO African regional office, in Brazzaville, Congo, as well as many countries in sub-Saharan Africa. A trip to South Africa was at that time out of the question, because of the prevailing political atmosphere. In October, researchers assembled in this beautiful country and enjoyed the hospitality of its rainbow-colored citizenry. This, indeed, is a good reason to celebrate.

In 1983, 14 countries were represented at the inaugural convention of AORTIC. Today, 25 years later, AORTIC draws its membership from 29 countries, including 5 non-African nations. This, indeed, is a good reason to celebrate.

At its inception more than 25 years ago, the WHO was AORTIC's only international supporter. Today, AORTIC can boast of associations with a plethora of international bodies, including the WHO, the National Cancer Institute of the United States, the American Cancer Society, the Canadian Cancer Society, the American Society of Clinical Oncology (ASCO), the AACR, the International Network for Cancer Treatment and Research (INCTR), as well as several other international bodies. With the help of these broad-based groups, one can be optimistic that there will be a renaissance of another "Golden Age" of cancer control in Africa. This is, indeed, a good reason to celebrate.

In the 25 years of its existence, AORTIC has demonstrated its ability to be a promoter of change. In its first decade, AORTIC organized a multicenter clinical trial involving five different African countries. It was a randomized study of the treatment of primary liver cancer comparing two anthracyclines, namely doxorubicin and epirubicin. This is probably the first and only study of its type ever held on this continent. The results of the study were presented at a meeting in Paris, France, in 1991, and later published. Several other studies were proposed. Unfortunately, prevailing socioeconomic problems made the realization of those goals unattainable.

In January 2007, AORTIC teamed up with ASCO to hold the Multidisciplinary Cancer Management course. It was held in Abuja, Nigeria, and was attended by 75 participants including physicians, surgeons, pharmacists, nurses, and social workers. This was the first time this type of cancer educational event was held in Africa after it had been held in other places such as China, and some Latin American countries.

At the 2005 meeting in Dakar, Senegal, AORTIC's activities received the endorsement of an important ally in the person of President Wade of Senegal. In his remarks at the opening ceremony, he expressed his enthusiasm for cancer advocacy in Africa. He followed up his words with action by implementing many of the recommendations emanating from the conference.

In 2007, AORTIC is alive and stronger than ever. Over 400 delegates from 46 nations, including more than 2 dozen African nations, and others from Europe, Asia, Australia and South America, gathered at the conference for 4 days of keynote presentations in 10 plenary sessions, 25 workshops, six "Meet-the-Experts" sessions, and grant-writing seminars — mingling and networking in scientific interchanges. A rich scientific agenda was embellished by a meaningful cultural experience. The sessions on the genitourinary malignancies constituted an integral part of the overall effort directed at the prevention, early detection, and successful treatment of a variety of malignancies in Africa.

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*This editorial is adapted from an address given at the 6th International meeting of the African Organization for Research and Training in Cancer (AORTIC), which was held in Cape Town, South Africa, from October 24 to 28, 2007.*

## What is the significance of the HPV epidemic?

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ANORLU RI. What is the significance of the HPV epidemic? *The Canadian Journal of Urology*. 2008;15(1):3860-3865.

*Human papillomavirus (HPV) is the most common sexually transmitted infection. The incidence of this infection has been on the rise in recent times. It is estimated that approximately 6 million new HPV infections are acquired each year in the United States alone, and prevalence data suggest that as many as 24 million American adults—that is, 1 in 5—may be infected with HPV. Unfortunately, there is little public awareness and knowledge about the infection and its sequelae. It is well known that more than 90% of cases of anogenital warts are caused by HPV. HPV has been implicated in cancers of the cervix, vulva, vagina, penis, anus, and oropharynx. The virus is a necessary cause of cervical cancer. HPV DNA is detected in almost 100% of cases of cervical cancer.*

*There have been major strides in recent years in the prevention of this infection and consequently, of diseases related to it. Vaccines are available and licensed in some countries. Two HPV vaccines are available: a quadrivalent (HPV types 6, 11, 16, and 18) vaccine and a bivalent (HPV types 16 and 18) vaccine. Both vaccines show a more than 90% protection against persistent HPV infection for up to 5 years after vaccination. The role of the vaccine in males is still controversial.*

*The vaccination cost, however, is beyond the reach of many individuals in developing countries where 80% of cervical cancer cases of are found. Many countries in Africa are battling with HIV, malaria, tuberculosis, maternal mortality, and childhood illness. Nevertheless, with increased awareness, political will, and engagement by pharmaceutical countries, HPV vaccines may become affordable in these countries.*

**Key Words:** HPV, human papillomavirus, sexually transmitted disease

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### Introduction

Human papillomaviruses (HPVs), a group of more than 100 viruses, are called papillomaviruses because certain types may cause warts, or papillomas. The “wart virus”

has been known since prehistoric times, but it was not until the 1970s and 1980s that it was studied extensively, and this has led to a tremendous understanding of the etiology of lesions associated with it. HPVs belongs to the family *Papovaviridae*.<sup>1</sup> The viral genome is enclosed in a 72-capsomere capsid.<sup>1,2</sup> HPV is the most common sexually transmitted infection.<sup>3,4</sup> It is estimated that approximately 6 million new HPV infections are acquired each year in the United States alone, and prevalence data suggest that as many as 24 million American adults—that is, 1 in 5—may be infected with

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## What is the significance of the HPV epidemic?

HPV.<sup>4</sup> The highest rates of new genital HPV infections, approximately 74% of annual infections, occur among young adults between the ages of 15 and 24.<sup>4</sup>

The virus affects mainly the mucocutaneous parts of the anogenital and oropharyngeal regions of the body. More than 100 genotypes of HPV have been isolated and about 40 types are associated with anogenital tumors. The HPVs are divided into two groups based on their association with risk for cancer. The low-risk HPV types 6, 11, 40, 42, 43, 54, 61, 72, and 81 are of low oncogenic potential, while the high-risk HPV types 16, 18, 26, 31, 33, 35, 39, 45, 51, 52, 53, 56, 58, 59, 66, 68, 73, and 82 are associated with cancer.<sup>1</sup> About 15 HPV types have been associated with anogenital cancers. High-risk HPV has been implicated in cancers of the cervix, vagina, vulva, anus, penis and oropharynx.<sup>5</sup> Non-melanoma skin cancer and cancer of the conjunctiva have also been causally linked with HPV.<sup>5</sup>

## The HPV genome and mechanism of tumorigenesis

HPV is a relatively small virus containing two strands of DNA within a spherical shell (capsid).

The HPV genome is a single stranded DNA that consists of 8000 base pairs and comprises three major regions.<sup>1</sup> The early region (E1-8) consists of genes responsible for transcription, plasmid replication, and transformation. The late region codes for the major (L1) and minor (L2) capsid proteins, and the control region contains the regulatory elements for transcription and replication. E1 and E2 proteins are essential for viral replication and transcription, and E6 and E7 proteins of high-risk HPV are of major significance in the process of carcinogenesis.

The HPV makes use of the normal process of turnover of epithelial cells, which involves upward migration and differentiation of cells from the basal layer to the superficial layer, to complete its life cycle. The basal cell leaves the cell cycle when it moves to the suprabasal layer of the epithelium, undergoes differentiation as it moves up to the superficial layer of the epithelium, gets disintegrated, and is released into the environment. The virus enters the epithelium through micro abrasions and enters the basal cell. It gets integrated into the chromosome of the cell, and the viral genome is replicated to a copy number of about 100 and is maintained for varying for a period of time within the cell.<sup>6</sup> Differentiation is delayed and less complete in the infected cell.<sup>6</sup> The virus continues its replication as the infected cell moves upwards, and when it gets to the superficial layer of the epithelium, the viral capsid proteins are expressed leading to the

production of mature virions. The cell disintegrates and virions are released into the environment ready to start another life cycle.

The key action of the E6 protein of high-risk HPV is to cause immortalization of the infected cell, a process that may eventually lead to malignant transformation. It does this by enhancing the degradation of p53 protein, a protein that promotes apoptosis. The E6 protein also activates the enzyme telomerase, which counteracts the shortening the chromosome telomeres — a cell-aging process. The high-risk E7 protein is the major transforming protein of the HPVs. It acts by binding pRb, a protein that binds and inhibits transcription factors of the E2F family. Binding of pRb by E7 will therefore lead to the release of E2F transcription factors that stimulate entry into the S-phase and lead to cell replication.<sup>1,6,7</sup> This process is normally checked by p53 protein, which causes apoptosis, but in HPV-infected cells, p53 protein is not available, as it is constantly being degraded by E6 protein. The continued actions of E6 and E7 proteins in a cell persistently infected with HPV leads to increasing genomic instability, accumulation of oncogene mutations, further loss of cell-growth control, and ultimately, cancer.<sup>5,7</sup>

The E6 protein of low-risk HPV does not bind p53 protein, and this may be the reason for the benign nature of the tumors that they cause.<sup>1</sup>

## Genital warts

Genital warts (condylomata acuminata) are the most common clinical, visible manifestation of genital HPV infection. They are highly infectious with a transmission rate of 65%, and the interval between exposure and infection is 3 weeks to 8 months.<sup>8,9</sup> It is well known that more than 90% of cases of genital warts are caused by low-risk HPV types 6 and 11.<sup>10,11</sup> Recent studies have shown that 20%-50% of lesions also contain coinfection with high-risk HPV types.<sup>9,12</sup>

It is estimated that 1% of the American population has genital warts, and women and men have similar rates of infection, with a female to male ratio of 1.4:1.<sup>11</sup> Between half a million to one million cases are diagnosed annually.<sup>11</sup> Cases of anogenital warts have been on the increase worldwide. Available data suggest that genital warts occur worldwide at similar rates to those observed in the United Kingdom and the United States.

Epidemiological studies have shown that the risk of acquiring an anogenital wart infection increases with cigarette smoking, oral contraceptive use, and increased sexual activity with multiple sexual

partners. Anogenital warts are also increased in situations where there is a deficiency of cell-mediated immunity, as occurs with HIV, diabetes, and the use of immunosuppressant drugs.

In males, the effects of genital warts are found on the glans penis, penile shaft, prepuce, and anal area. In about 5% of cases, the urethral meatus and urethra are involved; bladder involvement is rare.<sup>13,14</sup> In females, genital warts affect the vulva, vagina, cervix, groin, and anal area. Rarely, genital warts can also develop in the mouth or throat of individuals who engage in oral sex. Genital warts can have a negative psychological impact on an individual. It affects sexual activity. Very large warts may complicate vaginal delivery. Vertical transmission can occur at the time of delivery, and this could lead to juvenile-onset recurrent respiratory papillomatosis, a highly debilitating and potentially life-threatening condition.<sup>15</sup>

## HPV-related cancers

### *Cervical cancer*

Cancer of the cervix uteri is the second most common cancer among women worldwide, with an estimated 493000 new cases of this cancer and 274000 deaths due to this cancer worldwide in 2002.<sup>16</sup> It is projected that in the absence of any intervention, by 2020, 0.7 million cases will occur—about a 40% increase from 2002.<sup>17</sup>

HPV infection is now widely recognized as the principal etiologic agent in the development of cervical dysplasia and cervical cancer. The magnitude of this risk association is even greater than that between smoking and lung cancer.<sup>18,19</sup> HPV-DNA is found in 99.7% of cases of cervical cancer, which makes HPV a necessary cause of virtually all cervical cancer.<sup>20,21</sup> The most common HPV types identified are, in order of decreasing prevalence, HPV types 16, 18, 33, 45, 31, 58, 52, 35, 59, 56, 51, 39, 6, 68, 73, 66, and 70.<sup>21</sup> HPV types 16 and 18 are responsible for about 70% of all carcinomas of the cervix worldwide. Although HPV is a necessary cause of cervical cancer, it is not a sufficient cause. Cofactors are necessary for the progression from cervical HPV infection to cancer. The established cofactors include long-term use of hormonal contraceptives, high parity, tobacco smoking, and coinfection with HIV.<sup>5</sup> Coinfection with *Chlamydia trachomatis* (CT) and herpes simplex virus type-2 (HSV-2), immunosuppression, and certain dietary deficiencies are other probable cofactors.<sup>5</sup> Genetic and immunological host factors and other viral factors such as variants of type, viral load, and viral integration, are likely to be important, but these cofactors have not been clearly identified.<sup>5</sup>

### *Cancer of the vulva*

The majority (60%-90%) of vulva cancers and their precursor lesions found in young individuals are also strongly associated with HPV.<sup>5</sup> The HPV-related cancers of the vulva are of the basaloid or warty histological subtypes. Hording et al<sup>22</sup> found HPV types 16 and 33 in 12 of 17 (71%) invasive warty carcinomas and in 10 of 10 (100%) invasive basaloid carcinomas. The tumors diagnosed in young individuals are usually of the basaloid or warty histological subtypes. Less than 10% of vulva cancers in older individuals are associated with HPV.<sup>5,23</sup>

### *Cancer of the vagina*

Cancers of the vagina are less frequent than vulvar cancers: the age-standardized incidence rate (ASR) is 0.3 to 0.7 per 100000 individuals in most countries.<sup>17</sup> Many squamous cell carcinomas of the vagina are preceded by vaginal intraepithelial neoplasia (VAIN). HPV plays a similar role in cancer of the vagina as in cancer of the cervix. Between 64% and 91% of vaginal cancers and 82% and 100% of VAIN-3 lesions are HPV-DNA positive.<sup>5</sup>

### *Cancer of the penis*

Cancer of the penis is a rare malignancy, and it accounts for less than 0.5% of cancers in men.<sup>17,23</sup> In Western countries, the ASR is less than 1 per 100000 men.<sup>17</sup> HPV has been implicated in the development of dysplastic, precancerous, and cancerous lesions of the male genitalia, including squamous cell cancer of the penis, verrucous carcinoma of the penis, and penile squamous intraepithelial neoplasias (ie, squamous cell carcinoma in situ, bowenoid papulosis, erythroplasia of Queyrat, or Bowen's disease of the genitalia).<sup>1</sup> "B1"<sup>24-26</sup> A history of anogenital warts is associated with a 5- to 6-fold increase in risk of penile squamous carcinoma.<sup>27</sup> Studies using polymerase chain reaction (PCR) technology have reported a detection of HPV types 16, 18, 31, and 33 in up to 82% of invasive and in-situ penile carcinoma.<sup>27,28</sup> Preliminary reports have also linked HPV transmission with the subsequent development of bladder and prostate cancers.<sup>25,26</sup>

### *Anal cancer*

Anal cancer is a rare disease and accounts for up to 4% of all cancers of the lower gastrointestinal tract.<sup>29</sup> The annual incidence is about 1 in 1000000 in a heterosexual population. Each year there are about 500 new cases in the United Kingdom and 3500 new cases in the United States. The incidence amongst

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males who have anal-receptive sexual intercourse with males was estimated to be as high as 37 per 100000 person years.<sup>30</sup> It is also twice as common in HIV-positive than in HIV-negative individuals.<sup>29,30</sup>

Anal HPV infection is the most significant risk factor for the development of anal intraepithelial neoplasia (AIN), the precursor lesion to anal cancer. HPV DNA has been reported to be found in 88% of cases of squamous cell carcinoma of the anus.<sup>31</sup> HPV type 16 has been shown to be particularly associated with anal cancers.

### *Oral cavity and oropharyngeal cancer*

It has long been established that tobacco and alcohol are significant risk factors for cancers of the mouth and oropharynx. However, many studies in the last 20 years or so have demonstrated the role of HPV in the pathogenesis of cancers of the oral cavity and the oropharynx.<sup>32-34</sup> The prevalence of HPV DNA is higher in oropharyngeal cancers than in oral cancer.<sup>5</sup> A recent meta-analysis by Kramier et al<sup>35</sup> found that the prevalence of HPV-DNA was 35.6% (range, 11%-100%) in oropharyngeal squamous cell carcinomas (SCCs), 23.5% (range, 4%-80%) in oral SCCs, and 24.0% (range, 0%-100%) in laryngeal SCCs. HPV-DNA positivity is highest in tonsillar cancers: the prevalence is more than 50%. HPV type 16 is the predominant type and is found in 87% of HPV-infected oropharyngeal cancers and 68% of HPV-infected oral cavity cancers.<sup>36</sup>

Some studies have reported that individuals with HPV-positive oral and oropharyngeal cancers tend to be younger than those who are HPV-negative.

## Prevention of HPV infection

### *Sex education*

The best protection against HPV is to avoid sexual contact with any person who might be carrying this virus. It has also been reported that the risk of contracting HPV is directly proportional to the number of sexual partners an individual keeps.<sup>24</sup> Several studies have shown that there is generally a lack of awareness of HPV among different populations surveyed worldwide. There is also very poor knowledge of the economic and societal burden of HPV. There is therefore a great need for public enlightenment about this virus. Education messages about HPV should include information about the route of transmission of HPV, the risk factors for viral transmission (such as multiple sexual partners, smoking, and alcohol), and the sequelae of infection by this virus.

### *Condoms*

Anogenital HPV infections are transmitted by skin-to-skin or mucosa-to-mucosa contact and are not dependent upon exposure to semen or vaginal secretions.<sup>37</sup> The use of condoms during intercourse might reduce, but will not totally eliminate, transmission of HPV. Penetrative sexual intercourse is not strictly necessary for a person to become infected.<sup>37</sup> Many studies<sup>38-40</sup> have demonstrated the uncertainty of the protective nature of the condom in the acquisition of this infection. Educational messages must emphasize this finding.

### *Circumcision*

Many studies have reported the preventive role of circumcision in penile cancer and more recently, in HIV transmission.<sup>41-44</sup> A recent large study involving 1913 couples concluded that male circumcision is associated with a reduced risk of penile HPV infection and, in the case of men with a history of multiple sexual partners, a reduced risk of cervical cancer in their current female partners.<sup>45</sup>

### *HPV vaccines*

The development of vaccines against HPV is a major stride in the prevention of HPV infection and consequently reducing the societal and economic burden of HPV-related diseases such as cervical cancer. HPV vaccines contain the major capsid L1 proteins, which self-assemble into virus-like particles (VLP) resembling HPV.<sup>46,47</sup> These particles do not contain viral genetic material and thus are unable to multiply, and therefore are not infectious. Two HPV vaccines are now available, a quadrivalent (HPV types 6, 11, 16 and 18) vaccine and a bivalent (HPV types 16 and 18) vaccine. Both vaccines show greater than 90% protection against persistent HPV infection for up to 5 years after vaccination. They are given to girls between the ages of 9 and 13 years old.

