

Increased Risk of Penile Cancer among Men Working in Agriculture

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Abstract

Background: Previous Brazilian studies have indicated that working in agriculture could lead to an increased risk of penile cancer. The present descriptive study aimed at establishing a possible association between penile cancer and agricultural occupation. **Materials and methods:** Data on a total of 103 penile cancer patients were obtained from medical records of two reference centres for cancer treatment in the state of Paraíba, Northeast Brazil. Information about sexual behaviour was obtained in interviews for 48 cases. **Results:** Of 103 patients 38 and 52 were illiterate and had not completed graduation, respectively, and 60 earned less than twice the minimum wage. All together, 72 (70%) worked in agriculture and 39 confirmed involvement in application of agrochemicals. A history of phimosis was noted for 42 (69%) out of 61 patients and 40 (59%) out of 68 ever smoked. Pathological signs of HPV infection were detected in 45 (70%) out of 64 patients. Of the 48 interviewed patients, 27 (56%) confirmed sexual contact with prostitutes and eight (19%) out of 43 had sex with animals. **Conclusions:** Data confirmed the presence of several risk factors for penile cancer, like phimosis, smoking, HPV infection and promiscuous sexual behaviour. The high number of Brazilian agricultural workers with penile cancer was unexpected if compared with other professional groups. Future studies should focus on this group of men and elucidate possible reasons for their increased risk.

Keywords: Penile cancer- epidemiology- risk factors

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Introduction

Penile cancer is a rare and aggressive form of cancer in men (Siegel et al., 2015). In the United States, it accounts for about 2,000 new cases for less than 1% of all cancer in men and causes about 300 deaths each year (Siegel et al., 2015). The incidence of penile carcinoma is higher in several tropical countries of Africa, Asia and South America (Siegel et al., 2015). Brazil has one of the highest incidence rates worldwide, ranging from 2.9 and 6.8 cases per 100,000 men (Favorito et al., 2008).

Previous studies carried out in the US, Denmark, Paraguay and the Caribbean have identified phimosis and infection with human papillomavirus (HPV) as main risk factors for penile cancer (Daling et al., 2005; Madsen et al., 2008; Chaux et al., 2013; Ramdass et al., 2014). A recent study that was based on data obtained from 25 countries revealed that about a third to a fourth of penile cancers were related to HPV infection (Alemany et al., 2016). Circumcision in childhood was associated with a reduced risk of HPV infection (Castellsagué et al., 2002; Albero et al., 2012). As circumcision in childhood prevents phimosis and was associated with lower risk of HPV infection, it

was postulated to be a protective factor of penile cancer (Larke et al., 2011; Morris et al., 2011; Morris et al., 2012). Populations of countries with traditional circumcision during childhood, generally have lower rates of penile cancer, compared to uncircumcised populations (Larke et al., 2011). Several previous studies have associated the protective effect of circumcision exclusively regarding invasive forms of disease but not in situ penile cancer (Schoen et al., 2000; Tsen et al., 2001; Daling et al., 2005; Larke et al., 2011).

Promiscuous sexual behaviour can increase the chance of HPV infection and was also associated with increased risk of penile cancer (Madsen et al., 2008; Chaux et al., 2013). Other identified risk factors were conditions such as tear, rush or injury, penile lichen sclerosus and genital warts (Tsen et al., 2001; Daling et al., 2005; Madsen et al., 2008; Philippou et al., 2013). Smoking was also associated with increased risk of the disease (Tsen et al., 2001; Daling et al., 2005; Chaux et al., 2013). Furthermore, recent studies have identified obesity as a risk factor for penile cancer (Barnes et al., 2013; Barnes et al., 2016).

Previous Brazilian studies on risk factors of penile cancer aimed on sexual behaviour, phimosis,

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penile pre- malignancies, ethnic origin, smoking and socio- economic characteristics of patients (Favorito et al., 2008; Fonseca et al., 2010; Koifman et al., 2011; Zequi et al., 2012; Couto et al., 2014). Other studies have focused on skin lesions and other clinical risk factors for penile cancer among healthy men (Romero et al., 2013). Two previous studies conducted in Rio de Janeiro have exclusively focused on high risk of HPV infection (Gil et al., 2001; Scheiner et al., 2008). The authors of a previous study performed in the south- eastern state of São Paulo claimed that sex with animals could be a positive factor for penile cancer (Zequi et al., 2012). This could indicate that patients were mainly agriculture workers. However, the authors of this study did not show detailed information about professional background of patients (Zequi et al., 2012). In a study performed in northern state of Pará, including 208 cases of penile cancer, the authors pointed out that most patients were agriculture workers, but did not show detailed data about their profession (Fonseca et al., 2010). Data about the profession of Brazilian patients with penile cancer are important as agricultural work can provide an important socio-economic background and being associated with behavioural risk factors for penile cancer.

