The Importance of High-Risk Human Papillomavirus Types Other Than 16 and 18 in Cervical Neoplasia

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• ***Context.***—**Types 16 and 18 are the most widely studied high-risk types of human papillomavirus (HPV). However, other high-risk HPV types (HPV non-16/18) also play a significant role in cervical neoplasia. Currently, screening and management algorithms separate out HPV 16/18 from all other HPV non-16/18 types. In addition, most of the previously vaccinated population has only been vaccinated for these high-risk types, so many women are still vulnerable to HPV non-16/18 infections.**

Objective.—**To review the prevalence and role of HPV non-16/18 neoplasia and to review current surveillance, management, and vaccination strategies in view of these findings.**

Data Sources.—**The study comprised a review of the literature.**

Conclusions.—**Although HPV non-16/18 types are less frequently associated with cervical intraepithelial neoplasia and cancer, they are nonetheless a significant cause of disease. Further stratification of higher-risk HPV non-16/18 may be necessary to improve prevention and management, however, regional prevalence differences may make a unified approach difficult. As HPV 16/18 infections decrease owing to vaccination of at-risk women, the relative frequency of HPV non-16/18 will increase, although the latest vaccine covers several more high-risk types.**

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Most cervical cancers are associated with human papillomavirus (HPV) 16 (often squamous), with the second most common association being HPV type 18 (often adenocarcinomas).[1] Therefore, diagnosis and management of these 2 types have dominated medical studies. Current diagnostic paradigms incorporate the finding not only of a high-risk HPV type, but also of the presence or absence of HPV 16/18. The cobas HPV Test (Roche Diagnostics, Indianapolis, Indiana) can detect 14 high-risk types (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68); 12 of these are non-16/18. These other HPV types have been found in association with cervical precursor lesions. The prevalence of non-16/18 genotypes and their association with cervical lesions have considerable importance in diagnostic, management, and vaccination strategies. The current American Society for Colposcopy and Cervical Pathology (ASCCP) guidelines stratify management by HPV type.[2] Even though cancer risk is less for HPV non-16/18 types, they will still be associated with positive HPV screening test results and may be associated with abnormal cytology findings, with the need for further workup and management, low- and high-grade squamous intraepithelial lesions (LSILs and HSILs), and invasive cancer.

OVERALL PREVALENCE

There are multiple studies demonstrating the overall prevalence of various genotypes. For the purposes of clarity and brevity, we reviewed large-scale and more recent trials, and focused our work in North America, although we did include some additional international studies to demonstrate international variations. The overall prevalence of non-16/18 high-risk HPV genotypes varies with the population studied. The large Addressing the Need for Advanced HPV Diagnostics (ATHENA) trial of 40,901 women aged 25 years and older with both cytology and HPV testing found that HPV 16 was the most prevalent genotype, followed by HPV types 52, 31, and 18.[1] This was true for all age groups, highest at 3.5% in women aged 25 to 29 years, and ranged to 0.8% in women aged 50 years and older.[1] A study of 47,617 women in New Mexico showed the highest prevalence of HPV 16 followed by HPV 51, HPV 39, HPV 59, and HPV 52.[3] In contrast, in a rural Appalachian population, a retrospective review of 3515 Papanicolaou tests with subsequent HPV testing (via the Roche cobas 4800) demonstrated that the overall prevalence of HPV non-16/18 was 3 times higher than for HPV 16/18.[4] This population did not show any significant differences between HPV genotype (HPV 16/18 versus HPV other) and age, smoking, obesity, or oral contraceptive use.[4] In a study of Thai patients with cytologically normal findings with HPV

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cotesting, nulliparous women were about twice as likely to be infected with HPV non-16/18.[5]

Other large studies around the world have also reported a high prevalence of HPV non-16/18. A recent study of 38,000 women in China showed that HPV 52 was the most common genotype followed by types 16, 58, 39, 18, and 56.[6] In Greece, non-16/18 HPV types were detected in 45.9% to 52.6% of the study population, depending on the region.[7] Most studies show a peak of infection in the teens to early twenties, followed by a slow decline in prevalence rates over time.[1,3] The decrease appears to be most marked for HPV 16.[3]

