# Epidemiology of penile cancer from the 20th to the 21st century: a literature review

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**Background and Objective:** Penile cancer (PC) is a disease with great potential for physical and psychological mutilation, representing an important public health problem in underdeveloped regions. To reduce the incidence of PC, it is necessary to elucidate its causes and risk factors, as well as to understand the epidemiological profile of patients affected by this neoplasm. Therefore, the objective of this study was to evaluate, through the literature, the epidemiological profile of PC over the 20th and 21st centuries.

**Methods:** A literature review was conducted using as references the PubMed and Virtual Health Library (VHL) databases, using as descriptors the terms (penile) AND (neoplasms) AND (Epidemiology) AND (Risk Factors). For comparison, seven articles from the 20th century, published between 1963 and 1999, and eight articles from the 21st century published between 2000 and 2022 were selected, addressing the theme in an integrated manner without language restrictions. Those that addressed the descriptors in isolation were excluded.

**Key Content and Findings:** This review shows that the sociodemographic profile of patients with PC remains unchanged when compared to studies conducted in the 20th century and first decades of the 21st century. It is possible to verify that men with low income, low education, living in rural areas, and who work in farming characterize the public affected by PC over the two centuries.

**Conclusions:** It is evident that risk factors have always been closely related to socioeconomic conditions and the spatial distribution of the disease remains a problem in underdeveloped regions.

**Keywords:** Epidemiology; penile neoplasm; risk factors

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## Introduction

Penile cancer (PC) is a neoplasm with great potential for physical and psychological mutilations, associated with high morbidity resulting from the disease itself and/or its treatment (1). Despite being an aggressive disease with great impact on quality of life, PC remains a subject little studied in relation to other more prevalent neoplasms (2). Even in regions that have high incidence, there are still few published studies that provide a characterization of the population affected by the problem (3).

Its high incidence constitutes a public health problem in South American, Asian and African countries. In contrast, it is a rare disease and with decreasing incidence in developed countries, which reduces the interest in this pathology, limiting wide epidemiological studies and the understanding of risk factors (4).

Thus, the low incidence of this disease in developed countries, contrasting with the high incidence in underdeveloped countries, clearly indicates the association of PC with the socioeconomic conditions of the male population (3).

It is noteworthy that there are still few epidemiological data on the disease. Knowing better the patients' characteristics can provide important data for the improvement of educational and preventive measures, allowing early diagnosis and timely treatment (1).

In this sense, in order to reduce the occurrence of PC, it is necessary to invest in research that can elucidate its causes and risk factors, as well as understand the epidemiological profile of patients affected by this neoplasm. Therefore, the objective of this study was to evaluate the epidemiological profile of PC throughout the 20th and 21st centuries through the literature. We present this article in accordance with the Narrative Review reporting checklist (available at https://amj.amegroups.com/article/view/10.21037/amj-22-87/rc).

## Methods

To identify studies that evaluated the epidemiological characteristics of penile cancer in the 20th and 21st centuries, the PubMed and Virtual Health Library (VHL) databases were used from August 1st to 10th, 2022, searching for articles without language and date restrictions.

In the literature search, the search terms were selected using Medical Subject Heading (MeSH) and Health Science Descriptors (DeCS) and combined as described: PubMed: (penile) AND (neoplasms) AND (Epidemiology) AND (Risk Factors), BVS: (penile) AND (neoplasms) AND (Epidemiology) AND (Risk Factors). In addition, the identification of studies on the subject was also performed by reading the references of the research filtered in the databases.

The included studies published between 1963 and 2022, evaluated the epidemiological characteristics of penile cancer in the 20th and 21st centuries. We selected studies that provided an epidemiological profile and the spatial distribution of penile cancer as well as the identification of known risk factors.

After the selection of studies filtered by the descriptors, duplicates were excluded, and then the titles and abstracts were analyzed in order to exclude those that addressed the descriptors alone. The full texts of the remaining articles were analyzed, and the studies relevant to this review were included. From the selected studies, the following information was obtained: name of authors, year of publication, title, objectives, methods, results and conclusion.

## Discussion

It is important to highlight that the literature review is a retrospective study, so the results must be interpreted taking into account the limitations and biases inherent in observational studies. The main limitations that may affect this review are publication bias and methodological limitations of the primary studies.

As shown in *Figure 1*, in total 361 studies were identified and after exclusion of the 63 duplicates, 298 remained for analysis, but after applying the inclusion and exclusion criteria, 14 articles were included in the sample.

*Table 1* shows the year of publication of each study, database, countries where they were developed, title, and type of study selected for this review.

It is possible to observe that during the 60s, 70s, and 80s in the United States of America and Europe, penile cancer (PC) represented about 0.3% to 0.5% of malignant tumors in men, but, on the other hand, in some regions of Asia, Africa, and South America, this disease came to represent about 10% to 20% of male urogenital tumors (5).

