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Comparison of Subtypes of Penile Squamous Cell Carcinoma From High and Low Incidence Geographical Regions

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There is a worldwide geographical variation in the incidence of penile squamous cell carcinoma (PSCC); some subtypes are HPV-related (warty, basaloid) while others (keratinizing variants) are not. The aims of this study were to compare the distribution of different histological subtypes of PSCC from regions of low (Paraguay, 144 cases) and high (USA, 157 cases) incidence and to identify and compare tumors with and without warty and/or basaloid morphology. The distribution of subtypes in the Paraguayan and the American series was: usual, 49.3 and 46.5%; verrucous, 8.3 and 7.6%; papillary NOS, 7.6 and 5.7%; warty, 6.9 and 8.3%; basaloid, 4.2 and 7.0%; sarcomatoid, 0.7 and 0.6%; adenosquamous, 3.5 and 0.6%; and mixed, 19.4 and 23.6%, respectively. The distribution of mixed PSCC was: warty-basaloid, 50.0 and 59.5%; usual-verrucous, 21.4 and 21.6%; usual-warty, 14.3 and 8.1%; usual-basaloid, 7.1 and 0.0%; usual-papillary, 3.6 and 5.4%; and others, 3.6 and 5.4%, respectively. In conclusion, we found no geographical difference in the incidence of histological subtypes (p = 0.6501), mixed PSCC (p = 0.5937) or HPV-related tumors (p = 0.2505). Geographical variation may be the result of staging variation at clinical presentation or of pathological diagnosis. The identification of similar histological subtypes in both series validates this classification approach for penile cancer. The tendency for typical SCC to mix with verrucous and papillary carcinomas and of the basaloid to preferentially mix with benign condyloma and condylomatous (warty) carcinomas would support the hypothesis of the existence of an etiologically different dual population of penile tumors.

Keywords: penile cancer; squamous cell carcinoma; histological subtypes

There is a broad worldwide variation in the age standardized incidence (ASR) per 100 000 inhabitants of penile carcinoma ranging from about 2 to 4 per 100 000 in some countries of Africa, Asia, and South America to about 0.2 to 1 per 100 000 in North America and Europe.[1] Lowest ASRs are from Israel, Korea, Japan, and the Chinese population in San Francisco at rates of 0.1 to 0.2. Highest ASRs were reported from Paraguay, Brasilia, and Uganda with figures of 4.2, 3.7, and 2.8, respectively.[1,2] In the United States the national figure is 0.5 but there are population subsets at greater risk for penile cancer in Kentucky, West Virginia, and the American Indian population (1.0, 0.8, and 1.8, respectively). There are several environmental risk factors involved in the pathogenesis of penile cancer, such as phimosis, smoking, hygienic habits, treatment with Psoralen and ultraviolet A (PUVA) photochemotherapy, and a history of genital warts.[3-6] Lichen sclerosus have been found consistently associated with special subtypes of penile squamous cell carcinomas (SCC).[7-12] Presence of human papillomavirus (HPV) was found to be a risk factor for

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penile SCCs.[13-18] Considering that the incidence of penile and cervical cancers is high in the same geographical areas,[1] it is reasonable to assume that both types of cancer share the same etiological factors; however, less than half of penile cancers are related to HPV infection[18,19] whereas the virus is found in almost all cervical SCCs.[20-23] This difference is related to morphological differences in penile and cervical SCCs; the vast majority of cervical SCCs from higher risk geographical regions such as Paraguay presents a nonkeratinizing, basaloid, or warty morphology whereas only a subset of penile cancers shows these histological patterns.[13,14,18] Because of these findings, it was suggested that penile cancer, similar to vulvar cancer, presents a dual etiological pathway, one HPV-related and another non-HPV related[15,19,24-27] and that these etiological groups are morphologically distinct. The aims of this study were (*a*) to compare the distribution of different histological subtypes of penile SCC from regions of low and high incidence in a consecutive series of cases and (*b*) to identify tumors with and without warty and/or basaloid morphology and to compare their respective incidences.

Materials and Methods

Two consecutive series of patients were retrospectively assessed; the first series included 157 cases diagnosed between 1954 and 1998 at the MD Anderson Hospital, Houston, Texas and the second included 144 cases diagnosed at the Instituto de Patología e Investigación, Asunción, Paraguay between 1993 and 1998. Histological subtyping was done following the World Health Organization (WHO) classification system.[28,29] SCCs containing more than one histological subtype in 20% or more of the tumor were classified as mixed; tumors were also subclassified according to the presence or absence of basaloid and/or warty morphological features.

Statistical Analysis

Series were compared with the χ^2 and the Fisher exact test using the software Prism GraphPad version 5.0.1 (GraphPad Corporation, San Diego, CA). A 2-tailed $P < .05$ was required for statistical significance.

