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The value of human papillomavirus detection in primary cervical cancer screening

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Summary

Human papillomavirus (HPV) is present in the vast majority of high-grade gynecological abnormalities (high-grade squamous intraepithelial lesions and worse) and, therefore, HPV detection has a very high negative predictive value. Nevertheless, introduction of HPV detection into primary screening would result in large numbers of false positives: HPV positive women with normal cytology. The prevalence of HPV in women with cytologically normal smears is age-dependent as has been shown extensively. We hypothesize that women at the age of 50, who are HPV negative and have a cytologically normal smear might be encouraged to refrain from further screening. The data available from the literature on HPV prevalence in elderly women is presented. Data of cohort studies of elderly women with and without HPV infection as well as health-economical analyses to investigate the cost-effectiveness of the proposed hypothesis are still lacking.

Key words: Cervical cancer; Human papillomavirus; Primary screening.

Various studies on human papillomavirus (HPV) detection from different geographical regions around the world have shown very strong associations between HPV exposure and the occurrence of cervical cancers, with odds ratios ranging from 61-156 [1-13], which are much stronger than the association between smoking and lung cancer. Under optimal circumstances (fresh material, different HPV detection methods) HPV DNA was found in 99.7% of cervical cancer cases, suggesting that HPV-negative cervical cancer is extremely rare if it exists at all [14]. Mucosal HPV types can be divided into low-risk and high-risk types, the latter group consisting of 15 HPV types (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, 73, and 82); in addition three types are classified as probable high-risk types (26, 53, and 66) [15].

Although alternative routes for HPV transmission do exist (e.g., mother to child transmission at birth [16]), infection with HPV is primarily a sexually transmitted infection [17], which is underscored by the fact that HPV prevalence is much higher in commercial sex workers than in the general population [18, 19]. First infection frequently coincides with the start of sexual activity, and the prevalence of HPV in women with cytologically normal smears is age-dependent as has been shown by a number of studies [20-28]. The cumulative incidence of an HPV infection has been estimated at 75% or more [29], indicating that the majority of all women (and men) will encounter an HPV infection in their lifetime. In fact, longitudinal cohort studies in young female college students have shown that in the first three to five years after the start of sexual activity the cumulative risk of acquiring HPV is 60% [30, 31]. Generally, HPV infection is transient: in an American cohort study the median clearance time was eight months [30]. In fact, in that study the probability of clearing up an HPV infection was found to be 31% in the first six months and 39% in the second six-month period. If the infection was not cleared up within the first year, the probability of cure dropped to 11% in the third six-month period, indicating that the longer an infection persists, the more difficult it is to eventually clear up the infection [30]. After two years only 9% of the women continued to be infected with HPV. In a Dutch study on women with mild to moderate dyskaryosis at baseline, the median clearance time was 25 months and after five years of follow-up 67% of the women had cleared up the infection [32]. The much longer overall clearance time can be explained by the fact that in this study a high proportion of women had cervical intraepithelial neoplasia (CIN) grade 3, a condition in which HPV infection is poorly cleared. In contrast, the median clearance time of new infections in this study was six months, which is similar to the American study.

The strong relationship between HPV and the development of cervical cancer opens up possibilities for treatment and prevention. For instance, there is a strong interest in the development of a prophylactic vaccine against HPV. A recent randomised, placebo-controlled study of an HPV-16 vaccine has been reported [33]. The women were followed for a median of 17.4 months after completing the vaccination regimen. The incidence of persistent HPV-16 infection was 3.8 per 100 woman/year at risk in the placebo group and 0 per 100 woman/year at risk in the vaccine group (100% efficacy; 95% confidence interval, 90 to 100%; $p < 0.001$). All nine cases of HPV-16-related CIN occurred among the placebo recipients [33]. Cost-effectiveness of a prophylactic HPV vaccine has also been studied [34]. It was shown that vaccination of girls against high-risk HPV was cost-effective even when the vaccine efficacy was low. Although gains in life expectancy were modest at the individual level (4.0 quality-adjusted life days per person), population benefits would be substantial: if all 12-year-old girls currently living in the United States were vaccinated 224,255 cases of high-risk HPV infections, 112,710 cases of squamous intraepithelial lesions, 3,316 cases of cervical cancer and 1,340 cervical cancer deaths would be averted during their lifetimes [34]. A different study examined the potential health and economic effects of an HPV vaccine in a setting of existing screening. This study showed that vaccination at the age of 12 and biennial screening starting at the age of 24 years (a delay of 6 years) had the most attractive cost-effectiveness ratio compared with screening only beginning at age 18 years and conducted every three years. However, the cost-effectiveness of vaccination plus delayed screening was highly sensitive to age of vaccination, duration of vaccine efficacy, and cost of vaccination [35].