There have been many arguments for and against vaccination in men. The morbidity and mortality rates from HPV type 16- and type 18-related anal, penile, and oropharyngeal cancers among men are lower than the morbidity and mortality rates from cervical cancer among women.<sup>48</sup> Also, the efficacy of the HPV vaccine in preventing these diseases has not yet been established. HPV vaccines will, however, provide protection against genital warts in men. The strongest argument for immunizing men is that with high immunization coverage of both men and women, transmission of the virus may be significantly reduced or even eliminated, and, as a result, eventually women who have not been immunized will get protection.<sup>49</sup>

The cost of the vaccination—three doses cost about US \$400—is beyond the reach of many individuals in developing countries where 80% of cervical cancer cases are found. Many countries in Africa are seriously battling with the burden of high rates of HIV, malaria, tuberculosis, maternal mortality, and childhood illness. Cancer is generally not yet given the same priority as these other conditions. Nevertheless, with increased awareness of HPV and HPV-related diseases, greater political will, and engagement in this issue by pharmaceutical companies who make the vaccines, HPV vaccines may become affordable in these countries.

## Conclusion

HPV infection is a major sexually transmitted disease worldwide. In addition to causing condyloma acuminata in infected men and women, oncogenic subtypes have been associated with a large variety of cancers affecting both sexes. Among the most important, cervical cancer is a global disease of epidemic proportions, with 80% of cases diagnosed in women from Africa and other developing countries. Awareness and education are the key components of prevention, however vaccination has been recently made available. Healthcare providers involved with sexual and reproductive health, child and adolescent medicine, immunization, and cancer control must be aware of the key issues surrounding the introduction of HPV vaccines. □

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## *The worldwide epidemiology of prostate cancer: perspectives from autopsy studies*

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HAAS GP, DELONGCHAMPS N, BRAWLEY OW, WANG CY, DE LA ROZA G. The worldwide epidemiology of prostate cancer: perspectives from autopsy studies. *The Canadian Journal of Urology*. 2008;15(1):3866-3871.

**Introduction:** Prostate cancer is the most frequently diagnosed non-skin cancer in the United States and the third leading cause of cancer deaths. International trends in the incidence, mortality and prevalence of prostate cancer are assessed.

**Methods:** Databases from the Surveillance, Epidemiology and End Results (SEER) program of the National Cancer Institute and the International Agency for Research on Cancer (IARC), and the literature on autopsy studies on prostate cancer were reviewed and summarized in the article.

**Results:** Prostate cancer remains an important public health concern in Western countries and an emerging malignancy in developing nations. Prostate cancer incidence is dependent on efforts to detect the disease. Autopsy studies provide accurate and useful information regarding comparative prevalence rates of the disease among regions of interest.

**Conclusions:** Improved cancer registration is needed in developing nations. The prevalence of prostate cancer must be established to predict the expected incidence of the disease and in order to plan rational detection and treatment strategies. Clinically significant disease should be distinguished from insignificant disease which may pose little or no biological danger to the patient.

**Key Words:** epidemiology, prostate cancer

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### Introduction

Prostate cancer is a disease of increasing significance worldwide. In many industrialized nations such as the United States, it is one of the most common cancers and among the leading causes of cancer deaths.<sup>1</sup> In developing countries it may be less common, however its incidence and mortality has been on the rise.<sup>2</sup> It is

tempting to judge the public health significance of a disease by its incidence or mortality, but when it comes to prostate cancer this dogma is confounded by the very high prevalence of occult disease.<sup>3</sup> Incidence is therefore influenced by the intensity of diagnostic efforts, and the mortality figures reported for any particular geographic area depend on the reliability of cancer registries. The United States has one of the most active prostate cancer early detection programs in the world, and also the highest incidence. Once prostate specific antigen (PSA) tests became available for prostate cancer screening, the United States has experienced a huge increase in prostate cancer incidence.<sup>4</sup> Therefore, it is very important to understand the actual prevalence of prostate cancer in given areas of the world if we wish to compare incidence and mortality figures for various age and racial groups, or between different geographical regions.

### Estimation of prostate cancer prevalence

Prevalence is the number of cases of a particular condition that exists in a given population and consists of diagnosed cases plus those cases that are present but yet undetected. Prostate cancer prevalence can be estimated from a variety of sources.

Several decades ago, many prostate cancers were discovered during the pathological examination of specimens from transurethral prostatectomies. These patients were operated for suspected benign prostatic hyperplasia (BPH), but up to 25% were found to have malignancy.<sup>5,6</sup> However, the frequency of finding such incidental cancers has precipitously dropped since PSA came into existence, as most of the men undergoing surgery for BPH have their PSA tested and those with elevation are worked up.

Several authors investigated the prevalence of prostate cancer in cystoprostatectomy specimens, an operation usually carried out for the treatment of invasive bladder cancer. Twenty-five percent to 40% of prostates were found to contain unsuspected prostate cancer.<sup>7-10</sup> However, we have since then discovered that prostate and bladder cancers may share a common pathway of carcinogenesis, and therefore the association of prostate and bladder cancers may not be coincidental.<sup>11-14</sup> Nevertheless, these clinical studies demonstrated that prostate cancer is present in many patients unsuspected of harboring the disease, and the more thoroughly one examines the specimens, the more cancers will be discovered.

A very important clinical trial performed by Thompson and associates further elucidated the high prevalence of prostate cancer in the general

population. The results of the Prostate Cancer Prevention Trial were published in the *New England Journal of Medicine* in 2003.<sup>15</sup> In this trial, men with normal PSA and digital rectal examination results were biopsied at the end of the study. Fifteen percent of men were found to have prostate cancer. Sextant biopsies were performed in this study, had the authors utilized a more extensive biopsy regimen, most likely additional cancers would have been discovered. Even men with very low PSA values were at some risk for harboring prostate cancer.<sup>16</sup>

Much of what we know today about the prevalence of prostate cancer in various parts of the world comes from autopsy studies. If a representative cross section of a population is evaluated with post-mortem examination, one can determine the frequency of prostate cancer in that particular group. Autopsy studies of prostate cancer have been reported since the 1950s when some of the classical work has been performed by Franks.<sup>17</sup> This is the reference to the supposition that if a man lives to age 100, he will have a nearly 100% likelihood of developing prostate cancer. Breslow et al<sup>18</sup> investigated the incidence, mortality and autopsy prevalence of prostate cancer in a wide geographical area and concluded that while incidence and mortality rates varied greatly, the differences in prevalence were small. Similar conclusions were drawn by Yatani et al<sup>19</sup> who compared Japanese and American men. Guileyardo et al<sup>20</sup> compared an African American and Caucasian cohort of men, and concluded that despite major racial disparities in cancer incidence and mortality, prostate cancer prevalence was similar among the two groups.

These studies differed in their method of tissue processing, thoroughness of examination, and even in the selection of subjects. It is difficult to provide head-to-head comparisons among the reports. However, since the early 1990s, several investigators from very distinct geographical regions of the world utilized similar techniques of analyzing step-sectioned autopsied prostate specimens to report the prevalence of prostate cancer in their particular region.<sup>3</sup> Despite minor differences in their techniques, these authors contributed a wealth of data that can be used to draw meaningful comparisons about the epidemiology of prostate cancer around the world.

### Worldwide incidence of prostate cancer

Prostate cancer has no national boundaries and may be found on all continents. Table 1 is adapted from the database of the International Agency for Research on Cancer (IARC), and represents the most up to date

**TABLE 1. Age-standardized incidence of prostate cancer (per 100000) in the world**

Africa	Congo	29.0
	Kenya	16.6
	Senegal	7.5
	Uganda	38.0
	Zimbabwe	27.4
North America	Canada	78.2
	United States	124.8
	White	107.8
	African American	185.4
Asia	China	1.7
	Taiwan	3.0
	Israel	47.5
	Japan	12.6
	Korea	7.6
	Thailand	4.5
Europe	Austria	71.4
	Tyrol	100.1
	Vorarlberg	66.4
	France	59.3
	Hungary	34.0
	Iceland	75.2
	Norway	81.8
	Spain	35.9
	Sweden	90.9
	Switzerland	77.3
United Kingdom	52.2	
Oceania	Australia	76.0
	New Zealand	100.9

Rates are age-adjusted to the world standard population (WHO). Sources: <http://www-dep.iarc.fr/>.

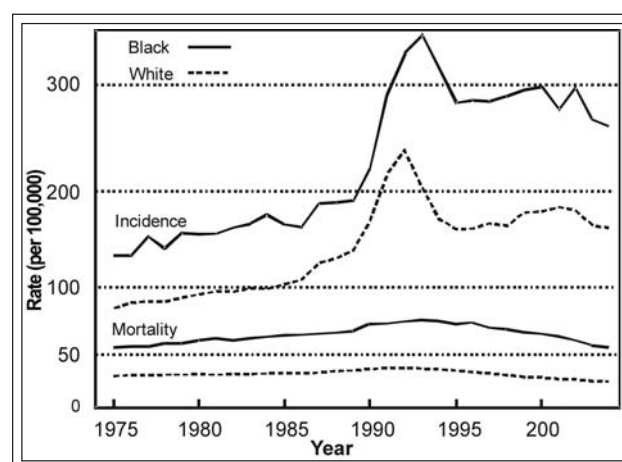
information on the incidence of prostate cancer around the world. The highest rates are from the United States, particularly among African American men. China has some of the lowest incidence rates. Among European countries, the incidence in Austria is notable, because there is wide variation within the country. Incidence rates are very high in the region of Tyrol compared to those reported from the eastern region. Tyrol has an organized, very thoroughly conducted screening program for prostate cancer. Incidence rates in the United States fluctuated during the last decade, Figure 1. We postulate that the great increase in incidence between the late 1980s and the mid 1990s was due to the large number of cases detected once PSA became available and widely utilized. This increase was followed by a dip in the curves as most detectable tumors were identified.

The current slow rise in incidence during the first half of the decade may be due to increased detection efforts with lower PSA thresholds and increased numbers of biopsy cores taken.<sup>21</sup>

### Worldwide mortality of prostate cancer

Table 2 shows prostate cancer mortality rates around the world. Mortality remains highest in Scandinavian countries. In many areas of the world, but particularly in the United States, a steady decline in mortality has been noted during the last decade, Figure 1. There is a great deal of controversy surrounding the role of prostate cancer screening on the reduction of mortality. Advocates attribute the reduction in mortality over the last several years to the delayed effect of early detection initiatives.<sup>22</sup> Some even believe that men who come to attention during prostate cancer screening or treatment are likely to benefit from additional medical attention for unrelated but potentially hazardous conditions, the treatment of which will result in an overall increase in survival.<sup>23</sup> Others believe that prostate cancer screening leads to over treatment of disease which is of low biological risk, therefore creating unnecessary morbidity and cost.<sup>24-28</sup> While it is beyond the scope of this work to resolve the issue, it is apparent that advocates of either side of the argument need reliable data not only of the incidence and mortality, but on the actual prevalence of prostate cancer and its various biological subtypes.

When national trends in mortality are contrasted against the incidence figures, a large disparity is noted



**Figure 1.** Age-adjusted total United States incidence and mortality rates for prostate cancer, all ages. 1995-2004. Age-adjusted to the 2000 United States Standard Population.

**TABLE 2. Age-standardized mortality of prostate cancer (per 100000) in the world**

Africa	South Africa	22.6
	Uganda	32.5
	Senegal	6.5
	Zimbabwe	23.5
Asia	China	1.0
	Israel	13.4
	Japan	5.7
Europe	Austria	18.4
	France	18.2
	Germany	15.8
	Hungary	18.4
	Iceland	23.0
	Italy	12.2
	Norway	28.4
	Spain	14.9
	Sweden	27.7
	United Kingdom	17.9
North America	United States	15.8
	Canada	16.6
Oceania	Australia	17.7
	New Zealand	20.3

Rates are age-adjusted to the world standard population (WHO). Sources: <http://www-dep.iarc.fr/>.

for the United States, where large numbers of men are diagnosed with prostate cancer, and relatively few die of the disease, Figure 1. In contrast, many Asian and African countries, where the incidence rates may be lower, most men will eventually succumb to prostate cancer. This suggests that American men may be either diagnosed earlier, in a more curable state of the disease, or that they may be diagnosed with many more biologically insignificant disease. In contrast,

Asian and African men may be diagnosed later, with advanced stage, incurable disease.

### Prevalence of prostate cancer around the world

Based on autopsy material, prostate cancer prevalence information according to age has been published by several authors, Table 3.<sup>3,19,28-31</sup> Prostate cancer prevalence is highest among American men of Caucasian and African origin, but the trends are similar among all countries reporting. Prostate cancers are identified at a much younger age than would be expected based on incidence data, and most men in the older age groups are effected. It appears that some prostate cancers may pass through a period of latency of up to 15 to 20 years, during which the disease is histologically present but has not come to attention yet. It is uncertain if this is equally true for aggressive, high-risk prostate cancers.

Although the current report does not contain contemporary African sources, earlier reports by Jackson and coworkers<sup>31</sup> documented similar trends from several African countries. Clearly, there is a great need to update this information.

Prostate cancer prevalence rates were lowest among men of Mediterranean origin.<sup>29,30</sup> One of the authors postulated that it is a diet rich in antioxidants from cereals, vegetables, olive oil, etc. which may be responsible for a diminished prostate cancer risk.<sup>29</sup>

Only one study reported an increase in the frequency of latent cancers between two time periods for the same location.<sup>19</sup> Therefore comparisons between time-related trends in incidence or mortality versus prevalence can not be established based on these data.

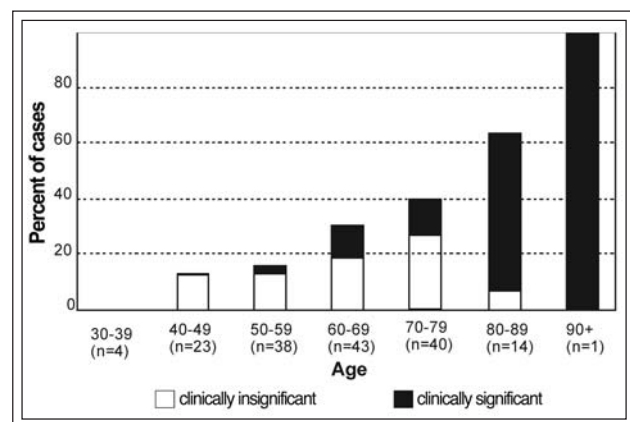
Most of the autopsy detected tumors in younger men are small volume, relatively well differentiated lesions. Histological criteria have been developed based on

**TABLE 3. Autopsy prevalence of prostate cancer in the world**

Age	United States White <sup>3</sup>	United States African American <sup>3</sup>	Japan <sup>19</sup>	Spain <sup>28</sup>	Greece <sup>29</sup>	Hungary <sup>30</sup>
21-30	8	8	0	4	0	0
31-40	31	31	20	9	0	27
41-50	37	43	13	14	3	20
51-60	44	46	22	24	5	28
61-70	65	70	35	32	14	44
71-80	83	81	41	33	31	58
81-90			48		40	73

radical prostatectomy specimens regarding differences between clinically significant versus insignificant prostate cancers.<sup>33,34</sup> Clinically significant cancers are defined as having a volume greater than 0.5 ml or have Gleason grades > 6, or are locally invasive. Tumors that do not meet any of these criteria are thought to represent clinically insignificant, low biological risk tumors that are unlikely to cause risk to the health of the patient. These definitions do not take into consideration patient factors such as age or existing comorbidities, which clearly influence not only the influence of the cancer over survival and life expectancy, but greatly impact on treatment decisions as well. Since the men investigated in the autopsy studies, by inclusion criteria, died of unrelated causes not knowing that they had prostate cancer, technically speaking, all of the specimens would have clinically insignificant disease.

In our most recent autopsy study, prostate cancer prevalence increased with age.<sup>21</sup> We first detected prostate cancer in a 42-year-old man. Although overall 43% of the tumors were clinically significant by histological definition, all but one of the tumors in men under the age of 60 were insignificant, and clinical significance correlated with age thereafter, Figure 2. Half the cancers were multifocal, the majority were Gleason score of 6 or less. It was the larger tumors which were also less well differentiated, while 80% of tumors less than 0.5 ml were of Gleason score of 6 or less. This data should not be interpreted that younger men would not be diagnosed with clinically significant or high-risk disease; we simply did not encounter this variety of prostate cancer in our autopsy study. Possibly men with such more aggressive disease would have presented with an elevated PSA or clinical manifestations of prostate cancer and could have been selected out.



**Figure 2.** Prevalence of prostate cancer in autopsy cases with increasing age.<sup>34</sup>

Our data also provided useful information for clinicians by mapping out the location of the tumors and indicating the recommended biopsy regimen to identify most of the clinically significant tumors.<sup>21</sup>

## Conclusions

The clinical incidence, mortality, and to a lesser degree prevalence of prostate cancer varies among various geographical regions of the world. The approach to screening, early detection initiatives, and availability of treatment modalities has a major impact on disease epidemiology. The differing role of genetic and environmental factors in prostate cancer carcinogenesis is yet to be elucidated. Autopsy studies provide important information toward the understanding of the prevalence of the disease, data which will lead to the rational design of diagnostic initiatives, and the diagnosis of those tumors which need to be identified and treated. There is a paucity of clinical and epidemiologic data from African populations, and this will need to be remedied in the immediate future as attention is focused on cancer care in Africa. □

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## *Genetic susceptibility to prostate cancer in men of African descent: implications for global disparities in incidence and outcomes*

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**Introduction:** Disparities in prostate cancer incidence and outcomes are a hallmark of the global pattern of prostate cancer, with men of African descent suffering disproportionately from this disease. The causes of these disparities are poorly understood.

**Methods:** A review of the literature was undertaken to evaluate the role that genetic susceptibility may play in prostate cancer etiology and outcomes, with a particular emphasis on disparities.

**Results:** The genetic contribution to prostate cancer is well established, and a number of candidate prostate cancer genes have been identified. Significant differences

in the frequency of risk alleles in these genes have been identified across the major races. These allele frequency differences may in part explain an increased susceptibility to prostate cancer in some populations. In addition, non-genetic factors contribute significantly to prostate cancer disparities, and the cumulative contribution of both genetic and non-genetic factors to poor-prognosis prostate cancer may explain the poorer outcomes experienced by men of African descent.

**Conclusions:** Prostate cancer disparities are a function of genetic susceptibility as well as environment, behavior, and health care factors acting in the context of this genetic susceptibility. Elimination of global prostate cancer disparities requires a full understanding of the effects of all of these factors on prostate cancer etiology and outcomes.

**Key Words:** prostate cancer, African descent, genetics, disparities

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### Introduction

Prostate cancer disproportionately affects men of African descent in terms of incidence, morbidity, and mortality. There are significant gaps in our knowledge about the factors that predict disparities in prostate cancer incidence and outcomes between men of African and European descent. This is true both in the United States as well as other geographic locations, including Africa and the Caribbean. In order to fully understand the source and solution to these disparities, it is imperative to integrate diverse scientific

disciplines, methods, and analytic approaches to understand the multiple contributions to disparities in prostate cancer, including factors associated with the social environment (e.g., economic status, access to health care, social isolation), the physical environment (e.g., location or type of residence or medical care setting), behavior (e.g., attitudes, beliefs, and practices associated with prostate cancer screening), and biology (e.g., inherited genotypes that may affect the development of prostate cancer or predict the aggressiveness of a prostate tumor).