The study carried out by Brumini *et al.* (6) shows that in the 20th century, PC was five times more prevalent in the poorest regions when compared to regions with a higher development index. Analyzing the studies published in the first two decades of the 21st century, it is observed that

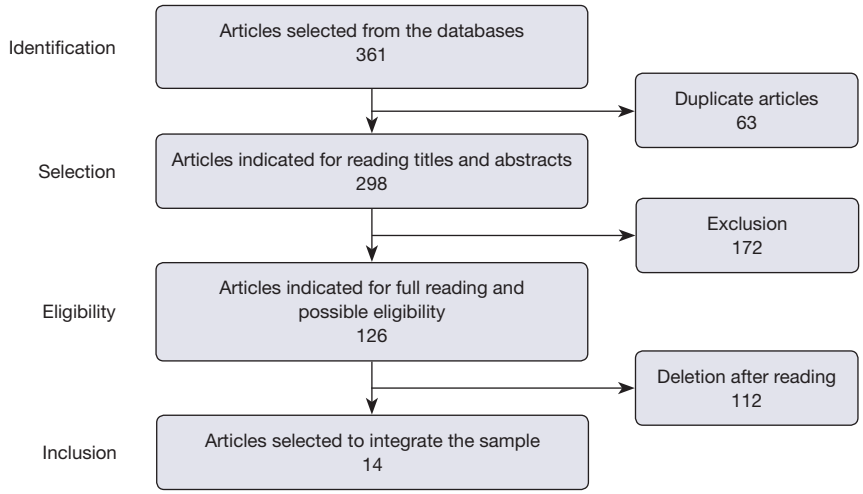


**Figure 1** Flowchart of the review article selection process.

**Table 1** Synthesis of articles selected for comparison of the epidemiological profile of penile cancer between the 20th and 21st centuries

| Year/country | Title/database | Methods |
|---|---|---|
| 1963/Indonesia | Observations on frequency of carcinoma of the penis at Macassar and its environs/PubMed | Study observational |
| 1977/Germany | Epidemiology of cancer of the penile/PubMed | Descriptive epidemiology |
| 1979/USA | Penile carcinoma in circumcised males/PubMed | Case study |
| 1982/Brazil | Cancer in Brazil: histopathological/LILASC | Descriptive epidemiology |
| 1987/Sweden | Penile cancer: Is there an epidemiological role for smoking and sexual behaviour?/PubMed | Retrospective study with matched controls |
| 1987/EUA | High prevalence of papillomavirus-associated penile intraepithelial neoplasia in sexual partners of women with cervical intraepithelial neoplasia/PubMed | Case study |
| 1993/Sweden | The prevalence of “high-risk” HPV types in penile condyloma-like lesions: correlation between HPV type and morphology/PubMed | Case study with 94 men |
| 2008/Brazil | Epidemiologic study on penile cancer in Brazil/SCIELO | Descriptive epidemiology |
| 2014/Brazil | Epidemiological study of penile cancer in Pernambuco: experience of two reference centers/SCIELO | Retrospective, observational and descriptive study |
| 2015/Brazil | Epidemiology of penile câncer/PubMed | Descriptive epidemiology |
| 2018/Brazil | Penile cancer in Maranhão, Northeast Brazil: the highest incidence globally?/PubMed | Retrospective study |
| 2020/Brazil | Profile of patients with penile cancer in the region with the highest worldwide incidence/PubMed | Prospective, cross-sectional, descriptive study |
| 2020/Brazil | Genomic profiling reveals the pivotal role of hrHPV driving copy number and gene expression alterations, including mRNA downregulation of TP53 and RB1 in penile cancer/PubMed | Case study |
| 2021/Italy | A global approach to improving penile cancer care/MEDLINE | Integrative review |
| 2022/Brazil | A comprehensive analysis of penile cancer in the region with the highest worldwide incidence reveals new insights into the disease/MEDLINE | Retrospective cohort study |

the prevalence of the disease remains low in developed countries, representing a public health problem in the poorest countries and regions of the world (7,8).

It is possible to relate this high prevalence of PC in underdeveloped countries to the low per capita income and low human development index. These factors, combined with the high rate of rural habitation, distance from health centres and little or no education, appear to create the ideal conditions for the development of penile cancer (3).

These socioeconomic characteristics are similar to those found in the study by Coelho *et al.* (4) where patients affected by PC generally have low socioeconomic status and face great difficulties in accessing health services. Thus, it is possible to realize that, as in the 20th century, socioeconomic conditions continue to be determinants for the high incidence of PC in less developed regions.

According to Bandini *et al.* (9), South America is one of the areas that concentrate the highest number of cases, and deaths from PC. This spatial distribution may justify the little interest in developing research, as well as the lack of implementation strategies to address the problem (4). Recent studies also show that the geographical distribution of PC remains as in the 20th century, with higher prevalence in the poorest regions, showing that PC continues to be a neglected disease (3).

The geographical distribution of PC contrasts with the rate of active registries contributing to research on the problem. In North America, there are a large number of active registries contributing to research on PC, but the prevalence of the disease is considerably low. On the other hand, in regions of higher prevalence, records of patients with PC are scarce and due to the difficulties in obtaining information hinder the improvement of prevention strategies and early treatment (9).

