

Epidemiologic Study on Penile Cancer in Brazil

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ABSTRACT

Objectives: To assess epidemiologic characteristics of penile cancer in Brazil.

Materials and Methods: From May 2006 to June 2007, a questionnaire was distributed to all Brazilian urologists. Their patients' clinical and epidemiological data was analyzed (age, race, place of residence, history of sexually transmitted diseases, tobacco smoking, performance of circumcision, type of hospital service), as well as the time between the appearance of the symptoms and the diagnosis, the pathological characteristics of the tumor (histological type, degree, localization and size of lesion, stage of disease), the type of treatment performed and the present state of the patient.

Results: 283 new cases of penile cancer in Brazil were recorded. The majority of these cases occurred in the north and northeast (53.02%) and southeast (45.54%) regions. The majority of patients (224, or 78.96%) were more than 46 years of age while only 21 patients (7.41%) were less than 35 years of age. Of the 283 patients presenting penile cancer, 171 (60.42%) had phimosis with the consequent impossibility to expose the glans. A prior medical history positive for HPV infection was reported in 18 of the 283 cases (6.36%). In 101 patients (35.68%) tobacco smoking was reported. The vast majority of the cases (n = 207; 73.14%) presented with tumors localized in the glans and prepuce. In 48 cases (16.96%) the tumor affected the glans, the prepuce and the corpus penis; in 28 cases (9.89%) the tumor affected the entire penis. The majority of the patients (n = 123; 75.26%) presented with T1 or T2; only 9 patients (3.18%) presented with T4 disease.

Conclusion: Penile cancer is a very frequent pathology in Brazil, predominantly affecting low income, white, uncircumcised patients, living in the north and northeast regions of the country.

Key words: penile cancer; epidemiology; phimosis

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INTRODUCTION

Penile cancer is an aggressive and mutilating disease that deeply affects the patient's self-esteem. Penile cancer is a rare neoplasia with low incidence in developed countries. One of the highest world incidence is found in India with rates of 3.32/100,000 inhabitants, and the lowest incidence is in Jewish men born in Israel with rates close to zero (1). In the United States, the incidence rate is 0.2 cases for each 100,000 inhabitants whereas in Brazil the incidence rate of penile cancer is 2.9 - 6.8/100,000 inhabitants, resulting in this country having one of the world's highest incidence rates for this neoplasia (2).

There are many proposed etiologies underlying the development to penile cancer however many aspects of the pathophysiology of this disease are still poorly elucidated. What is known is that there is a strong association between the presence of the prepuce and the development of the disease (3). The risk of developing this neoplasia was studied by Maden et al. (4) in three groups of individuals. In those that had never been circumcised, the risk was 3.2 times higher than in those that were circumcised at birth and 3 times higher than the ones who were circumcised during the neonatal period. Similarly, Paymaster and Gangadharan (5) reported an incidence of 3.3% among non circumcised individuals and 0% in those circumcised after birth.

Furthermore, among those with phimosis or excess prepuce, a low socioeconomic level of the patients and poor personal hygiene were the most important risk factors for the development of penile cancer (6). The importance of the association of these three risk factors is well established; nevertheless in the work of Frisch et al. (7), a low incidence of penile cancer was observed in Scandinavia, even though the population studies reported from this geographical area showed a low incidence of circumcisions.

Also smegma has been implied in the carcinogenesis of penile cancer. Experiments have demonstrated that cancer of the uterine cervix can be induced in female rats through the local application of smegma (8); however the specific carcinogenicity of this substance has yet to be defined (3). A common risk factor for penile cancer includes a clinical history of sexually transmitted diseases such as gonorrhea, Chlamydia, and/or syphilis, even though there is no evidence of a causality relationship between these infectious pathogens and the development of this neoplasia (4).

There is an association between Human Papilloma Virus (HPV) infection and penile cancer in 30 to 50% of cases, primarily HPV 16 (9), although the exact role of the infection in the genesis of this neoplasia has not yet been entirely clarified (10).

Prospective epidemiological studies about penile cancer are rare. In Brazil there are no multicenter epidemiological studies regarding this neoplasia. The aim of this study was to prospectively evaluate the epidemiological characteristics of penile cancer in Brazil, assessing the presence of predisposing factors, the places where the incidence of the disease is higher, the age of the manifestation and the clinical characteristics of the disease.