### Evidence of global prostate cancer disparities

Prostate cancer has one of the highest incidences and prevalences of any cancer in the world, accounting for 6.9% of all cancers diagnosed. Prostate cancer accounts for 9.7% of all cancers in men, including 15% of cancers in developed countries and 4% of cancers in less developed areas of the world. It is also responsible for almost 6% of cancer deaths in men worldwide. About 600000 new cases of prostate

cancer are diagnosed each year, and approximately 200000 deaths are attributed to prostate cancer. Three-fourths of prostate cancer cases occur in men over the age of 64 years.<sup>1</sup>

Prostate cancer rates vary significantly by geographical region, Table 1. The incidence of prostate cancer is highest in countries where prostate-specific antigen (PSA) screening for prostate cancer is common.<sup>1</sup> These rates are influenced greatly by the detection of latent or asymptomatic prostate cancers through the use of screening modalities. Screening with PSA has not been applied in all regions, including Africa, to the same degree as in the United States.

While rates of prostate cancer are high in Europe and North America, the incidence of prostate cancer is highest among men of African descent in North America and the Caribbean. African American men are at particularly high risk for prostate cancer. Recent SEER data (2006) indicate that the incidence of prostate cancer in African American men is higher than in any other group, with an age-adjusted incidence of 255.5 per 100000 versus 161.4 per 100000 in European

TABLE 1. Sample prostate cancer incidence and mortality rates (per 100000)

Region	Subgrouping	Age-specific incidence	Age-specific mortality	Source
World		25.3	8.2	
Developed countries		56.2	13.5	IARC <sup>105</sup>
Developing countries		9.4	5.2	
Africa	Eastern Africa	13.8	11.8	
	Middle Africa	24.5	21.1	
	Northern Africa	5.8	4.9	IARC <sup>105</sup>
	Southern Africa	40.5	22.4	
	Western Africa	19.3	16.0	
Americas	The Caribbean	52.4	28.0	IARC <sup>105</sup>
	Brazil	53.2	15.8	
	United States: all races	168.0	27.9	
	African American	255.5	62.3	
	European American	161.4	25.6	SEER, 2004
	American Indian/ Alaskan Native	68.2	21.5	
	Asian or Pacific Islander	96.5	11.3	
	Hispanic	140.8	21.2	
Asia	Eastern Asia	3.8	1.9	
Europe	Northern Europe	57.5	19.7	IARC <sup>105</sup>
	Western Europe	61.6	17.5	
Oceania	New Zealand	79.9	18.1	

Americans. African American men also present with more advanced disease at initial diagnosis,<sup>2</sup> and have a worse prognosis than white men.<sup>3</sup> However, the reason for these differences is not completely understood. It has been hypothesized that genetics and environmental exposures may play a role in determining these high rates.<sup>4,5</sup>

Like incidence, prostate cancer mortality rates are highest in populations of African descent. A study by Thompson et al<sup>6</sup> found that after controlling for prognostic variables, African American men were more likely than European American men to have inferior outcomes after receiving hormonal therapy for prostate cancer. This ethnic disparity suggests that there may be a biological difference in prostate cancer as it manifests in African Americans versus European Americans.

Reported prostate cancer rates are low in native Africans, perhaps due to underreporting of the disease. Although not reflected in many international reports, prostate cancer appears to be one of the most prevalent urological malignancies in native Africans.<sup>7</sup> Rates in East and West African populations have been reported to be higher than those in North Africa and other developing countries. However, the validity of these rates in West African populations is not known, and it is possible that rates are substantially higher than those reported in the existing registries.<sup>8</sup>

Prostate cancer may pose a significant public health burden in some African countries, as the majority of newly diagnosed cases present with advanced disease, including poor differentiation of the tumor, metastasis, and neurological symptoms.<sup>9-12</sup> Diagnosis at this later stage of disease often is associated with poor prognosis, which has devastating effects in countries with limited medical resources.<sup>9,12</sup> Because of differences in screening practices which increase the number of low grade or asymptomatic cancers detected, prostate cancer survival is estimated at 80% in the United States compared to 40% in developing nations.<sup>1</sup> A combination of low socioeconomic status, late disease presentation, and limited health care access for prostate cancer treatment in many African countries may contribute to the poor prognosis that African men face after being diagnosed with prostate cancer.<sup>13</sup>

Because African and African American men have common ancestry, knowledge of prostate cancer in African men, and comparisons of prostate cancer in African American men and men of the African Diaspora may provide valuable clues about the causes, prevention and treatment of prostate cancer. International comparisons of prostate cancer rates are complicated by differences in prostate cancer screening, diagnosis and reporting systems.<sup>11,14</sup>

Research on prostate cancer disparities by ethnicity has revealed that there are ethnic differences across populations in terms of diagnostic characteristics and prognostic characteristics, with African Americans having an earlier age at diagnosis and higher PSA levels compared with European Americans.<sup>10,15,16</sup> However, these ethnic disparities are not explained entirely by inequities in socioeconomic status or access to and use of health care.<sup>17</sup>

Despite this evidence, the reasons for disparity in prostate cancer etiology and outcomes in men of African descent are not well understood. Previous research has largely identified individual factors that may be associated with prostate cancer risk or disparities, including family history, age, race, and possibly exposures. However, this research has not generally considered the interaction of multiple factors and the neighborhood context in which they act in determining the causes of disparities. A transdisciplinary approach that considers multiple causative agents may be required to fully understand disparities in prostate cancer and the translation of this information into meaningful disparities reduction approaches. Here, we focus on the possible role of genetic susceptibility in affecting prostate cancer disparities.

## Genetic susceptibility

Genetic contribution to prostate cancer risk is well established. Men with one, two or three first-degree affected relatives have a 2-, 5- and 11-fold increased risk of developing prostate cancer, respectively.<sup>18</sup> In a study of the risk of prostate cancer among 44788 pairs of twins in the Scandinavian countries, 42% of cases were attributed to inheritance, with the remainder considered to be most likely due to environmental factors.<sup>19</sup> These findings have been confirmed by other studies as well.<sup>20,21</sup> Epidemiological studies also suggested that about 9% of familial prostate cancer cases diagnosed by age 85 are caused by transmission of a rare high risk allele, and that this allele accounts for approximately half of the prostate cancer cases diagnosed before age 55.<sup>18</sup> Examples of the genes that may explain these effects are provided below.

### *Candidate androgen metabolism genes*

Of the potential candidate gene pathways, a substantial amount of work has been focused on androgen metabolism genetics. Testosterone is a major determinant of prostate growth and differentiation. There are numerous lines of evidence that support the role of androgen metabolism in prostate cancer etiology. Circulating levels of

androgens have been reported to be higher in populations at increased prostate cancer risk, including African American men,<sup>22</sup> and lower in populations at decreased prostate cancer risk, such as Chinese men.<sup>23</sup> Although serum levels of testosterone do not correlate well with prostate cancer risk,<sup>24</sup> serum levels of dihydrotestosterone (DHT) and other testosterone metabolites do correlate with prostate cancer risk.<sup>22,24</sup> Second, there is abundant clinical evidence that androgens are related to the growth and development of prostate cancers. Androgen ablation in men with hormone-sensitive prostate cancer reduces tumor size, and decreases the associated disease burden.<sup>25</sup> This evidence suggests that the disposition of testosterone may be important in determining prostate cancer risk.

There are several enzymes that determine the activation or inactivation of testosterone, which subsequently influences the signaling capability of testosterone metabolites in androgen-sensitive cells. These genes include the 5 alpha-reductase type II (SRD5A2) and the cytochromes p450 CYP3A4, CYP3A5 and CYP3A43. In addition, the androgen receptor (*AR*) gene encodes a ligand-activated receptor that mediates androgen signaling response.

The SRD5A2 gene encodes the steroid 5 $\alpha$ -reductase type II, which converts testosterone to DHT. The valine to leucine missense variant at codon 89 (V89L) and the alanine to threonine missense variant at codon 49 (A49T) are common SRD5A2 variants that have been associated with prostate cancer etiology or severity.<sup>26-31</sup> The V89L polymorphism on the SRD5A2 is believed to decrease the conversion of testosterone to DHT<sup>32</sup> while A49T is believed to increase the conversion of testosterone to DHT.<sup>30</sup> However, associations of prostate cancer risk involving these variants have not been consistent in all studies.<sup>29,33-40</sup>

The CYP3A multigene family lies in a region of chromosome 7q21-q22, which includes CYP3A4, CYP3A5, CYP3A7 and CYP3A43 in addition to pseudogenes. Only CYP3A4, CYP3A5, CYP3A7, and CYP3A43 are expressed in adults. Previous reports suggested that linkage disequilibrium exists at the CYP3A locus.<sup>41-43</sup> Linkage disequilibrium between CYP3A4 and CYP3A5 in particular, suggests that associations at one locus could be the result of causative effects at the other locus.<sup>42</sup>

The CYP3A genes are involved in the metabolic deactivation (hydroxylation) of testosterone.<sup>44,45</sup> These genes convert testosterone to 2 $\beta$ -, 6 $\beta$ -, or 15 $\beta$ -hydroxytestosterone, and therefore shunt testosterone away from the more biologically active DHT. However, the function of CYP3A4\*1B has been

controversial. In addition to epidemiological evidence that CYP3A4\*1B is associated with prostate cancer, the basic science literature has not consistently supported a functionally significant effect. A number of authors have studied the relationship of CYP3A4 expression or function of CYP3A4\*1B.<sup>46-52</sup> Most of these authors concluded that no biologically meaningful effects existed given the small magnitude of effects that were observed. However, almost all studies have reported consistent elevations in expression associated with CYP3A4\*1B in the range of 20%-200% increase over the consensus CYP3A4\*1A.

CYP3A5\*1 is the only CYP3A5 allele to date that produces high levels of full length CYP3A5 mRNA and expresses CYP3A5.<sup>41</sup> The more common CYP3A5 polymorphism in European Americans, CYP3A5\*3, produces an aberrantly spliced mRNA with a premature stop codon. Therefore, there is ample reason to believe that the CYP3A5 alleles studied here could have a functionally meaningful effect on disease etiology. CYP3A5\*1 has been inversely associated with prostate cancer.<sup>43</sup>

In addition, reports have shown a significant association of CYP3A4 and CYP3A43 with occurrence of prostate cancer.<sup>42</sup> While CYP3A5\*1 had no effect on disease occurrence alone in that study, CYP3A43 increased risk of disease in men with a family history of disease, while CYP3A4\*1B had an overall protective effect. It is unclear why CYP3A43 is associated with prostate cancer when examined alone. CYP3A43 is preferentially expressed in the prostate,<sup>53</sup> but it has rarely been studied. As a result, there is not enough basic science about these genes that can explain the associations with family history-positive prostate cancer. However, one might speculate that this variant is more commonly inherited in men who have a family history of prostate cancer and may be a candidate hereditary gene for prostate cancer.

When CYP3A4 and CYP3A43 were considered in pairwise interactions in our earlier study to determine the effect of having genotypes with at least one CYP3A4\*1B and at least one CYP3A43\*3 allele, there were highly significant protective effects for early onset prostate cancer.<sup>42</sup> This is an interesting finding, as it suggests an association that may have its greatest impact in African Americans. While only 4% of European Americans carry this allelic combination, it was a more common haplotype observed in our African American sample (35%). Therefore, a subset of men who carry the CYP3A4\*1B and CYP3A43\*3 combination and are likely African American are significantly less likely to have been diagnosed with prostate cancer before age 60. The reasons for this

association are not understood, as African Americans, in general, are at high risk to be diagnosed with prostate cancer prior to the age of 60 years.

The androgen receptor (AR), located on the X chromosome, plays a major role in the development and functioning of the prostate gland. AR is expressed in all histologic types and stages of prostate cancer and its transactivation domain is highly polymorphic.<sup>54</sup> Several regions of repetitive polymorphic DNA sequences exist in AR, including CAG trinucleotide repeats encoding polyglutamine residues and GGN repeats encoding polyglycine residues. Several studies have demonstrated an inverse association between the number of CAG and GGN repeats and risk of prostate cancer, advanced cancer, and risk of associated mortality.<sup>55-62</sup> Still, some studies suggest that a positive association exists between prostate cancer and long GGN repeats in combination with short CAG repeats<sup>62</sup> Vijayalakshmi.<sup>63</sup> The combination of GGN/CAG repeats may be the key to understanding how the AR is functioning to promote or inhibit prostate cancer development and progression.<sup>62-64</sup>

### *Race-specific effects*

Genotypes involved in prostate cancer etiology differ significantly across ethnicities. For example, the allele frequencies in candidate prostate cancer susceptibility genes such as CYP3A4 and SRD5A2 differ substantially by ethnicity. We have reported a 4-5-fold higher rate of this CYP3A4 variant in African Americans relative to European Americans.<sup>65</sup> Similarly, Ross et al<sup>66</sup> and Jaffe et al<sup>29</sup> have reported significant ethnic variation in SRD5A2 genotype frequencies that track with race-specific differences in prostate cancer risk. More recently, Zeigler-Johnson et al<sup>67</sup> reported significant differences in the frequency of V89L variant in the SRD5A2 gene by ethnicity, with an L allele frequency of 30% in European Americans, 27% in African Americans, 19% in Ghanaians, and 18% in Senegalese ( $p = 0.002$ ). Differences were also observed for CYP3A4\*1B, with \*1B frequencies of 8% in European Americans, 59% in African Americans, 81% in Ghanaians, and 78% in Senegalese ( $p = 0.0001$ ). When these data were pooled with data from previous studies, significant ethnic differences were observed for each of the polymorphisms. Overall, Asians were least likely to have SRD5A2-V89L and CYP3A4\*1B while Africans, followed by African Americans, were most likely to have those alleles. These results suggest that ethnicity-specific differences in allele and genotype frequencies exist for candidate prostate cancer genes. They further suggest that prostate cancer risk across ethnicity (lowest in Asians and highest in

African Americans) may be correlated with allele frequencies at candidate prostate cancer susceptibility genes. It remains unknown whether or how these inherited genotypes may explain prostate cancer risk and variability in that risk across racial or ethnic groups. However, these findings suggest that African populations may be at genotypically increased prostate cancer risk, even though the actual magnitude of risk is not well characterized. Because so little is known about the genetics of prostate cancer in Africa, research in this area will provide insight into disease etiology and ethnic disparities worldwide that are associated with prostate cancer incidence and mortality.

### *Non-candidate susceptibility genes identified by other methods*

Family-based studies have yielded numerous prostate cancer susceptibility genes, including ELAC2/HPC2 at 17p (MIM 605367),<sup>68</sup> 2'-5'-oligoadenylate-dependent RNase L (RNASEL/HPC1) (MIM 180435)<sup>69</sup> and macrophage scavenger receptor 1 (MSR1) (MIM 153622).<sup>70</sup> Two of these genes, RNASEL and MSR1 have been shown to play a major role in inflammation and innate immunity.

2'-5'-oligoadenylate-dependent RNase L (RNASEL) is a constitutively expressed latent endonuclease that mediates the antiviral and proapoptotic activities of the interferon-inducible 2-5A system.<sup>71,72</sup> Initial linkage analysis studies revealed the presence of two deleterious mutations, Met1Ile and Glu265X in African American and European American families, respectively, that segregated with the disease.<sup>69</sup> Glu265X was also associated with hereditary prostate cancer in other patients from European origin,<sup>73</sup> while Met1Ile was not found in other studies. Two additional deleterious frameshift mutations, 471delAAAG and 147dupCAAT, in this gene was detected in Ashkenazi Jewish and Asian Indian men, respectively.<sup>74</sup> Several missense variants in RNASEL have also been detected.<sup>73,75</sup> One of these variants, Arg462Gln, was implicated in up to 13% of prostate cancer cases using a family-based case-control study.<sup>76</sup> Although there is a low frequency of deleterious mutations in RNASEL, functional studies strongly implicate this gene in the disease. Prostate cancer patients carrying the Glu265X or the 471delAAAG mutation showed loss of heterozygosity of the wild type allele in microdissected tumor DNA,<sup>69,74</sup> while the Arg462Gln had a significantly lower RNASEL enzymatic activity compared to the normal protein.<sup>76</sup>

Macrophage scavenger receptor 1 (MSR1; Chromosome 8p22) is a member of an expanded family of membrane receptors collectively termed scavenger receptors. MSR1 can bind many chemically

modified molecules ranging from bacteria to modified lipoproteins. Correspondingly, MSR1 has been associated with a wide variety of normal and pathological processes, including inflammation, innate and adaptive immunity, oxidative stress and apoptosis.<sup>77</sup> MSR1 maps to the 8p22 chromosome region, which is commonly deleted in prostate cancer.<sup>78</sup> Six rare missense variants and one nonsense mutation within MSR1 were observed to co-segregate with the disease in hereditary prostate cancer families.<sup>70</sup> Furthermore, the prevalence of MSR1 mutations in prostate cancer cases of European and African American descent was substantially higher compared to unaffected men.<sup>70</sup> Arg293X and Ser41Tyr were the most common mutations detected among prostate cancer patients of European and African American descent, respectively.<sup>79</sup>

ELAC2/HPC2 was predicted to encode an evolutionarily conserved, metal-dependent hydrolase, which could partially explain environmental effects on human prostate epithelial cells by postulating differential interactions with environmental exposures.<sup>68</sup> ELAC2 was also shown to encode a 3' processing endoribonuclease, an enzyme responsible for the removal of a 3' trailer from precursor RNA<sup>80</sup> and to interact with  $\gamma$ -tubulin, a component of the mitotic apparatus,<sup>81</sup> suggesting a possible role for ELAC2 in cell cycle control. Initial sequence analyses of the ELAC2 gene identified rare mutations and two common missense changes, Ser217Leu and Ala541Thr that were reported to be associated with prostate

cancer risk.<sup>68,82,83</sup> However, confirmation of these results has been difficult with only weak consensus among studies.<sup>84-85</sup>

#### Race-specific effects

Rennert et al<sup>86</sup> observed significant differences in ELAC2, RNASEL and MSR1 allele frequencies by race. Although no significant association has been found with prostate cancer risk overall, certain effects for MSR1 IVS7delinsTTA and RNASEL Arg462Gln were observed when stratified by race, family history or disease severity in both African American and European American men. No association between the common ELAC2 Ser217Leu and Ala541Thr sequence variants and prostate cancer risk was found. Moreover, Ala541Thr was very rare among African Americans compared to European Americans, and therefore was unlikely to explain the higher rate of prostate cancer in the African American racial group. RNASEL Arg462Gln gene variation is of particular interest since it was clearly associated with reduced functional activity, and although not statistically significant, it was more common among African American cases compared to controls (0.12 versus 0.16), Table 2. When stratified by prostate tumor characteristics, Arg462Gln was associated with low-grade (OR = 1.5, 95% CI 1.04-2.2) and early-stage (OR = 1.5, 95% CI 1.02-2.1) disease in family history negative European Americans, while in family history positive individuals, Arg462Gln was inversely associated with low grade (OR = 0.43 95% CI 0.21-

TABLE 2. Allele frequencies and SIFT analysis of missense polymorphisms in ELAC2, MSR1 and RNASEL genes

Gene	Nucleotide sequence variant	Amino acid change	Substitution probability (Pi)	Allele frequency (total no. of alleles in sample)			
				African American		European American	
				Controls	Cases	Controls	Cases
ELAC2/	650C > T	Ser217Leu	0.15	0.228 (254) <sup>a</sup>	0.211 (180)	0.296 (656)	0.301 (1020)
HPC2	1621G > A	Ala541Thr	0.26	0.004 (268) <sup>a</sup>	0 (190)	0.027 (698)	0.033 (1072)
MSR1	520G > T	Asp174Tyr	0.13	0.015 (266) <sup>a</sup>	0.022 (186)	0 (696)	0 (1064)
	876C > T	Arg293X	0	0 (262)	0 (166)	0.012 (694) <sup>b</sup>	0.007 (994)
	-14,742A > G	None	N/A	0.269 (260) <sup>a,b</sup>	0.253 (186) <sup>b</sup>	0.105 (686)	0.105 (1060)
	IVS5-59C > A	None	N/A	0.012 (246) <sup>a</sup>	0.006 (170)	0.059 (628)	0.050 (968)
	IVS7delTTA	None	N/A	0.264 (220) <sup>a,b</sup>	0.218 (156)	0.057 (562)	0.045 (894)
RNASEL/	793G > T	Glu265X	0	0 (268)	0 (188)	0.001 (714)	0.003 (1080)
HPC1	354C > T	None	N/A	0.004 (266)	0 (182)	0.003 (682)	0.002 (1002)
	1385G > A	Arg462Gln	0.02	0.119 (252) <sup>a</sup>	0.159 (176)	0.361 (642)	0.370 (1010)

<sup>a</sup>Frequency in control groups differs by race (two-sided Fisher's exact tests:  $p < 0.05$ ).