Table 1. Geographical Comparison of Subtypes of Squamous Cell Carcinoma of Penis[a]

	No. of Cases (%)	
Subtypes of Squamous Cell Carcinoma	Paraguay (n = 144)	Houston (n = 157)
Usual	71 (49.3)	73 (46.5)
Verrucous	12 (8.3)	12 (7.6)
Papillary	11 (7.6)	9 (5.7)
Condylomatous (warty)	10 (6.9)	13 (8.3)
Basaloid	6 (4.2)	11 (7.0)
Sarcomatoid	1 (0.7)	1 (0.6)
Adenosquamous	5 (3.5)	1 (0.6)
Mixed	28 (19.4)	37 (23.6)

[a] $P = .6051$.

Results

The distribution of the various histological subtypes is presented in Table 1 and their morphological features are depicted in Figures 1 to 7. We found no geographical difference in the incidence of histological subtypes between the 2 regions. The usual SCC comprised almost half of the tumors, followed by the mixed category, diagnosed in one fourth of the cases in both geographical regions. Verruciform neoplasms (verrucous, papillary not otherwise specified [NOS], and condylomatous carcinomas) comprised 23% and 22% of all cases in the Paraguayan and the American series, respectively. Basaloid carcinomas, present in 4% and 7% of the cases, respectively, were slightly more frequent in the Houston series, but this difference was not statistically significant.

The mixed tumor category was present in 19% and 24% of the Paraguyan and US groups, respectively (Table 2). About a half of mixed tumors were combinations of usual SCC with special subtypes such as verrucous, papillary, warty, or basaloid carcinomas; the other half consisted of a distinctive and hitherto not well-characterized mixed tumor identified as the warty–basaloid variant. In this subtype, the superficial verruciform or papillomatous component was undistinguishable from classical condylomatous carcinoma and the deeply invasive component was that of a typical basaloid carcinoma. Sometimes the combination of warty and basaloid features was observed in deep invasive tumor nests. Benign typical condylomas were associated with warty–basaloid

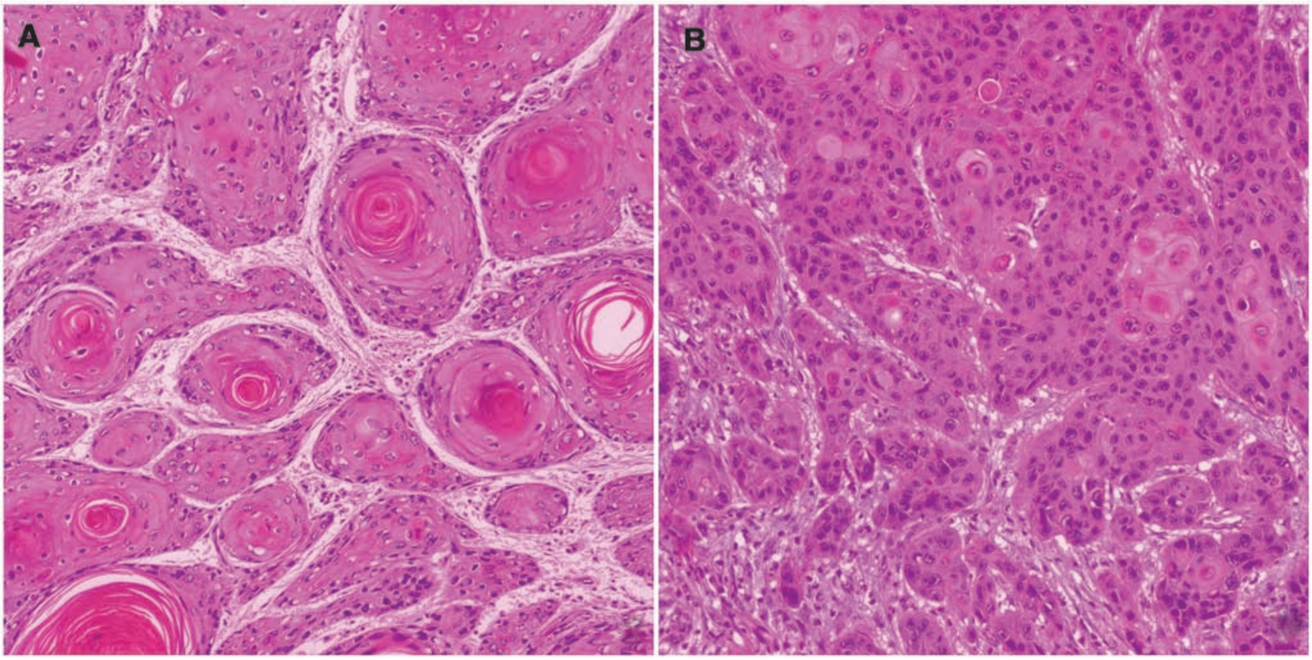

Figure 1. Usual squamous cell carcinoma. A, Well-differentiated squamous cell nests, most of them showing keratinized centers. B, Irregular nests composed of moderately differentiated squamous cells.

