HPV Today

Newsletter on Human Papillomavirus

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EVALUATION OF A PROPHYLACTIC HPV VACCINE SHOWS GREAT PROTECTION AGAINST HPV INFECTIONS

INTERVIEW WITH LAURA KOUTSKY

With the discovery that human papillomaviruses (HPVs) are central to the development of cervical cancer, scientists began working on vaccines to prevent HPV infections. One strategy for HPV vaccine development involves using certain viruses or species of yeast as miniature factories. Such microscopic factories have been engineered to produce large quantities of the protein shell from papillomaviruses. These empty shells are called virus-like particles (VLPs), and cannot cause infection; however, they are highly immunogenic. Furthermore, studies on cows, rabbits, dogs, and now humans have shown that VLP-based vaccines prevent papillomavirus infections in their human or animal hosts.

What was the purpose of the vaccine trial published in December 2002 (Koutsky et al.[1]**)?**

The primary goal of the trial was to determine whether an HPV-16 VLP vaccine would effectively prevent persistent HPV-16 infection, including HPV-16-related cervical intraepithelial neoplasia (CIN), which is the precursor lesion for cervical cancer.

How was it designed and where was it conducted?

The study was designed as a randomized controlled trial with 50% of study participants assigned to receive three injections of HPV-16 VLP vaccine (manufactured by Merck Research Laboratories, Bluebell, PA, USA) and 50% assigned to receive three doses of a placebo injection. The vaccine and placebo injections were visually indistinguishable and none of the researchers or study participants knew who received vaccine or placebo.

Study participants included 2,392 young women (16 to 23 years of age) who were enrolled from 16 clinical centers in the United States. At the enrollment visit, women underwent an examination including collection of cervical samples for Pap testing and multiple genital

(*continues on page 3*)

Nº 03 September 2003

EDITORIAL

CERVICAL CANCER PREVENTION USING HPV TECHNOLOGY. ADVANCING ON ALL FRONTS

The first "proof of principle" vaccination trial with an HPV-16 VLP product has shown protection of all vaccinated women from the persistent presence of HPV-16 DNA for a median time of 17 months. Dr Laura Koutsky (see cover page) explains that additional trials are underway in several parts of the world with a new HPV-16, -18, -6 and -11 VLP vaccine. Some of these trials include long-term observations destined to evaluate the reduction of high grade intraepitelial lesion (HGSIL) among vaccinated women and to confirm the absence of side effects.

Early in 2003 the Food and Drug Administration (FDA) issued an expert evaluation recognizing the HPV test Hybrid Capture 2 (HC2) as a valid instrument for primary screening. This resolution specifically focused on women over 30 years of age in combination with cytology (see also news section). It has taken over two decades to move from the hypothesis of an association of HPV with cervical cancer to the recognition that HPV screening has a net gain to offer to cytology. The bulk of evidence is nowadays beyond reasonable doubt. Medical societies are now considering this landmark resolution and adapting their clinical protocols to what may well evolve into a new standard for screening.
The American Cancer Society (ACS), for example, issued guidelines late in 2002 that underscored the negative predictive value (NPV) of a screening event that reports negative for HPV DNA and normal for cytology. Women in such a class have an extremely low probability of having, or developing, a high-grade lesion in the years to come. The combined NPV at 2 to 3 years has been estimated in most instances to be greater than 97% and close to 100% if the tests are performed under expert conditions. For women over 30, the report clearly specified that the combined tests should not be performed more often than every 3 years to avoid redundant screening and lowering of the cost-benefit ratios. Other review parties such as the US Preventive Services Task Force have issued more conservative conclusions until the completion of ongoing trials.

The choice of technology and its intimate links with the length of the intervals between each screen and associated costs are thus becoming a topic of relevance. It faces substantial vested interests and demands renewed professional training efforts. It may be necessary to re-discuss the intrinsic value and the contents of the regular visit to the gynecologist/general practitioner for preventive oncology. This "revisited annual visit" could perhaps expand their protocols to the current cancer priorities among women in most developed countries (i.e. lung, breast and colorectal cancers) and, at the same time, should support the gentle adoption of the current progress in screening technology.
It is a great time to talk about it.

