Genital Human Papillomavirus (HPV) Infections and Their Associations with Squamous Cell Cancer: Reappraisal of the Morphologic, Epidemiologic and DNA Data

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ABSTRACT

The reliable assessment of epidemiology of genital human papillomavirus (HPV) infections is hampered by a number of technical problems. Because of the lack of tissue-culture systems, methods based on morphological approaches (colposcopy, cytology, and histopathology) play a central role in HPV diagnosis. Even the DNA-hybridization techniques and the recently introduced DNA amplification with PCR are extremely difficult to standardize, and they are thus subject to major interlaboratory variation. The situation is further complicated by the complex biological behavior of HPV infections. As established by the long-term prospective follow-up study run in Kuopio since 1981 for over 500 women, clinical progression and regression seem to be significantly related to grade of the lesion when first diagnosed (p < 0.00001, and p = 0.0005, respectively), as well as to the type of HPV (p = 0.0012). Most importantly, however, genital HPV infections seem to run an extremely fluctuating course, a transition from a manifest to a subclinical or latent infection frequently being encountered in individual patients when examined at 6-month intervals for prolonged periods. This explains the highly divergent prevalence figures reported in different series (ranging from a few percent to 80%), which are completely dependent on the technique used to analyze the presence of HPV, i.e., whether by (1) PAP smear, (2) biopsy, (3) DNA hybridization, or (4) PCR amplification. The first two are capable of disclosing only manifest (clinical) infections, the latter two also the subclinical and latent ones, respectively. Because of major practical relevance, the criteria for subclinical and latent HPV infections are defined in this paper for the first time. In an unselected population of 22-year-old Finnish females, the prevalence of clinical HPV infections was 3%, and the adjusted annual incidence was 8%. According to estimates for the life-time risk, up to 79% of Finnish females would contract at least one HPV infection between ages 20 to 79 years. When related to long-term trends in
invasive cervical cancer in Finland, it is evident that this 79% life-time risk of getting HPV-infected or the observed 15% clinical progression rate for HPV infections during a long-term prospective follow-up are far above the established risk ($5/10^5$, annual incidence) for the development of cervical cancer (ie, $0.79 \times 0.15 = 11\%$). A theoretical model was constructed to explain the complex biological behavior of genital HPV infections, according to which clinical lesions represented only a small minority (2%–5%) of the problem, subclinical and latent infections accounting for over 90% of all HPV infections. It seems clear that in countries where effective mass-screening programs exist (and precancerous lesions are traced), the increasing prevalence of clinical HPV infections is not necessarily reflected as increased prevalence and incidence figures of invasive cervical carcinomas. As long as HPV infections are not associated with a morphologically manifest epithelial lesion, they are probably of lesser clinical significance (ie, subclinical and latent). Accordingly, our major attempts should be focused on the clinical HPV lesions to develop accurate means by which to predict the lesions at risk for malignant transformation from those regressing spontaneously. This would have major implications in therapeutic considerations of genital HPV infections.

**NEW ERA IN HPV RESEARCH STARTED FROM THE MID 1970s**

Condyloma acuminatum (genital wart) known to be caused by human papillomavirus (HPV) since 1968 has been recognized as a disease entity since antiquity. During the past 15 years, significant new data on epidemiology, molecular biology, and biological behavior of HPV infections as well as their intimate associations with a variety of human squamous cell tumors have been published. HPV infections in the genital tract are a sexually transmitted disease. (STD), and their reported rapid increase in most countries has been attributed to dramatically changed sexual habits during the past two decades (ie, early onset of sexual activity, large number of sexual partners, poor sexual hygiene, and inadequate preventive measures).

Since 1976, it has been well recognized that HPV-induced lesions in the female genital tract (flat, inverted and papillary condylomas) are frequently (from 50% to 80% in different series) associated with cervical intraepithelial neoplasia (CIN), carcinoma in situ (CIS) and invasive squamous cell carcinomas, on light microscopic examination. The same has been subsequently shown to be true with the newly described lesions of Bowenoid papulosis (morphologically consistent with CIS), exclusively confined to external genitalia in both sexes.

Using immunohistochemical (IP-PAP) techniques, viral structural protein expression can be demonstrated in CIN lesions, CIS, and less frequently, in invasive carcinomas. With the rapidly developed molecular biological techniques, >60 different HPV types have been recognized in less than 10 years. More than twenty of the known HPV types are known to infect the genital tract (ie, HPV 6, 11, 16, 18, 31, 33, 34, 35, 39, 40, 42, 43, 44, 45, 50, and 51–59) (Table 9-1). So far, the DNA of a few HPV types has been found integrated into the host cell DNA. Based on these integration properties (including the integration site close to cellular oncogenes, c-onc), and their close association with either benign condylomas/papillomas or invasive carcinomas, HPV types have been classified as low risk types (eg, HPV 6 and 11) and high risk types (eg, HPV 16 and 18). A significant risk for the development of an invasive cancer has been ascribed to infections by the latter.

Evidence on the definite progressive potential of certain HPV lesions has been obtained by prospective cohort studies as well. Histologically documented clinical progression has been established for genital HPV infections in a prospective follow-up study conducted in our clinic since 1981 for over 500 women without therapeutic interventions. During the 5-year mean follow-up, a considerable percentage of the HPV infections regressed