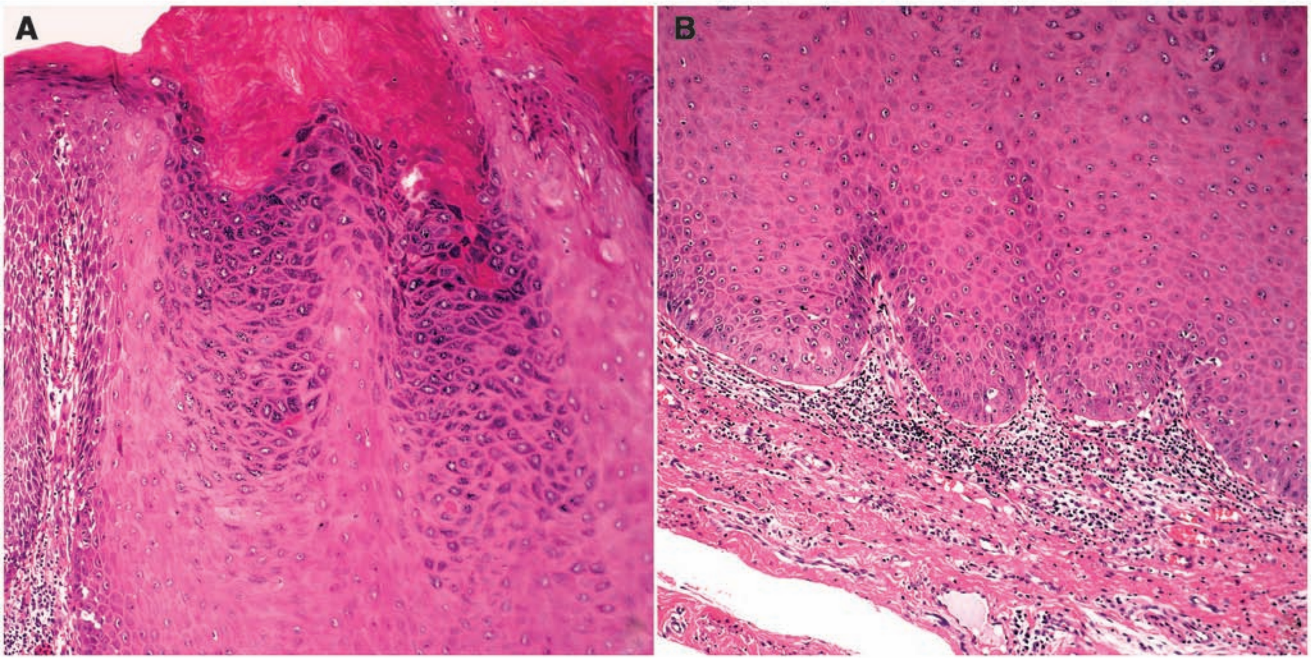

Figure 2. Verrucous carcinoma. A, Papillomatosis with acanthotic and hyperkeratotic features. B, The tumor is broadly based with a sharp delineation in the interface of tumor and stroma.

carcinomas in 9 (64%) and 10 cases (45%) of the Paraguayan and American series, respectively. We found no condylomas in association with other subtypes of penile cancer.

The geographical comparison of the WHO subtypes of SCCs with and without warty and/or basaloid features disclosed no difference between the 2 series (Table 3). A slight predominance of tumors