MATERIALS AND METHODS

Over the period from May 2006 to June 2007, an epidemiological study was conducted among Brazilian urologists to further elucidate the incidence, risk factors, and patient characteristics of newly diagnosed penile cancer patients within Brazil. Each urologist treating a newly diagnosed penile cancer was asked to complete a patient directed questionnaire with no

patient identifiers provided in order to maintain patient confidentiality. These questionnaires were sent back to our institution and the results were entered into a prospectively collected database.

The patient's clinical and epidemiological data was assessed in the questionnaire: age, race, place of residence, degree of education, history and type of sexually transmitted diseases, presence of phimosis (patients with incapacity to expose the glans), presence of HPV, age the circumcision was performed (childhood, adolescence and adulthood), tobacco smoking, type of hospital service (public or private network).

Also assessed were: the time between the appearance of the symptoms and the diagnosis of penile cancer; the presence of pre-neoplastic diseases (balanitis xerotica obliterans, Bowen's disease or erythroplasia of Queyrat); the anatomical pathological characteristics of the tumor, such as the histological type, degree, localization of the lesion (glans, prepuce, corpus, shaft or the entire penis); size of the lesion; presence of palpable inguinal lymph nodes; stage of the disease; presence and localization of metastasis and the type of treatment performed, if surgical (partial penectomy, radical penectomy, lymphadenectomy) or palliative (chemotherapy, radiotherapy).

All patients filled out an informed consent form to be included in the sample. The present study was approved by the Bioethics Committee of our institution.

RESULTS

Study accrual and analysis was performed from May 2006 to August 2007. During this study period, 283 questionnaires were received containing 283 new cases of penile cancer. We observed that the majority of the cases (149 cases - 53.02%) were reported in the north and northeast regions of the country with the lowest human development index. The region with fewer reports of cases was the Southern region, a region with a high human development index presenting less than 2 cases (0.71%).

The age range of the patients affected by the disease is shown in Table-1. We can observe that the vast majority of the patients (n = 224; 78.96%) were

Table 1 – Distribution of the cases of penile cancer in relation to age.

Age Range	N of Cases (%)
< 26 years	10 (3.53)
27-35 years	11 (3.88)
36-45 years	34 (12)
46-55 years	53 (18.72)
56-65 years	60 (21.2)
> 66 years	111 (39.22)
Total	283 (100)

older than 46 years of age, while only 21 patients (7.41%) were less than 35 years of age. Of the 283 patients with penile cancer, 214 (75.61%) were Caucasian, 63 (22.26%) were Black and only 6 (2.12%) were Oriental.

Of the 283 patients presenting with penile cancer, 171 (60.42%) presented with severe phimosis not allowing the possibility of exposing the glans and 37 (13.07%) had a circumcision. Of these 37 patients, only 1 underwent the procedure in childhood, 4 during adolescence and 32 in adulthood. The patients that had a circumcision in childhood or adolescence presented a low grade penile tumor (Grade 1 - 3 patients, Grade 2 - 2 patients). Of the 32 patients who had a circumcision in adulthood, 28 presented low grade tumors and 4 (12.5%) presented high grade tumors. Of all 37 patients that had a circumcision, only 5 (all belonging to the group of those who underwent circumcision while adults) presented a tumor affecting the corpus penis.

Table 2 – Staging of 283 cases of penile cancer studied.

Staging	N of Cases (%)
Tis	7 (2.47)
T1	102 (36.04)
T2	111 (39.22)
T3	44 (15.54)
T4	9 (3.18)
Total	283 (100)

A history of HPV was reported in 18 of the 283 cases (6.36%). In 101 patients (35.68%) there was a report of tobacco smoking. The number of cigarettes per day that the patients consumed tobacco was not reported, nor was the length of time those patients had been tobacco smokers preventing further statistical analysis to be conducted. Of the 101 tobacco smoking patients, 87 (86.13%) presented with a low grade tumor and 14 (13.86%) presented with a high grade tumor.

The vast majority of cases (n = 207; 73.14%) presented with tumors localized in the glans penis and prepuce. In 48 cases (16.96%), the tumor affected the glans, prepuce, and corpora cavernosa of the penis; in 28 cases (9.89%) the tumor affected the entire penis. The frequency distribution of newly diagnosed penile cancer cases stratified by stage of disease is shown in Table-2. The majority of the patients 213 (75.26%) presented stage T1 or T2 tumors; only 9 patients (3.18%) presented stage 4 tumors.

