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Penile Cancer

Role of Human Papillomavirus in Penile Carcinomas Worldwide

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Abstract

Background: Invasive penile cancer is a rare disease with an approximately 22 000 cases per year. The incidence is higher in less developed countries, where penile cancer can account for up to 10% of cancers among men in some parts of Africa, South America, and Asia.
Objective: To describe the human papillomavirus (HPV) DNA prevalence, HPV type distribution, and detection of markers of viral activity (ie, E6*I mRNA and $p16^{INK4a}$) in a series of invasive penile cancers and penile high-grade squamous intraepithelial lesions (HGSILs) from 25 countries. A total of 85 penile HGSILs and 1010 penile invasive cancers diagnosed from 1983 to 2011 were included.
Design, setting, and participants: After histopathologic evaluation of formalin-fixed paraffin-embedded samples, HPV DNA detection and genotyping were performed using

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DNA
mRNA
p16
Vaccine

the SPF-10/DEIA/LiPA$_{25}$ system, v.1 (Laboratory Biomedical Products, Rijswijk, The Netherlands). HPV DNA–positive cases were additionally tested for oncogene E6*I mRNA and all cases for p16^{INK4a} expression, a surrogate marker of oncogenic HPV activity.

Outcome measurements and statistical analysis: HPV DNA prevalence and type distributions were estimated.

Results and limitations: HPV DNA was detected in 33.1% of penile cancers (95% confidence interval [CI], 30.2–36.1) and in 87.1% of HGSILs (95% CI, 78.0–93.4). The warty-basaloid histologic subtype showed the highest HPV DNA prevalence. Among cancers, statistically significant differences in prevalence were observed only by geographic region and not by period or by age at diagnosis. HPV16 was the most frequent HPV type detected in both HPV-positive cancers (68.7%) and HGSILs (79.6%). HPV6 was the second most common type in invasive cancers (3.7%). The p16^{INK4a} upregulation and mRNA detection in addition to HPV DNA positivity were observed in 69.3% of HGSILs, and at least one of these HPV activity markers was detected in 85.3% of cases. In penile cancers, these figures were 22.0% and 27.1%, respectively.

Conclusions: About a third to a fourth of penile cancers were related to HPV when considering HPV DNA detection alone or adding an HPV activity marker, respectively. The observed HPV type distribution reinforces the potential benefit of current and new HPV vaccines in the reduction of HPV-related penile neoplastic lesions.

Patient summary: About one-third to one-quarter of penile cancers were related to human papillomavirus (HPV). The observed HPV type distribution reinforces the potential benefit of current and new HPV vaccines to prevent HPV-related penile neoplastic lesions.

1. Introduction

Invasive penile cancer is a rare disease with an annual burden of 22 000 estimated cases [1]. The incidence is higher in less developed countries, where penile cancer can account for up to 10% of cancers among men in some parts of Africa, South America, and Asia [2].

Two major pathways have been described to occur in penile cancer carcinogenesis: one related to a number of penile conditions such as inflammation, phimosis, or history of lichen sclerosus and lichen planus, and another related to human papillomavirus (HPV) infection [2,3]. Circumcision acts as a protective factor, presumably by reducing HPV transmission or penile pathologic conditions associated with penile carcinogenesis [2,4].

Previous literature suggests that HPV DNA is detected in approximately half of penile cancers with variations between studies. HPV16 is the most common type detected, followed by HPV18 [5]. It remains unclear whether the differences in prevalence between studies reflect a real variation across populations or differences in sample selection or in the technology used. Given the wide range of estimates, a further insight may be gained by increasing study sample size, geographic representativeness, and standardized HPV DNA detection protocols. Additional signature of HPV activity and induced carcinogenicity such as markers of viral transcription and HPV-induced cellular transformation should be used to distinguish whether the HPV DNA detected in tumor tissue is likely an active viral infection, a transient infection, or a contaminant [6]. These additional markers are essential to get closer to the proportion of penile cancers linked etiologically to the virus.

Our objective was a comprehensive description of HPV DNA prevalence and type distribution, HPV E6*I mRNA detection, and p16^{INK4a} expression in a series of 85 penile high-grade squamous intraepithelial lesions (HGSILs) and 1010 invasive penile cancers from 25 countries.

2. Materials and methods

2.1. Study design

A retrospective cross-sectional study was designed and coordinated by the Institut Català d'Oncologia (ICO), Barcelona, Spain. Formalin-fixed paraffin-embedded (FFPE) HGSILs and invasive penile cancer specimens diagnosed from 1983 to 2011 were obtained from pathology archives in 25 countries from Europe, North America, Latin America, Africa, Asia, and Oceania (the countries are listed in Supplementary Table 1). Information about age and year of diagnosis and the original histologic diagnosis were also obtained from the participating centers.

2.2. Histopathologic evaluation

FFPE tissue blocks were processed under strict pre/post polymerase chain reaction (PCR) separation conditions to avoid potential contamination as described in a previous publication [7]. At least five FFPE sections were performed; first and last sections were used for histopathologic evaluation after hematoxylin and eosin (HE) staining. This evaluation was performed following the consensus criteria established by a panel of expert pathologists and based on schemes published by the Armed Forces Institute of Pathology and the World Health Organization [8,9]. All cases were reviewed by an expert pathologist (A.C.), and doubtful and discordant diagnoses with the original diagnosis were again reviewed by the panel to come to a specific diagnostic decision. A block was determined to be adequate for HPV DNA testing if invasive cancer or a HGSIL was observed in the two HE-stained sections of the specimen. To control for possible sources of contamination, blocks containing tissues a priori non-related to HPV infection and processed in the local pathology laboratory at the same time as the penile specimens under study were blindly processed.

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