

Can we really beat cervical cancer?

Vaccination has the potential to reduce the global burden of disease from genital HPV infection

CERVICAL CANCER is the third most common cancer worldwide and, for women, the second most common after breast cancer. Each year there are about 466 000 new cases globally, and around 232 000 women die of cervical cancer.¹ Eighty per cent of cases occur in developing countries, where it is the leading cause of cancer-related death among women.¹

Precursor lesions (high-grade dysplasias) precede the development of cancer by years. With appropriate screening programs and early diagnosis and treatment, this reproductive health problem becomes a preventable public health issue. However, data for the past 5 years indicate that only about 5% of women in developing countries are screened, compared with 40%–50% of women in developed countries. Further, because of the insensitivity of the Papanicolaou (Pap) test, even in countries with appropriate screening programs, 50% of adenocarcinomas and at least 25% of squamous cell carcinomas occur in adequately screened women.

Association between human papillomavirus and cervical cancer

Molecular biology has finally established the causal association between persistent infection with certain human papillomavirus (HPV) genotypes and cervical cancer, supporting previous observations relating cervical cancer to sexual activity.²⁻⁴ HPV genotypes 16 and 18 are now categorised as human carcinogens,² and it is noteworthy that these two HPVs are present in over 70% of cases of cervical cancer worldwide.²⁻⁴ Further, in a study of almost 1000 cervical cancer cases worldwide, the prevalence of HPV infection

was 99.7%.³ Recently, less prevalent oncogenic HPV genotypes (31, 33, 45, 52, 58, 59) have also been found to be strongly associated with cervical cancer, with odds ratios several hundredfold.⁴ With such high relative risks, the association between persistent oncogenic HPVs and cervical cancer is the strongest for any environmental factor and human cancer.

From recently completed longitudinal studies, we now know that genital HPVs are the commonest sexually transmitted viral infection. They are largely transient, usually asymptomatic and most are of no clinical consequence. The mean duration of carriage is 4 months for low-risk oncogenic types and 8 months for high-risk oncogenic types, with HPV-16 carriage being even longer.⁵ Genital warts are caused by genotypes 6 and 11 (low-risk HPVs), while persistent infection with oncogenic genotypes (over years and in a minority of patients) results in severe dysplasia or, ultimately, carcinogenesis. This process involves other cofactors (host and/or exogenous factors, such as high parity, cigarette smoking) and complex pathways, which are not completely understood.

HPV DNA as a marker for precursor lesions

Persistent infection with oncogenic HPVs precedes virtually all high-grade dysplasias or neoplasias. Thus, persistent positivity for high-risk HPV DNA is a marker for current or subsequent development of precursor lesions,⁵ with persistent HPV DNA type-specificity being an even stronger predictive factor.⁶ Cohort analyses show that negative baseline Pap and HPV DNA tests are associated with very low

A controlled trial of a human papillomavirus (HPV) type 16 vaccine, by Koutsky et al⁹

Study population: 2392 young women, 16–23 years old (no more than five male sexual partners during their lifetime).

Intervention: Intramuscular vaccination with three doses of placebo or HPV-16 virus-like particle (VLP) vaccine (Day 0, Month 2, Month 6).

Follow-up: Month 7, 12 and thereafter 6 monthly to 48 months (Pap test, and HPV DNA 16 and HPV-16 antibody assayed). Colposcopy biopsy tissue evaluated for cervical intraepithelial neoplasia (CIN).

Primary endpoints: Persistent HPV-16 infection (the detection of HPV-16 DNA in samples obtained at two or more visits \geq 4 months apart, in those HPV DNA negative at Day 0 and Month 7) and HPV-16-related CIN.

Results: After a median follow-up of 17.4 months, the incidence of persistent HPV-16 infection was 3.8/100 woman-years (placebo group) and 0/100 woman-years (vaccine group) (100% efficacy; 95% CI, 90–100; $P < 0.001$). Nine cases of HPV-16-related CIN occurred, all in the placebo group. 99.7% of the women vaccinated seroconverted and with a robust antibody response.

Conclusion: HPV-16 vaccine reduced the incidence of both HPV-16 infection and HPV-16-related CIN. The study is continuing.

risks of high-grade disease (0.16%). By comparison, women with positive HPV DNA tests and abnormal Pap smear results have a 4.54% cumulative incidence of high-grade dysplasia or cancer.⁷ HPV DNA testing, with its higher sensitivity for detecting underlying high-grade lesions than the Pap test (and the advantage that it can be performed on self-collected samples), is being reviewed for its clinical utility, either in triage of inconclusive or minimally abnormal smears, in conjunction with the Pap test, or as a stand-alone test in primary screening.⁵ It may also have a role as a test of cure after ablation for cervical dysplasia; persistence of HPV DNA after treatment could be an accurate predictor of residual disease or relapse.⁵ Of note, in the United States, HPV DNA (Hybrid Capture 2) testing was recently approved for use with the Pap test for women 30 years and over.⁸

Vaccination prevention at last?