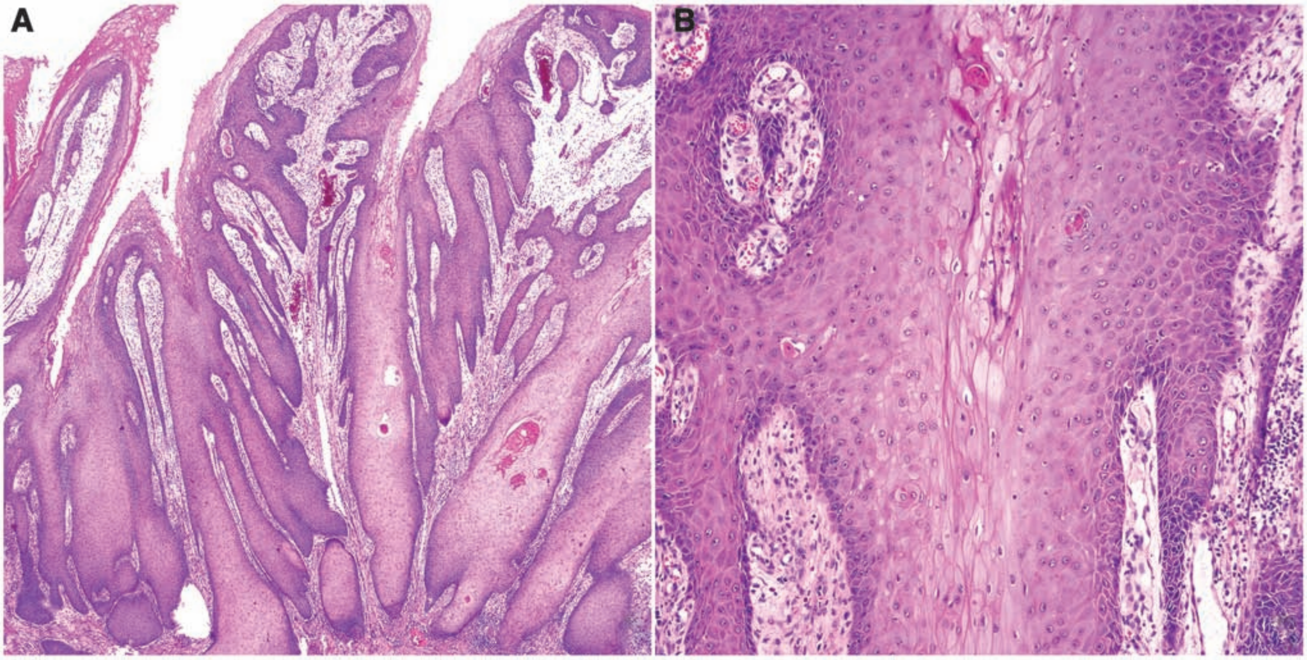

Figure 3. Papillary carcinoma. A, Papillomatosis with a jagged pattern at the base. Keratinized invasive nests are seen in underlying tissues. B, High-power view showing acanthotic papillae composed of well-differentiated cells with no koilocytotic features.

with warty and/or basaloid features was observed in the Houston series (25% vs 31%), but it was not statistically significant.

Discussion

There are geographical differences in the incidence rates of some malignant tumors and this phenomenon is usually attributed to ethnic or environmental factors.[30-32] The differences may be associated with variations in the prevalence of specific histological subtypes, such as the predominance of intestinal and diffuse gastric adenocarcinomas in high-risk Japanese and low-risk American populations, respectively.[33,34] We were hoping to find a difference between histological subtypes of penile cancer but the comparison of 2 consecutive large series from areas of high and low incidence of penile cancer disclosed no such dissimilarities. Basaloid carcinomas were present in 4% of Paraguayans and 7% of American patients, but this difference was not statistically significant and the number of cases was too small. In fact, the apparent higher frequency of basaloid carcinomas detected in a previous study[13] between patients from the Unites States when compared with patients from Paraguay led us to speculate that the geographical variation between these 2 regions was due to a different regional incidence of HPV infection, which could in turn explain the difference in the incidence of HPV-related tumors. However, our finding of similar and equally distributed tumors in both series and the overall rarity of HPV-related tumors would contradict the hypothesis of a geographical variation based on differences in the incidence of HPV-related neoplasms. The previously detected slight higher frequency of basaloid carcinoma in the US population could be related to the fact that cases in that study were selected and they were not consecutive as in this study.

A recent study of the geographical distribution of in situ carcinomas comparing the ratio of in situ versus invasive carcinomas from high and low incidence countries (Paraguay and France) revealed a much higher frequency of carcinomas in situ in France than in Paraguay.[35] In the same study, HPV-related penile intraepithelial neoplasia (PeIN; warty and basaloid variants) were more prevalent in France whereas the predominant variant in Paraguay was the differentiated PeIN. If we believe that tumoral progression evolves through a continuous spectrum of lesions initiating as a precancerous state, future incidence studies should require encompassing preinvasive and invasive lesions as well. Most comparative epidemiologic or pathologic studies usually include