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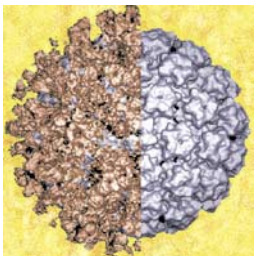
(from page 1) samples for HPV-16 DNA testing. Follow-up visits with specimen collection for Pap and HPV-16 DNA testing were scheduled 1 month following the third vaccination (month 7), 6 months following the third vaccination (month 12), and every 6 months thereafter until month 48. Serum samples for HPV-16 antibody titers were obtained at enrollment and follow-up visits. During follow-up, women with Pap test findings suggestive of CIN were referred for colposcopy and biopsy. Cervical biopsy specimens were reviewed by an independent, masked panel of four pathologists without knowledge of other clinical or laboratory data.

The published report of the study (Koutsky et al.[1]) is based on an interim analysis that was specified before the study began. Although the study will continue until all subjects complete four years of follow-up, the primary pre-specified analysis was conducted as soon as at least 31 cases of persistent HPV-16 infection were known to have occurred (August 31, 2001).

The 1,533 subjects (768 vaccine recipients and 765 placebo recipients) included in the pre-specified primary analysis included all subjects who received the full regimen of study vaccine or placebo and who were HPV-16 seronegative and HPV-16 DNA negative at enrollment and HPV-16 DNA negative at month 7 and on any cervical biopsies performed between enrollment and month 7.



What are the key results?

We found that a three-dose regimen of HPV-16 VLP vaccine reduced the incidence of persistent HPV-16 infection and of HPV-16-related CIN. All 41 cases of persistent HPV-16 infection, including nine cases of HPV-16-related CIN, occurred among placebo recipients. The vaccine was estimated to be at least 90% effective in preventing persistent HPV-16 infection and HPV-16-related CIN. Data from this study and previous studies also demonstrate that this vaccine is highly immunogenic, and generally well tolerated. These findings provide evidence of a highly efficacious and generally safe prophylactic HPV vaccine.

At what stage is the research on HPV vaccines? What should be done next?

The next stage of the research is to conduct a phase-III trial, which is a large randomized trial designed to demonstrate that a vaccine not only prevents infections but also prevents a clinically important disease such as high grade CIN, the lesion that is most strongly linked with cervical cancer. Regulatory agencies, such as the Food and Drug Administration (FDA) in the US, use results from phase-III trials to make decisions about vaccine licensing. Additionally, it is important to determine whether these HPV VLP vaccines effectively prevent infection in young men and how long protection lasts in both male and female vaccine recipients.

Which vaccine products will be tested in Phase III?

Merck Research Laboratories is currently conducting phase-III trials of an HPV vaccine that contains VLPS from four HPV types. Because this vaccine has the potential to prevent infection and disease from four HPV types, it is referred to as a tetravalent or quadrivalent HPV vaccine. Included in this tetravalent vaccine are VLPs from HPV-16 and -18, the two HPV types that are linked with 60-70% of invasive cervical cancers worldwide, and VLPs from HPV-6 and -11, the two HPV types that are linked with at least 90% of genital warts.

If tetravalent vaccines are effective, there is reason to believe that the valency of HPV vaccines could be increased to include VLPs from other cancer-associated HPV types including HPV-45, -31, -33, -35, -52, and -58.

What are the perspectives of your results for cervical cancer prevention?

Our results suggest the possibility of preventing cervical cancer and cervical cancer deaths through vaccination. Furthermore, since anal, vaginal, vulvar, penile and a small proportion of head and neck cancers are linked with these same HPV types, vaccination should eventually reduce the morbidity and mortality caused by these cancers as well. A shorter-term goal for countries with effective Pap screening programs will be to reduce the number of women with abnormal Pap smears and CIN, the number of men and women with genital warts, and the number of young children with juvenile-onset recurrent respiratory papillomatosis.

When do you think the vaccine will be marketed?

The vaccine could be marketed within 5 to 7 years.

How would an HPV vaccine against HPV-16 and -18 combine with screening strategies?

Even after achieving widespread population coverage with a prophylactic vaccine that prevents HPV-16 and -18 infections, Pap screening will continue for many decades. Thousands of women will remain at risk from cervical cancer either because they were infected with HPV-16 or -18 before the vaccine was available or because they are infected with a cancer-associated HPV type that is not prevented by the vaccine. Although Pap screening will continue, a smaller percentage of women will develop abnormal Pap smears and a smaller percentage will require colposcopies, biopsies and treatments for intraepithelial lesions and cancers. Ideally, a screening test that is more accurate than the Pap smear will be developed and, over a lifetime, a woman will require fewer screening tests.

