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What are the Implications of Distinct HPV Genotypes in Women of Different Ethnic/Racial Ancestry?

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Abstract

Invasive cervical cancer incidence and mortality continue to disproportionately affect racial/ethnic minorities, and the distribution of HPV genotypes varies by race/ethnicity, providing a potential explanation for such differences in incidence and mortality. It remains unclear whether such differences could be explained by host genetics or epigenetics that increase susceptibility to particular HPV genotypes, viral genetics, differences in HPV genotypes harbored by different social and/or economic networks, or by differences as simply as function of sexual networks. Determining if race-specific vaccines will benefit some subgroups will depend on addressing these questions. In general, it is our opinion that given population admixture, race/ethnicity based vaccine development may have limited value. Necessary to resolving this question will be the deliberate inclusion of minority populations into observational studies and clinical trials, as well as increase efforts in the study of other less racially admixed populations.

Keywords: HPV; Vaccines; Race/ethnicity

Abbreviations:

HPV: Human Papilloma Virus; HR: High Risk; CIN: Cervical Intraepithelial Neoplasia; ICC: Invasive Cervical Cancer; ASCUS: Atypical Squamous Cells of Undetermined Significance; US: United States; GSK: GlaxoSmithKline

Introduction

More than 12,000 American women are diagnosed with invasive cervical cancer annually (American Cancer Society). For poorly understood reasons, the incidence is 60% higher and mortality is more than two-times higher in women of African ancestry, compared to Americans of European ancestry, despite comparable screening rates to detect precancerous lesions. Recent evidence suggests that African American women are two times less likely to be infected with high-risk (HR) human papilloma virus (HPV) 16 and 18 [1,2]. HPV 16 and 18 genotypes are found in 70% of invasive cervical cancer (ICC) and are included in bivalent and quadrivalent vaccine regimens. We also recently found that among African American women undergoing colposcopic evaluation following detection of cytological abnormalities, the most prevalent HR HPV genotypes were 35, 45, 58 and 68 when compared to European American women [3]. In general, this pattern of racial/ethnic differences in HPV type distribution between European American and African American women also persists among women with cervical intraepithelial neoplasia (CIN), the precursor lesion to ICC, including high grade lesions (see Figure 1). HR-HPV 16 and 18 were statistically significantly less likely to be present in African American women with CIN2/3 ($p<0.05$), compared to European American. While HPV genotypes 45, 58 and 68 are part of the nonavalent vaccine currently in Phase III clinical trials, HPV 35 is not (Table 1). The singular importance of high-risk HPV 68, 35 and 58, as well as co-infections with multiple HPV types remain unclear, these findings support the contention that some of the racial differences seen in patients with high-grade CIN, and perhaps ICC, may be due to the different genotype distribution inherent in different ethnic groups not identified earlier in the disease process. These intriguing findings raise the question of what the population attributable risk of HPV 35 is, and whether it ultimately is worth trying to add yet another type, to reduce disparities in cervical cancer incidence and mortality.

Vaccine	HPV type	Country*	Year Implemented
Cervarix®, GlaxoSmithKline (GSK)	16, 18	USA, Australia, Europe	2007
Gardasil®, Merck	6, 11, 16,18	USA, Canada, South Korea, New Zealand, Mexico United Kingdom	2007 2008 2012
Cervarix®, GSK/ Gardasil®, Merck	-	Ghana, Kenya, Magadascar, Malawi, Niger, Sierra Leone, Tanzania	2013
V503*, Merck (phase 3 clinical trial)	6, 11, 16, 18, 31, 33, 45, 52, 58		*Pending FDA approval

Table 1: HPV Vaccines Used World-wide

*This list is not meant to be exhaustive

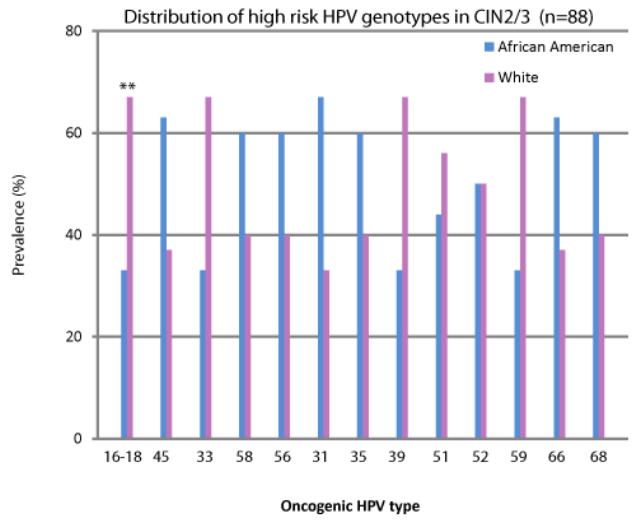

Figure 1: Distribution of high-risk HPV genotypes. HPV genotypes 16 and 18 were most commonly found in European American women with CIN2/3 lesions, **p<0.05. Though a trend for significance was observed, the differences of HPV 33, 31, and 39 distribution were not statistically significant (p>0.05), probably due to small sample size.