Although these results are very promising, several issues need to be addressed: what is the target population (girls only or also boys), at what age should vaccination start, which HPV types should be included in the vaccine? Furthermore, since the greatest potential for vaccination is in the developing world, another issue is whether a vaccine can be developed that can be delivered in a single dose, preferably by the oral or nasal route (and not by injection) and which is stable under variable conditions.

Progress in the development of a therapeutic vaccine has been much slower. Although a number of Phase I studies have been performed, and these have shown that the vaccines are generally safe and well-tolerated, only few studies have demonstrated statistically significant regression of lesions [36]. In fact, even a reversed pattern can be observed. In one study using a DNA vaccination approach to deliver HPV-16 E7 oncoprotein, enhanced tumor growth, delayed regression or tumor outgrowth in vaccinated mice were consistently noted, probably due to an effect on cytokine production. Splenocytes from E7-gene vaccinated animals responded to restimulation in vitro with E7-bearing tumor cells with a tumor induced immune deviation by producing IL-4 but only low levels of IFN-gamma [37]. In light of the safety and tolerability of the vaccines in Phase I studies, further studies are needed, especially as women in Phase II studies will be less immunocompromised, and may therefore be better equipped to respond to vaccination.

Another possible application of the strong relation between HPV and cervical cancer is the use of HPV detection in the triage of minimally abnormal Pap smears. The ASCUS-LSIL Triage Study (ALTS) has investigated in a prospective, randomized fashion the optimal management of both atypical squamous cells of undetermined significance (ASCUS) [38] and low-grade squamous intraepithelial lesion (LSIL) [39] by three management strategies: 1) immediate colposcopy, 2) HPV triage (referral for colposcopy only if enrollment HPV test was positive) or 3) conservative management (repeat cytology in follow-up and referral for colposcopy after cytological diagnosis of a high-grade squamous intraepithelial lesion - HSIL). Because the cytology interpretation of LSIL is fairly reproducible and the majority of LSIL cases (84%) are HPV positive, the use of HPV testing for the management of LSIL is not cost-effective, since the majority of women in that case would be referred for colposcopy [39]. It should be noted that the two alternative management strategies were also not effective for the management of LSIL; thus, immediate colposcopy would detect only 56% of the cumulative CIN 3 cases (102 of 673 women, or 15.2%, of women with LSIL developed CIN 3) and repeat cytology would detect 48% of the cumulative CIN 3 cases [39]. For the management of women with ASCUS, however, HPV triage is at least as sensitive as immediate colposcopy in the detection of underlying CIN 3, while the number of women referred for colposcopy is halved [38], and would therefore appear to be the most effective strategy for the management of women with ASCUS. This has been further strengthened by a meta-analysis of 15 studies (including the ALTS study) in which HPV triage and histological outcome was documented [40]. It was shown that HPV detection by Hybrid Capture II assay has a higher sensitivity with equal specificity to repeat cytology.