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HPV IN SCREENING AND TRIAGE

REALIZING THE

Traditional cervical cancer screening by means of dry slide cytology is hampered in practice both by modest sensitivity, thereby requiring frequent testing, and, perhaps more importantly, by low positive predictive value (PPV) for CIN 2/3 and cancer (CIN 2/3+). While the sensitivity issue has been well documented, (Nanda et al.[1], Fahey et al.[2]) the limitation of low PPV, particularly in older women, has received less attention and deserves emphasis because the consequences are important for both the patient and the screening system. Sawaya et al.[3] have recently published their experience with the entry cervical cytology in the Heart and Estrogen/Progestin Replacement Therapy (HERS) study, an evaluation of hormonal replacement therapy. They described smears from 2,561 participants which included 110 positives (1–2 years after a negative smear), 231 interventions to evaluate the positives, and one CIN 1-2 diagnosed (Sawaya et al.[3]). When this pattern is multiplied by a population of millions of women, the majority of whom undergo cytological screening annually, the magnitude of the unnecessary expenditure of patient and health-care system resources can be readily appreciated.

HPV testing provides the first effective tool for risk assessment in women with minimally abnormal smears, and women with normal smears at ages 30 and over. This presents an opportunity to focus the most intensive evaluation and the most frequent screening on that small minority of women who are actually at risk of cervical cancer. Effective use of this tool in clinical practice requires that the testing works as well in the clinic as it does in the research setting. It also requires a massive and sustained educational effort so that we, as a society, can come to grips with the idea of an untreatable commensal sexually transmitted disease. In addition, the information systems by which screening registries, patients, laboratories and providers communicate must all then be modified to accommodate and reflect this new understanding.

The Kaiser experience has shown the importance that all members of the screening team are aware of the changes introduced in the protocols that offer combined cytology and HPV testing. As part of the communication effort, the staff needs to understand the benefits and help the participants to adapt to a novel scheme of cervical cancer prevention. In the picture the screening team at Point West.
Courtesy of Dr W Kinney

Our experience with the institution of HPV testing for atypical squamous cells of undetermined significance (ASCUS) triage is in some ways encouraging. In the mid-1990's Manos et al.[4] demonstrated the efficacy of the 11-type prototype of Hybrid Capture 2 for ASCUS triage in our population. Application of testing in routine clinical practice started at some facilities in 1999 and was institutionalized as a policy recommendation in January 2001. Unpublished evaluation of the histology of those patients with atypical squamous cells (ASC) and atypical glandular cells (AGC) smears, HPV testing and biopsy in the year 2001 indicates that 97% of the CIN 2/3 and 100% of the adenocarcinoma in situ (AIS) and squamous and glandular invasive cancers were HPV positive. Because in clinical practice not all women were biopsied regardless of HPV result, the sensitivity and specificity cannot be calculated, but the recognition that test performance in the hands of clinicians appears to be comparable to that in the research setting is profoundly reassuring.

Our very early experience with general population screening with cytology plus HPV testing in women of 30 years of age and over indicates that, this new approach holds the potential for much greater benefit than the use of HPV triage of ASC smears, although the barriers to its adoption are commensurately more daunting.

At present the majority of our patients with multiple consecutive negative smears choose to be rescreened at an annual interval despite the recommendation for biennial screening following 2 negative smears that was made to our patients and providers in December of 1996. In addition, Miller et al.[5] recently demonstrated that in our population, the risk of cancer doubles with extension of screening intervals from one to 2–3 years. Three-quarters of our Pap smears and 95% of our cancers are in women 30 years of age and older. These observations, plus the poor PPV of conventional cytology for CIN 2/3+, prompted us to consider taking on the challenges of implementing a system whereby 1) patients who are cytology positive receive colposcopy, 2) patients who are cytology-negative, HPV-positive are-screened with both tests in 12 months, and 3) women who are cytologically and HPV negative are rescreened in 3 years. Essential components of this task affect every group involved in cervical cancer screening.

BENEFIT OF HPV TESTING IN CLINICAL PRACTICE: THE KAISER NORTHERN CALIFORNIA EXPERIENCE

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- **Patients** must have adequate educational materials so that they can understand the benefits to them associated with this medical advance. We have written a brief summary sheet that the Medical Assistant provides to the patient when she is escorted to the exam room. The most important component of the information provided is the repeated assurance that the patient may see her provider whenever she needs to do so regardless of whether or not she chooses to participate in Pap plus HPV screening. We have observed that if this information is properly presented the patients are uniformly pleased to be able to receive this advance in medical care which provides them the protection of annual screening with fewer visits and biopsies.