Several global studies have reported variability in the prevalence of HPV genotypes associated with cervical lesions by geographic region and race/ethnicity, with obvious potential implications for vaccine development [4-6]. A key question that remains to be answered, if interventions (including vaccines) aimed at reducing disparities are to be effective, is whether or not race/ethnic differences observed are the consequence of a higher propensity for infection with specific HPV type variants in different race/ethnic groups. If so, this may suggest differences in immunological response to HPV or co-infections. Alternatively, can HPV infections be explained by differences in sexual networks and/or social strata? A recent US study examined HPV genotypes in the context of poverty factors and found that a higher degree of poverty is a strong predictor of lower HPV 16 and 18 infections, a factor that was also highly correlated with being African American and Hispanic [2]. Given that, in general, socio-economic status is intricately linked to geographic regions and race/ethnicity, disentangling the associations between HPV genotype distributions by race/ethnicity will require larger studies that include women representing several sexual networks or social strata.

A general consensus of HPV type distribution based on global studies of high-grade CIN and ICC led to the development of the current HPV vaccines [7]. Findings showing that 70% of ICC cases carried high-risk HPV 16 and 18 logically indicated that vaccines targeting these HPV types would have the highest impact on reducing ICC risk. However, few studies have investigated which HPV types are causing the remaining 30% of ICC and if there is a racial/ethnic HPV distribution pattern that emerges from this group. Small sample size notwithstanding, it has recently been shown that HPV 35 and 58, but not HPV18, were among the most commonly found genotypes in CIN1-3 and ICC among East African women [5]. On the other hand, few studies have examined HPV prevalence in the US where women predominantly have CIN1 and atypical squamous cells of undetermined significance (ASCUS). This is important because current screening strategies focus on the presence of HPV 16 and 18 to make decisions on follow-up surveillance and treatment. Given that African American women are less likely to be infected with these high-risk HPV genotypes, these women may not be recommended for further workup to detect lesions until the tumor has invaded the basement membrane.

An alternative explanation for race/ethnicity differences in HPV genotype distribution could be the presence of HPV type variants. HPV viral isolates that differ by less than 2% of the DNA sequence for the L1 gene are defined as variants, and this is true for any given HPV type. The L1 gene encodes the viral coat protein used as the antigen in the vaccines. HPV type variants appear to segregate geographically [8-11] and to be race-specific [12]. Xi et al. raised the intriguing argument, based on their data from ASCUS and low-grade lesions, that the distribution of HPV 16 and HPV 18 variants may be related to race among women presently living in the same geographic region. However, current HPV screening with HPV genotyping triggered by an abnormal cytology findings, and HPV vaccines do not differentiate between HPV 16 and HPV 18 DNA variants. Differences in the adaptation of the HPV virus to the host after many generations of exposure may be one of the factors that contribute to the endemic nature of HPV variants [12]. In support of this, persistence of infections with HPV 16 and HPV 18 were race-associated; that is, European variants were more likely to persist in white women, while African variants were more likely to persist in African American women [13]. Among white women, HPV 16 European variants were associated with a higher 2-year prevalence of CIN3 as compared to African American women [13].

Oncogenic HPV 31 type variants may also be race-specific [14]. Among a Caucasian and African American population with CIN2/3, HPV 31 variants A, B and C occurred with different frequencies depending on race/ethnicity and correlated differently with ICC [14]. Moreover, infections with B variants were most likely to resolve, whereas variants A and C resolved in Caucasian women, while the C variant was more persistent in African American women. The race-associated distribution of HPV variants may result from long-term sexual mixing patterns in the population or genetic influences of the host which preferentially predispose women to establish and/or retain infection with particular variants [14]. Host epigenetics has also been investigated and suggested to influence HPV infection predisposition and concurrently, CIN and ICC development [15-17]. Furthermore, viral DNA methylation allows many viruses to adopt different tactics to regulate gene expression and evade the host immune system [18]. Viral methylation may even affect the methylation status of the host [19]. In support of this, increased methylation of HPV 16, 18, 31 and 45 is associated with progression of cervical lesions and ICC [20]. Together, these prior findings paint a complex picture that suggests the development of race-specific HPV vaccines may be premature until we better understand whether and how they influence infectivity and tumorigenicity.

In summary, ICC incidence and mortality continue to disproportionately affect racial/ethnic minorities, and the distribution of HPV genotypes varies by race/ethnicity, providing a potential explanation for such differences in incidence and mortality. It remains unclear whether such differences could be explained by host genetics or epigenetics that increase susceptibility to particular HPV genotypes, viral genetics, differences in HPV genotypes harbored by different social and/or economic networks, or by the differences in sexual

networks. Determining if race-specific vaccines will benefit some subgroups will depend on addressing these questions. In general, it is our opinion that given population admixture, race/ethnicity based vaccine-development may have limited value. Necessary to resolving this question will be the deliberate inclusion of minority populations into observational studies and clinical trials, as well as increase efforts in the study of other less racially admixed populations.

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