<sup>b</sup>Deviations from Hardy-Weinberg proportions based on  $\chi^2$ . Test at  $p < 0.05$ .

0.88) and low stage (OR = 0.46 95% CI 0.22-0.95) disease. In African Americans however, Arg462Gln was associated with positive family history high stage disease (OR = 14.8 95% CI 1.6-135.7).<sup>86</sup>

These conflicting associations among the different studies may be explained by clinical and genetic heterogeneity of prostate cancer, heterogeneity of study populations, incomplete penetrance, or non-genetic etiologies (e.g., environmental factors). Screening practices for prostate cancer and the inclusion of patients with clinically insignificant disease probably play a role as well. Follow-up meta-analysis studies on the association of prostate cancer with ELAC2, RNASEL, or MSR1 variants found no association or very weak effects of gene variations in these genes with prostate cancer risk overall in either European Americans or African Americans.<sup>84,85,87-90</sup> However due to power constraints, these studies did not evaluate gene variation effects by disease or prostate tumor characteristics. Taken together, these results suggest that although MSR1 and RNASEL do not seem to be associated with disease risk overall, they may still influence disease severity and that this effect possibly varies by family history of cancer and by racial background.

### *8q24 locus*

Recently, a genome-wide linkage study in Iceland<sup>91</sup> and an admixture study among African Americans<sup>92</sup> independently detected markers associated with prostate cancer risk on chromosome 8q24. Of these, a single nucleotide, rs1447295, at 8q24.21 (denoted region 1) was most strongly associated with prostate cancer risk in pooled case-control studies of Caucasians from several countries.<sup>91,93-95</sup> Weaker effects, however, were noted for this SNP among African American men.<sup>93</sup> SNP marker rs1447295 was also reported to be associated with prostate cancer aggressiveness, but this effect varied widely by population and study group.<sup>96,97</sup> Moreover, a second region approximately 350 kb upstream to the previously reported rs1447295, denoted region 2, also demonstrated strong association with prostate cancer<sup>93,94</sup> in both Caucasians and African Americans. These effects were independent of those detected for region 1. Finally, a third region located between regions 1 and region 2 approximately 70 kb centromeric to rs1447295 was also found to be strongly associated with prostate risk in a large nested case-control study of Caucasians, suggesting the presence of at least two independent loci within 8q24 that may contribute to prostate cancer risk in this population.<sup>95</sup>

## Relationship of genotypic susceptibility and other factors

Genetic susceptibility represents only one piece of the very complex nature of prostate cancer etiology. Underlying differences in susceptibility to develop prostate cancer is manifest through exposure to environmental agents, social environmental and neighborhood context, behavior, access to quality health care, and other factors. To fully understand the causes of prostate cancer disparities across groups, a comprehensive approach to the study of many factors involved in prostate cancer causation is required.

### *Environmental exposure*

Relatively few exposures have been consistently associated with prostate cancer risk, and very little information about the role of exposures in establishing prostate cancer disparities is available. Thus, expanded definitions of "the environment" could be developed to include social environment (e.g., socioeconomic status, access to health care, social isolation, cultural beliefs and values); physical environment (e.g., location or type of residence, access to computer and internet resources, or medical care); and behavioral factors (e.g., attitudes, beliefs and practices associated with cancer screening). Thus "environment" could include both individual-level factors as well as neighborhood- or community-level factors using a multilevel approach. For example, neighborhood-level factors could include housing density, measures of social capital such as cultural/civic participation or neighborhood cohesiveness, neighborhood stability such as the percent of rental housing, measures of deprivation such as violent crime rate, and social conditions such as percent of individuals in the neighborhood who live below the poverty level or average educational attainment. Similarly, institutional factors such as health care patterns, access to care, insurance, and type and quality of health care that has been accessed could also be considered. In general, research has focused on individual-level variables, and therefore has not been able to address the larger context in which genes, biological factors, or individual environmental exposures are acting.

### *Health care*

Access to and choice of prostate cancer treatment may have a profound effect on disparities in outcome.<sup>98</sup> African American men are more likely than European American men to undergo watchful waiting instead of

aggressive therapy for localized prostate cancer<sup>99-101</sup> and differences in treatment and mortality persist after adjusting for individual factors such as stage, grade, and socioeconomic status.<sup>99</sup> This remains true despite the observation that mortality differences can be explained by lower rates of aggressive treatment in African American men.<sup>102,103</sup> A strong relationship exists between cancer outcomes and hospital and provider characteristics, prevalent distrust of research/teaching hospitals among African Americans, and links between residential segregation and racial alienation.<sup>98</sup> However, there remain little data about the role of social environment, including factors that affect access to care, contributes to racial disparities in access to quality prostate cancer treatment.

### *Social environment and behavior*

Social environment, including culture, is increasingly recognized as having an important impact on cancer outcomes in ethnically diverse populations.<sup>98</sup> Environmental stressors such as life stress, racism, and discrimination may have a deleterious impact on physiological (i.e., immune functioning, cardiovascular reactivity) and behavioral (i.e., coping efforts, dietary behaviors, smoking) responses to prostate cancer.<sup>104</sup> While African ancestry is a marker for other factors that might better explain quality of life, ethnicity alone does not provide information on the causes of these disparities. Incorporating biological and other factors into the application of assessment of risk and outcomes could improve interventions that could be addressed through psycho-educational approaches designed to facilitate stress reduction and increased confidence to cope with treatment-related side effects<sup>98</sup>.

### Implications for prostate cancer disparities

Our limited knowledge about the genetic and other biological events that cause prostate cancer disparities presents a major barrier to eliminating these disparities. The accumulating knowledge of the human genome provides an opportunity to apply knowledge of carcinogenic mechanisms to the problem of prostate cancer disparities. The incorporation of biomarkers in cancer disparities research provides new opportunities for clinical and public health research and practice, and has the potential to catalyze needed improvements in the prevention and management of cancer to eliminate cancer disparities.

Prostate cancer may be a major cancer burden in African men, so it will be important to understand etiological factors including inherited genotypes that confer risk of developing prostate cancer. Understanding

prostate cancer in Africa may inform us about inherited predisposition, modifiable risk factors, and disease prevention in the high risk African American population. Additionally, knowledge of the interactions of prostate cancer susceptibility genes, environment, and behavior could be used to identify individuals at risk of developing prostate cancer with poor outcomes for heightened screening or prevention modalities, and to identify optimal treatment strategies for men of African descent. □

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# *A study of PSA values in an unselected sample of Senegalese men*

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JALLOH M, ZEIGLER-JOHNSON C, SYLLA-NIANG M, NIANG L, LABOU I, KONTE KA, REBBECK TR, GUEYE S. A study of PSA values in an unselected sample of Senegalese men. *The Canadian Journal of Urology*. 2008;15(1):3883-3885.

**Objectives:** Limited data exist about prostate cancer screening in Africa. The goal of this study was to describe the distribution of prostate-specific antigen (PSA) values in an unselected population of Senegalese men being screened for prostate cancer, and to assess the role of PSA screening tests in the early detection of prostate cancer in this population.

**Patients and methods:** We undertook a cross-sectional study in a community outreach setting with 113 unselected Senegalese men. Participants completed a questionnaire, underwent a digital rectal examination (DRE), and provided a blood sample for PSA testing. The questionnaire focused on demographic data, voiding problems, PSA values, and cigarette smoking. The Kruskal-Wallis test and the Fisher exact test were used to describe differences in PSA values among the groups.

**Results:** The median age of the participants was 65 years

(range, 36-87 years). Five percent of the men knew about PSA screening and 3% had ever been tested for PSA. The median PSA value overall was 1.28 ng/ml (range, 0.14 ng/ml-50.16 ng/ml). In the first 3 age quartiles (< 55, 55-64, and 65-72 years), the median PSA increased with age (1.0, 1.3, and 2.3 ng/mL, respectively;  $p = 0.012$ ) as did the percentage of men with PSA  $\geq 4.0$  ng/ml (4%, 7%, and 28%, respectively;  $p = 0.034$ ). The percentage of men with a PSA  $\geq 4$  ng/ml was higher in the abnormal versus normal DRE group ( $p = 0.023$ ), while the median PSA was lower in the smoking versus nonsmoking group ( $p = 0.022$ ). We found no relationship between PSA and occupation or ethnic group. **Conclusion:** PSA screening is not widely used in Senegalese men. In this sample, the likelihood of having an abnormal PSA increased with age and was more common in men with abnormal DREs. These results may motivate additional studies to determine if wider use of PSA testing in this population could lead to the detection of more prostate cancer cases and improve clinical outcomes among cancer cases.

**Key Words:** PSA, prostate cancer, early detection, ethnicity

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## Introduction

Prostate cancer is the most common non-cutaneous male cancer and its incidence has increased since the wider use of prostate-specific antigen (PSA) screening for early cancer detection.<sup>1,2</sup> In 2004 in the United States, the estimated incidence of prostate cancer was

145.3 cases/100000 men.<sup>3</sup> The greater use of PSA testing has led to an increase in the number of prostate cancer cases that are diagnosed early.<sup>2</sup> To date, there is no nomogram for prostate cancer screening relevant to sub-Saharan Africa (the area of Africa south of the Sahara desert) and few studies have examined the epidemiology and management of prostate cancer in this region. The aim of this study was to examine the awareness of PSA screening and to determine the distribution of PSA values in a nonselected population of Senegalese men, and to explore whether PSA testing could play a role in the early detection of prostate cancer in these men.

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## Materials and methods

We undertook a cross-sectional study in a community outreach setting in Senegal in which 113 unselected men with no known history of prostate cancer or prostate disease completed a questionnaire, underwent a digital rectal exam (DRE), and provided a blood sample for PSA testing. All participants were from two regions of Senegal: the region around Dakar, the capital city — partly in the city (urban) and partly in Sendou village (rural) — and Fimla village in the Fatick region (rural). The questionnaire focused on demographic details, knowledge of PSA testing, previous PSA values and DRE results, and tobacco use. Descriptive analyses were carried out for discrete traits. The Kruskal-Wallis test and Fisher exact test were used to compare discrete traits among different groups. Medians were used to summarize continuous traits.

## Results

The median age of the study participants was 65 years (range, 36-87 years). Most of the men (85%) were from rural regions. Only 5% of them knew about PSA screening and only 3% had ever undergone PSA testing. The distribution of the population by ethnic groups is summarized in Table 1. The two largest ethnic groups were the Serere (48%) and Wolof (39%) groups. Most participants were either farmers (35%) or fishermen (27%), as summarized in Table 2.

The median PSA of the study participants was 1.28 ng/ml (range, 0.14 ng/ml-50.16 ng/ml). A total of 16% of the participants had total PSA values  $\geq 4.0$  ng/mL. We found an abnormal DRE in 11% of cases, and 47% of the men admitted to smoking cigarettes.

TABLE 1. Distribution of the study population among ethnic groups

Ethnic group	Number of participants (n = 113)
Serere	48 (42%)
Wolof	39 (35%)
Peulh	15 (13%)
Manding	6 (5%)
Maure	2 (2%)
Soninke	2 (2%)
Sonrai	1 (1%)

TABLE 2. Distribution of the study population among occupations

Occupation	Percentage (n = 113)
Farmers	35%
Fishermen	27%
Bricklayers	5%
Civil servants	5%
Drivers	5%
Others	< 5% each

The comparison of PSA values among the different groups is summarized in Table 3. In the first 3 age quartiles (< 55, 55-64, and 65-72 years), the median PSA increased with age (1.0, 1.3, and 2.3 ng/ml, respectively;  $p = 0.012$ ) as did the percentage of men with PSA  $\geq 4.0$  ng/ml (4%, 7%, and 28%, respectively;  $p = 0.034$ ). The percentage of men with a PSA  $\geq 4$  ng/ml was higher in the abnormal versus normal DRE group ( $p = 0.023$ ), while the median PSA was lower in the smoking versus smoking group ( $p = 0.022$ ). We found no relationship between PSA  $\geq 4$  ng/ml and occupation ( $p = 0.915$ ), ethnicity ( $p = 0.533$ ), existence of voiding dysfunction ( $p = 0.123$ ), or geographic origin ( $p = 0.465$ ).

TABLE 3. Comparison of PSA values among 113 Senegalese men

Group	Median PSA (ng/ml)	PSA $\geq 4.0$ ng/ml
Age quartile		
< 55 (n = 25)	1.0	4%
55-64 (n = 29)	1.3	7%
65-72 (n = 29)	2.3	28%
> 72 (n = 30)	1.3	23%
	$p = 0.012$	$p = 0.034$
Abnormal DRE		
No (n = 101)	1.3	13%
Yes (n = 12)	1.8	42%
	$p = 0.229$	$p = 0.023$
Cigarette smoking		
No (n = 60)	1.4	20%
Yes (n = 53)	1.1	11%
	$p = 0.022$	$p = 0.208$

## Discussion

The purpose of this study was to examine PSA levels in an understudied Senegalese sample. We found that increases in PSA levels were associated with advancing age, nonsmoking status, and abnormal DRE. We found no relationships between PSA levels and occupation ( $p = 0.915$ ), or ethnicity ( $p = 0.533$ ), or the existence of a voiding dysfunction ( $p = 0.123$ ).

Some study participants in this sample were relatively young (36 years old). The study included these young participants since some data in the literature supports the possibility of prostate cancer occurring at this age.<sup>4</sup> We found an increase in median PSA values in the first 3 age quartiles up to age 72. This finding is consistent with the results of Kohayashi<sup>5</sup> in Japan and Lee<sup>6</sup> in Korea, although in the later study, median PSA values increased even in older age groups. The increase in the prevalence of PSA  $\geq 4.0$  ng/ml with increasing age could lead to a higher rate of detection of prostate cancer with increasing age, according to some studies.<sup>5-8</sup> This increase in the rate of PSA  $\geq 4.0$  ng/ml with age is also consistent with some data that suggest that an age-specific cut-off for PSA should be used.<sup>9</sup> The two main ethnic groups (Serere and Wolof) in this study are predominant in the geographic regions where the study was conducted. These areas are close to the sea and also offer land suitable for farming, and most people who live there are farmers or fishermen.

Data in the literature suggest that a PSA cut-off value of 4 ng/ml gives the highest sensitivity and specificity for the detection of prostate cancer.<sup>10</sup> In our study, 16% of participants had a PSA  $\geq 4.0$  ng/ml. This prevalence is higher than that found by Mettling<sup>11</sup> in a study from the United States where 13% of a population of 2996 men aged 55 to 70 years had a high PSA value. In Japan, Egawa et al<sup>12</sup> and Uchida et al<sup>13</sup> found a lower prevalence of PSA  $\geq 4.0$  ng/ml in screened populations, reporting that 3.6% of 1227 men aged 55 years or older had a PSA  $\geq 4.0$  ng/ml, and 5.6% of a population of 899 men had a PSA  $\geq 4.0$  ng/ml, respectively. One limitation of our study is the small number of participants compared to these other studies. However, with a small sample, we were unable to detect differences in PSA by demographic variables. Our study should be continued to include more participants and perhaps other variables (i.e. body mass index, diet) that may help to identify men at highest risk for prostate cancer.

## Conclusion

A wider use of PSA testing in this population could lead to the detection of more prostate cancer cases. Even more

important, we need to determine PSA cut-off values specific to this population. Some authors suggest there is a need to adjust PSA cut-off values for ethnic groups other than white men. Discussions about ways to effectively treat prostate cancer in developing countries are still needed. However, such conversations may suggest that men who are found to have high PSA values should undergo follow-up examinations that include a repeat PSA test and a prostate biopsy, to better assess the place of PSA screening in the early detection of prostate cancer. □

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## Teaching radical prostatectomy in sub-Saharan Africa

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RUENES JR A, GUEYE SM. Teaching radical prostatectomy in sub-Saharan Africa. *The Canadian Journal of Urology*. 2008;15(1):3886-3889.

