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Human papillomavirus infection: Natural history and vaccine development

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Abstract

Molecular and epidemiological studies conducted over the last 25 years led to the recognition of certain types of human papillomavirus (HPV) as the etiologic agents of cervical cancer, a very common neoplasia, particularly in developing countries. More than 100 HPVs have been described, including both cutaneous and mucosal types. About half of the known HPVs, and an even higher number of variants, have been isolated from genital mucosas. The association of certain types primarily with normal tissues and benign lesions, as opposed to cancer-associated types has led to the concept of low and high oncogenic risk HPVs, respectively. The latter express oncogenic proteins that interfere with cell growth control functions. As a consequence of the continuous expression of these viral genomes, chromosome instability may occur, leading to fully transformed cells.

Natural history studies have shown that HPV infections are very common in sexually active women, particularly those at younger ages. However, only a small fraction of women infected with high-risk HPV types will eventually progress to high-grade intraepithelial lesions (HSIL) and cervical cancer. This establishes an important role for co-factors, such as oral contraceptives use, parity, tobacco smoking, co-infection with HIV or other STDs, diet, and immune response-related co-factors, including HLA polymorphisms. Recent studies indicate that persistence of high-risk HPVs may determine progression to more severe stages of cervical disease, while the majority of HPV infections are transient and do not seem to be important in cervical carcinogenesis. The risk for disease progression seems also to be associated with viral burden.

Species-specific papillomavirus L1 Virus-like particles (VLP) vaccines prevent disease in animal models. In studies in women, monovalent HPV L1 VLP vaccines induced high titer serum antibodies and an HPV 16 L1 VLP vaccine was shown to prevent HPV 16 infection. We evaluated a quadrivalent HPV (Types 6/11/16/18) L1 VLP vaccine in a double-blind, placebo-controlled phase II study conducted by Merck, Sharp and Dohme. These VLPs are generated in yeast and formulated with aluminum. In the study's interim analysis, the quadrivalent HPV L1 VLP vaccine was generally well tolerated and highly immunogenic. If proven safe and effective, a vaccine that prevents infection with common pathogenic HPV types will be a major advance in anogenital cancer control.