In this sense, it is possible to observe that, as in the last century, the challenges that surround the confrontation of PC continue to be related to the timely diagnosis, the time between diagnosis and beginning treatment, inadequate surgical technique and the unavailability of chemotherapy and radiotherapy (9,10).

When analyzing the men affected by PC over the two centuries, it was also verified that the sociodemographic profile of these patients remains as pointed out in the study by Hellberg (10), where the most prevalent occupation among men affected was that of farmer. Similarly, Vieira *et al.* (3) found that most patients affected by PC live in rural areas, work in farming and have little or no education.

In the same way, the study by Teixeira Júnior *et al.* (1) shows that most patients affected by PC experience socioeconomic vulnerability. In addition, Coelho *et al.* (4) show that, similar to the sociodemographic profile of PC in the 20th century, currently, men affected by the disease are predominantly individuals of low socioeconomic status and low education, residents of rural areas and who work in farming.

It is possible to observe that over the years, PC has remained more prevalent in individuals after the fifth decade of life, although it can affect men in any age group regardless of race (3). Given the above, Teixeira (1) corroborates the finding that there was no change in relation to the sociodemographic profile of men affected by PC, and that the population over 50 years of age and living in rural areas continues to face the same difficulties of access to measures of prevention, diagnosis and timely treatment.

It is possible to verify that cancer started to be a discussed and studied disease during the first decades of the 20th century. In great measure, this was due to the increase of research about the functioning of the cells, which brought a greater knowledge of the risk factors that contribute to the development of neoplasms (11). Studies of that time already pointed out that the smoking habit had a significant effect on the prevalence of all types of cancer, including penile cancer (10).

It is observed, as corroborated by the study of Costa (12), that tobacco use remains an important risk factor established for PC and other neoplasms. Therefore, investment in educational campaigns and guidance on smoking cessation can considerably impact the pathogenesis of precancerous lesions of the penis (1).

Evidence suggests that the chemical components of tobacco have a mutagenic potential that causes DNA damage and epithelial cell modification, in addition to causing a local and systemic immunosuppressive effect, which creates an opportunistic environment for the development and prevalence of certain viruses such as HPV. Thus, one third of men worldwide who are active smokers are exposed to an increased risk of infection and the viral persistence of HPV, one of the main risk factors for carcinogenesis of penile neoplasm (8).

It should also be remembered that over the years the scientific community has been devoting efforts to determine the influence of risk factors on the onset and development of neoplasms. In this sense, the literature points out that younger men seem to develop mainly HPV-associated PC, being more prone to recurrence, infiltrative patterns and perineural invasion (1). It is also worth noting that since the

mid-20th century there was already a significant correlation between "high-risk" types of HPV and PC (10).

Thus, in the last decade, there was huge progress in the identification of genes associated with cancer; the improvement and reduced costs of research methods in molecular biology will facilitate the emergence of new diagnostic molecular markers (8). Recent studies show that HPV remains an important risk factor for the development of PC as pointed out in the study by Macedo (13) where they observed a frequency of HPV in 96.4% of patients affected by PC, with HPV 16 being the most prevalent.

However, there is still a lack of studies on the association between HPV and penile carcinomas, which are necessary to intensify prevention campaigns, passing on to the general population the knowledge about the carcinogenic effect of HPV infection (13).

Another prevalent factor among PC cases is phimosis, which can hinder genital hygiene, cause accumulation of smegma, increase the risks of chronic inflammation such as balanitis and lichen sclerosus, besides making more favorable the transmission of HPV, factors that are closely related to the development and progression of cancer lesions (3).

The history of phimosis stands out as an important risk factor for the development of PC, being found in approximately 85% of patients (7,11). Similarly, in the study by Vieira *et al.* (3) where 116 patients with PC were evaluated, phimosis was present in 66% of cases and most circumcised men had the procedure done in adulthood, after presenting symptoms of the disease.

In the background, in the same study, genital hygiene was classified as bad/moderate in 73% of patients, in agreement with the study published in 1963 by Tan (14), which provided evidence that precarious conditions of intimate hygiene were associated with PC. Such conditions form a set of risk factors already known since the middle of the 20th century, increasing the chances of balanitis and lichen sclerosus, which can also contribute to the development of PC (1).

## Conclusions

Based on the aspects analyzed, this review demonstrates that the epidemiological profile of PC remains unchanged when comparing the studies conducted in the 20th century with those conducted in the first two decades of the 21st century. It is possible to observe that the risk factors have been known since the middle of the last century and have always been closely related to socioeconomic conditions.

In view of the above, PC continues to be an important public health problem in the poorest regions of the world, where the men affected remain as in the past, of low income, low education, who are mostly farmers and rural residents.

Thus, the geographical distribution of PC is closely related to the knowledge gap generated by the lack of research funding, combating risk factors, and changing socioeconomic conditions that can gather data capable of mitigating this serious health problem.

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*Ethical Statement:* The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.



 

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