*In the United States alone, approximately 220000 new cases of prostate cancer will be detected in 2007, and 27000 men will die of that disease. African American men will suffer disproportionately, having a prostate cancer incidence that is nearly 60% higher than their Caucasian counterparts. In fact, it is widely accepted that African American men have the highest incidence of prostate cancer in the world. This observation has led investigators to study the prostate cancer risk among African men in an effort to identify factors responsible for the high incidence of prostate cancer that plagues the African American population. Findings suggest that the public health burden of prostate cancer to native African men is substantial.*

*Effective management of prostate cancer depends on early detection of the disease and its definitive treatment. Cost-effective management can be elusive. Radical prostatectomy*

*can cure clinically localized disease and may offer long-term cancer control in patients with stage T3 disease. Of the various forms of radical prostatectomy, radical perineal prostatectomy is ideally suited to accomplish these goals in sub-Saharan Africa.*

*A program to teach radical perineal prostatectomy has begun in Dakar, Senegal. It is a system based on graded surgical responsibility. High-quality audiovisual guides familiarize surgeons with the procedure's unique anatomic concerns. They then observe live procedures, assist in live procedures and eventually begin performing the live procedures under direct supervision. Repeated performance of the operation with simultaneous critique is the hallmark of this program, the goal of which is to establish a center of excellence where surgeons throughout the continent can come to learn this technique.*

**Key Words:** prostate cancer, radical perineal prostatectomy, sub-Saharan Africa, prostate specific antigen

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### Introduction

In the United States alone, approximately 220000 new cases of prostate cancer will be detected in 2007, and over 27000 men will die of the disease.<sup>1</sup> African American men will suffer disproportionately, having a prostate cancer incidence that is nearly 60% higher

than their Caucasian counterparts.<sup>2</sup> In fact, it is widely accepted that African American men have the highest incidence of prostate cancer in the world. Several other populations of African descent, particularly in the Caribbean, are afflicted by unusually high incidences of the disease as well.<sup>3</sup> These observations have led investigators to study the prostate cancer risk among African men in an effort to identify factors responsible for the high incidence of prostate cancer that plagues the African American population. Findings suggest that the public health burden of prostate cancer to native African men is substantial.<sup>4</sup>

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Effective management of prostate cancer depends on early detection of the disease and its definitive treatment. Cost-effective management can be much more elusive. Radical prostatectomy can cure clinically localized disease and may offer long-term cancer control in patients with stage T3 disease.<sup>5,6</sup> Of the various forms of radical prostatectomy, radical perineal prostatectomy is ideally suited to accomplish these goals in sub-Saharan Africa. It can be performed under general or regional anesthesia. Blood transfusion is not generally needed. It does not require the costly technology associated with laparoscopic or robot-assisted prostatectomy. It is comparable to other forms of radical prostatectomy in terms of positive margin rates, nerve-sparing capability and in the incidence of postoperative stress urinary incontinence.

A program to teach radical perineal prostatectomy has begun in Dakar, Senegal. It is a system based on graded surgical responsibility. High-quality audiovisual guides familiarize surgeons with the procedure's unique anatomic concerns. They then observe live procedures, assist in live procedures and eventually begin performing the live procedures under direct supervision. Repeated performance of the operation with simultaneous critique is the hallmark of this program, the goal of which is to establish a center of excellence where surgeons throughout the continent can come to learn this technique.

### Cancer risk and obstacles to diagnosis and treatment

Several authors have identified and documented the African American male's increased risk of developing adenocarcinoma of the prostate when compared to men of other races. Like men with a family history of prostate cancer, being of the African American race mandates tight surveillance and screening for prostate cancer since these men are at risk to develop prostate cancer at a relatively early age.<sup>7,8</sup> Additionally, they are more likely than men of other races to be diagnosed with high-grade disease, and according to some reports, advanced stage disease.<sup>9</sup>

Socioeconomic and cultural factors have been implicated in the race disparity, particularly with regard to prostate cancer stage at the time of presentation.<sup>10</sup> Access to quality healthcare in the United States often hinges upon financial well being. Poverty creates a major obstacle toward receiving care even for acute medical problems. Health maintenance and screening can be seen as an unaffordable luxury by the impoverished or uninsured. As a result, scheduled digital rectal exams and prostate specific antigen (PSA) blood testing are

neglected. The cost of travel to the nearest medical professional can prove prohibitive. Among the poorer communities, public awareness campaigns are either non-existent or fall far short of their aim. Faced with potential treatment-related erectile dysfunction and stress urinary incontinence, many with access to care choose not to be evaluated.

The same barriers that prevent adequate prostate cancer screening, early detection and definitive treatment for the African American male also plague the native sub-Saharan male. Further complicating the effective management of prostate cancer in sub-Saharan Africa is the general unavailability of radiation therapy, leaving radical prostatectomy the sole curative therapeutic option. It is therefore critical that a center of excellence be established in sub-Saharan Africa to perform and teach affordable, minimally invasive, nerve sparing radical prostatectomy.

### Radical perineal prostatectomy

Radical perineal prostatectomy was made popular in the United States in the early 1900's. Hugh Hampton Young, working at Johns Hopkins Hospital in Baltimore, Maryland used the perineal route, first described by Buchler, for surgical extirpation of the prostate. The procedure remained in favor until the 1970's.<sup>11</sup> When the importance of lymphadenectomy as a critical staging tool was recognized, surgeons began approaching the prostate through the retropubic approach, which allowed simultaneous access to the pelvic lymph nodes. The anatomic localization of the neurovascular bundles by Patrick Walsh increased the appeal of the retropubic prostatectomy. Radical perineal prostatectomy remained in decline until the 1990's, when a resurgent interest in the procedure was born out of the advent of PSA and algorithms that could predict the likelihood of lymphatic metastases based on blood levels of the serine protease and the Gleason grade determined by prostate biopsy.<sup>12</sup> The push toward minimally invasive procedures also helped enhance the popularity of radical perineal prostatectomy, yet even today fewer than 5% of urologic oncologists perform radical prostatectomy using this approach.

Radical perineal prostatectomy is performed through a curvilinear incision placed between the two ischial tuberosities, approximately 2 cm from the anus. Once the central tendon of the perineum and the rectourethralis muscles are incised, the prostate becomes palpable, lying just beyond Denonvillier's fascia. A vertical midline incision into Denonvillier's fascia allows mobilization and preservation of the

neurovascular bundles and identification of the membranous urethra at the apex of the prostate. The dorsal venous complex is avoided during removal of the gland, limiting blood loss. The vesicourethral anastomosis is performed in a widely open, shallow surgical field with excellent visualization of the bladder neck and membranous urethra, making anastomotic suture placement simple. An indwelling Foley catheter remains 10 to 14 days postoperatively. Short-term and long-term complications of radical perineal prostatectomy and the incidence of positive surgical margins parallel those of radical retropubic prostatectomy,<sup>13,14</sup> however, postoperative pain and the need for blood transfusion are less with radical perineal prostatectomy.

Radical perineal prostatectomy is well suited to sub-Saharan Africa where financial limitations, access to an untainted blood supply and a cultural aversion to the potential postoperative sexual dysfunction and urinary incontinence can be significant concerns.

All the instruments used in performing a radical perineal prostatectomy are durable and reusable, therefore the average cost per case is quite low. The only case by case expenditures are the Foley catheter, a Penrose drain, sutures, hemostatic clips (optional), sponges (compresses), and dressings. The average cost of these items is \$260 (US) per case, including the hemostatic clips. In Senegal, as opposed to in the United States, surgical drapes, electrocautery equipment and suction devices are reusable and further curtail costs.

The average blood loss during radical perineal prostatectomy at our institution is 314 ml. Blood transfusion is required in less than 8% of cases. Where autologous blood donation programs are not available or where a reliable source of untainted blood cannot be guaranteed, radical perineal prostatectomy can provide results equivalent to laparoscopic or robot-assisted prostatectomy in terms of this outcome parameter.

Unlike laparoscopic or robot-assisted prostatectomy, radical perineal prostatectomy can be performed under either general or regional anesthesia. Anesthetic costs associated with the procedure can therefore be more tightly controlled. Also limiting anesthesia costs, regardless of the route of the anesthetic chosen, is the relatively short operative time. At Doylestown Hospital the average radical perineal prostatectomy is accomplished within 82 minutes.

The incidence of post-prostatectomy urinary incontinence is approximately 3% one year after surgery at our institution. The severity of the urinary incontinence is generally mild and manageable with a light pad. The incidence of postoperative erectile

dysfunction is dependent upon a number of preoperative and intraoperative factors, including patient age, preoperative erectile function and the ability to perform a bilateral nerve sparing prostatectomy. In healthy males under age 60 years who are fully potent and receive a bilateral nerve-sparing procedure, nearly 40% will remain impotent 2 years postoperatively. Sixty percent of our patients will be potent at that same end point, some relying on PDE5-inhibitors. Proper preoperative counseling and education will likely determine whether the average sub-Saharan male finds the risk of post-prostatectomy incontinence and erectile dysfunction acceptable.

### Training program

In June 2004 the first radical perineal prostatectomies were performed at Hôpital Général de Grand-Yoff in Dakar, Senegal as part of a nascent training program. Present were Dakar University staff physicians and residents along with a number of visiting professors from Dakar and neighboring West African nations. The surgeries were preceded by an audiovisual presentation to familiarize participants with the procedure they were to observe. Visiting professors and residents participated in the procedures as first assistants. Live recordings of the operations were made and a video teaching library was begun. Between the summer of 2004 and the spring of 2007 urologists from Dakar University and Doylestown Hospital in Doylestown, Pennsylvania visited one another's institutions to advance the teaching process. A second formal training program was held in Dakar in April 2007. Participants took a more active role in the surgeries performed at this time. Once again, didactic sessions were scheduled as part of the program and included presentations in anatomy and pathology.

The hallmark of the Dakar surgical training program is active participation with direct supervision. It is styled after typical Western surgical residency programs characterized by graded surgical responsibility.<sup>15</sup> To best prepare West African surgeons to perform radical perineal prostatectomy on their fellow countrymen it is critical that they be trained in their own facilities. A strength of this program is that it has been established in West Africa. Using equipment and technologies already available in the region, radical perineal prostatectomy has been successfully performed and taught. The goal of this program is to establish a center of excellence where surgeons from throughout the African continent can travel to learn this form of radical prostatectomy. To realize this goal, future training programs will be scheduled in Dakar, surgeons in training will review instructional videotape recordings

between scheduled live demonstrations and a select few will be chosen for most intense training. Hopefully, with adequate financial support, a surgeon-in-residence program can be developed to provide continuous instruction for periods of months at a time. □

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## *Management of advanced prostate cancer in Africa*

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**Background:** Carcinoma of the prostate (CaP) is the most common male malignancy in developed and developing countries and has been termed the "malignant epidemic of blacks." Despite this, clinicians managing men with advanced CaP in Africa have to contend with significant limitations in the healthcare systems. This article reviews the current and future options for the management of these patients on the African continent.

**Methods:** We searched PubMed and Google for articles on CaP with an emphasis on those focusing on subpopulation differences. Information was also obtained from ongoing studies and interviews with urologists and other specialists and executives in hospitals in our locality.

**Results:** In Africa, most patients with CaP present with advanced disease, and surgical castration is the most

common treatment option, as most modern treatment strategies for the disease are unavailable or unaffordable. Unfortunately, a significant proportion of these men progress to hormone-resistant disease shortly after first-line hormonal treatment, and a majority die within 2 years. Problems that are peculiar to the African continent include poor health facilities, scarcity of expert care, high cost of treatment, lack of data, low level of awareness of the disease, absence of early detection and treatment programs, cultural limitations, and the prominence of alternative medical practice.

**Conclusion:** Most Africans with CaP present with advanced disease, and treatment is mostly limited to bilateral orchiectomy, but the results are poor. The care of these patients can be improved by increased funding of healthcare institutions and projects directed at prevention, early detection, and treatment.

**Key Words:** prostate, prostate cancer, native African men, African health, palliative care

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### Acknowledgement

This paper was presented in part at the Scientific Meeting of the African Organization for Research and Training in Cancer, Cape Town, South Africa, on October 27, 2007.

This paper is dedicated to all African patients with prostate cancer and to those who care for them.

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### Introduction

Carcinoma of the prostate (CaP) is the most commonly diagnosed male malignancy worldwide, and is now the second major cause of death from cancer in the United States.<sup>1</sup> CaP has been termed "the malignant epidemic of blacks," as the highest incidence of the disease has been recorded in native and migrant black subpopulations worldwide.<sup>2-5</sup> African-American men (AAM) are also twice as likely as Caucasian Americans to die from the disease,<sup>6</sup> and black men worldwide are more likely to present at a younger age with more

advanced disease and are known to have a poorer prognosis.<sup>7,8</sup>

In Africa, CaP represents 14%-22% of prostatic diseases presenting to health institutions with a peak incidence in the seventh decade.<sup>9-13</sup> The commonest disease cell-type is adenocarcinoma (98%), with 34%-52% of adenocarcinomas being moderately or poorly differentiated.<sup>10-13</sup> Due to the absence of widespread CaP screening programs in African countries, almost all patients present with either irritative and/or obstructive lower urinary tract symptoms, while symptoms and signs of metastatic disease are seen in up to half of the patients.<sup>7,14</sup> At the final diagnosis at presentation, 50% to 80% of patients have advanced disease (T2-T4) at presentation with almost two-thirds having evidence distant/extra-capsular (M1) involvement.<sup>2,7,15</sup>

The late presentation of most CaP patients in Africa presents a challenge to healthcare practitioners (urologists and others). This paper reviews the management strategies currently available for advanced CaP in Africa, identifies the limitations, and proffers suggestions for improving the care of these patients.

### Current management of advanced prostate cancer in developed countries

Most patients with CaP in developed countries have localized disease at presentation and are treated with radical surgery and radiotherapy with good results.<sup>1</sup> Advanced disease is seen at presentation only in a few cases (with blacks comprising a higher proportion of these), and only 15% of patients with localized disease who are treated with radical prostatectomy will progress to advanced stages at 10 years.<sup>16</sup> The Scher and Heller dynamic model of CaP is widely used to guide the management of CaP in the developed world.<sup>17</sup> This model divides CaP into five timelines (localized CaP, biological relapse, clinical metastatic non-castrate disease and clinical metastatic castrate disease and hormone refractory disease) and the last three are considered to be advanced disease. Treatment of this stage is mainly palliative and involves androgen ablation, usually by medical (anti-androgens and/or luteinizing hormone-releasing hormone (LHRH agonists) or rarely surgical castration, which is effective in 80% of patients.<sup>1,18</sup> Hormonal ablation therapy, however, is not curative, and the duration of response to the treatment rarely lasts more than 2 years.<sup>19</sup> Most patients will eventually develop resistance to first-line hormonal therapy and require second-line hormonal manipulation, which most respond to at least for awhile.<sup>20</sup> Symptomatic treatment

with radiotherapy and bisphosphonates may also then be instituted. Although CaP was previously considered to be chemo-resistant, recent success has been reported with chemotherapy,<sup>20,21</sup> and these drugs have now being approved for use in the clinical setting.

### Current management of advanced prostate cancer in Africa

In Africa as a whole, the protocol for the management of advanced CaP described above is inapplicable due to the limited availability of prostate-specific antigen (PSA) testing, and of radical surgery and radiotherapy as treatment options for locally advanced CaP.<sup>22</sup> As such, advanced stages of the disease are often determined clinically with minimal investigations and usually include locally advanced (inoperable/T2-T3) disease, along with metastatic and hormone-resistant disease. Most patients with CaP in Africa present with advanced disease and hormone ablation remains the only treatment of these stages of the disease in most of these patients. In contrast to developed countries, however, this is usually achieved with bilateral orchiectomy (75%) or stilboestrol, with only a few patients being treated with either anti-androgens (Flutamide/Casodex) or LHRH agonists.<sup>14,15,23</sup> Symptomatic treatment is also given as is required and could include analgesia, blood transfusion for anemia, channel- trans-urethral resection of the prostate (TURP) or catheterization for relief of urinary retention, and dialysis for correction of electrolyte derangement. Second-line treatment of hormone-resistant disease is usually with stilboestrol, or anti-androgens and/or LHRH agonists where available/affordable and not already utilized as first-line management. Bilateral orchiectomy has also been shown to be effective in a few patients in whom LHRH-induced combined androgen blockade has failed and who have normal serum testosterone.<sup>24</sup> External beam radiotherapy is available for palliative care in a few centers. Chemotherapy has recently been introduced to the African continent, but it is only available in a few cities.

Similar to results in the developed nations, symptomatic improvement occurs in up to 80% of patients following first-line hormonal ablation, including full (50%-78%) or partial (22%) recovery of function in almost all of those who present with paraplegia.<sup>14,15,25</sup> In contrast to the developed world, however, despite the initial positive response, the prognosis of native African men (NAM) with CaP is poor, and the overall death rate has been cited as being as high as 64% in 2 years.<sup>2</sup> The survival rate of patients with well-differentiated cancers

is, however, quite good with a > 80% 4-year survival, compared to 0%-33% of patients with moderate-to-poorly differentiated cancers.<sup>15,23</sup> Patients with neurological deficits have the worst prognosis with 44% dying within 6 months of presentation.<sup>25</sup>

### Limitations to the effective management of advanced prostate cancer in Africa

The goals of the management of patients with advanced CaP in Africa are similar to those in all other diseases and in other parts of the world. However, there are peculiar challenges to achieving this objective in the management of this stage of CaP on the African continent.<sup>22</sup>

#### *Peculiarities of CaP in Black men (native Africans and African-American men)*

The aggressive nature of CaP in black men is a limitation to effective management of the advanced stages of the disease in Africa. This is because men of the subpopulation have less favorable postoperative outcomes compared to others.<sup>1,26,27</sup> Interestingly histo-pathological comparative studies of CaP in (Nigerian) native African men (NAM) and AAM reported that the peak age of NAM men at diagnosis with CaP was significantly lower than AAM, and that a significantly greater proportion of NAM presented with advanced disease as compared to AAM.<sup>28,29</sup>

Thus, the unfavorable phenotype observed in the black subpopulation with CaP may be even more pronounced in the native African population.

#### *Poorly funded and inadequate healthcare systems*

Most people in Africa are poorly educated and poorly informed about health issues including CaP,<sup>30</sup> resulting in late presentation to hospitals. Furthermore, attendance of patients at these health facilities is reducing due to a multitude of factors, Table 1 prominent amongst which are the high cost of treatment (which is borne almost completely by the patient and his/her family due to the absence of health insurance in most countries,<sup>31</sup> and the patient/community unfriendliness of the hospital protocols and staff. Hence, most patients prefer to patronize alternative medical practitioners (traditional and faith healers or other alternative health providers) who are considered cheaper, friendlier, and more accessible.

