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Abnormal Pap tests after the HPV vaccine

Background
Worldwide, cervical cancer affects 500 000 women and causes 275 000 deaths annually. Persistent infection with one of 13 oncogenic types of human papillomavirus (HPV) is now known to be the cause of both squamous and adenocervical carcinomas of the cervix. The Pap test involves the examination of exfoliated cells from the cervix and has been shown to be an effective way of detecting the precursors of squamous cell carcinoma. In Australia, commencing in 2007, a free quadrivalent HPV vaccine was offered to all females aged 12–26 years.

Objective
This article looks at why a substantial number of young women who have been vaccinated with the HPV vaccine will still have Pap test abnormalities.

Discussion
Prophylactic efficacy of the two HPV vaccines against specific HPV types is almost 100%. This knowledge has created an expectation of the demise of both cervical cancer and Pap test abnormalities. Efficacy of the vaccine is dependent upon the recipient not having been infected with that HPV type. It is likely that most of the women aged 18–26 years who have had the HPV vaccine were already sexually active and therefore exposed to one or more HPV types. We can still expect to see a substantial number of young vaccinated women with Pap test abnormalities, due to both HPV exposure before vaccination and to the many HPV types not covered by the vaccine. A noticeable reduction in cancers and Pap test abnormalities will not be seen for some years.

Worldwide, cervical cancer affects 500 000 women and causes 275 000 deaths annually.[1] There are two major types of cervical cancer: squamous cell carcinoma (SCC) and adenocarcinoma. Squamous cell carcinoma arises at the transformation zone of the cervix; adenocarcinoma arises higher (and often deeper) in the canal. Persistent infection with one of at least 13 oncogenic HPV types is now known to be the cause of both squamous and adenocervical carcinomas.[2]

In Australia, 734 new cases of cervical cancer and 221 deaths from cervical cancer were recorded in 2005.[3] The incidence of disease and mortality rates are now among the lowest in the world due to the success of the National Cervical Screening Program, introduced in 1991.

The Pap test or 'smear' was first described by George Papanicolau in 1928 and involves the examination of exfoliated cells from the cervix. The Pap test has been shown to be an effective way of detecting the precursors of SCC. In an optimal cervical screening program it has been estimated that around 90% of cervical cancers could be prevented.[4] Pap test screening cannot prevent 100% of cervical cancers as the test has imperfect sensitivity and is unable to readily detect precursors of adenocarcinoma.[4]

Pap tests look at cellular changes at the cervix. If an abnormality is seen, it is classified as low grade squamous intra-epithelial lesions (LSILs) or high grade squamous intra-epithelial lesions (HSILs) according to specific criteria. Nearly 3.5 million women aged 20–69 years participated in the National Cervical Screening Program in the 2 year period 2005–2006.[5] The majority of Pap tests (about 94%) were negative, but others showed abnormalities, mostly low grade. Approximately 90 000 LSILs and 15 000 HSILs are reported annually in Australia.[4]

Low grade cellular changes mostly represent transient infection with any of the 40+ HPV types that can infect the genital tract. High grade changes are more likely to signify persistent or integrated HPV infection, most often with one of the oncogenic HPV types. Women with high grade changes should be referred for colposcopy

and biopsy. If these high grade changes are histologically confirmed, treatment is recommended.

Pap screening is a secondary prevention strategy. The aim of detecting cellular changes due to persistent HPV infection is to allow treatment before there is an opportunity for the development of cancer. It has been estimated that if left untreated, about 30% of women with a high grade lesion would develop cervical cancer over a 30 year period.[6] By contrast, HPV vaccination is a primary prevention strategy. It is only of value in an individual when provided before infection with the vaccine targeted HPV types. It has no therapeutic effect on existing infections.

Two HPV vaccines are currently available: a quadrivalent vaccine against HPV types 6, 11, 16 and 18 (Gardasil™) and a bivalent vaccine against types 16 and 18 (Cervarix™). Both vaccines stimulate the production of very high titres of antibodies against the targeted HPV types. This results in protection against type specific HPV infection and related cervical disease. Because vaccination does not cover all HPV types that may cause cervical lesions and cancer, it is a complementary strategy, not a replacement for cervical screening.

Importantly, the two HPV vaccines do not contain live virus nor any oncogenic viral proteins or infectious material. Therefore, the vaccine is not responsible for any smear detected abnormalities that may be found after it has been given.

The expected impact of HPV vaccination in Australia

Australia was the first country in the world to introduce a fully funded, population based HPV vaccination program. Commencing in 2007, HPV vaccine was offered to all females aged 12–26 years through school and general practice/community settings, with vaccination courses to be completed by 31 December 2009. Routine HPV vaccination of 12–13 year old girls at school will continue as part of the National Immunisation Program. Estimates of vaccine uptake to date are promising, with 70–80% three dose uptake in Victoria and New South Wales school programs in 2007.[7] In addition, in 2008 a New South Wales family planning clinic survey found that 58% of females aged 15–26 years had received at least one dose 10 months into the program.[8]

There has been considerable excitement about anticipated reductions in both cervical cancer and Pap test abnormalities from HPV vaccination. This might seem logical given:

- the very high efficacy of the vaccines in trials (90–100% efficacy against infection and disease due to HPV types 6, 11, 16, 18)[9,10]
- the high vaccine coverage in Australia, and
- that 70–80% of cervical cancers are due to HPV types 16 and 18.[11,12]

We anticipate that the vaccine will eventually have a major impact on the incidence of cervical disease and cancer. However, a significant effect on Pap test abnormalities will not be seen for some years. We can still expect to see a substantial number of young vaccinated women with Pap test abnormalities because of the following three factors.