The present descriptive study was conducted in the state of Paraíba, North-eastern Brazil and aimed on the socio-economic profile and clinical characteristics of penile cancer patients. The authors investigated if penile cancer in this region was mainly found among men working in agriculture and if they applied agrochemicals. Furthermore, the study investigated signs of infection with HPV among patients.

Materials and Methods

Study population

The sampling protocol was reviewed and approved by the Brazilian National Research Ethics Committee (CAAE plataforma Brasil: 46957515.8.0000.5175). Data from patients were sampled in two reference centres for cancer treatment in the state of Paraíba, North-eastern Brazil: The “Fundação Assistencial da Paraíba” public hospital (FAP) in Campina Grande and the “Napoleão Laureano” Hospital (HNL) in João Pessoa. Both hospitals together treat most cancer patients in the state. Patients seeking for treatment come from regions as far as 600 km from the reference centre. João Pessoa, capital of the state of Paraíba, has about 0.8 million inhabitants and is located on the coast (IGBE, 2010). Campina Grande, with about 0.4 million inhabitants, the second most populated urban centre in Paraíba, is located about 120 km away from the capital in the inland of the state (IGBE, 2017). Like other states of North-eastern Brazil, Paraíba has mixed-ethnicity population composed of Indigenous, African and European ancestry.

Data sampling

Data were obtained from 103 patients with invasive penile cancer that were treated in the years between 2012 and 2017. Of 103 patients, 82 (80%) and 21 (20%) were from the HNL and FAP hospital, respectively. Patients

with any other type of cancer were excluded from the study. Information about clinical and histopathological characteristics of the disease and history of phimosis, penile trauma or injury was obtained from medical records of both hospitals. Tumour tissue alterations, suggesting infection with HPV was defined according to established histological criteria (Krustrup et al., 2009). Trained pathologists of both hospital evaluated available paraffin section of penile cancer patients on signs of HPV infection. Information about income, defined as minimum wage and multiple values, was obtained from medical records. Furthermore, information about educational level, marital status, profession, ethnic origin, smoking, alcohol consumption and application of agrochemicals was also obtained from medical records. Information about ethnic origin was self-reported by patients. Patients were given the choice of European, African, Indigenous or any other ethnical background.

A semi- structured questionnaire was applied to interview 40 former patients directly and in eight cases telephone interviews were performed. Interviews were performed by one of the authors in both hospitals. Penile cancer patients were asked about behavioural sexual factors that could increase the risk to develop the disease. Data of medical records about profession, smoking, alcohol consumption, application of agrochemicals, history of phimosis and penile injury or trauma was confirmed again during interview, indicating that data of medical records were highly incomplete, but reliable for all interviewed patients. In 55 out of 103 cases, it was impossible to interview patients due to the following reasons: In seven cases patients had died, 18 did not want to participate on interviews and in 30 cases, it was impossible to establish telephone contact with patients. All together, interviews were performed with 48 patients. Descriptive statistics was performed using EXCEL software (Microsoft®; version 14).

Results

Clinical and histopathological characteristics of 103 patients are summarized in Table 1. Data of medical records were in many cases incomplete. Of 95 patients, 92 (97%) had squamous cell carcinoma and in 42 (51%) out of 82 cases, tumours were stage II (Table 1). Of 59 cases, 41 (69%) were lymph node negative and in one (2%) out of 55 cases, distant metastases were detected (Table 1). In 57 (64%) out of 79 cases, tumour was grade II (Table 1). Histopathological analysis of paraffin specimens suggested in 45 (70%) out of 64 cases an infection with HPV (Table 1).