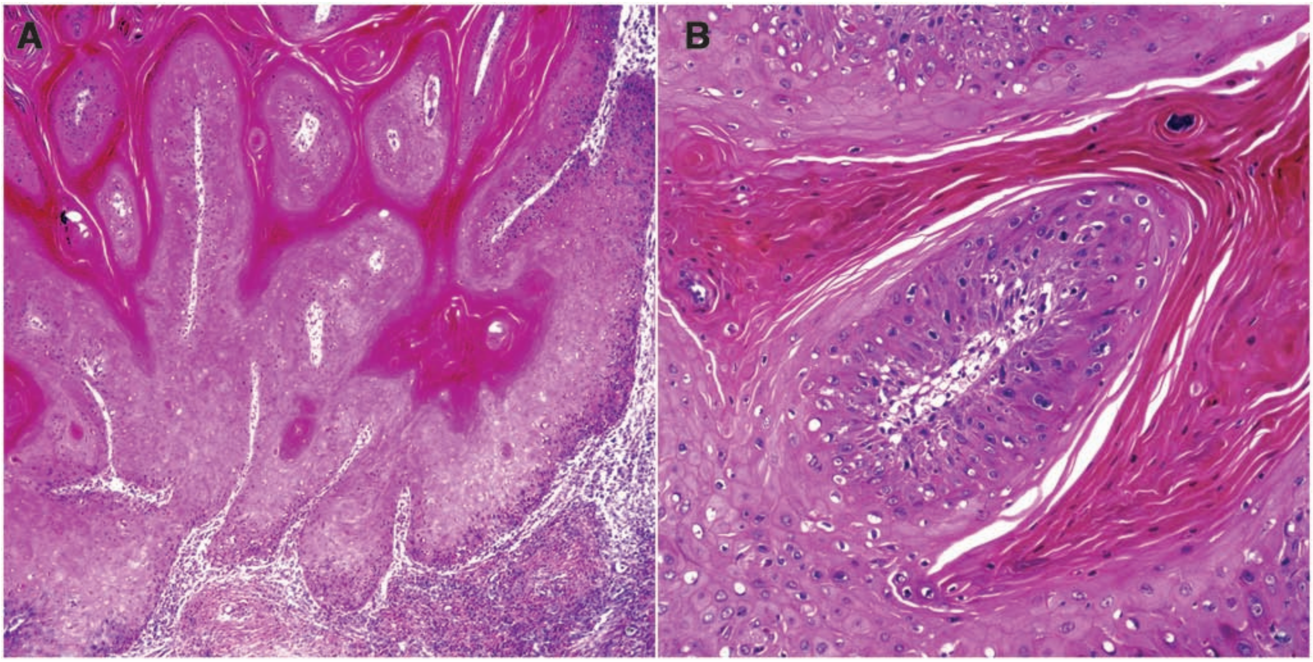

Figure 4. Warty (condylomatous) carcinoma. A, Low-power view shows the typical arborescent condylomatous features. Papillae with fibrovascular cores can be observed. B, High-power view shows an acanthotic epithelium with parakeratosis and pleomorphic koilocytotic changes.

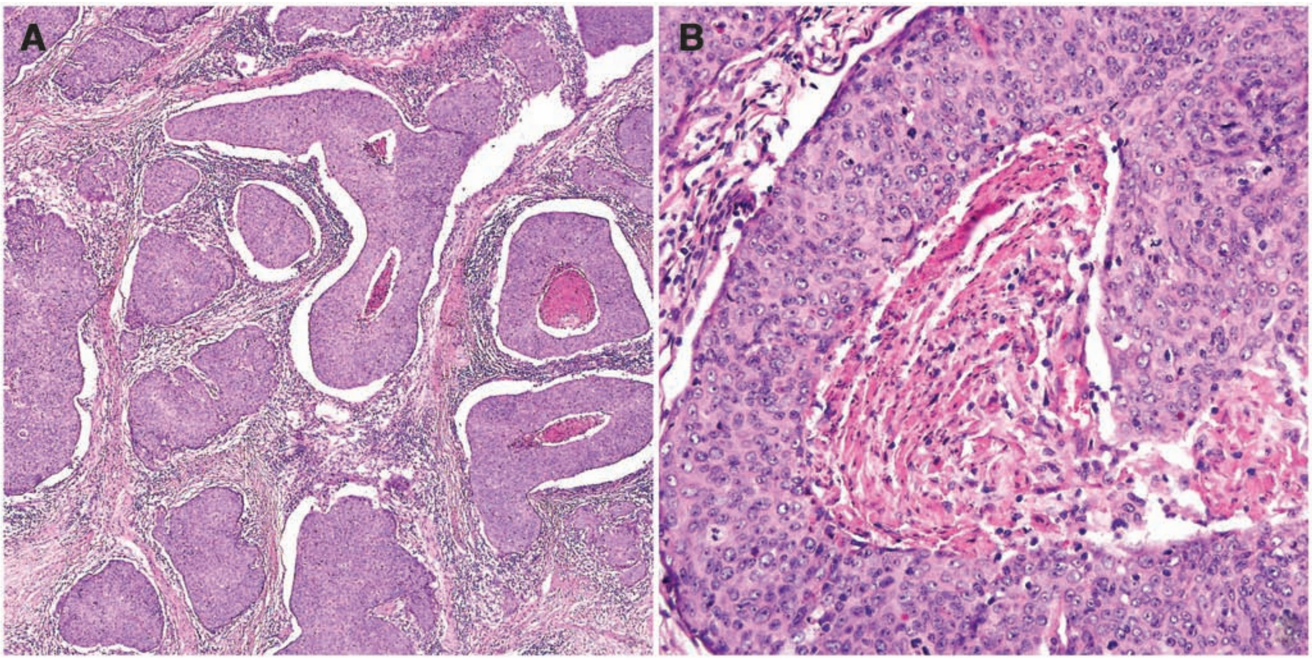

Figure 5. Basaloid carcinoma. A, An infiltrating nesting pattern. Each nest is either solid or centrally necrotic (comedocarcinoma). Note the clear cleft artifact surrounding some nests. B, Bluish nests of small anaplastic cells with high nucleus-to-cytoplasm ratio centered by necrotic and keratinous materials. Note the abrupt keratinization.

