



Original contribution

# Warty/basaloid penile intraepithelial neoplasia is more prevalent than differentiated penile intraepithelial neoplasia in nonendemic regions for penile cancer when compared with endemic areas: a comparative study between pathologic series from Paris and Paraguay<sup>☆</sup>

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**Summary** Penile squamous cell carcinoma shows an ample geographic variation in its prevalence with regions of low (North America, Europe, Japan, and Israel) and high (Africa, Asia, and South America) incidence. However, the geographic variation in the distribution of penile intraepithelial neoplasia is not well established. The aim of the present study was to compare the distribution of in situ and invasive lesions between geographic areas with low (France) and high (Paraguay) penile cancer incidence using a series of consecutive cases. The French series included 86 cases (57 in situ and 29 in situ + invasive squamous cell carcinoma), and the Paraguayan series, 117 cases (31 in situ and 86 in situ + invasive squamous cell carcinoma). Incidence of invasive squamous cell carcinoma in the overall samples was higher in the Paraguayan series ( $P < .00001$ ). Comparing the Paraguayan and the French series, differentiated penile intraepithelial neoplasia was more prevalent in the former (65.0% versus 19.8%), whereas lesions showing warty and/or basaloid features predominated in the latter (35.0% versus 80.2%) to a significant level ( $P < .00001$ ). This distinctive pattern of differential distribution was maintained when cases with associated invasive squamous cell carcinoma were excluded. The pattern of distribution of lichen sclerosus was also distinctive, with a significantly higher prevalence in the Paraguayan population when compared with the French series (32.5% versus 12.8%,  $P = .0015$ ). In summary, there appears to be a distinctive distribution of penile precursor lesions depending on the

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geographic region in consideration. Penile intraepithelial neoplasia with warty and/or basaloid features predominated in low-incidence areas, whereas differentiated penile intraepithelial neoplasia was more prevalent in endemic regions for penile cancer. Further prospective studies in matched populations and from different geographic regions are needed to further clarify the reasons for this discrepancy.

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## 1. Introduction

There is a significant worldwide geographic variation in the incidence of penile squamous cell carcinomas (SCCs), with regions of low incidence in North America, Europe, Japan, and Israel (age-standardized rate [ASR], 0.2-0.8 per 100 000 inhabitants) and high incidence in Africa, Asia, and South America (ASR, 2-4.2 per 100 000 inhabitants) [1,2]. Other geographic differences include the higher frequency of precancerous over invasive lesions reported in European and American series, with opposite results in countries with high penile cancer ASR [3,4]. In addition, evidence of human papillomavirus (HPV) infection is found in 60% to 100% of all in situ carcinomas [5,6], whereas HPV-related invasive SCC accounts only for 22% to 48% of all penile tumors either in regions of low or high incidence [7-11]. There are no satisfactory explanations for these phenomena. Previous studies have found a close similarity in the distribution of histologic subtypes of penile cancer in high- and low-incidence areas [9,10,12], but none has focused exclusively in the comparison of preneoplastic lesions between these regions. Taking into account the recently proposed classification of penile intraepithelial neoplasia (PeIN) [3], the striking association of these PeIN subtypes with specific variants of invasive penile SCC [3,13], and the preferential association of HPV infection with certain subtypes of SCC [9-11], we designed this study to compare the distribution of in situ and invasive lesions between geographic areas with low (France; ASR, 0.3-0.8 per 100 000) and high (Paraguay; ASR, 4.2 per 100 000) penile cancer incidence [1,2].

## 2. Materials and method

The surgical pathology databases at the Hôpital Cochin (Paris, France) and the Instituto de Patología e Investigación (Asunción, Paraguay) were searched for all consecutive cases diagnosed as precancerous penile lesions (dysplasia, carcinoma in situ, PeIN/atypical intraepithelial lesion, erythroplasia of Queyrat, or Bowen disease) with or without associated invasive carcinoma; cases previously diagnosed as squamous hyperplasias and lichen sclerosus without atypias were excluded. Pathology reports were retrieved, and cases were selected according to the availability of slides for histologic examination; surgical specimens consisted of biopsies, circumcisions, wide local excisions, and penec-

tomies. The number of cases available for review included 90 cases in the French series and 126 cases in the Paraguayan series; 1 to 5 slides were reviewed for each case. A workshop was conducted in the Department of Pathology at the Hôpital Cochin (Paris, France) to standardize the uniform morphological criteria for identification and classification of precursor lesions; cases were collectively reviewed afterward by the authors using a multihead microscope, and a consensus diagnosis was reached for each one of them. When present, subtypes of invasive SCC were classified following the criteria given in the latest Armed Forces Institute of Pathology Atlas of Tumor Pathology [14]. The presence of lichen sclerosus, diagnosed using previously published criteria [15], was also recorded for each case. Medical records were examined in all cases for determining the presence of concurrent HIV infection. After the workshop, 4 cases from the French series were excluded based on insufficient morphological changes to warrant a diagnosis of PeIN and were reclassified as atypical condylomas. In 9 cases of the Paraguayan series, the distinction between a squamous hyperplasia and an early/minimal differentiated PeIN was not possible based solely on the hematoxylin and eosin findings; those cases were also excluded from the main group. In all the remainder cases of the French (n = 86) and Paraguayan (n = 117) series, the diagnosis of PeIN with or without an invasive component was confirmed.

### 2.1. Criteria for PeIN subtyping

Penile precancerous lesions were classified in one of the following subtypes of PeIN: differentiated, warty, basaloid, or warty-basaloid [3]. Criteria for diagnosis of PeIN subtypes were for differentiated PeIN, presence of atypical epithelial cells, usually more prominent at bottom layers, with retained squamous maturation, including eosinophilic cytoplasm, well-defined cellular borders, and prominent intercellular bridges (Fig. 1A); elongated, irregular rete ridges, acanthosis, parakeratosis, hypergranulosis, and hyperkeratosis were also seen but not required for diagnosis. Basaloid PeIN was characterized by a proliferation of small- to medium-sized monotonous cells with basophilic, scant cytoplasm, indistinctive cellular borders, and high mitotic/apoptotic rate, totally replacing the epithelium (Fig. 1B); epithelial surface was flat or slightly irregular, frequently acanthotic, and parakeratotic. Warty PeIN exhibited a spiky, undulating surface with evident parakeratosis, conspicuous koilocytosis,

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