#### *Poor funding of tertiary and specialist hospitals*

In the midst of the poor funding of the health systems in Africa, tertiary and specialist institutions are even more poorly funded as a policy of most governments on the continent. This is due, in part, to a World Bank's report that called for 'a reduction of government expenditure in tertiary facilities, specialist training, and intervention that provide little gain for money spent'.<sup>32</sup> This policy has had the following effects:

TABLE 1. Factors responsible for the reduction of patient attendance of orthodox hospitals in Africa

1. The number of general and specialists are too few for the populations they serve
2. The urban location of most of the specialist hospitals makes them distant and difficult to access by the majority of the population
3. Poor funding of these institutions resulting in inadequate infrastructure and equipment which are poorly maintained and are therefore frequently non-functional
4. Patients often require multiple visits in the course of their investigations and treatment (may be further prolonged by equipment failures).
5. High cost of health care which is unaffordable by majority of the people and is further increased by the cost of travelling to and from hospital visits.
6. The hospital staff and protocols are socially unresponsive (community/patient unfriendly)
  - Use of foreign languages for communication (by staff) and for hospital operating systems
  - Lack of patient information leaflets
  - Limited information given to patients and families about their diseases and plans of action
  - Lack of consideration of the culture and religion of the patient or community
  - Limited signs to direct patients around hospital
  - Inadequate hospital beds
  - Poor facilities for traveling patients and accompanying family members
7. Absence of, or poorly organized, patient support groups.

- a) A significant number of primary health<sup>33</sup> and tertiary and training institutions<sup>34</sup> now run 'cost-recovery' programs that have further driven orthodox care out of the reach of the average African patient. A recent study has shown that more than half of patients admitted to a hospital in Northern Nigeria had to sell personal and family assets to be able to pay the admission fees, while 20% and 10% could only come up with the funds after a month and a year, respectively.<sup>35</sup> But most disturbing of all, 16% had to abandon treatment due to their inability to afford unforeseen costs of their care. Not surprisingly, government hospitals have acquired the reputation of being neocolonialist and extortionist.
- b) There is a shortage of medical specialists and other support healthcare practitioners required for optimal management of CaP patients in Africa. This is because relatively few urologists, other specialists, and support staff are trained on the continent, and a significant proportion of those trained migrate to the developed countries during, or after completing, their residency programs (i.e. the brain drain).<sup>36</sup> Worse still is that the quality of training is now being affected by the decreased number of patients attending training institutions (as mentioned above) and the inability of those who do attend to afford the costs of prescribed investigations and treatment.<sup>34</sup> These factors make accurate diagnosis, staging, and effective treatment of patients with all stages of cancers difficult. In addition, most specialists who remain on the African continent are located almost exclusively in the cities, whereas most of the populace dwell in rural areas, creating access problems for the patients.
- c) Modern investigations (such as bone, CT and MRI scans), modern drugs (e.g. bisphosphonates, taxel-based drugs and opiates), radiotherapy, and other supportive treatments are largely unavailable in Africa,<sup>14,22</sup> and where available are too expensive for most patients to afford (e.g. in Nigeria the cost of a course of docetaxel is over 15 times the cost of a monthly dose of stilboestrol and more than 10 times the minimum monthly wage). As a result, often times all that can be offered is a clinical examination, a few basic investigations ( $\pm$  biopsy) and bilateral orchiectomy in the first instance, and when the disease becomes hormone resistant, most patients are simply unable to afford anything other than simple analgesics, as even opiates are either unavailable or beyond their reach.

Consequently, as mentioned above, these patients are sometimes abandoned by their families due to their inability to pay for their care.<sup>35</sup>

- d) Palliative care is established in only a few African countries (South Africa, Uganda, Kenya, Zimbabwe, and Egypt) and is largely unknown in the rest of the continent.<sup>37</sup> As such, most patients with advanced cancers (including CaP) do not have access to palliative care facilities or specialists, especially since most African hospitals do not have hospice facilities, palliative-care strategies, or protocols, and their staff are largely untrained in the specialty.<sup>38</sup> This has meant that most terminally-ill African patients are discharged into the care of their families who are mostly unable to cope with the demands (financial, psychological, and nursing) in the home settings, further alienating orthodox hospitals and physicians from the community.

#### *Peculiarities of the African culture*

The lack of awareness of the disease mentioned above is not limited to the patient alone but to the entire family and community, which largely remains distrustful of orthodox medicine and its practitioners. Thus patients are more likely to be directed to the 'trusted' and 'friendly' traditional/alternative health practitioners, thus delaying their presentation to the hospital. Unfortunately, some of these practitioners are quacks.<sup>34</sup> Furthermore, there is a high usage rate of nonstandardized and unregulated complimentary and alternative medications amongst advanced CaP patients, which may counteract or synergize the desired effects of orthodox medicines, or result in complications, all of which worsen the patient's situation, which is then blamed on the orthodox drugs and/or physician.

#### *Limited research and published data*

Little is known about the epidemiology and natural history of CaP in NAM due to insufficient research and published data in the literature. In addition, the information in the published papers often do not use standardized indices and/or are not detailed enough to allow comparison with papers from other parts of the world. There is also a discrepancy between the (low) ranking of African countries in the World Health Organization (WHO) CaP statistics and the (high) incidence published from the countries.<sup>39</sup> The former has led to the relatively poor interest of the international agencies in funding research projects about the disease on the continent.

### *Lack of effective homegrown healthcare policies*

The poor culture of data collection in Africa makes healthcare planning complicated and difficult. Consequently most African countries do not have adequately-planned, well-resourced, homegrown national healthcare policies and strategies. In the absence of effective homegrown healthcare and training policies, most of these nations adopt healthcare policies designed in foreign nations, sometimes without adapting them to the peculiarities of their communities, thereby making the policies unacceptable and ineffective.

### *Lack of awareness, early detection, and treatment and prevention programs*

Like other black men,<sup>40</sup> NAM have a poor knowledge of CaP and the methods of its early detection and screening.<sup>30</sup> The lack of counselors and public-health educators trained in CaP detection and care has also meant the absence of community outreach programs to disseminate such knowledge. Further, although the value of PSA screening is now being debated,<sup>41</sup> its value in monitoring CaP is without question. However, few African nations have standardized PSA reference values for their community,<sup>42</sup> and worse still, black Africans with elevated PSAs are reluctant to undergo prostate biopsies.<sup>43</sup> Cancer prevention is also virtually unknown in Africa. As such, native African blacks continue to consume high-fat diets and are obese (factor that have been closely associated with the invasiveness and progression of CaP<sup>44,45</sup>) and are not involved in any of the chemoprevention studies (Prostate Cancer Prevention Trial [PCPT]<sup>46</sup> or The Selenium and Vitamin E Cancer Prevention Trial [SELECT]<sup>47</sup>).

### *Politics and prostate cancer research*

There is a glaring disparity in the funding given to CaP, breast cancer, and HIV/AIDS. In the United States, the comparative amounts invested in each life lost to the three diseases are: \$16700 for CaP, \$21800 for breast cancer, and \$160000 for AIDS.<sup>48</sup> This relative lack of interest in CaP by the scientific community in general and the international research funding agencies in particular has meant that there is even less interest in providing funds for CaP research and its management in Africa.

### *The way forward*

Prostate cancer is a major healthcare problem in Africa and initiatives for improving its management (especially the advanced stages) are urgently required. These programs would include, but would not be limited to

the improvement on, or reversal of, the limitations listed above. However, it would be difficult to improve the care of these patients in isolation. The measures described below are therefore directed toward improving healthcare on the African continent generally and the management of (advanced) CaP specifically.

### *Improving healthcare in Africa*

This can be achieved by:

- a) Improving the performance/function of African healthcare institutions.
  - i. *Improved funding* – The health budgets of most African nations are between 3%-10%,<sup>31</sup> see Table 2, and therefore need to be increased, as they are below the African Union recommendation of 15%.<sup>49</sup> Most importantly, a reversal of the World Bank's advice<sup>32</sup> is required, and more funds need to be spent on tertiary and specialist hospitals. In addition, a policy on national health insurance is required in all countries on the continent. This scheme would ensure the provision of affordable, efficient, equal access healthcare to those whose income would enable them to afford the contributions, with the governments taking on the responsibility for those who cannot afford the cost of insurance.
  - ii. *Making the hospitals more patient-friendly* – There is a need to develop culturally-oriented hospital environments and patient and family awareness and treatment programs. Improved staff attitudes and access to these facilities, especially for patients in the rural areas, must also be emphasized.
  - iii. *Capacity building (employment and training) of healthcare specialists especially urologists, medical oncology and palliative care teams (including nurses, counselors, etc.)* - This should be done with a view to developing homegrown interdisciplinary management protocols for the treatment of oncology patients. Frantic efforts must be also made by all governments in the continent to reduce and eventually reverse the brain drain.
- b) Development of culture-friendly, homegrown healthcare policies with achievable objectives, which should also be formulated with the involvement of all stakeholders, especially the people and their leaders. Also to be included are outreach programs during which the ethos of orthodox healthcare practices and policies are explained to those in the communities. For example, a small survey in our department revealed that orchiectomy is acceptable to most African men if they are properly counseled about the benefits and side effects (unpublished data).

TABLE 2. Health Expenditure in Africa<sup>31</sup>

Country	THE* as % of GDP	GGEH as % of TEH	PEH as % of TEH	GGEH as % of TEH	ERH as % of TEH	SSEH as % of GGEH	OPE as % of PEH
Algeria	3.6	72.5	27.5	8.4	0.0	33.2	94.60
Libya	3.8	74.9	25.1	6.1	0.0	n/a	100.0
Egypt	6.1	38.2	61.8	7.9	0.9	26.7	94.3
Tunisia	6.2	52.1	47.9	8.8	0.2	19.4	83.00
Morocco	5.1	34.3	65.7	5.5	0.9	0.0	76.00
Nigeria	4.6	30.4	69.6	3.5	5.6	0.0	90.40
Cameroun	5.2	28.0	72.0	10.5	5.3	0.0	94.50
Chad	4.2	36.9	63.1	9.5	7.0	n/a	95.80
Niger	4.2	52.5	47.5	10.3	21.3	n/a	85.10
Mali	6.6	49.2	50.8	12.8	13.8	n/a	99.50
Benin	4.9	51.2	48.8	9.8	10.2	n/a	99.9
Togo	5.5	20.7	79.3	6.9	8.9	14.4	84.90
Ghana	6.7	42.2	57.8	8.4	29.9	n/a	78.2
Burkina Faso	6.1	54.8	45.2	15.3	26.8	0.4	97.90
Cote d'Ivoire	3.8	23.8	76.2	4.6	5.0	n/a	88.70
Liberia	5.6	63.9	36.1	20.1	37.8	0.0	98.50
Guinea	5.3	13.2	86.8	4.5	9.5	1.6	99.50
Sierra Leone	3.3	59.0	41.0	7.8	35.4	0.0	100.0
Guinea Bissau	4.8	27.3	72.7	3.5	31.6	3.5	90.0
Gambia	6.8	27.1	72.9	5.9	23.0	0.0	68.20
Senegal	5.9	40.3	59.7	9.8	12.8	14.7	94.50
Mauritania	2.9	69.4	30.6	5.3	20.2	0.0	100.00
Ethiopia	5.3	51.5	48.5	9.4	35.2	0.4	78.30
Eritrea	4.5	39.2	60.8	4.2	59.6	0.0	100.00
Sudan	4.1	35.4	64.6	7.2	5.1	12.5	98.10
Kenya	4.1	42.7	57.3	8.2	18.3	8.4	81.90
Uganda	7.6	32.7	67.3	10.0	25.2	0.0	51.30
Rwanda	7.5	56.8	43.2	16.5	37.1	4.6	36.9
Burundi	3.2	26.2	73.8	2.3	17.6	n/a	100.00
Tanzania	4.0	43.6	56.4	8.5	27.1	1.8	83.20
Congo	2.5	49.2	50.8	4.4	3.6	0.0	100.00
Gabon	4.5	68.8	31.2	13.9	1.3	1.7	100.00
Equatorial Guinea	1.6	77.1	22.9	7.0	3.8	0.0	75.10
Central African Rep.	4.1	36.8	63.2	10.9	47.7	n/a	95.40
Angola	1.9	79.4	20.6	4.4	9.1	0.0	100.0
Botswana	6.4	62.9	37.1	10.5	2.5	n/a	27.9
Namibia	6.8	69.0	31.0	13.5	16.9	1.7	18.10
Malawi	12.9	74.7	25.3	28.8	59.4	0.0	35.2
Mozambique	4.0	68.4	31.6	9.1	55.9	0.0	38.5
Madagascar	3.0	59.1	40.9	8.7	45.5	n/a	52.50
South Africa	8.6	40.4	59.6	10.8	0.5	4.3	17.2
Zimbabwe	7.5	46.1	53.9	8.9	13.1	0.0	48.7
Lesotho	6.5	84.2	15.8	13.4	8.7	0.0	18.20

Note\* - TEH = Total expenditure on health, GDP = Gross domestic product, GGEH = General government expenditure on health, PEH = Private expenditure on health, ERH = External resources for health, SSEH = Social security expenditure on health, OPE = out-of-pocket expenditure on health.

- c) In light of the culture and widespread use of alternative and traditional medications amongst patients in Africa, governments must reach out to alternative and traditional medical practitioners with a view to standardizing and integrating their practice into the national health policies. These fields should also be included in the curriculum of medical schools.
  - d) Improved data collection in Africa can be achieved by better documentation and record keeping in hospitals and other healthcare facilities and during research projects. This would result in publications of higher standards with improved knowledge of the epidemiology of diseases and would also provide support for applications for grants from national and international funding agencies.
  - e) Similar to current trends in the developed world, cancer prevention is a must in Africa. As such, programs about a healthy diet and lifestyle should be emphasized, as diet is known to be responsible for approximately 30%-50% of all cancers.<sup>50</sup> These efforts should also include research into the genetic and epigenetic factors involved in cancers as well as their biomarkers, with a view to identifying targets for preventive intervention.<sup>51-53</sup> Oncologists in African should also take advantage of established training workshops/programs in cancer prevention such as the Summer Curriculum in Cancer Prevention of the National Cancer Institute (<http://cancer.gov/prevention/pob>).
  - f) Recognition of palliative care as a specialty and establishment of palliative care centers and care-in-the-community programs to improve the care of patients with advanced cancer. Healthcare practitioners should also be taught about end-of-life issues as part of their training.
- and Caucasian American men (CAM) are conflicting.<sup>7-42</sup> In addition, markedly elevated PSA levels in NAM may be due to chronic prostatitis and not CaP.<sup>55</sup>
- b) Repositioning CaP in research and funding.
    - i. National and international governments and scientific bodies should take due cognizance of the health burden posed by CaP both as a reproductive and a noncommunicable disease in Africa. Such recognition should result in an increase in the publicity and funding for research projects into all aspects (basic, clinical, and public health science) of the disease and its management on the continent. Importantly, more comparative studies of the indices of the disease are required between NAM and blacks in the diaspora in order to determine the effects of genetic and epigenetic factors on the natural history of the disease.
    - ii. Modern anti-CaP drugs/strategies should be provided at subsidized rates in Africa. Furthermore, phase III trials of these drugs should be carried out in African prior to their introduction as effective treatment, to detect any differences in drug kinetics. The assistance of international health organizations such as the World Health Organization (WHO), African Organization for Research and Training in Cancer (AORTIC ) and Pan African Urological Surgeons Association (PAUSA) should be enlisted to support these initiatives.
    - iii. Prostate cancer prevention programs and organizations similar to those in the developed countries (e.g. Alliance for Prostate Cancer Prevention [APCaP] [www.apcap.org](http://www.apcap.org). must be established in Africa. These would provide information on the disease and its prevention to the general public via the electronic and print media and via community outreach projects. Africa should also be included in chemopreventive programs,<sup>46</sup> especially those involving diet.<sup>47</sup> These efforts should also include research into factors involved in the initiation and progression of CaP in Africans as well as the determinants of its aggressive biology in the subpopulation.<sup>56</sup> Furthermore, targets for modern molecular interventions should also be identified in CaP in Africans.<sup>57</sup>

### *Improving care of CaP patients*

- a) Institution of awareness and early detection and treatment programs are a priority for Africa, as late presentation is a major contributor to the poor prognosis of the disease on the continent. Fortunately, health education programs have been shown to improve the knowledge and awareness of CaP and its early detection and treatment in NAM.<sup>53</sup> Prior to the establishment of CaP screening programs, however, there is a need to have PSA reference levels determined for Africans, as reports on mean PSA values in NAM as compared to AAM

### *Making progress slowly*

Despite the limitations in the management of CaP in Africa, some progress is being made in the care of patients with advanced CaP. Notable amongst these are:

- 1) The increasing awareness of the magnitude of the problem posed by CaP by governmental and nongovernmental policy makers, healthcare managers, and the public.
- 2) The increase in demand and funds for the care of the elderly in whom cancers (including CaP) are more prevalent, due to the (slowly) increasing life expectancy and economic power in Africa.<sup>58</sup>
- 3) There is increasing research into basic and public health science of CaP in NAM.<sup>7,12,42,59,60</sup>
- 4) Health insurance schemes are now being introduced in African countries (e.g. Nigeria).<sup>61</sup>
- 5) Palliative care is now being recognized as a specialty in Africa and hospices and palliative care programs are being established across the continent.<sup>38,62</sup>

## Conclusion

Most patients with CaP in Africa have advanced disease, and their management is presently unsatisfactory, for which the inadequate and materialistic operation of the health systems are partly to blame. As such, the quality of life and the prognosis of these patients are poor. CaP is a major reproductive and general men's health burden in Africa and should be recognized as such, as this would result in the initiation or improvement of (research and treatment) programs that would improve the care of the patients. Research projects to determine the epidemiology of CaP in Africa and the role of genetic/ethnic and environmental factors in the natural history of the disease in NAM are required as are comparative studies with blacks in the diaspora. Better funded and staffed patient-friendly hospitals, hospices, and community-health centers that are accessible to most patients are a priority, as are culturally acceptable health policies that involve the alternative and traditional healthcare practitioners. Equally important are health education programs that emphasize prevention and early detection and treatment of CaP. □

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## *Bladder cancer in Africa*

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*Accurate epidemiological data about the incidence and mortality of bladder cancer are unavailable for most African countries. Transitional cell carcinoma (TCC) of the bladder is probably less common in rural African regions than in industrialized countries, due to lower levels of exposure to carcinogenic chemicals. In areas with endemic schistosomiasis (bilharzia) caused by parasitic schistosomes (blood flukes), most bladder cancer cases are comprised of squamous cell carcinoma (SCC). However, with increased urbanization, industrialization, and cigarette smoking in many African countries, there is an increasing incidence of TCC relative to SCC of the bladder.*

*SCC of the bladder presents in patients who are on average 10 to 20 years younger than those with TCC. In Egypt and other North African countries, SCC is more common in men (the male to female ratio ranges from 3:1 to 5:1), probably because boys and men performing*

*agricultural work are more exposed to schistosomiasis-infested water. In some sub-Saharan countries, SCC of the bladder is equally common in men and women, probably due to equal schistosomiasis exposure of girls and boys, and because women obtain household water and perform most agricultural tasks.*

*Although SCC of the bladder often presents at a locally advanced stage, the tumors are usually well differentiated, with a relatively low incidence of lymphatic and hematogenous metastases. Patients with localized SCC are ideal candidates for cystectomy and orthotopic neobladder construction, because they are relatively young and healthy, and there is no risk of urethral recurrence, unlike with TCC. Unfortunately, many patients in Africa still present with advanced and inoperable bladder cancer, and many do not have access to healthcare facilities that can provide a cure and a good quality of life by means of radical cystectomy and neobladder construction.*

**Key Words:** bladder, transitional cell, squamous cell, carcinoma, schistosomiasis, Africa

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### Introduction

The aim of this paper is to review the literature on bladder cancer in Africa, focusing on how bladder cancer seen in Africa differs from that seen in the rest

of the world. Whereas much medical literature from Europe and North America deals with bladder cancer, relatively few reports about bladder cancer in Africa have been published. This paper attempts to include most of the available reports on the epidemiology, pathology, etiology, and treatment results of bladder cancer in Africa.