only invasive cancers. In fact, many population-based cancer registries document only invasive neoplasms, excluding precancerous lesions and this approach may also need revision in the future if meaningful geographical comparisons are intended. A prospective study comparing population-based pathological

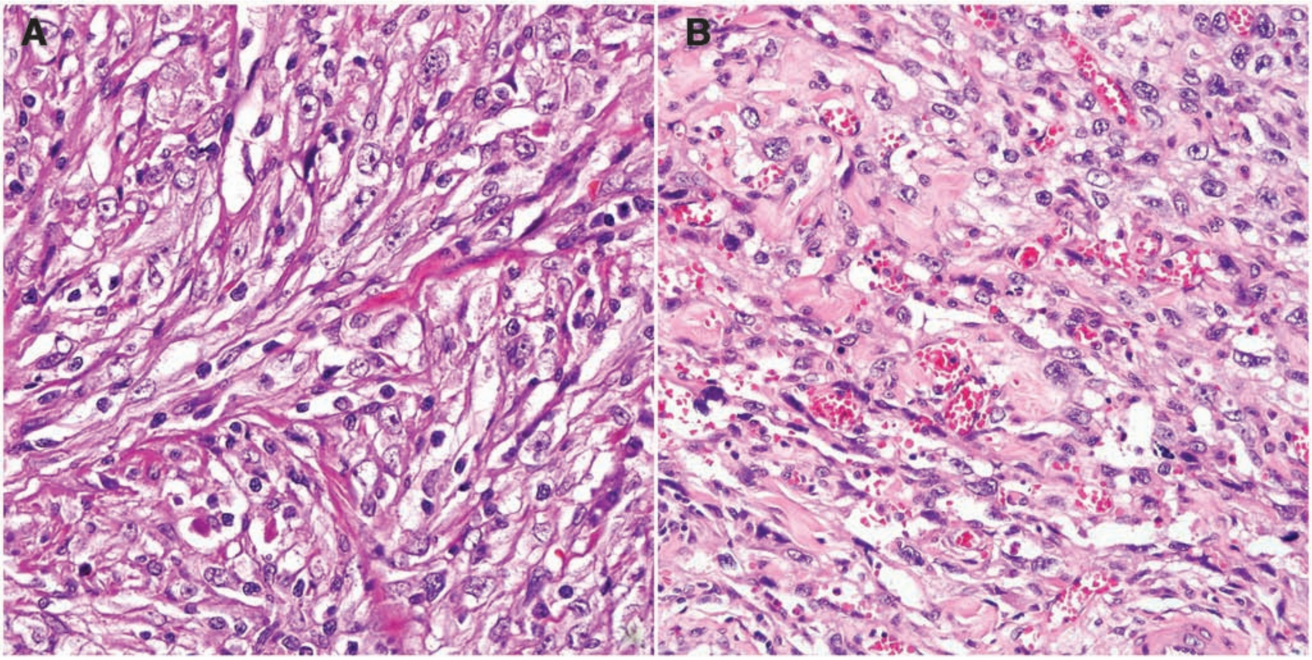

Figure 6. Sarcomatoid carcinoma. A, Anaplastic spindle cells with pleomorphic nuclei and no obvious evidence of carcinomatous differentiation. B, Sarcomatoid lesion resembling angiosarcoma.