COMMENTS

Brazil is a country with one of the highest incidences of penile cancer in the world; the frequency of this neoplasia is variable depending on the region considered, and is directly related to the local socio-economic conditions. The overall relative incidence was 2.1% of the male neoplasias, reaching 5.7% in the Northeast region, 5.3% in the North region, 3.8% in the Center-east region, 1.4% in the Southeast region and 1.2% in the Southern region (11). According to the data from the Brazilian Ministry of Health, there is an estimated 850 partial or complete penile surgical procedures performed in the context of malignancy yearly within Brazil, with approximately 50% of these procedures being performed in the North and Northeast regions of the country. In our study we observe a predominance of reports of penile cancer in the North and Northeast (53.02%), which are regions with lower human development indexes.

The age range where penile cancer is more frequent is in the sixth decade of life (1,12). This sample included 78.96% of patients older than 45 years of age. However, 7.41% of the patients were less than 35 years of age. The occurrence of this neoplasia

in a younger age range serves as an alert that research of penile neoplasia in young non circumcised patients with suspected lesions is important (13).

There is very limited data in the scientific literature regarding the preponderance of penile cancer among various racial ethnicities. Busby and Pettaway (14) reports that the probability of Africo-American patients developing more aggressive penile cancer is higher than Caucasians; however, this article does not discuss socioeconomic factors that could influence these indexes, i.e. early medical assistance. In our sample the vast majority of the patients (75.61%) were Caucasian. Only 22.26% of the patients were Black and 2.12% Oriental. Since more than 90% of the patients originated from the public service network, this disease tends to affect poorer, non-circumcised patients with precarious hygiene habits. Race does not seem to be a determinant risk factor for the occurrence of this type of tumor.

The most important risk factor for the development of penile cancer is phimosis (4). Men who do not undergo neonatal circumcision have a 3.2 times higher risk to develop penile cancer than patients submitted to the removal of the prepuce after birth (37 patients (13.07%), who had a postectomy compared to 32 who had to the procedure in adulthood and 5 in childhood or adolescence. Only 4 (12.5%) of the 37 patients who had a circumcision presented with a high grade tumor. These data are interesting and may suggest that circumcision prevents the occurrence of penile cancer only if performed in the perinatal period, despite the fact that the patients that had circumcision in their majority (more than 87%) tended to develop low grade tumors.

An important epidemiological study conducted in 244 patients presenting penile cancer with a control group of 232 patients without penile cancer demonstrated that tobacco smoking is a risk factor for the development of penile cancer (15). Of the 283 patients in our study, 101 were tobacco smokers (35.65%). Of the tobacco smoking patients, 87 (86.13%) presented with a low grade and 14 (13.86%) with a high grade penile tumor. This correlation between tobacco smoking and the grade of penile cancer has not previously been reported. Our study, even though it does not offer a control group, demonstrates that more than one third of the patients

presenting with penile cancer were tobacco smokers, suggesting that tobacco smoking is one of the risk factors for the development of this neoplasia. More than 85% of the tobacco smoking patients presenting with penile cancer had a low grade tumor.

Our study underlines the fact that even within the context of a contemporary series of penile cancer patients, 58% of patients were diagnosed with advanced disease (Grade T2 or higher). This finding is of concern because it is well established that the advanced stage is strongly correlated with degree of invasion and probability of regional and systemic metastases suggesting a worse prognosis for these patients (16-18).

These data suggest that patients delay in their search for medical care either because of fear or ignorance, or find it difficult to get access to specialized services. Independently from this, a national campaign to alert the greater public about this presently poorly known disease is fundamental. This campaign should also serve as an alert to the Brazilian authorities about the high incidence of this malignancy within our society.

CONCLUSION

Penile cancer is a very frequent pathology in Brazil, predominantly affecting low income, non-neonatal circumcised males, Caucasian patients living in North and Northeast regions of the country where there may be a delay in obtaining specialized medical assistance.

CONFLICT OF INTEREST

None declared.

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EDITORIAL COMMENT

The authors present an epidemiologic study including 283 patients with penile carcinomas. A questionnaire was distributed to all the Brazilian urologists and epidemiological data was analyzed. Penile cancer is an uncommon tumor with a significantly higher incidence in some areas of underdeveloped countries.