Pap screening in Australia commences at the age of peak HPV infection

During the 2 year period 2005–2006, 47% of eligible women aged 20–24 years had a Pap test.[5] Both low and high grade Pap test abnormalities are more common in this age group than other age groups. High grade lesions are diagnosed at an overall rate of 7.3 per 1000 smears; in the 20–24 years age group the rate is more than double this at 18.4. This means that about one in 50 women screened in this age group will have a HSIL on her Pap smear.[5]

Most Pap test abnormalities are caused by HPV types not preventable with current vaccines

It is estimated that about 50% of high grade lesions are due to HPV types 16 and 18; the other half are due to other HPV types.[10] Low grade squamous epithelial lesions generally represent infection with any of the 40 or so HPV types. Types 6, 11, 16, and 18 are detected in about 30% of LSILs.[13] This is in contrast to genital warts which are overwhelmingly (90–95%) attributable to infection with HPV types 6 and 11.[14] Multiple infections with HPV (ie. more than one type) are more common than single infections in young women. This means that, even if types 6, 11, 16, and 18 are prevented, other types not covered by the vaccines may still cause abnormalities.[15,16]

HPV vaccination is less effective when sexually active women are vaccinated

Efficacy of the vaccine against specific HPV types is dependent upon the recipient not having existing infection with that HPV type. Acquisition of genital HPV in the first few years after commencing sexual activity is remarkably high – probably at least 60%.[17–20] In trial populations, high vaccine efficacy rates (98–100%) were seen because the vaccinated population was naïve to the relevant HPV vaccine type. When the entire population (including sexually active women previously exposed to HPV) was considered, the reduction in high grade Pap test abnormalities due to any HPV vaccine type among vaccinated women was only 18% (with a lower confidence interval of 7%) at a mean of 3 years postvaccination.[9]

In Australia, around 50% of young people are sexually active by the age of 16 years.[21] It is likely that the majority of young women aged less than 27 years who took the opportunity to have the free HPV vaccine (commencing before 30 June 2009) were already sexually active and had thus been exposed to one or more HPV types.

Long term impact of vaccination

State run Pap test registers and the National HPV Vaccination Program Register (see *Resources*) will carefully monitor the population level impact of the vaccination program to determine the vaccine's effectiveness at preventing cervical disease. As time goes on, more women will receive the HPV vaccine before the onset of sexual activity. This will result in a fall in positive predictive value of the Pap test and will necessitate modifications to the

National Cervical Screening Program. These modifications will be considered through evidence based reviews, modelling, and cost effectiveness analyses. Modifications might include a change in the age of commencement of screening, a change to the screening interval, or the addition of primary triage with HPV DNA tests.

Conclusion

It is unlikely that individual practitioners will notice any difference in Pap test abnormalities in their female patients over the next few years. This should not be seen as a cause of concern as most Pap test abnormalities are low grade lesions that represent transient HPV infection and need no treatment. High grade abnormalities should continue to be managed according to current National Health and Medical Research Council guidelines. However, a clear message must be given to women that the vaccine is not a substitute for Pap tests and it is not the cause of any smear detected abnormalities that may be found after it has been given.

Modifications to the National Cervical Screening Program will be necessary in the long term. Meanwhile, HPV vaccination represents a remarkable new tool in the fight against cervical disease and other anogenital cancers. To succeed in this fight we need to understand the impact over time of both screening and vaccination and how the two strategies can complement one another. In this way we can get the best benefit from both strategies.

Summary of important points

- Both low and high grade lesions on Pap tests are most commonly seen in women aged 20–24 years.
- Most Pap test abnormalities are caused by HPV types not preventable with current vaccines. Multiple infections with HPV (ie. more than one type) are more common than single infections in young women.
- Pap test abnormalities in vaccinated women are likely to be caused by one of the nonvaccine HPV types or an infection acquired before vaccination.
- HPV vaccination does not cause Pap test abnormalities that might be detected after it has been given.
- Pap test abnormalities will still occur in vaccinated women and are not a cause for alarm.
- HPV vaccination is not a substitute for Pap tests.

Resources

- The National HPV Vaccination Program Register: www.hpvregister.org.au/
- Details of state run Pap test registers are available at: www.cancerscreening.gov.au/internet/screening/publishing.nsf/Content/register.

Conflict of interest: Julia Brotherton has been a chief investigator on a study of HPV sero prevalence in Australia, which received funding for the laboratory component from CSL. She is also an investigator on a HPV prevalence study partially funded by equal and unrestricted grants from CSL and GlaxoSmithKline.

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