Experimental and epidemiologic data have established a causal link between infection with human papillomaviruses (HPVs) and all grades of cervical intraepithelial neoplasia (CIN)\(^1\) and invasive cervical cancer (\(I\)). While about 30 types of HPV are known to infect the genital tract, studies have shown that not all HPV types are created equal. Some types (most notably HPV types 16, 18, 31, 33, and 45) have been shown in epidemiologic studies to be more strongly associated with CIN 2-3 and cancer than others (most notably, HPV types 6 and 11, which cause mainly exophytic warts). Experimental evidence supports these observations, having shown that the HPVE6- and E7- transforming proteins from high-risk HPV types such as HPV16 have a higher transforming ability than those from low-risk HPV types such as HPV-6 and 11. In this issue of the Journal, Xi et al. present evidence that minor variations within HPV types\(^2\) might also affect the magnitude of association with disease risk. Their results support those from previous small studies suggesting an association between HPV variants and persistence of infection or development of CIN2-3 and cancer (\(3,4\)). In their report of 19 cases of CIN2-3 arising from a group of 123 women followed longitudinally, Xi et al. suggest that infection with variant forms of HPV16 might be more strongly associated with the risk of developing CIN2-3 than infection with the prototype European HPV16 virus. This finding, if confirmed in larger studies, might influence both our understanding of the natural history of HPV-related diseases and our efforts to develop HPV vaccines. Each of these will be discussed in turn.

With the confirmation that HPV infection is the main causal agent involved in the etiology of cervical cancer, more recent research efforts have attempted to uncover factors that influence the progression of HPV infection and its early cytologic manifestation, CIN 1 and koilocytic atypia, to CIN2-3 and invasive cervical cancer.

Genital HPV infection is known to be common among sexually active individuals while cervical cancer is a relatively rare event. This suggests that the majority of women infected with this common virus are capable of controlling the virus and never develop cancer. This is partially explained by the fact that a sizable proportion of women infected with HPV are infected with types possessing only low or moderate oncogenic potential. However, even among women infected with high-risk HPV types such as HPV16, most infections are known to regress spontaneously over time and only a fraction develop into CIN2-3 or cancer. The search for determinants of persistent and/or progressive HPV infection has focused on exogenous and lifestyle factors (such as other infectious agents, parity, oral contraceptive use, and cigarette smoking) and host factors, particularly the host immune response to HPV infection (\(5,6\)).

A third possibility is suggested by Xi et al. (2): that viral variants might impart different risks of disease and therefore partially explain why some women infected with high-risk HPV types have persistent or progressive infection while others do not.

The findings by Xi et al. might also potentially have important implications for the design of HPV vaccines. Efforts to develop effective therapeutic and prophylactic vaccines are now under way (7,8). Therapeutic vaccine efforts have focused primarily on the stimulation of a host cellular immune response against the virus to enable individuals with HPV-related diseases to target their host defenses against the HPV-infected neoplastic lesion. Since the HPV-transforming proteins, E6 and E7, are known to be expressed in invasive tumors, therapeutic efforts have focused largely on E6- and E7-based vaccine formulations. In contrast, the aim of the more recent prophylactic vaccine efforts is to induce an antibody response capable of neutralizing HPV and to prevent or limit initial infection with the virus. These efforts have therefore focused primarily on structural protein-based vaccines (i.e., L1 and L2, which together form the HPV viral capsid). To the extent that antigenic determinants of the L1, L2, E6, or E7 proteins differ in naturally occurring HPV variants, effective vaccines will need to incorporate these variations into their formulations.

While the potential implications of HPV variants to our understanding of the natural history of HPV-related diseases and to vaccine development efforts are clear, there is still little evidence to support that variants are indeed important. Studies (2-4) linking HPV variants to persistent or progressive cervical disease, including the present study by Xi and colleagues, are small and inconclusive. Also, studies are not directly comparable, because variations in different regions of the viral genome have been examined in different studies, and in some instances specific variations in HPV coding and/or regulatory regions are not identified. These studies are further complicated by the fact that variations in different regions of the HPV genome are correlated, making it difficult to determine the independent effect of specific variations. Experimental evidence providing a biologic basis for viral variants to act as determinants of disease and/or immune response is also limited to a handful of studies, and our understanding of the biologic implications of naturally occurring variations detected within coding and regulatory regions of the HPV genome is far from complete (9-12). Furthermore, it is not

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known whether any association between HPV variants and disease results from specific differences in the biologic activity of the virus itself (in which case the same variants should be more risky in all populations) or to specific co-evolution and adaptation of specific viral variants in different populations (in which case different variants could be worse for different populations). Finally, almost no data are available on the potential role in the natural history of HPV-related diseases of variants of high-risk cancer-associated HPV types other than HPV16 (3).

For those interested in elucidating the etiology of HPV-related diseases, the challenge is to conduct large studies capable of examining specific variants to determine the association between these variants and disease in different populations and to uncover biologic plausibility for these associations. For those involved in vaccine development efforts, the challenge is to determine whether these variations result in differences in antigenicity, i.e., differences in how the host immune system responds to the different variants.

References


Notes

1Recent U.S. nomenclature changes now classify cervical intraepithelial neoplasia (CIN) type 1 (along with koilocytic atypia) as low-grade squamous intraepithelial lesions and CIN 2/CIN 3 as high-grade squamous intraepithelial lesions.
2Different human papillomavirus (HPV) types are defined as having less than 90% nucleotide similarity in the L1, E6, and E7 genes. Variants detected with HPV types are defined as having more than 0% but less than 2% nucleotide dissimilarity in these same genes.

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