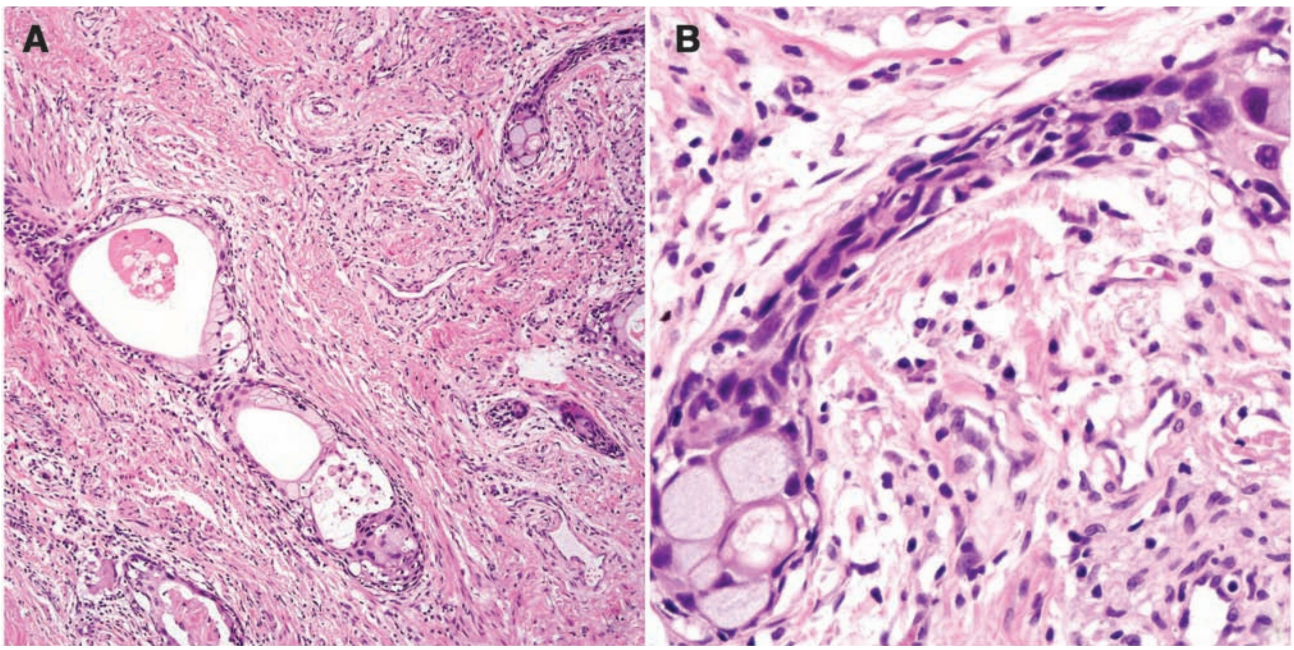

Figure 7. Adenosquamous cell carcinoma. A, Mixed tumor showing both glandular and squamous features. Clear mucin cells lining glandular spaces containing mucinous and necrotic material. B, Higher-power view disclosing the squamous and glandular patterns of the neoplasm.

materials from presumed high-risk and low-risk regions of the world, with emphasis in environmental-associated factors and, especially, stage of the disease (including precancerous lesions) would be of great interest. We may predict that in developed countries many lesions would be diagnosed in the precancerous

Table 2. Carcinomas of the Penis With Mixed Features[a]

Subtypes of Carcinoma	No. of Cases (%) Paraguay (n = 28)	Houston (n = 37)
Warty–basaloid[b]	14 (50.0)	22 (59.5)
Usual–verrucous	6 (21.4)	8 (21.6)
Usual–warty	4 (14.3)	3 (8.1)
Usual–basaloid	2 (7.1)	0 (0)
Usual–papillary	1 (3.6)	2 (5.4)
Others[c]	1 (3.6)	2 (5.4)

[a] $P = .5937$.
[b] Nine cases in the Paraguayan series and 10 cases in the American series were associated with typical condylomas.
[c] Including 1 polymorphous case in the Paraguayan series and 1 adenobasaloid and 1 mucoepidermoid case in the American series.

Table 3. Geographical Comparison According to the Presence of Warty and/or Basaloid (W/B) Features[a]

	No. of Cases (%) Paraguay (n = 144)	Houston (n = 157)
With W/B features	36 (25)	49 (31)
Without W/B features	108 (75)	108 (69)

[a] $P = .2505$.

or in situ stages (a phenomenon parallel to that observed for cervical cancer[36]), and consequently treated and cured, with few lesions remaining in the invasive stage. The opposite would occur in developing countries, so that the apparent geographical variation might be explained by a variation in the clinical stages in which the disease is diagnosed, a presumed confounding variable that should be taken into account for designing and interpreting those data.

Another factor to be prospectively investigated is the role of phimosis and circumcision in areas of high and low risk for penile cancer, because it is well known that the impossibility in the retraction of the foreskin represents a major risk factor associated with penile cancer[5,6,37-40] and that circumcision is the best preventive measure against the neoplasm.[37,38,41-43] Circumcision is more frequently practiced in the American population than in the Paraguayan population and the impact of this difference in explaining the geographical variation should be prospectively investigated. The concept of phimosis is poorly defined; hence, its retrospective documentation is difficult. In the Paraguayan general population we found 3 types of foreskin, classified according to their anatomical relation with the urethral meatus, glans corona, and sulcus, in long, medium, and short. The majority of the foreskins in our population were of the long type and 78% of the patients with penile cancer showed a long foreskin. Phimosis, detected in half of these cases, is an important predisposing factor but it is not present in all patients.[6] We suggest that an international study be done comparing types of foreskin in different populations as related to the frequency of penile cancer.