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### Incidence

Bladder cancer is almost never found incidentally at autopsy, making it unlikely that differences in incidence rates among different gender, race, and age groups are due to underdiagnosis in certain groups. Different incidence rates among different countries may, however, be due to underdiagnosis (patients not presenting to hospital), or to underreporting of

diagnosed cases, or unreliable population statistics.

In the United States, in a 1995 report, almost all bladder tumors were transitional cell carcinoma (TCC; 93.6% of cases). The remaining cases were squamous cell carcinoma (SCC; 2.1%), adenocarcinoma (1.4%), or sarcoma or other histological types (3%).<sup>1</sup> In addition, bladder TCC incidence rates were considerably lower among black (African-American) patients compared to white (Caucasian) patients. The yearly incidence rates of bladder TCC per 100000 were 30.3 for white males, 14.2 for black males, 7.1 for white females, and 4.3 for black females. However, SCC was more common among black patients, especially females; the rates of SCC were 1.4% among white males, 3.3% among white females, 5.3% among black males, and 10.4% among black females.<sup>1</sup>

Incidence data for bladder cancer in Africa show large variations between countries, suggesting that the incidence rates may not be reliable, due to incomplete reporting of diagnosed cases and/or incorrect population statistics. The frequency of bladder cancer as a percentage of all malignancies, and the age-standardized incidence rates (ASR) of bladder cancer differ by as much as 10-fold between some African countries, Table 1.

In countries such as Malawi and Zambia where schistosomiasis (bilharzia) — which is caused by parasitic schistosomes (blood flukes) — is endemic, bladder cancer has been reported to be the leading type of malignant disease. In schistosome-free countries such as the United States, England, and Germany, bladder carcinoma is reported to rank from the 5<sup>th</sup> to the 7<sup>th</sup> most common cancer in men and from the 7<sup>th</sup> to the 14<sup>th</sup> most common cancer in women.<sup>2</sup>

In Egypt, during 1970 to 1974, bladder cancer accounted for 30.8% of the total cancer incidence. It was the most common cancer in Egyptian males and second

only to breast cancer in females. In 1980, bladder cancer accounted for 27.6% of all cancers in Egypt — 38.5% of cancers in males and 11.3% in females.<sup>3</sup> Currently, bladder cancer accounts for 16.2% of male cancers in Egypt; it is the most common cancer in men and the 4<sup>th</sup> most common in women, and it occurs in 10.1% of the total population.<sup>4</sup>

Studies from Nigeria reported that bladder cancer represented 2.7% to 6.4% of all cancers, and its prevalence was estimated as 6.7 per 100000 cancer cases.<sup>5-7</sup>

### Age

In 1995 it was reported that in the USA the median age of patients with bladder cancer was 69 years for males and 71 for females with TCC, and 71.5 years for males and 72 for females with SCC. As a proportion of all urinary bladder cancers, the prevalence of SCC steadily increased among both males and females along with advancing age, reaching 2.1% among males and 4.4% among females in the 85+ age group.<sup>1</sup>

In schistosome-free countries, the peak incidence of bladder cancer is in the seventh or eighth decade of life reaching a maximum between age 65 to 75 years, and only 12% of bladder cancer cases occur in people younger than 50 years old. In countries with endemic schistosomiasis, the peak age of incidence of bilharzial-related bladder cancer is between 40 and 49 years.<sup>2</sup>

The mean patient age at presentation in African countries with a high incidence of SCC of the bladder due to endemic schistosomiasis has been variously reported as 43 to 49.4 years in Egypt, 47 years in Sudan, 49 years in Nigeria, and 50 years in South Africa.<sup>5-9,10-12</sup> In other countries and population groups with a predominance of TCC of the bladder, the mean age at presentation has been reported as 57 years in Kenya and 73 years in South Africa.<sup>10,13,14</sup>

TABLE 1. Frequency and age-standardized incidence rates of bladder cancer in some African countries\*

Country	% of cancers that are bladder cancer: in males	Bladder cancer ASR/100000 males	% of cancers that are bladder cancer: in females	Bladder cancer ASR/100000 females	Male:Female ratio
Algeria	11.7	10.8	2.4	2.3	4.7:1
The Gambia	1.4	1.2	0.6	0.5	2.4:1
Mali	10.1	11.3	4.2	5.8	2:1
Uganda	0.8	2.9	0.4	1.2	2.4:1
Zimbabwe	2.5	8.3	2.7	8.3	1:1

\*based on data from the International Agency for Research on Cancer (IARC)  
ASR = age-standardized incidence rates

## Male to female ratio

In the United States, in 1995, the male to female ratio for bladder cancer was reported to be 2.8:1 for bladder TCC and 1.2:1 for bladder SCC.<sup>1</sup> A 1999 report found that the male to female ratio of bladder cancer in countries with endemic schistosomiasis varied from 4:1 to almost 6:1, compared to 3:1 in countries without endemic schistosomiasis. One possible explanation is that in rural areas with endemic schistosomiasis, the main route for infection is through contact with infected water during agricultural activities that are normally performed by men.<sup>2</sup>

Different male to female prevalence of SCC and TCC of bladder are found in Northern African countries (such as Egypt and Sudan) compared to sub-Saharan countries such as Nigeria, Kenya, Zimbabwe, and South Africa.

In African countries with endemic schistosomiasis and a predominance of SCC of the bladder, the reported male to female ratio of bladder cancer has varied from 3:1 to 5.6:1 (Egypt), 2.5:1 to 5:1 (Nigeria) to as high as 12:1 (Sudan).<sup>5-9,11</sup> In Kenya, with a predominance of TCC of the bladder, the male to female ratio of bladder cancer was 4:1.<sup>13,14</sup> In Zimbabwe the male to female ratio for SCC of the bladder was 1:1 and in South Africa the ratio for TCC of the bladder was 2:1, whereas for SCC of the bladder it was 1:1.<sup>10,15</sup>

The fact that the male to female ratio for SCC of the bladder in Southern African countries such as Zimbabwe and South Africa is 1:1 versus a ratio of 3:1 and higher for Northern African countries such as Egypt is possibly due to sociocultural differences, equal exposure to schistosomiasis infestation at a young age by boys and girls in Northern Africa, and the fact that women in rural sub-Saharan areas usually obtain household drinking water and perform agricultural tasks.<sup>10</sup>

## Histological type, grade and stage

A study from Egypt in the mid 1990s reported SCC in 53% of bladder cancer patients, TCC in 23% of these patients, and adenocarcinoma in 13% of these patients; 90% of the patients had schistosomiasis.<sup>16</sup> A more recent study of bladder cancer patients from Egypt reported TCC in 59% of patients, SCC in 28% of patients, and adenocarcinoma and sarcomatoid carcinoma in 13% of patients.<sup>12</sup>

In a study of 1095 Egyptian patients with bladder cancer treated by radical cystectomy during 1967 to 1978, schistosome eggs were present in 82.4% of the

bladders. SCC was more frequent in egg-positive cases and TCC was more frequent in egg-negative cases. Grade 1 carcinomas predominated in the egg-positive group and grade 3 predominated in the egg-negative group. The tumors were locally advanced in most patients, with a limited tendency to lymphatic and hematogenous spread.<sup>8</sup>

In another large series of 1026 patients with invasive bladder cancer treated during 1969 to 1990 in Mansoura, Egypt, SCC was present in 59%, TCC in 22% and adenocarcinoma in 11% of cases. Bilharzial eggs were seen in 85% of the specimens. SCC was mostly well differentiated, and most TCC was moderately differentiated: SCC was grade 1 in 50%, grade 2 in 33%, and grade 3 in 17% of cases; whereas TCC was grade 1 in 14%, grade 2 in 53%, and grade 3 in 33% of cases. The most common pathological stage was pT3. A total of 80% of SCC, 58% of TCC, 73% of adenocarcinoma, and 85% of mixed/unclassified tumors were pT3. The correlation between clinical and pathological staging was good in 67% of cases; understaging occurred in 20% of cases and overstaging occurred in 13% of cases. Regional lymph nodes were involved in 18% of pT3a and 42% of pT3b tumors.<sup>11</sup>

A study from Sudan reported that SCC constituted 27% of all bladder tumors; 31% of the patients had a previous history of urinary bilharziasis; 60% of patients had locally advanced (T3 N0 M0) tumors at presentation; and the 5-year survival rate after radical cystectomy was 75%.<sup>9</sup> Another report from Sudan found carcinoma of the bladder in 10% of patients presenting with hematuria, and of these, 50% had SCC of the bladder in association with urinary bilharziasis.<sup>17</sup>

Studies from Nigeria have reported that SCC constituted 39% to 53% of bladder cancers, with TCC in 26%, mixed tumors in 16%, and adenocarcinoma in 5% of cases.<sup>5-7</sup> In Nigerian patients presenting with hematuria, the cause was bladder carcinoma in 31% of cases.<sup>18</sup>

A changing trend was observed in Nigeria during 1979 to 1989. Whereas earlier reports indicated a preponderance of SCC, there has been a rise in the frequency of TCC relative to SCC. However, among patients aged 50 years and younger, SCC was more frequent (45.5% of bladder cancer cases) than TCC (18% of cases). Increasing urbanization and industrialization may be factors leading to the increasing incidence of TCC of the bladder.<sup>19</sup>

A study from Tanzania reported that SCC represented 72% of bladder cancers and of these, 46% had *schistosoma haematobium* (*S. haematobium*) infestation.<sup>20</sup>

A study from Kenya during 1977 to 1984 reported TCC in over half (53%) of bladder tumors (which constituted only 0.75% of all reported cancers), while anaplastic cancer occurred in 17% of cases, and SCC occurred in the minority of cases (13%), mostly from schistosoma-endemic areas.<sup>13</sup> A more recent study from Kenya also reported TCC in the majority (67%) of bladder tumors, with advanced disease in 60% of cases.<sup>14</sup>

In one report from Zambia in the 1970s, SCC was the most common form of bladder cancer; patients almost always presented at a late stage.<sup>21</sup> In another study from Zambia from the same period, bladder cancer was the third most common malignancy. The bladder tumors were well-differentiated; SCC accounted for 75% of cases, and 65% of cases had concomitant schistosomiasis.<sup>22</sup> In a later study from Zambia, it was reported that bladder cancer, predominantly SCC, was the commonest urological tumor (51%), and in nearly 32% of cases, bilharzial ova were demonstrated histopathologically.<sup>23</sup>

A study from Zimbabwe during 1963 to 1977 found that 71% of bladder cancer cases were SCC.<sup>24</sup> Another study from Zimbabwe during 1984 to 1987 reported that SCC comprised 69% of bladder cancers and 31% were TCC.<sup>15</sup>

One study reported that in Mozambique, which has a high prevalence of bilharziasis, the incidence of SCC of the bladder is the highest in the world, with a yearly frequency of 24 cases per 100000 of the male, and 19 cases per 100000 of the female population. Bladder cancer was the second most common malignancy in men (after primary liver cancer) and the third most common malignancy in women (after liver and cervix cancer).<sup>25</sup>

Researchers from South Africa reported that in a histology study of bladder tumors from Natal (a region with endemic schistosomiasis) during 1971 to 1982, TCC was found in 62% of cases, SCC in 56% of cases, and adenocarcinoma or undifferentiated cancer in 10% of cases. Among black patients with bladder tumors, 61% had SCC, and among Asians (Indians), 29% had SCC. The prevalence of schistosomiasis was higher in blacks (44%) than in Indians (23%), and schistosomal infection was most commonly associated with SCC (61%).<sup>26</sup>

In a 1980 to 1990 study from the same region, the distribution of histological types of bladder cancer differed between races. Among white patients TCC constituted 95%, SCC 2%, and undifferentiated/mixed histology cancers 3% of cases; in black Africans TCC occurred in 30%, SCC in 53%, and undifferentiated/mixed tumors in 17% of cases; whereas among Asians (Indians), TCC occurred in 75%, SCC in 18% and

undifferentiated/mixed histology in 7% of cases. In Caucasians, TCC was early stage (T1 or T2) in 76% of cases; whereas in Africans, SCC was advanced disease in 90% of cases, and 27% of cases were regarded as inoperable due to local fixation or distant metastases.<sup>10</sup>

A 1975 study from South Africa reported that the Western Cape region (which is non-endemic for bilharzia) had a low percentage of SCC bladder cancer compared with other parts of Africa. TCC constituted 79%, SCC 6%, TCC with squamous metaplasia 5%, undifferentiated cancer 6%, and adenocarcinoma 2% of bladder cancer cases.<sup>27</sup> In a more recent study from the same area reporting on 112 cystectomy cases, 83% were TCC, 9% SCC, 5% adenocarcinoma, and 3% sarcoma. The low frequency of SCC is similar to that seen in the United States and Europe, and underlines the importance of bilharziasis in the etiology of SCC.<sup>28</sup>

## Etiology

In a recent study, researchers estimated that 75% of men in Egypt with bladder cancer were smokers, in contrast to studies from Western countries reporting that about 50% of men with bladder cancer are smokers. Urinary schistosomiasis was estimated to account for 16% of bladder cancer cases in Egypt; thus, for men, tobacco smoking was a far greater risk factor than schistosomiasis.<sup>29,30</sup> This was not the case for Egyptian women, who had low rates of smoking. The study authors estimated that combined exposure to tobacco smoking and a high-risk occupation or schistosomiasis led to an approximately 10-fold higher risk of bladder cancer.<sup>29</sup>

A study from Zimbabwe during 1963 to 1977 found that schistosomiasis was associated with a significantly increased risk of bladder cancer in both genders. The proportion of bladder cancer attributable to schistosomiasis was estimated to be 28%. Tobacco smoking in men had no effect on the risk of SCC. For TCC or adenocarcinomas, there was a nonsignificant increased risk of 2.0 for men in the highest smoking categories.<sup>24</sup>

Schistosomiasis may lead to malignancy through local tissue damage, mechanical irritation, bilharzial toxins, or secondary bacterial infection. Exposure to carcinogenic N-nitroso compounds is probably the most important mechanism. Inflammatory cells such as macrophages and neutrophils are important sources of endogenous oxygen radicals, which are implicated in the formation of carcinogenic N-nitrosamines. Hydroxyl radicals released from inflammatory cells induce genotoxic effects, such as mutations, sister chromatid

exchanges, and DNA strand breaks. Inflammatory cells participate in the activation of procarcinogens, such as aromatic amines and polycyclic aromatic hydrocarbons, to their ultimate carcinogenic metabolites.<sup>2</sup>

Nitrate-reducing bacteria in the urine of *S. haematobium*-infected patients can mediate nitrosation reactions between secondary amines and nitrate, producing high concentrations of N-nitrosamines that act like carcinogenic alkylating agents. Host cell DNA damage due to alkylating agents, together with inefficiency in the capacity of relevant enzymes to repair this damaged DNA, may lead to SCC.<sup>2,31</sup> Schistosomiasis may cause liver involvement and dysfunction, which disturbs tryptophan metabolism, leading to the excretion of carcinogenic metabolites. In addition, vitamin A deficiency may be responsible for squamous metaplasia in the bladder, predisposing to SCC.<sup>3</sup> N-nitroso compounds and N-nitrosodimethylamine in the urine of *S. haematobium*-infected patients might have a role not only in the initiation of the carcinogenic process, but also in its progression.<sup>32</sup>

More than 90% of bilharzia-related bladder carcinoma (BBC) cases at presentation are advanced-stage tumors. The frequency of p53 nuclear overexpression in BBC is lower than that reported for conventional TCC. Nevertheless, tumors with p53 alterations have a greater propensity to progress. The prominent number of cases displaying an mdm2-positive phenotype suggests that this may be an early incident in BBC and should be regarded as a potential oncogenic phenomenon. The association of an aggressive clinical course with the coexpression of both p53 and mdm2 products might be viewed as a cooperative effect that develops in tumor progression.<sup>33</sup>

A 9p gene, possibly CDKN2, may contribute to the development of the majority of schistosomiasis-associated bladder tumors, but genes on 9q play a much less important role.<sup>34</sup> The frequency of human papillomavirus (HPV) was reported to vary from 23% to 46% in bladder cancers in Egypt, but HPV was not detected in bladder cancers from South Africa, indicating that it does not play a role in schistosomiasis-associated bladder carcinoma there.<sup>35</sup>

The fact that in Egypt over the past three decades the incidence of bladder cancer has decreased from 30.8% to 10.1% of total cancers may be due to a decreased prevalence of schistosomiasis as a result of eradication of the snails that host the parasites, decreased contamination of water sources through improved sanitation, decreased population exposure to infested water, or better treatment of acquired

bilharzia. The relative increase of TCC versus SCC of the bladder in Egypt may be partly due to schistosomiasis control, but appears to be largely due to increased cigarette smoking and industrialization. The apparent decrease of bladder cancer as a percentage of all other cancers in Egypt is more difficult to explain, but may be due to increasing rates of lung cancer (due to smoking) and prostate cancer (diagnosed with prostate specific antigen).