Of 103 patients, 24 (24%) were under 50 years, whereas 79 (76%) were aged 50 years or older (Table 2). The mean age of patients was 60.65 (s= 15.66) years. Of 95 patients, 38 (40%) were illiterate and 52 (55%) had not completed graduation (Table 2). Of 64 patients, four (6%) earned more than two minimum wages and all together, 72 (70%) worked in agriculture (Table 2).

Of 66 patients, 39 (59%), applied agrochemicals (Table 3). History of phimosis, was reported by 42 (69%) out of 61 patients (Table 3). Of 68 patients, 40 (59%)

Table 1. Clinical and Histopathological Characteristics (N= 103)

Histological type of tumour	
Squamous cell carcinoma	92 (97%)
Other one	3 (3%)
Missing	8
Tumour status	
T1	26 (32%)
T2	42 (51%)
T3	10 (12%)
T4	4 (5%)
Missing	21
Lymph node status	
N0	41 (69%)
N1	8 (14%)
N2	7 (12%)
N3	3 (5%)
Missing	44
Presence of distant metastases	
M0	54 (98%)
M1	1 (2%)
Missing	48
Tumour grade	
I	28 (31%)
II	57 (64%)
III	4 (5%)
Missing	14
Infection with HPV	
Yes	45 (70%)
No	19 (30%)
Missing	39

smoked or were former smokers and 39 (68%) of 67 patients consumed alcohol (Table 3). When asked about sexual behaviour, 27 (56%) out of 48 patients had sexual contact with prostitutes and 28 (61%) out of 46 never used condoms (Table 4). Of 46 patients, 19 (41%) reported history of sexually transmitted infections and 8 (19%) out of 43 have had sex with animals (Table 4).

Discussion

Previous Brazilian studies about association of penile cancer and HPV reported infection rates of 31% and 28% (Gil et al., 2001; Scheiner et al., 2008). Present results in contrast, have indicated HPV infection in 70% of analysed cases. The difference may be due to the methodological approach, as both previous studies focused on high risk HPV 16 and used a direct approach of detection by PCR, whereas the present study focused on general cellular alterations of HPV infection. In agreement with present results, previous studies carried out the USA and Denmark reported similar high infection cases analysed of about 65% and 80%, respectively (Daling et al., 2005; Madsen et al., 2008).

Table 2. Socio- Economic Characteristics of Patients (N= 103)

Age	
20 – 39 years	12 (12%)
40 – 49 years	12 (12%)
50 – 59 years	26 (25%)
60 – 69 years	22 (21%)
≥ 70 years	31 (30%)
Education	
Analphabetic	38 (40%)
Incomplete graduation	52 (55%)
Complete graduation	5 (5%)
Missing	8
Income	
≤ 2 minimum wages	60 (94%)
> 2 minimum wages	4 (6%)
Missing	39
Profession	
Working in Agriculture	72 (70%)
Other one	31 (30%)
Marital status	
Married	75 (82%)
Single	17 (18%)
Missing	11
Ethnic origin	
Mixed ethnic origin	75 (78%)
Caucasian	18 (19%)
Afro- descendent	3 (3%)
Missing	7

Table 3. Information of Risk Factors Obtained from Medical Records (N= 103)

Application of agrochemicals	
Yes	39 (59%)
No	27 (41%)
Missing	46
History of Phimosis	
Yes	42 (69%)
No	19 (31%)
Missing	42
Penile trauma or injury	
Yes	11 (21%)
No	41 (79%)
Missing	51
Smoking	
Ever	40 (59%)
Never	28 (41%)
Missing	35
Alcohol consumption	
Yes	49 (68%)
No	18 (32%)
Missing	36

Table 4. Sexual Behaviour and History of Sexually Transmitted Disease (N= 48).

Sexual contact with prostitutes	
Yes	27 (56%)
No	21 (44%)
Use of condoms	
Never	28 (61%)
Sometimes	18 (39%)
Missing	2
Genital hygiene after sexual contact	
Always	28 (58%)
Sometimes or never	14 (42%)
Missing	6
History of sexually transmitted infections	
Yes	19 (41%)
No	27 (59%)
Missing	2
Sex with animals	
Yes	8 (19%)
No	35 (81%)
Missing	5

Nearly one quarter of patients were under 50 years old and the mean age was 60.65 years. Similarly, in a Brazilian multicentre study, most patients were also aged 60-79 years and 29% of patients were 50 years old or younger (Koifman et al., 2010). However, in a study including 206 patients of penile cancer from the state of Pará, Northern Brazil, 42% of patients were 50 years or younger and in a Brazilian multicentre study, mean age of 58.72 years was reported (Fonseca et al., 2010; Zequi et al., 2012). Comparable to present results, a high percentage of younger penile cancer patients had also been reported in the USA: In the study from Daling and colleagues (2010) of 107 patients, 26% were also less than 50 years of age.

