

Human papillomavirus vaccines and the potential for cross-protection between related HPV types

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Abstract

The majority of human papillomavirus (HPV) belong to the genus alpha-papillomavirus, which can be further subdivided into species and then strains. Approximately 200 strains of HPV have been identified, and the whole genomes of approximately 100 strains have been (discovered) and completely sequenced. Between 13 and 18 HPV strains have been characterized as conferring a high oncogenic risk, with 12 of these strains belonging to the HPV species 7 (HPV-18, -39, -45, -59, -68) and species 9 (HPV-16, -31, -33, -35, -52, -58, -67). While strains belonging to the same species are phylogenetically related, they may differ biologically. The available data on whether natural HPV infection infers cross-protection against other related strains from the same species are equivocal. There are data to indicate that following HPV infection, there appears to be a reduced risk of contracting the same strain of HPV. However, there is also evidence to indicate that natural infection with HPV does not confer group-specific immune protection or general protection from reinfection with genital HPV mucosal types. Recent studies conducted with HPV vaccines show data on cross-protection against related HPV strains. In vitro experiments with serum from recipients of the quadrivalent HPV vaccine (HPV-6/8/16/18) show neutralization of HPV 45 pseudovirions. Cross-protection following vaccination of women ($n=776$) with three doses of bivalent HPV vaccine (HPV-16/18) demonstrated that, over a period of up to 4.5 years, long-term vaccine efficacy was observed for HPV-16 and -18, and vaccine efficacy was also observed against incident infection with HPV-31 and -45. These findings are supported by the results of a large study ($n=18,644$) in women aged 15 to 25 years vaccinated with the adjuvant bivalent HPV vaccine (HPV-16/18). Over a period of 6 months, cross-protection was observed against persistent infections with HPV-45, -31 and -52, and at 12 months, modest protection was demonstrated against persistent infections with 12 combined oncogenic HPV types.

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Human papillomavirus phylogenetic tree

The human papillomavirus (HPV) belongs to the papillomavirus family, within which there are different genera [1,2]. These different genera are phylogenetically related but may be biologically diverse. The genus alpha papillomavirus is most common in humans, however, the genus beta papillomavirus can be found in a small proportion of individuals, such as those who are immunocompromised [1–3]. Closely related HPV strains have been categorized into species. At present, approximately 200 strains of HPV have been identified; the

whole genomes of approximately 100 strains have been isolated and completely sequenced [1]. An HPV strain is defined as a complete genome whose L1 gene sequence is $\geq 10\%$ dissimilar to that of any other HPV type.

HPV types have also been categorized according to whether they are associated with a high or low oncogenic risk [4,5]. In total, between 13 and 18 HPV strains have been characterized as conferring a high oncogenic risk; 12 of these strains belong to the HPV species 7 (HPV-18, -39, -45, -59, -68) and species 9 (HPV-16, -31, -33, -35, -52, -58, -67) [5,6]. For example, all HPV strains that are classified as belonging to HPV species 9, along with HPV-16, are found in cervical cancer and its precursor lesions [2]. However, the overlap within each of these species is not complete, and some strains within a species (e.g.,

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HPV species 7 and strain HPV-70) have not been definitively classified as high risk [1]. Research has focused on several high-risk strains of HPV, including HPV-16, -18 and -31. While it can be suggested that the molecular and clinical characteristics of strains belonging to species 7 and 9 are similar to these three high-risk strains, further research is needed to fully clarify the similarities and differences within each species.

Cross-protection following natural infection with HPV

After an initial infection with HPV, subsequent infections are common [7]. However, with subsequent HPV infections, there may be a reduced risk of contracting the same strain of HPV. A US-based cohort of female students ($n=608$; mean age 20 years) was monitored at 6-month intervals for a period of 3 years [7]. A total of 141 women were HPV-positive at baseline; the 24-month cumulative incidence of subsequent HPV infection was 71.6%. During follow-up, initial HPV infection was detected in a further 106 women; the 24-month cumulative incidence of subsequent HPV infection in these women was 67.3%. Overall, the 24-month cumulative incidence in women with ≥ 1 follow-up visit after their initial HPV infection was 70.2%. Detection of the initial HPV infection at baseline or during subsequent follow-up had no significant effect on the risk of subsequent infection with additional HPV types ($p=0.682$).

In this cohort of women, analyses were performed to determine whether the development of antibodies to HPV-16 virus-like particles (VLP) were associated with a reduced risk for the acquisition of non-HPV-16-related strains [7]. The VLP is capsid protein for HPV. Following adjustment for age, ethnicity, number of male sexual partners, use of oral contraceptives and persistence of HPV DNA or antibodies, it was determined that high levels of IgG to HPV-16 VLPs in ≥ 2 previous visits conferred a moderate protective effect (relative risk [RR] 0.57; $p=0.131$). Women with persistent seropositivity to IgG and IgA antibodies had a risk reduction of 32% for subsequent infection with a non-HPV-16-related strain. Persistent HPV-16 infection for ≥ 2 visits also appeared to confer a group-specific protective effect [7].