The final aspect in which HPV might play a role is cervical smear screening. Although HPV is present in the vast majority of high-grade abnormalities (HSIL and worse) and, consequently, has a very high negative predictive value [41-43], introduction of HPV detection into primary screening would result in large numbers of false positives: HPV positive women with normal cytology. Especially in younger women, between the ages of 20 to 30, both HPV infections and low-grade abnormalities are frequent and usually transient [31]. HPV screening should, therefore, not be performed before the age of 30. However, so far little attention has been focused on the use of HPV detection to define an upper age limit for screening. Within countries with population-based screening programs, some attention has been paid to withdrawal of women with consecutive normal smears [44-47]. However, in a country without population-based screening, where women are not bound to one general practitioner, and where no continuous patient record accompanies the woman upon switching healthcare providers, withdrawal of low-risk women necessarily needs to be based on the last smear. In that case, the addition of HPV testing to cytology at the time point of the final smear would provide optimal information to distinguish between low-risk and high-risk women. We have hypothesized that women at the age of 50, who are HPV negative and have a cytologically normal smear might be encouraged to refrain from further screening [48].

Recently, it has been shown that after an initial decline in HPV prevalence a higher prevalence after the age of 55 may be encountered [8, 49, 50]. A group of 3,024 women from Costa Rica were tested by polymerase chain reaction for more than 40 HPV genotypes [8]. Among the women with normal cytology, HPV infections first peaked before the age of 25, and peaked again in women of 55 years and older. It was suggested that the increased HPV prevalence after menopause could lead to a second peak of HSIL, as described by others. However, the second peak in HPV prevalence could be attributed almost entirely to low-risk (non-cancer associated) HPV types [8]. A second study, performed in Canada, also showed an increase in the prevalence of HPV in women of 60 years and older [49]. However, in this Canadian study the second peak was entirely due to high-risk HPV types. Multiple regression analysis showed that age less than 20 years at first intercourse and apparent absence of a stable sexual partnership (marital status) were significantly related to the presence of HPV [49]. We have studied the HPV prevalence in a group of 1,936 elderly women (50 years and older), screened either by their gynecologist or their general practitioner [50]. There was no consistent difference in the prevalence of specific HPV types with age. The presence of multiple infections, however, was much more pronounced in women between 50 and 60. The prevalence of HPV type 16 in women aged 70 and older was 2.25%, which was the highest prevalence of all age groups in this study. It has been shown previously that women with multiple infections are at higher risk for the development of cervical lesions [30]. The presence of HPV type 16 per se has also been shown to convey a higher risk of cervical lesions [8, 30, 31]. The results of our study were somewhat puzzling in this aspect, since on the one hand they seemed to suggest a lower risk because fewer multiple infections were detected, while on the other hand more HPV type 16 infections were detected, which suggests a higher risk [50]. The presence of a second peak in HPV prevalence might imply that the natural decline in immune competence with increasing age promotes infection with or reactivation of HPV. However, all of these studies are cross-sectional studies rather than cohort-studies and, consequently, cannot rule out differences between the women in the different age groups, for instance in exposure to HPV. Although the studies are consistent with an increase in HPV prevalence with older age, only a cohort-study can actually prove this increase as a consequence of age.

Nevertheless, it was shown in this study that based on the hypothesis, 94% of the women could be withdrawn from the screening program [50]. The 6% of women that cannot be withdrawn consists of women with negative beta-globin PCR, women with cytological abnormalities and women with normal cytology but a high-risk HPV infection. Similarly, results of a study in the Grampian area (Scotland) showed that 90% of the women could be withdrawn from the screening program [51], indicating that this research is also valid for countries with population-based screening programs. HPV detection in the Scottish study was performed on stained Pap smear slides, resulting in a higher number of beta-globin negative samples (inadequate DNA isolation). If HPV detection could be performed on the residual material from thin-layer cytology, the number of women withdrawn could potentially be higher.

It is our firm belief that further studies in this area are needed. We imagine that this type of research should comprise the follow-up of elderly women with and without HPV infection to estimate the frequency of (re) infection as well as the course of such infections in elderly women, a health-economical analysis to investigate the cost-effectiveness of the hypothesis and finally an appropriately sized randomized clinical trial.

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