Human papillomavirus – enigmas and persistent questions

Since the 1970s the association between cancer and the human papillomavirus (HPV) has been known. Zur Hausen's belatedly awarded Nobel prize bears testament to this. We know that HPV is associated with cervical cancer, vulval cancer, anal cancer, vulvovaginal warts, and other non-gynaecological cancers. The place of HPV in the modern management of gynaecology may at first seem clear. Vaccination with the bivalent vaccine against HPV 16 and 18 (Cervarix, GlaxoSmithKline (GSK)) may prevent cervical, vulval and some anal cancers; vaccination with the quadrivalent vaccine (Gardasil, Merck) may prevent those conditions plus warts. The 9-valent vaccine (Gardasil 9, Merck) is currently recommended, as are the other two, by the American College of Obstetricians and Gynecologists (ACOG).[1] The UK initiated vaccination with the bivalent vaccine and now recommends the quadrivalent vaccine.[2] So far studies have demonstrated a significant decrease in dysplasia and warts, particularly in HPV-naive subjects. Whether these benefits translate to the prevention of cervical and other cancers has not yet been shown, but if one considers the natural history of the progression of dysplasia to cancer, this is quite reasonably presumed.

Some have asked why young girls only are to be vaccinated, and not boys. Both sexes are involved in the process of transmitting the viruses. Australian, Austrian, Canadian, Danish, US and lately Swiss national health authorities have recommended vaccination of boys.

A persistent question is the suitability of vaccination in subjects who have previously been exposed to HPV. Efficacy is significantly reduced. Some continue to recommend vaccination; others feel that the benefit in this group is too limited.

Anxiety has been expressed about possible sequelae to vaccination, particularly neurological sequelae. Japan has withdrawn from vaccination programmes. Some have described this as irresponsible, a reaction influenced by previous vaccination controversies in that country. A former Merck employee has travelled the world lecturing on the inadequately discussed serious adverse effects that are reported. This may or may not be similar to an early anxiety regarding the Salk polio vaccine, which induced cancer in primates. The caution was ignored. Polio vaccination has remained, and has prevented millions of polio cases.

Not all populations are similarly affected by the HPV family of viruses, of which there are over a hundred subtypes. So far, much of the effort in vaccination has concentrated on HPV 16 and 18. Many other HPV family members are known to be implicated in cervical cancer. The bivalent and quadrivalent vaccine manufacturers claim cross-reactivity and benefit in suppressing other subtypes that are found in cervical cancers; the 9-valent vaccine (Gardasil 9, ACOG recommended) is now available. Multiple HPV subtypes, beyond the more obvious HPV 16 and 18, have been found in cervical cancer biopsies, particularly in Africa.[3] Would current bivalent and quadrivalent vaccines be as effective in these populations as in Europe, North America, and Australia? The data are limited. Will this particular situation be adequately treated by the 9-valent vaccine? Newer vaccines with directed wider reactivity among HPV subtypes are being developed.

The ACOG has previously recommended either the bivalent or quadrivalent vaccine for individuals with HIV. More recently (January 2016) the 9-valent has also been recommended.[1] HIV-affected individuals are highly likely to be HPV carriers before vaccination. The benefits of vaccination, as explained above, are more limited in the previously affected. However, there is a second even more contentious issue, i.e. that HIV-affected individuals may also be seriously affected by massive proliferation of vulvovaginal warts, which are covered by the quadrivalent (and now the 9-valent) but definitely not the bivalent vaccine. The ACOG recommends both bivalent and quadrivalent vaccines to HIV-positive subjects, with equal merit.[1] This recommendation is bizarre. It ignores the heavy burden of massive vulvovaginal warts in HIV-positive individuals, and seems to be more concerned with promoting free trade than medical sense or safe practice.

There may be a particularly strong case for vaccination in the developing world, where poverty and lack of infrastructure development inhibit cancer prevention by routine screening. Yet, firstly, the uncertainty of vaccine efficacy in some regions differently affected by multiple HPV subtypes remains; and secondly, many countries in the developing world might be better advised to conserve scarce allocated resources to better develop the basic medical infrastructure which they lack. Cancer is, however, costly and true cost calculations are not straightforward; preventing cancer might represent a significant cost saving, as well as avoiding the enormous cost in suffering.