CERVICAL PRECURSOR LESIONS

The large New Mexico study showed 25% of LSILs to be associated with HPV 16/18.[3] A meta-analysis of HPV genotypes in LSIL confirmed this observation, finding HPV 16 was the most common HPV genotype in LSIL and accounted for slightly more than a quarter of LSILs.[8] This was followed in decreasing order by HPV 31, HPV 51, HPV 53, HPV 56, HPV 52, HPV 18, HPV 66, HPV 58, HPV 6, HPV 39, HPV 33, HPV 59, HPV 35, and HPV 45.[8] In this study, LSIL associated with HPV 16 was twice as likely, and HPV 18 was 1.5 times more likely, to progress to cancer.[8] However, another smaller study that followed up LSIL cases for up to almost 4 years found that the rate for non-HPV 16/18 was higher in women whose disease progressed to HSIL than for those whose lesions regressed, particularly for types 31, 39, and 52.[9]

In most studies, HPV non-16/18 was more likely to be associated with low-grade cytologic abnormalities and the rate of HPV 16/18 rose with increasing cytologic severity.[3,4,10] In addition, LSIL cytology was more likely associated with infections with multiple genotypes.[10] In terms of immediate follow-up to an abnormal cytology finding, HPV 16/18 was more likely associated with an HSIL on biopsy when the cytologic diagnosis was atypical cells of undetermined significance (ASC-US), while HPV non-16/18 was equally likely to be found in HSIL on biopsy following LSIL cytology.[11] The current ASCCP guidelines mandate that all women with ASC-US undergo colposcopy, while those with negative cytology findings should undergo colposcopy only if HPV 16/18 is present.[2] Further studies will need to determine if this is the best screening strategy for all HPV non-16/18 types.

In the ATHENA trial, HPV 16 was most likely associated with high-grade dysplasia (cervical intraepithelial neoplasia [CIN] 2 or greater), followed by HPV 31, 52, and 18.[1] The New Mexico prospective study found that HPV types 16/18 were found in almost 55% of HSIL cases.[3] However, there are important geographic variations, as a Chinese study found the greatest risk for developing HSIL involved types 16, 31, and 58.[12] HPV non-16/18 may demonstrate a different time course. HPV non-16/18 infections have been associated with a longer time for progression in contrast to HPV 16, which appears to progress quite rapidly.[13] Confirming this observation, Sideri et al[13] found the probability of developing HSIL (CIN 2+) decreased over time for women infected with HPV types 16/18, but the probability increased with HPV non-16/18.

Much of the difficulty in interpreting results from the literature comes from the genotyping methodology. The ATHENA trial demonstrated that HPV 16 was most likely associated with high-grade lesions for all ages; some HPV non-16/18 subtypes may have a greater association with CIN 3+ than HPV type 18.[1] In this study, individual genotypes were compared to HPV 16 and HPV 18.[1] This required more testing than is generally clinically available. Most studies report on clinical paradigms in which data are lumped into 2 categories: HPV 16/18 and HPV non-16/18. As noted, HPV types 16 and 18 each have different associations and risks while non-16/18 genotypes, which convey high-risk, may be lumped with those types that are not as likely to progress. Given the geographic variations in those HPV non-16/18 types and their association with HSIL, risk stratification for enhanced follow-up and vaccination strategies may need to include several non-16/18 types and may need to be regional. One such stratification would involve higher-risk HPV non-16/18 including HPV-31/33/35/45/52/58 versus HPV 39/51/56/59/66/68.[14]

INVASIVE CANCER

Although it is not the most prevalent genotype in all studies, HPV 16 is the most prevalent HPV type found in invasive cancers. A worldwide study of HPV in tissue blocks from 10,575 cancers from 38 countries in Europe, North America, central South America, Africa, Asia, and Oceania showed that 8977 (85%) of these were positive for HPV DNA.[15] The authors detected HPV types 16, 18, 31, 33, 35, 45, 52, and 58 in decreasing order.[15] This accounted for 91% of cases, while HPV types 16 and 18 were detected in 71% of invasive cancer. Types 16, 18, and 45 were most common in cervical adenocarcinomas and were also found in younger patients, and the ATHENA trial found that HPV 18 was associated with half of cervical adenocarcinoma in situ and half of all cervical adenocarcinomas.[1,15]