## Early detection

A study conducted to detect early bladder carcinoma by selective cytologic screening in a rural Egyptian population infested with *S. haematobium* targeted a high-risk group, i.e., farmers aged 20 years and older. Bladder carcinoma was detected in 11 patients among the 4769 individuals screened in the high-risk group, which translated into 2.3 cases per 1000 high-risk individuals. No tumors were detected in the 3975 individuals in the low-risk group. The primary tumors included 5 SCC, 4 TCC and 1 undifferentiated carcinoma; 7 of the tumors were in early stages. The authors concluded that selective cytologic screening in the high-risk group in Egypt is feasible and effective for the early detection of bladder carcinoma associated with schistosomiasis.<sup>36</sup>

The use of urine cytology in the diagnosis of SCC was studied in a schistosomiasis-endemic area of Kenya. The prevalence of inflammation (39%), hyperkeratosis (30%), metaplasia (33%), and frank atypia (0.4%) was higher than in previously studied, non-endemic populations. Overall, *S. haematobium* infection was strongly associated with increased risk for cytologic abnormality. The data suggested an age-dependent progression of cellular abnormalities in the urinary epithelium that is associated with chronic *S. haematobium* infection, which becomes independent of concurrent infection intensity as subjects grow older.<sup>37</sup>

A study from Egypt reported that the BTA stat and BTA TRAK tests were extremely sensitive (99% and 94%, respectively) in both SCC and TCC, but specificity was only 15% in patients with bilharziasis, i.e., false positive results for cancer were observed in 85% of patients with active bilharziasis.<sup>38</sup> A significant elevation of urinary cytokeratin 19 (CYFRA21-1) was found in 82.3% of bladder cancer patients and 11.4% of patients with bilharzia.<sup>39,40</sup> The authors concluded that urinary CYFRA 21-1 and BTA stat are valuable non-invasive urinary markers for the detection of bladder cancer, with a high sensitivity compared to urine cytology.<sup>41</sup>

## Prevention

Educational and marketing campaigns about effective and convenient treatments for schistosomiasis, aimed to increase awareness in the general public and the medical community have contributed dramatically to the primary prevention of bladder cancer in Egypt.<sup>42</sup> Primary prevention could be possible if the schistosomiasis parasite is eliminated. Chemoprevention using retinoids or cyclooxygenase 2 (COX-2) inhibitors is a possible alternative.<sup>43</sup>

## Treatment of superficial TCC

A study from South Africa was one of the first to report on the use of intravesical Bacillus Calmette-Guerin (BCG) immunotherapy in patients with recurrent superficial TCC of the bladder. Among 13 patients who received BCG prophylactically to reduce recurrence, 70% were in remission after 2 years, and of the 14 patients who received BCG therapeutically for in situ carcinoma, 69% responded favorably. Most patients (78%) experienced irritable bladder symptoms, but only one patient discontinued treatment. A statistically significant reduction in the number of recurrences was experienced by the patients who received BCG prophylactically.<sup>44</sup>

Intravesical therapy for superficial TCC of the bladder was studied by a group in Egypt who prospectively randomized 156 patients with superficial (Ta and T1) TCC to treatment with 150 mg BCG weekly alternating with 50 mg epirubicin for 6 weeks, and maintenance with monthly doses of BCG alternating with epirubicin for 1 year (Group 1). Group 2 patients were treated with the same protocol, but in a reversed order, with epirubicin being used initially. At a mean follow-up of 42.8 months, the cancer recurrence rate was 18% and the progression rate was 12%. Side effects occurred in 26% of the patients and were most often mild cystitis. The two groups were comparable in terms of cancer recurrence and progression rates. The side effects were less frequent than in historical controls treated with BCG alone. The authors concluded that it does not make any difference whether treatment is started with epirubicin or BCG.<sup>45</sup>

In a more recent study by the same authors, 84 patients in Egypt with T1 TCC were prospectively randomized, following an initial 6-week course of sequential BCG and epirubicin. Group 1 received 3-week courses of 120 mg BCG at 3, 6, 12, 18 and 24 months, while Group 2 received monthly BCG at the same dose for 1 year. At a mean follow-up of 31 months, the recurrence rates of the two groups (24% and 18%, respectively) and the progression rates (6%

and 4%, respectively) were comparable. Toxic side effects were more frequent in Group 1 than in Group 2 (50% versus 20%, respectively). The authors concluded that monthly BCG maintenance is as effective and is less toxic than multiple 3-week courses in recurrence prophylaxis of T1 bladder TCC.<sup>46</sup>

In another study from Egypt, 66 patients with superficial TCC were treated at Cairo University with either Nd:YAG laser therapy (16 patients) or transurethral resection (TUR) of the bladder (50 patients) and followed for a mean of 5.5 years. Local tumor recurrence at the site of the original tumor occurred in 39% of patients and remote recurrence occurred in 33% of patients. The total recurrence rate was 59%. Tumor progression to invasive cancer occurred in 11% of patients, while 4.5% of patients died of disease-related causes. The authors concluded that superficial TCC is a serious condition that merits close, long-term follow-up.<sup>47</sup>

## Treatment of invasive bladder cancer

In a large series of 1,026 patients with invasive bladder cancer treated during 1969 to 1990 in Mansoura, Egypt, SCC was present in 59%, TCC in 22%, and adenocarcinoma in 11% of the patients. At a median follow-up of 4 years after cystectomy, postoperative mortality was 4%. The 5-year overall survival rate was 48%-50% for patients with SCC, 47% for those with TCC, 46% for those with adenocarcinoma, and 36% for those with mixed/unclassified tumors. Only tumor stage and grade and lymph node status had a significant impact on survival.<sup>11</sup>

A study from Sudan reported that SCC constituted 27% of all bladder tumors. A total of 60% of patients had locally advanced (T3 N0 M0) tumors at presentation, and the 5-year survival rate after radical cystectomy was 75%.<sup>9</sup>

Researchers from South Africa reported on 100 consecutive patients with infiltrating TCC who underwent cystectomy during 1978 to 1989. Radiotherapy was given preoperatively in 39% of cases and postoperatively in 15% of cases, and systemic chemotherapy was used postoperatively in 12% of cases. The tumors were pathological grade 1 in 5%, grade 2 in 21% and grade 3 in 53% of cases, and the pathological stage was T0 in 10%, T1 in 17%, T2 in 12%, T3 in 43%, and T4 in 15% of cases. At a mean follow-up of 40.8 months, the overall 5-year survival was approximately 70%.<sup>48</sup>

Another study from South Africa reported on 112 patients who underwent radical cystectomy and Bricker diversion for bladder cancer during 1978 to

1989 in a university teaching hospital. The overall perioperative mortality was 11%, but perioperative mortality was 3% for surgeon A who performed 30 surgeries and assisted in 2, 8% for surgeon B who performed 26 surgeries and assisted in 4, and 26% in a group of 12 surgeons (E-P) who performed 29 surgeries and assisted in 46. The mean operation times were 206 minutes for surgeon A, 265 minutes for surgeon B and 285 minutes for surgeons E-P. Perioperative mortality and major early complications were greater in patients older than 71 years old versus those younger than 60 years old. Perioperative mortality was also lower in patients with T0-1 tumors than in those with T2-4 tumors. The authors concluded that perioperative mortality was higher in the following patient groups: those operated on by surgeons with limited experience, those older than 71 years old, those who had not received preoperative radiotherapy, and those with locally advanced tumors.<sup>28</sup>

A further study from South Africa reported on 63 patients (73% male) who underwent radical cystectomy during 1988 to 1994. The patients' mean age was 61 years (range, 33-77years). A total of 14% of the patients had clinical stage T1 disease and 24% had pathological stage T1 disease; the corresponding numbers for prevalence of clinical and pathological stage T2 disease were 24% and 6%, respectively; for stage T3 disease 46% and 45%, respectively; and for stage T4 disease 16% and 25%, respectively. Node metastases occurred in 0% of pT1-2 tumors, 29% of pT3 tumors, and 38% of pT4 tumors. The operative mortality was 2%, and the overall survival rate was 33% at a median follow-up of 42 months. The estimated 5-year survival rates were 91% for pT1, 75% for pT2, 31% for pT3, and 29% for pT4 disease. The authors concluded that cystectomy is the standard against which other treatments for bladder cancer must be measured.<sup>49</sup>

Investigators from Nigeria recently reported on 58 patients with bladder carcinoma treated from 2000 to 2005. Cystectomy was performed in 30 patients (25 male and 5 female) who had a mean age of 50 years; 28 patients with metastases were excluded from analysis. Surgery consisted of construction of an orthotopic ileal neobladder in 15 cases (50%), a continent cutaneous reservoir in 11 cases (37%) and non-continent drainage in 4 cases (13%). A 40% survival was achieved with follow-up ranging from 6 to 60 months.<sup>50</sup>

A recent study from Cairo reported on 27 patients selected for laparoscopic cystectomy. The procedure was aborted in seven patients and was completed laparoscopically in 20 patients (16 male, 4 female). The

mean operative time was 8 hours and the mean blood loss was 680 ml. Postoperative complications occurred in five patients (25%), and four patients (20%) died in the postoperative period.<sup>51</sup>

### Radiotherapy

A study from South Africa reported on 46 patients who underwent salvage cystectomy during 1981 to 1992 for persistent or recurrent carcinoma after radical irradiation for bladder carcinoma. The overall 5-year survival rate was 43%. There were three deaths (a mortality rate of 7%) and 12 nonfatal major complications due to prior irradiation or surgery — an overall rate of fatal and nonfatal 5-year complication of 33%. The authors concluded that salvage cystectomy is indicated for selected patients with persistent or recurrent disease after radical irradiation for bladder cancer, but that the expectation of a survival rate similar to that found in patients treated with immediate cystectomy may not be justified.<sup>52</sup>

In a prospective study of neoadjuvant radiotherapy in Egypt from 1996 to 2000, 104 patients with infiltrating bladder cancer were treated with a total preoperative dose of 45 Gy given over 3 weeks (1.5 Gy/fraction, 2 fractions/day, 5 days/week). Three weeks later, this was followed by radical cystectomy with pelvic node dissection. Only 56 of the 104 patients completed the treatment program. At a median follow-up of 26 months, disease-free survival was 64%, with 50% of failures due to pelvic cancer recurrence. The authors found no increased operative difficulty or increased postoperative morbidity related to irradiation.<sup>53</sup>

### Bladder conservation

A bladder conserving approach has been used in some African centers. A study from South Africa reported on the use of neoadjuvant chemotherapy (cisplatin, methotrexate, and vinblastine) and radical irradiation in 18 patients with T3 or T4 bladder cancer. After chemotherapy, a complete response was obtained in four patients (22%) and a partial response in eight patients (44%). After irradiation, a complete response was obtained in 12 patients (67%). The 3-year continuously disease-free survival rate (with preserved bladders) was 44%, and the overall 3-year survival rate was 61%. The authors concluded that the local control rate was unsatisfactory.<sup>54</sup>

In a study from Egypt, 27 patients (24 males, 3 females; mean age 58 years) with invasive nonmetastatic bladder cancer for whom radical

surgery was not suitable were treated with three cycles of chemotherapy (carboplatin, methotrexate, and vinblastine) and radiotherapy (65 Gy) in two phases. The authors concluded that DNA ploidy status seems to be a useful prognostic factor when bladder sparing therapy is applied.<sup>55</sup>

## Mortality

The management of bladder cancer is mainly surgery, and 5-year survival rates after radical cystectomy have increased from 35% in the 1970s to around 50% in the 1990s. The addition of adjuvant and neoadjuvant radiotherapy and chemotherapy to surgery since 1976 significantly improved both disease-free and overall survival rates.<sup>43</sup>

In 1995 it was reported that in the USA males had higher 5-year bladder cancer survival rates than females, while African-American women had the lowest survival rates. The survival rates were 84% in white males, 71% in black males, 76% in white females, and 51% in black females. One reason for the lower survival rates among black patients may be presentation with more advanced stages of disease. TCC at first diagnosis was localized in 76% of white males, 74% of white females, 66% of black males, and 56% of black females. Factors that may lead to a more advanced stage at diagnosis in black Americans, particularly women, include possible underreporting of superficial cancers, delayed diagnosis, and/or more frequent occurrence of more aggressive variants of TCC in African-Americans. A contributing factor to the lower survival rates may be differences in therapy. In a study that looked at treatment from 1978 to 1985, black American males were more likely than whites to go untreated after diagnosis, suggesting that differences in initial therapy may have contributed to the survival differential.<sup>1</sup>

From 1979 to 1985, bladder cancer mortality among North African migrants of both sexes<sup>56</sup> and among migrant males from West Africa<sup>57</sup> living in France was higher than the rate among the native population. Among people of European origin living in Southern Africa for over 30 years, bladder cancer rates were higher than normally seen in white populations elsewhere.<sup>58</sup> These findings indicate that environmental factors may be more important than ethnicity in determining bladder cancer mortality.

## Summary

Bladder cancer in parts of Africa with endemic schistosomiasis (bilharzia) is different from that seen in

North America and Europe. There is a predominance of SCC rather than TCC of the bladder. The patients with SCC are on average 10 to 20 years younger than those with TCC of the bladder. The male to female ratio for bladder cancer is high in areas where more men than women are exposed to schistosomiasis or are smokers, and the ratio is equal where bilharzia exposure is equal between men and women. In many parts of Africa, the population is unaware that bilharzia is transmitted via snail-infested water sources, and they regard hematuria almost as a normal rite of passage into adulthood. Consequently, SCC of the bladder usually presents at a locally advanced stage and is often inoperable.<sup>59</sup> However, SCC of the bladder is usually well differentiated, with a low incidence of lymph node and distant metastases, possibly due to capillary and lymphatic fibrosis resulting from chronic schistosomal infection. There is a changing pattern in Africa from SCC to TCC of the bladder, probably due to decreased schistosomiasis infestation and increased cigarette smoking and industrialization. □

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## *Challenges of anticancer chemotherapy in Africa*

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NDOM P. Challenges of anticancer chemotherapy in Africa. *The Canadian Journal of Urology*. 2008;15(1):3909-3911.

**Background:** Cancer patients in Africa face unique challenges beyond the issues of disease pathology and treatment. Most patients present in advance stages beyond hopes of a cure and their management is confounded by complex socioeconomic and cultural issues unique to underdeveloped countries.

**Methods:** Critical assessment of the state of cancer care in Africa with focus on the management of advanced stages of the disease. The impact of a shortage of resources, difficulty with access to care and cultural attitudes that impact on the ability to provide state-of-the-art therapies are reviewed.

**Results:** In contrast to AIDS, malaria, and tuberculosis, malignancies kill more patients than all three of these high profile infectious diseases combined. The lack of adequate social and economic resources results in direct limitation on the effectiveness of care in many African nations.

**Conclusions:** Effective cancer treatment strategies in Africa need to focus on providing basic care, making efforts to diagnose cancers earlier, making treatments more accessible and affordable, promoting research that is more applicable to local conditions in an African setting, and striving for public health initiatives that will benefit the vast majority of patients with advanced-stage disease.

**Key Words:** chemotherapy advanced, challenges

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### Introduction

The International Agency for Research on Cancer (IARC) estimates that worldwide, in 2020 there will be 15 million new cases of cancer a year, of which 70% will occur in developing countries.<sup>1</sup> It is feared that most cases of cancer in Africa will be diagnosed at advanced or metastatic stages, when chemotherapy is often crucial.<sup>2,3</sup>

There have been some extraordinary recent developments in cancer treatment. Discoveries about the mechanisms of the malignant process involving oncogenes and antioncogenes have led to the development of new oncolytic drugs and the consolidation of therapeutic cancer management protocols.<sup>4</sup>

Africa, however, is still beset by multiple and varied challenges related to providing anticancer chemotherapy. Challenges surround early cancer detection; managing chemotherapy; clinical, diagnostic and therapeutic good practices; accessibility of drugs; competent healthcare workers; research; and healthcare policies.<sup>5</sup>

### Early cancer detection

African countries require policies to promote early cancer detection, by means of campaigns to increase public awareness, and screening programs to detect cancer.

### Managing chemotherapy

Chemotherapy can be augmented by adjuvant radiotherapy or surgery, or be replaced by hormone therapy. However, management of chemotherapy remains complex due to its significant physical effects as well as effects on morale, and even social effects. Increased care is needed to try to control, or at least minimize, side effects of chemotherapy.<sup>6</sup>

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## Clinical, diagnostic, and therapeutic good practices

Chemotherapy requires hospital infrastructures and technical expertise. Advances in these aspects are noticeable in southern Africa (South Africa) and northern Africa (Algeria, Tunisia, Egypt) where specialized chemotherapy units are available.<sup>4</sup>

Antimitotics are generally administered to physically and psychologically fragile patients who are at high risk of getting infections. Yet most African countries lack the ideal framework to administer these treatments: there might be no room to prepare antimitotics, no isolation room, no laminar flow hood, or no sterile syringes. In addition, there might be problems in referrals among oncology, hematology, pediatric, gynecology, or surgery services. Qualified staff to administer the treatment is often lacking.

## Accessibility of drugs

Economic barriers to treatment include the high cost of drugs, the frequent lack of a national healthcare system or health insurance, and the high prevalence of poverty (from close to 50% of the population in some countries to even higher rates).<sup>7</sup> Thus, to promote the availability of drugs against cancer, it is necessary to promote the listing of antimitotics by national purchasing centers, and to also encourage the generosity of pharmaceutical firms, the support of associations such as the African Organization for Research and Training in Cancer (AORTIC), and the support of families of cancer patients.

It is also difficult to control some side effects inherent to antimiotics (pain, vomiting, and lowered blood cell levels) due to difficulties in obtaining timely, affordable analgesics, 5-HT antagonists (antiserotonins), 5-hydroxytryptamine<sub>3</sub> (5-HT<sub>3</sub>) receptor antagonists, and erythrocyte/leukocyte/platelet pellets, which are required with large doses of chemotherapy.

Cultural barriers to receiving chemotherapy will remain a primary concern for some time to come, given that some African cultures hold a widespread belief that cancer is a disease induced by supernatural forces and/or an incurable disease.<sup>8</sup>

## Competent healthcare workers

The administration of antimitotics requires devoted and qualified healthcare personnel. In most African countries, the quality of cancer care is poor. Very often, neither a qualified oncologist, nor an experienced

oncology nurse is available to administer treatment. Reasons for this deficiency include low salaries paid to specialists, which is also reflected in the fact that educated specialists from southern Africa tend to migrate to northern Africa. Policies regarding the training, promotion, and coordination of healthcare personnel have to be re-examined to ensure the availability in Africa of a critical core of personnel who are technically competent to provide chemotherapy.<sup>5</sup>

## Research

Cancer research in Africa is not usually in the form of international, multicenter studies of chemotherapies. There is a need to promote the dissemination of results of African research by publishing findings in renowned medical journals. Currently, there is an absence of support for publishing results of African studies, particularly in specialized journals.

## Healthcare policies

Despite continuing problems such as a lack of essential drugs, there is an increasing awareness about the need for improved cancer care in Africa. The 2006 World Cancer Declaration presented during the 2006 UICC World Cancer Congress is one example of this. In addition, renewed interest led to the March 2007 London Declaration on Cancer Control in Africa.

National cancer control plans need to be established in Africa and given priority. Resources need to be mobilized to develop a cancer registry (to certify cancer cases), to establish prevention and screening programs (given that 1/3 of cancers in Africa could be largely avoided), to set up a financial framework, to set up training programs, and to establish regional or local training institutes, centers of excellence for treating cancer patients, and centers for cancer research.<sup>9</sup>

## Conclusion

Anticancer chemotherapy challenges in Africa are real and varied. Many challenges could be met if they were given a significant importance in healthcare budgets. This is especially important given that worldwide, 12.5% of deaths are due to cancer, more than deaths from HIV/AIDS, tuberculosis and malaria combined. To address these challenges in anticancer chemotherapy in Africa, the issues should be studied in-depth and a platform to mobilize resources should be developed. □

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