Unfortunately, delay on the part of the physician in initiating diagnosis may be considerable and many patients are referred to treatment after developing advanced disease. There is a large volume of data on penile cancer in Brazil. Losing patients to follow-up is common and in some areas of the country, penile

cancer accounts for 17% of all malignancies in men (1). In these less developed areas, penile carcinoma represents one of the most important health problems. In Brazil, it is very difficult to get access to specialized services and unfortunately, in this article it was not possible to discuss socioeconomic factors that could influence the indexes analyzed by the study. This epidemiological study and another sponsored by the Brazilian Society of Urology (SBU) gave us an idea about the complexity of the problem (2). For example, the highest incidence rates of penile carcinoma were found in Maranhão and São Paulo. Maranhão is situated in an underdeveloped area and São Paulo is the richest state of the country. An explanation for this contradiction is the large migration of the poor from underdeveloped areas to São Paulo.

The SBU and the federal government are now waging a campaign to increase early diagnosis and improve health measures in order to eradicate the disease in the future. The authors are to be congratulated for their national campaign to alert the Brazilian urologists and the greater public about this poorly known disease.

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EDITORIAL COMMENT

Penile cancer is a rare malignancy in most countries however Brazil has one of the highest incidences of this malignancy. The present study offers a unique opportunity to better define the socio-epidemiological characteristics of this patient population within Brazil. Several important conclusions can be made from this study that I would like to highlight. Firstly, the study illustrates that 283 newly reported cases of penile cancer were treated by Brazilian urologists over a one year period clearly representing one of the highest incidences of this malignancy worldwide. Furthermore, most newly identified cases of penile cancer were treated in 3 distinct parts of the country (north, northeast, and southeast) and most patients (79%) were more than 46 years of age. This study better defines the relative contribution of risk factors for penile cancer carcinogenesis within Brazil, particularly phimosis, previous HPV infection, and a history of tobacco smoking. Furthermore, the study as well highlights that most patients (58%) present with advanced disease (T2 or higher) clearly emphasizing

the importance for better patient education and accessibility to early medical services. In this reviewer's opinion, studies such as this are important as they help better define the socioeconomic characteristics of those affected with penile cancer whereby the specific patient population at increased risk of this malignancy can be targeted for education on the signs and symptoms of penile cancer. Furthermore, the study brings attention to the high incidence of advanced disease at diagnosis and need for improved accessibility to early treatment diagnosis and intervention (raising question of the potential role of screening in high-risk populations like some regions of Brazil) in an attempt to optimize the treatment related outcomes for this highly aggressive tumor phenotype.

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EDITORIAL COMMENT

This study attempts to get grip on epidemiological data regarding penile cancer. This is a laudable attempt as penile cancer has a high incidence in Brazil. These basic data are essential for health strategies not only for the male population in Brazil but also for females. It is sobering to realize that the incidence of cervical cancer in Brazil ranks also as one of the highest in the world.

Some findings are remarkable.

The association of phimosis and penis cancer is well known amongst urologist. Is it equally known among other doctors and laymen? It is time to spread the gospel. This is unique opportunity for preventive medicine. Physiologic phimosis after the age of 6 year is not physiologic anymore. All involved in primary and pediatric medicine (health authorities, primary health care workers, general practitioners, gynecologists, pediatricians etc.) should be on the alert for this condition. Moreover, the public should be informed as well.

It is a riddle why circumcision done at a later stage than shortly after birth, does not have the same

protective properties anymore. It is reasonable to assume that sexarche and the risk of acquiring high-risk HPV has a profound effect on the etiology of penile cancer. Could factors even before the start of sexual activity play a role?

It is remarkable that tumors arising after circumcision in adulthood seem to have a different biological make up (the majority are well differentiated).

This study has nevertheless some shortcomings. Considering the fact that according to the authors, more than 800 cases of penile cancer are treated in Brazil and considering the fact that some 200 + cases are described in this study, selection has occurred. It is unclear what sort of selection took place. Also we are not informed on the response rate after sending the questionnaires.

Restricting their epidemiological data to the clinical stage of the primary only and not expanding their data to the clinical stage of regional lymph nodes is a missed opportunity to have more insight in the incidence of lymph node invasion.

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