Patients of the present study were characterized as with low educational level and low income. Other studies that analysed socio- economic background of penile cancer patients, based on populations of Brazil and Paraguay, revealed similar results (Fonseca et al., 2010; Koifman et al., 2011; Couto et al., 2014; Chaux et al., 2013).

Most patients have worked in agriculture and over 59% had used agrochemicals. This result corroborates two previous Brazilian studies that had indirectly indicated an increased number of agricultural workers among penile cancer patients (Fonseca et al., 2010; Zequi et al., 2012). A similar observation was made in Costa Rica, where many cases of penile cancer were found among banana crop workers (Wesseling et al., 1996). Wesseling and colleagues also postulated an association of penile cancer among these workers and application of agrochemicals (Wesseling et al., 1999). However, this interpretation has to be considered with care, as the socio- economic background of agricultural workers can lead to an increased behavioural risk and confound the true impact of use of agrochemicals. Furthermore, in addition to the socio- economic background, late treatment of phimosi-

and other etiological important penile conditions may also obscure this impact.

Information obtained from 61 individuals indicated high frequency of phimosi: In the present study, 42 (69%) patients had history of phimosi. Overwhelming amount of data indicate that penile inflammatory conditions like phimosi and balaniti are most important etiological factors of penile cancer (Tsen et al., 2001; Daling et al., 2005; Favorito et al., 2008; Madsen et al., 2008; Morris et al., 2011; Morris et al., 2012; Zequi et al., 2012; Chaux et al., 2013; Morris and Krieger, 2017).

In the present study, about 59% of patients smoked or were former smokers. This is comparable with Daling et al., (2005) for example, who reported a frequency of 67% of former or current smokers. However, compared to present results and several previous Brazilian studies, the frequency of smokers among penile cancer patients was somewhat low: It varied from 33% to 57% (Favorito et al., 2008; Zequi et al., 2012; Couto et al., 2014; Koifman et al., 2011).

The study of Zequi et al., (2012) revealed that 53 (45%) out of 118 penile cancer patients had sex with animals. In the present study, this percentage was lower: Eight (19%) of 43 interviewed patients admitted to having had sex with animals. Additionally, more than a half of patients reported to have had sexual contact with prostitutes. Of patients interviewed 28 (61%) and 19 (41%) admitted never using condoms and to have had a sexually transmitted infection, respectively. These data indicated a promiscuous sexual behaviour of patients. Such behaviour may increase the chance of high risk of HPV infection and other etiological conditions that favour penile cancer. Present data are in agreement with previous studies that reported increased promiscuous sexual behaviour and history of sexually transmitted infections among penile cancer patients (Madson et al., 2008; Zequi et al., 2012; Chaux et al., 2013).

The present study has some limitations. Due to incomplete medical records and the low number of participants, the study was based on few data and this may have caused biases. As only 48 of 103 patients participated on interviews, selection bias cannot be ruled out. As time span between initiation of disease and recruitment was long, recall bias cannot be ruled out. Most patients who had worked in agriculture did not remember which agrochemicals they had applied. The study did not determine at which time of life patients had phimosi. The study did not include detailed quantitative and time -related smoking habits of patients.

In summary, present data confirmed results of previous studies. A high number of penile cancer patients in the state of Paraíba had history of phimosi, had ever smoked during their life time, showed promiscuous sexual behaviour and had tumours with pathological signs of HPV infection. Present results confirmed two previous studies from other regions in Brazil that had indicated that most penile cancer patients worked in agriculture. This is also notable because data were obtained in two urban reference centres of cancer treatment, where most patients do not work in agriculture. Future studies about penile cancer are necessary to elucidate why this disease

is more common among this group of workers. Ideally, the use of agrochemicals, behavioural and etiological risk factors should be compared in a prospective study with a larger group of men working in agriculture.

Conflict of interest

There is no conflict of interest.

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