A Swedish nested case-control study reviewed HPV testing in women who subsequently developed squamous carcinoma (within the next 7 years).[16] When HPV 16/18 was present initially, there was an 18.6 times higher risk for subsequent development of squamous carcinoma as compared with women who were negative for HPV; persistence of HPV 16 conferred a 20 times higher risk.[16] Infection with HPV non-16/18 types in the first sample increased risk by 3-fold; individual non-16/18 types were not reported.[16] Thus, although HPV types 16 and 18 are the most frequently found types in invasive cancers and confer the greatest risk, a substantial minority of cervical cancers develop in association with HPV non-16/18.

ROLE OF HPV NON-16/18 IN IMMUNODEFICIENT INDIVIDUALS (INCLUDING HUMAN IMMUNODEFICIENCY VIRUS)

HPV non-16/18 types are also important in those with other disease states. A 2010 review article[17] reported that women infected with human immunodeficiency virus (HIV) are more likely to be infected with HPV non-16/18. These findings are consistent with more recent studies.[18] In fact, a recent large time-trend analysis in Brazil demonstrated increasing frequency of HPV non-16/18 infection in HIV-infected unvaccinated women, an acceleration potentially associated with the introduction of the HPV vaccination.[19] Further bolstering these observations, in studies of anal neoplasia and carcinoma, non-16/18 subtypes have been the common subtypes found in specimens from immunodeficient individuals, particularly type 39 in HIV-infected patients and type 58 in chemotherapy-associated immunodeficiency.[20,21] In the setting of HIV, infections with multiple

types are common.[22] In contrast, HPV type 16 is the most common type isolated from lesions in immunocompetent individuals.[20,21] Both of these genotypes (ie, HPV types 39 and 58) are considered lower-risk HPV non-16/18 types and may need coinfection with HIV or immunodeficiency from another cause for neoplastic progression.

HPV VACCINES

The US Food and Drug Administration has approved 3 vaccines, namely, Gardasil, Gardasil 9 (both manufactured by Merck & Co, Kenilworth, New Jersey), and Cervarix (GlaxoSmithKline Biologicals, Brentford, United Kingdom), although the latter vaccine is no longer available in the United States. All 3 vaccines target HPV 16/18, but only Gardasil 9 targets other high-risk HPV types (31, 33, 45, 52, and 58).[23] Gardasil 9 covers the most significant HPV non-16/18 types and should be the vaccine of choice whenever possible. In addition, both Gardasil and Gardasil 9 prevent infections with HPV types 6 and 11, associated with genital warts. As Gardasil 9 is a later version of the vaccine as well as the most comprehensive, many patients previously vaccinated or vaccinated with a less comprehensive vaccine may still be susceptible to HPV non-16/18 infections. Not surprisingly, previously vaccinated women are more likely to be infected with HPV non-16/18.[4,24] Women who were vaccinated early with the quadrivalent Gardasil or with Cervarix will need to be screened for those types not covered in these vaccines, although the incidence of invasive cervical cancer should decrease. Finally, in the setting of HIV infection and/or immunodeficiency, even the Gardasil 9 vaccine may not be sufficient to prevent HPV-associated neoplasia.

SUMMARY

In the future, we will need to continue cervical screening for those women infected with HPV non-16/18. As the prevalence of HPV types 16 and 18 decreases, the incidence of cervical cancer should likewise fall. However, other types will become relatively more prevalent and the risk of progression in these types is not well studied. When reviewing the literature, a significant issue is testing methodology and reporting. The current clinical method lumps a substantial number of high-risk HPV non-16/18 types together. First, since HPV 16 confers the single greatest risk, and HPV 18 confers significant risk for glandular lesions but less risk for squamous lesions than some HPV non-16/18 types, reporting for HPV 16 and HPV 18 separately is probably warranted in the future. Furthermore, since there is variability both in future risk for developing HSIL and cancer as well as geographic variability, other non-16/18 subtypes should also be singled out and reported separately rather than lumped together. Geographic patterns of infection and the overall risk associated with each subtype should determine the screening and vaccination priorities. An international strategy to eradicate most cases of cervical cancer may need to target many HPV non-16/18 types.

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