HPV screening as an adjunct to cervical cytology to detect premalignant disease and to identify the at-risk individual is also not without controversy. Cervical cytology, developed by the Greek immigrant pathologist Papanicolaou in the 1940s, has a quoted sensitivity of 60 - 85%. It is relatively costly, manpower-intensive without computerisation, and dependent on the skill of the observer. Screening individuals for high-risk HPV subtypes is obviously attractive.

HPV is highly prevalent and thought to be transitory in the under-30 age group; therefore this group is not recommended for testing (except HIV-positive patients). For the over-30s, current protocols (HPV screening is recommended by the ACOG[1] and the British College[4] (Royal College of Obstetricians and Gynaecologists (RCOG)) still require use of conventional cytology for 'co-testing' protocols, but not for the ACOG newly recommended protocol and RCOG-considered HPV testing alone; colposcopy would still be required.

Does the addition of HPV testing streamline the process? Some studies have shown increased and not decreased rates of colposcopy rendering HPV screening more and not less labour intensive. In other studies there is a clear advantage, enabling the extension of the screening interval to 5 years in those negative for 'high-risk' HPVs and permitting less concern for atypical squamous cells of uncertain significance in HPV-negative persons with an extended screening interval of 3 years. The addition of 'biomarkers', e.g. p16 and Ki67, into testin, may increase specificity and decrease the number of test positives.[4]

Population screening for HPV in the over-30s is also not without significant further questions. It is predicated on prevalence rates in the target population of ~10%[5] or a little more. Yet, in the developing world, and perhaps in some populations in the developed world, high-risk HPV carriage in the over-30s may

exceed 50%.[6] The mathematical models of cost and efficiency become meaningless and completely erroneous as background HPV rates increase. Current American guidelines[1] recommend colposcopy in Pap smear-negative HPV 16- and 18-positive individuals. This is completely unfeasible in the situation mentioned above. Furthermore, should the attribution of high-risk to HPV 16 and 18 in North America be extended to other cervical cancer-associated HPV types elsewhere, the rate of colposcopy would increase.

HPV testing benefits primarily the HPV-negative individual, extending a cost benefit to medical systems by a decrease in testing frequency. An actual *benefit* for high-risk HPV positives may not appear – the majority of recently occurring cervical cancers represent inadequate screening rather than cytology screening failures.

A further question is the immense potential for psychological damage in HPV positives. A high-risk HPV-positive individual may at first be reassured by healthcare professionals, but access to the internet may reveal that testing is recommended in the over-30s because infection is more likely to be permanent and damaging. Further reading will show that the HPV viruses in question are 'highly oncogenic' – this clearly means *highly likely to cause cancer*. Once tested positive, there may be no turning back. This may affect quality of life and may nullify the effect of normal annual Pap smears, and may greatly damage that most fragile of phenomena – sexual health. There may be requests for more radical procedures (i.e. hysterectomy), more commonly associated with the response to BRCA1 and 2; to the lay person the two situations might be comparable.

Much about the cellular mechanisms of HPV remains unknown. How do the seemingly catastrophic effects of the E6 and E7 proteins in nullifying p53 and retinoblastoma protein, the genome guardians, not lead to carcinogenesis in all those affected? Other harmful mechanisms involving E2 and E5 and a variety of other molecular/genetic effects damaging to the genome are less well publicised but present. The answer is that 'redundant' unused pathways seem to exist to provide protection. These remain unidentified.

Much is written about HPV, and much benefit may come from vaccination and testing. However, the actual numbers and ramifications are important and may be overlooked. We know that for many there is more at stake than pure science: GSK, the bivalent vaccine manufacturer, clearly has work to do to compete in the market with the quadrivalent (and now the 9-valent) vaccine of Merck. GSK published a brochure[7] containing a comparison of efficacy of its own vaccine by perfect use – 'per protocol' use – with Merck's data on clouded population-based analysis, 'intention to treat'. The latter always produces worse results. This was an unfair, scientifically illegitimate comparison. At the same international meeting, GSK's advertising poster for the bivalent Cervarix[8] depicted the graph showing the higher antibody titres achieved with its bivalent vaccine compared with the levels achieved with Merck's quadrivalent vaccine. There is no simple relationship, however, between antibody titres and biological effect, which is as well known for HPV as it is for hepatitis and other vaccinations. This was not a scientifically valid comparison.

It is important to realise, therefore, that there is a need to inspect the data carefully. We need look no further than hormone replacement therapy, or more recently statins, to see that cost and benefit may not be uniform in different groups; calculations in some situations may not be applicable in others. So much rests in the numbers, and a careful consideration of the consequences.

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Editor

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