

Serum Antibodies to HPV 16 Virus-Like Particles Are Not Associated with Penile Cancer in Chinese Males

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Ecologic studies showing geographic clustering of penile and cervical cancers in central China (14), along with earlier observations of marital clusters in other populations (6,17,22), led to the hypothesis of a common sexually transmitted etiologic agent for these two diseases. However, in a study of 141 penile cancer cases and 150 controls in Hunan, China, no associations were observed with various sexual factors, including age at first intercourse, number of sexual partners, and number of marriages. Modest associations were seen with the sexual risk factors of extramarital sexual relations (relative risk = 1.7; 95% confidence interval 0.9-3.1) and history of venereal disease (3.5; 0.9-13.8). In contrast, increases in risk of a 10-fold or greater magnitude were associated with correlates of chronic penile inflammation, such as phimosis, paraphimosis, presence of smegma, and medically indicated adult circumcision (4).

Sexually transmitted oncogenic human papillomavirus (HPV) infection is the central risk factor for cervical cancer (9), and has been linked to penile cancer as well, based on prevalence estimates of HPV DNA in invasive and *in situ* penile cancers in populations of North America (13,16,20), Latin America (15,18), and Europe (1,8,21). To further explore the relationship of HPV infection with penile cancer in the Chinese study, frozen serum samples, available for 55 cases and 60 controls who had been prospectively ascertained, were screened for the presence of IgG antibody to HPV 16 virus-like particles (VLPs) using a previously described enzyme-linked immunosorbent assay (ELISA) (10). The VLPs are empty HPV 16 capsids that self-assemble in SF-9 insect cells after expression of L1 and L2 structural genes via baculovirus expression vectors.

The cases consisted of males with newly diagnosed invasive penile cancer who lived in three geographic areas within Hunan province. One community control was selected per case, matching on age and commune of residence. The mean age of cases and controls was 55 years. Each serum sample was tested three times and the three optical density (OD) values from these tests were averaged to obtain the final ELISA result. The cutpoint for seropositivity, an OD of 0.72, was derived by adding the overall mean OD of the controls (0.39) to 2.5 times the standard deviation of the overall mean [i.e., $0.39 + (2.5 \times 0.13) = 0.72$]. A cutpoint of 0.75 had been derived by this method in previous studies of cervical neoplasia (11,23). The

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results of the ELISA test were negative for all penile cancer cases and controls. When the triplicate assay results were averaged, the median OD value was 0.39 for cases and 0.36 for controls.

In contrast to HPV 16 VLP studies of cervical (19), anal epidermoid (7), and vulvar cancer (A. Hildesheim, manuscript submitted), these findings imply that HPV 16 infection is not a major cause of penile cancer in this population. Previous research suggests that the proportion of anogenital cancers that is attributable to oncogenic HPV infection varies by body site. While over 90% of cervical squamous cell carcinomas are associated with oncogenic HPV types (3), a survey of studies on penile, vaginal, vulvar, and anal tumors indicates that the attributable proportion in these sites may be lower, in some approximating 50% or less (5). Variation in the attributable proportion by histology within site has also been noted in vulvar cancers, where HPV prevalence is elevated in basaloid and warty carcinomas but not in keratinizing squamous cell carcinomas (12).

An association of penile cancer with HPV infection cannot be entirely ruled out in the present study, however. For example, it is possible that HPV types other than 16 were associated with the penile cancers, or that HPV infection of the penile epithelium, in general, does not readily result in a systemic antibody response to viral antigens. These questions could be further addressed in studies that employ serologic assays for multiple HPV types, which are currently under development and evaluation, along with standard polymerase chain reaction testing for viral DNA, also of multiple types.

In conclusion, in this study, penile cancer was not linked to HPV 16 infection using a characterized HPV 16 serologic marker, which is consistent with the epidemiologic findings that phimosis and chronic inflammation, rather than a sexually transmitted agent, are the major risk factors for penile cancer in this population.

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