The relative frequency and distribution of the various subtypes of SCC of the penis in both series is similar to previously reported studies: half of the tumors were of the typical squamous subtype, 20% were verruciform, 4% to 10% basaloid, and the remainder were mixed variants or rare types.[29,44] The most common tumor, usual SCC, was similar to equivalent lesions of other sites, specially vulva, peripheral zone of anus and oral regions, and different from cervical and anal canal cancers. The peripheral tumors (ectocervix-vulvar, perianal skin, and foreskin) are highly keratinized and of lower grade, and the latter, originating in epithelial transitional areas (ecto-endocervix, rectal–perianal, urethral–glans), are less keratinized and higher grade tumors.[45-50] Usual type SCC of the penis comprised a spectrum from low to high grade. Nonexophytic invasive tumors with extremely differentiated cells were difficult to distinguish from pseudoepiteliomatous hyperplasias. High-grade solid variants and sarcomatoid carcinomas simulated malignant melanomas and sarcomas.

The verruciform tumors were clearly separated into 3 subtypes, after the elimination from both series of large, histologically benign or atypical, and locally destructive condylomas (giant condylomas). In the recent past, condylomatous (warty) carcinomas were not recognized as specific tumors and verrucous carcinomas and giant condylomas were considered to be the same, but a new approach in the categorization of verruciform tumors is emerging, based on the pattern of papillae, presence of koilocytosis, cell atypia, and evaluation of the interface between tumor and stroma. In a previous study,[51] condylomatous (warty) carcinomas were difficult to distinguish from giant condylomas, especially when broad and noninvasive tumoral fronts were present; the growth pattern and the shape of papillae in both tumors were similar. However, the cells in giant condylomas were benign and clearly atypical and malignant in warty carcinomas. In addition, the koilocytosis was superficial and orderly in giant condylomas and pleomorphic, diffuse and invading deep tissues in warty carcinomas. Verrucous carcinomas were easier to diagnosed using the strict morphological criteria outlined in Ackerman's[52] original descriptions.[53] The differential features with either benign condyloma or warty carcinoma were the more acanthotic pattern, the shape of the papillae, the presence of orthokeratosis and keratin-filled cysts in the acanthotic epithelium, and the lack of koilocytosis in verrucous carcinoma. The main confusing feature in the differential diagnosis of verrucous carcinoma and giant condyloma was the benign appearance of tumor cells in both cases. But everything else was different. We have seen, however, few very unusual examples of complex mixed tumors with unequivocal focal features of both verrucous carcinoma and benign condyloma in the same specimen. But benign condylomata may be present in association with other subtypes of penile SCC as well, preferentially basaloid and warty carcinomas, as showing in this study. The papillary SCC, NOS, was an exclusion category of exophytic papillomatous SCC, where the papillae were of variable shape, without koilocytosis, and, unlike verrucous carcinoma, the interphase of the tumor with the stroma was by definition irregular.

Heterogeneous mixtures of the various patterns of SCC of the penis appeared to follow a pattern. SCC of the usual type tended to be preferentially mixed with either verrucous or papillary subtypes, which presumably are non-HPV related.[54] On the contrary, basaloid carcinomas tended to mixed with either warty or benign condylomata, well-known HPV-related lesions. The relationship between HPV-related warty and basaloid tumors was substantiated by the finding of distinctive penile tumors showing mixed warty–basaloid features and behaving as aggressive basaloid carcinomas.[15,17,55,56]

In a study of precancerous lesions associated with invasive SCC of the penis, it was also found that penile intraepithelial neoplasia of the simplex or differentiated type tended to associate with typical SCC and that warty or basaloid PeIN were preferentially associated with their corresponding warty or basaloid invasive counterparts and rarely with the usual variant of SCC.[57,58] These findings would support the hypothesis of a dual population of etiologically distinct penile neoplasms, one being HPV-related and the other non-HPV related.[59]

There is little knowledge about nonurethral glandular tumors of the penis,[60] but the potential of the surface squamous epithelium of the penis to differentiate along glandular lines was proven in this study by the identification in both series of adenosquamous carcinomas.[61,62] Similar to other subtypes, we found no differences in their incidence.

Conclusions

No geographical differences were found among the histological subtypes of penile cancer or in the frequency of HPV-related subtypes. A critical review of the concept of geographical variation of penile cancer is mandatory using population-based pathological materials, including all stages of the disease and precancerous lesions. Geographical variation may be the result of staging variation at clinical presentation or of pathological diagnosis. The identification of similar histological subtypes in both series validates this classification approach for penile cancer. The tendency for typical SCC to mix with verrucous and papillary carcinomas and of the basaloid to preferentially mix with benign condyloma and condylomatous (warty) carcinomas would support the hypothesis of the existence of an etiologically different dual population of penile tumors.

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