The preliminary results of a recent trial of a monovalent HPV genotype 16 vaccine were received with great interest and enthusiasm (Box). The vaccine provided vaccinees with high-level protection for incident and persistent HPV-16 infection (as a surrogate for invasive cancer) and HPV-16-related cervical intraepithelial neoplasia (CIN).⁹ Now awaited are larger studies to prove that clinical disease is prevented by vaccination, and the results of current clinical trials evaluating multivalent vaccines (HPV types 6, 11, 16 and 18). If these vaccines are as successful as the interim monovalent vaccine,⁹ they have the potential to prevent genital warts and over 70% of dysplasias and cancers, as well as reduce the occurrence of abnormal Pap smear results and the costs of their follow-up and management.

Pivotal in the development of these vaccines was the production of virus-like particles (VLPs) — an Australian first.¹⁰ The VLPs used for the HPV-16 vaccine are viral

subunits, composed of the major capsid protein L1 or outer shell of HPVs. Being devoid of DNA, they are not infectious. In Phase 1 and 2 clinical trials, VLPs have been shown to be not only immunogenic and safe, but able to induce strong cell-mediated and humoral immune responses. Most encouraging is that VLPs produce neutralising antibodies in animal models that are protective against challenge as well as long lasting. We need to see whether VLPs induce similar long-lasting immunity in humans.

Second-generation vaccines

Second-generation vaccines will need to be easier and cheaper to develop, give a broader coverage, have a better delivery system, allow better mucosal delivery, and possibly incorporate both prophylactic and therapeutic cover. The initiatives of the Gates Foundation to reduce cervical cancer in developing countries, where the disease is most common, are to be commended.¹¹ Initiatives to promote second-generation vaccines (eg, vaccines that are cheaper to manufacture and available in a non-injectable form) have been discussed at a meeting of HPV vaccine experts, convened by the Gates Foundation in Seattle, Washington, in September 2002.

Therapeutic vaccines have been successful in animal models, and there have been various Phase I and II trials in humans using HPV subunits (modified fragments of the HPV *E6* and *E7* genes), as well as chimeric and DNA viral approaches.¹² These trials have shown some encouraging results for intraepithelial neoplasias, although clinical trials are not as advanced as for the prophylactic vaccines.

An important question for vaccine development is whether there will be any cross-protection between types (immunity induced by natural infection is type specific), or whether effective vaccine-induced immune responses to one common high-risk HPV might simply open the door to another, currently less common type.

In Australia, mortality from cervical cancer has been reduced substantially by an effective Pap screening program, but this comes at a considerable cost, both to the health budget and to women who face the psychological impact of having an abnormal Pap smear result. Ultimately, successful vaccination has the greatest potential to reduce the global burden of disease from genital HPV infection. Development of a vaccine for a sexually transmitted infection, the infective agent of which can not be grown by traditional methods in the laboratory, could be seen as a very important breakthrough, particularly for Australia (as VLPs were developed here).¹⁰ An effective prophylactic vaccine could ultimately obviate the need for population-based Pap smears, while an effective therapeutic vaccine could provide a change to conventional management of cervical disease, including reducing the need for colposcopy. However, lowering the incidence of dysplasia and neoplasia will take many years. In the meantime, the various prevention strategies still need to be endorsed and maintained.

Apart from cervical cancer, other anogenital cancers and some non-melanoma skin cancers are also attributed to oncogenic HPVs. A successful vaccine could ultimately have an even greater impact on HPV-related diseases.

Other challenges

Besides vaccine delivery, vaccine implementation would include educating the general public about HPV (public awareness and acceptance), de-stigmatising HPV infection, and gaining acceptance for vaccinating adolescents (or pre-adolescents), possibly of both sexes, for a sexually transmitted infection before their sexual début. For the future, we need a better understanding of the transmission dynamics of HPV. A public health policy will need to be guided by mathematical modelling of the impact of an HPV vaccine on Pap screening. This also applies to the interrelationship between HPV and abnormal Pap smear results, and any concomitant psychological impact on women faced with an abnormal result of an HPV DNA test or a Pap smear.

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