

# The Tango and Tangle of Human Papillomavirus and the Human Genome

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Human papillomavirus (HPV) oncogenic types, especially type 16, are some of the most potent human carcinogens described. The odds ratio of squamous-cell cancer in HPV16-infected women has been estimated to be 435 (95% confidence interval [CI] = 278 to 679) and appears to be high throughout the world (1). The public health burden of both HPV and cervix neoplasia is profound; cervical cancer is the second most prevalent cancer in the developing world with nearly half a million cases diagnosed per year (2). In contrast, the risk of lung cancer associated with cigarette smoking varies throughout the world, with odds ratios of 4.0 and 40.0 in Japan and United States, respectively (3).

The final link in the etiologic trail of HPV and cervical cancer is about to be tested. The availability and widespread use of prophylactic vaccines for HPV16 and HPV18 (4), with an anticipated two-thirds reduction in cervical cancer incidence in vaccinated women, will be the final fulfillment of Hill's criteria, as previously discussed (5). Nevertheless, HPV infection and cervical cancer will remain a major health burden for decades to come. Studies on the molecular basis and viral-host dynamics of HPV-associated disease will continue to contribute to clinical screening and management strategies, as well as to models of solid tumor pathogenesis. Moreover, in the upcoming HPV vaccine era, it will be important to understand the modes of HPV evolution and adaptation to immunized hosts. In this issue of the Journal, the study of Xi et al. (6) provides insights into the ability of the most clinically relevant HPVs to evolve over a relatively short evolutionary period.

Xi et al. (6) take advantage of samples from a large multi-center randomized clinical trial sponsored by the National Cancer Institute. The Atypical Squamous Cells of Undetermined Significance–Low-Grade Squamous Intraepithelial Lesion (ASCUS–LSIL) Triage Study (ALTS) investigated the management of common cervical cytologic abnormalities in 5060 predominantly young women (median age = 25 years, interquartile range = 21–31 years) (7). The 3488 women with ASCUS and 1572 with LSIL were monitored for 2 years at 6-month intervals, and all women had an exit colposcopy to diagnose high-grade cervical neoplasia. HPV DNA was amplified by use of PGMY09/11 L1 consensus primers and typed by a reverse line blot (8). HPV16 was the most common type identified in women with either ASCUS (501 [14.9%] of the 3362 women with ASCUS) or LSIL (327 [21.1%] of the 1550 women with LSIL) (8). The 2-year cumulative risks for cervical intraepithelial neoplasia of grade 3 or for cancer in women with HPV16 detected at baseline with ASCUS or LSIL were 33% and 39%, respectively (8).

In contrast, women with HPV18 and ASCUS or LSIL had a 9% and 15% risk, respectively, which was not different from the risks for other non-HPV16 oncogenic HPV types. The samples from participants with HPV16 and/or HPV18 constitute the study group of the report by Xi et al. (6). They further characterized the HPV16 and HPV18 genomes into phylogenetic variant lineages. Phylogenetic lineages of HPV16 and HPV18 correspond to the geographic locations from which the samples were obtained, suggesting genetic drift or perhaps selection or co-evolution as a mechanism resulting in this association (9,10). Enigmatically, this geographic pattern of phylogeny was not as robust when other oncogenic and nononcogenic types were analyzed with samples from different geographic regions [for review, see Bernard et al. (11)], possibly suggesting a difference in recent evolution of HPV16 and HPV18, the most pathogenic of HPV types.

Persistence of oncogenic HPV types has been shown to be a critical factor in the development of cervical cancer (12). Thus, Xi et al. (6) ask whether different lineages of HPV16 and HPV18 had different rates of clearance over the 2-year observation period. For simplicity, they limit their major analyses to 624 cases of HPV16 (560 with European lineages and 64 with African lineages) among 483 white and 141 African American women and to 182 cases of HPV18 (108 with European lineages and 74 with African lineages) among 101 white and 81 African American women. As expected, African variants of both HPV16 and HPV18 were more common among African American women than among white women, and European variants were more common among white women than among African American women. Overall, there was difference neither in the clearance of HPV16 African variants compared with European variants nor in HPV18 African variants compared with European variants. However, when they stratified the analyses by race, HPV16 and HPV18 European variants compared with African variants had a longer

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time to clearance among white women, and African variants compared with European variants had a longer time to clearance among African American women.

The implication of these results is that variants of these highly pathogenic types of HPV have coevolved with their host and that coexistence has selected for variants with increased duration of infectivity, a presumably selectable trait. Although these observations have intriguing biologic ramifications, the issue of clinical importance is whether there is an increased risk for cervical cancer associated with specific variants in individuals of a particular genotype, for which race is a surrogate (13–15). If we assume that the increased time to clearance translates into increased risk of cancer, then it is difficult to resolve these data with other studies that found a stronger association between cancer and non-European HPV16 variants in white women (16) and in women from Mexico and Costa Rica (17,18) and between cancer and European variants that are more common in cervical cancer among African women (19). Thus, it appears that the HPVs that did not coevolve with a specific race are more pathogenic. A corollary exists with animal papillomavirus: Cottontail rabbit cutaneous papillomavirus causes carcinomas in domestic rabbits but not in cottontail rabbits, and bovine papillomavirus causes sarcoid lesions in horses (20). It would have been informative to combine the HPV16 Asian American variants and the African variants into a non-European variant class for additional analyses because a dichotomy in HPV lineage (European versus non-European) is supported by analyses of the complete genomes of representative HPV16 variants (21).

The biologic question is what is the relationship between virus and host. The notion that selective pressure for HPV intratypic variants has developed since the migration of humans from Africa suggests that HPV16 and HPV18 are still evolving and likely have the potential to evolve under selective pressure of host immunity elicited through vaccination. Can we posit that a selective advantage will correspond to an increased prevalence? What host factors might the virus need to overcome to increase the duration of viral persistence and presumably to be infective over a longer period? Host immunity is at the top of the list. In fact, in a study in Costa Rica (17), infection with non-European variants was associated with a specific human leukocyte antigen haplotype but not with markers for genetic stratification. Costa Rica's population being admixed confuses the definition of race as a surrogate marker for a specific genotype. Thus, the HPV16 and HPV18 variants appear to be in a "tango" with some unknown characteristics of the human genome associated with race. The "tangle" is trying to figure out what these factors might be and how the relationships among virus variation, host variation, and persistence lead to cancer. Long-term follow-up of vaccinated individuals should reveal whether the virus is eliminated or is planning any more "tango steps."

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