To date conflicting data are available regarding cross-protection from naturally occurring HPV infection. There is also evidence to indicate that natural infection with HPV does not confer group-specific immune protection or general protection from reinfection with genital HPV mucosal types [8]. Viscidi et al. [8] investigated the association between IgA seroreactivity to HPV-16, -18 or -31 VLPs and the risk of subsequent HPV infection after 5 to 7 years in a population-based cohort of Costa Rican women ($n=7046$). In general, seropositivity to HPV-16 or -31 was not associated with a significant reduction in the risk of infection with HPV-16 or related strains. Similar results were demonstrated for seropositivity to HPV-18. A total of 2.6% of seronegative and 3.5% of seropositive women had new infections with an HPV-18-related type. However, a nonsignificant 40% reduction in the risk of subsequent HPV infection was observed in women with high levels of antibodies to HPV-16 VLPs. A total of 4.4% of

seronegative and 3.6% of seropositive women had new infections with HPV-16-related types. In a stratified subgroup of women selected according to baseline and follow-up HPV-16 DNA status, 6.9% of IgA seropositive and 7.6% of IgA seronegative women had a new HPV infection (RR 0.91; 95% CI 0.38–2.18). In contrast to Ho et al. [7], the results of this study suggest that IgA reactivity to HPV-16 VLPs is not a correlate of immunity.

Trial data on cross-protection with HPV vaccination

Recent studies conducted with HPV vaccines have demonstrated promising data on cross-protection against related HPV strains [9–11]. Vaccination against one HPV strain may in turn confer protection against heterologous HPV infections.

Preclinical data

Preclinical data have shown that immunization of rabbits with an HPV VLP vaccine displaying HPV-16 L2 epitopes induces cross-neutralizing antibodies to HPV-11 [9]. The L2 minor capsid protein is antigenetically subdominant to the L1 structural protein; in an effort to induce a strong anti-L2 antibody response with cross-neutralizing activity to other mucosal types, chimeric VLPs were generated based on the bovine papillomavirus type 1 L1 major capsid protein. These chimeric particles displayed the HPV-16 L2 peptides (69–81 and 108–120) on an immunogenic capsid surface loop. The immunization of rabbits induced L2-specific serum antibodies. In addition, in this animal model, antisera to both chimeric proteins partially neutralized HPV-16 pseudovirions, and immune serum to chimeric protein comprising L2 69–81 was partially neutralizing for infection by HPV-11 virions. Although these data show that cross-protection can occur after vaccination of rabbits with HPV L2 epitopes, current vaccines (quadrivalent and bivalent) against HPV are comprised of L1 epitopes.

Healthy volunteers

In healthy volunteers ($n=16$), response to vaccination with HPV-16 L1 VLP was shown to predict the response to other HPV strains [10]. As would be expected, the strongest correlations were between HPV-16 and HPV-31 ($p<0.0001$), both of which belong to the HPV species 9. Proliferative and cytokine responses were evaluated to determine whether vaccination in these individuals induced cellular immunity. Post-vaccination, fewer women responded to heterologous strains than to HPV-16 (73%). However, increased proliferative and cytokine responses to more than one heterologous strain (HPV-18, -31 and -53) were induced in 45% of women and 18% of women responded to all three strains.

Clinical data

Harper et al. [11] reported evidence of cross-protection following vaccination of 776 women with three doses of bivalent HPV vaccine (HPV-16/18) who were followed-up over

a period of up to 4.5 years. While long-term vaccine efficacy was observed for HPV-16 and -18, vaccine efficacy was also observed against incident infection with HPV-31 and -45.

Cross-protection has also been demonstrated following vaccination of women aged 15 to 25 years ($n=18,644$) with the adjuvant bivalent HPV vaccine (HPV-16/18) [12]. Vaccine efficacy against cervical intraepithelial neoplasia grade 2+ containing HPV-16 or -18 was 90.4% after a mean follow-up of 14.8 months. At 6 months, cross-protection was also demonstrated against persistent infections with HPV-45, -31 and -52, with vaccine efficacy ranging from 31.6 to 59.9%. At 12 months, modest protection was demonstrated against persistent infections with 12 combined oncogenic HPV types, with vaccine efficacy of 27.1%.

Serum collected from 10 patients, who were enrolled in a phase II dose finding and efficacy study with the quadrivalent vaccine (HPV-6/11/16/18), showed as expected the ability to neutralize pseudovirions of HPV 18 in vitro [13]. Six of the ten sera also neutralized HPV 45 pseudovirions. These data suggest that the quadrivalent vaccine-induced antibodies have the ability to neutralize HPV 45 in vitro which is closely related to HPV 18. Clinical trials on in vivo cross-protection are in progress.

Summary

It is unclear whether natural HPV infection confers a reduced risk of subsequent infection with related HPV strains. However, there are preliminary data to indicate that vaccination against one HPV strain may, in turn, confer protection against heterologous HPV infections. Available in vitro data suggest that the quadrivalent vaccine (HPV-6/8/16/18) induces cross-neutralization antibodies against HPV-45. Clinical data have demonstrated that the bivalent HPV vaccine (HPV-16/18) induces cross-protection against heterologous strains (HPV-31/45/52). Further clinical trials are needed to fully clarify the cross-protective properties of the bivalent and quadrivalent vaccines in clinical use. In addition, recent preclinical data have indicated that the induction of cross-neutralization antibodies by L1 or L2 epitopes may be a possible strategy for the generation of broad-spectrum vaccines to protect against relevant mucosal HPV infection and associated neoplasia.

Question and answer

What type of cross-protection has been demonstrated by HPV vaccines?

Both the bivalent and quadrivalent vaccines have demonstrated cross-protection. While the bivalent vaccine offers cross-protection against HPV types 33 to 45, preliminary data from a recent pre-planned subgroup analysis of the

FUTURE I and II trials, presented during the 47th Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC), demonstrate that the quadrivalent vaccine provides cross-protection against 10 HPV types (i.e., 31, 33, 35, 39, 45, 51, 52, 56, 58, and 59) with a reduced risk of infection against these subtypes of 38%.

Conflict of interest statement

KA has received grant/research support and is a consultant for Genzyme, GlaxoSmithKline, Merck, Gen Probe and Advaxis.

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