> Providers need to have confidence in the underlying science and adequate materials for patient education, to reassure the patient who equates a positive HPV test with a positive test for gonorrhea or syphilis

- **Providers** (physicians and nurse practitioners) must receive sufficient education that they are absolutely sure that their participation does not interfere with other patient-care goals in any way. Specifically, they too need to understand that they can see their patients as frequently as they feel is needed and that the medical and economic rationale of Pap plus HPV screening is in no way compromised. They need to have confidence in the underlying science and adequate materials for patient education, including materials with sufficient depth of information to reassure the patient who equates a positive HPV test with a positive test for gonorrhea or syphilis.
- **Support staff** are every bit as important as the care providers in making this new system work, and they require education at least comparable to that of the providers to understand and participate effectively in the patient's care. There are literally thousands of clinic registration personnel, Medical Assistants and Call-center employees for whom there is no standardized method of, or occasion for, continuing medical education. Yet the introduction of this testing cannot function without the understanding and approval of these personnel, who provide patient information, answer questions and schedule appointments. The need for educational opportunities and materials specifically for these essential members of the care system has been one of the more important realizations.
- **Information technology (IT) systems and administrators** are central to communication between the providers, the laboratory and the patients. We have identified four areas where revision of IT practice is essential:

-First, a variety of manual systems are in place at different facilities to track Pap results. These are in the progress of being supplanted by a centralized automated system that tracks both Pap and HPV results and provides assurance that providers are aware of abnormal results and that patients with abnormal results receive appropriate evaluation.

-Second, communication of negative Pap results to patients in the past has consisted of a postcard sent directly from the lab. We have written letters that inform patients who elect to participate in combined testing of different results and the appropriate response.

-Thirdly, the computerized "Preventive Health Prompting System" which prints out a list of preventive healthcare goals for each patient at the time of registration for each visit must be revised to understand and respond appropriately to previous cytology and HPV results.

-Finally, the scripts that the Teleservice Representatives at the Call Centers use to discern which patients are overdue for screening and to make appointments need to be revised and implemented.

Each of these activities requires the approval of one or more committees, and a separate budget.

The task before us seems Herculean: We must successfully communicate the benefit of better screening practices to the policy makers, healthcare providers, and society at large. If we are successful, then unnecessary visits and procedures will be decreased, access to healthcare providers will improve, and if we are able to recruit the underscreened, cancer incidence will decrease. It is up to us. The tools are in our hands.

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EUROGIN 2003

International Charter: www.eurogin.com/2003

J. Monsonego
Chairman of the Scientific Programme

The 5th international EUROGIN Conference was held in Paris from April 13–16 2003 and focused on the latest research and recent developments in the prevention, control and treatment of human papillomavirus infection and neoplasia throughout the world. More than 1,200 delegates from 70 countries gathered to share and increase their knowledge and skills in disease prevention. One of the highlights of the conference was the Conclusions session, during which a panel of experts presented their recommendations on cervical cancer control, priorities and new directions in both high- and low-resource settings. As well as the presentations at the conference, each team of experts contributed a paper for an International Charter which provides the rationale, current evidence, clinical practice and recommendations for the core areas of epidemiology, HPV testing, cytopathology, colposcopy/management, screening techniques in developed and developing countries, and prophylactic and therapeutic vaccines.

Progress in cytology testing techniques, the role of HPV testing in cervical cancer screening protocols, technology platforms, and vaccines for primary prevention were cited as promising breakthroughs. These advances have opened up new areas of research, including the evaluation of biomarkers to further stratify HPV-positive women at risk of progression to CIN 3 and cervical cancer, the investigation of associated factors that may increase the risk of developing cervical cancer or precursor lesions, and the role of the HPV DNA male carrier in the epidemiological chain of HPV and cervical cancer. Improvements in sensitivity and specificity with combined cytology and HPV testing raise the issue of whether screening intervals can be lengthened to compensate for the higher cost of this strategy.

The major challenges that still need to be faced were also identified. There is still a huge gap in the availability of prevention and education programmes, screening techniques and treatment options between high- and low-resource settings. Access to appropriate, cost-effective prevention, screening and treatment options is still required for a large number of women, and this problem needs to be addressed through international collaborative efforts to truly win the fight against cervical cancer. With vaccine approval likely in the near future, issues of acceptance, distribution, funding and administration require urgent attention.

The overriding message that comes through loud and clear is the ongoing need for information, training, communication and coordination of resources to ensure that best-practice solutions to prevent, control and treat cervical cancer are implemented throughout the world.

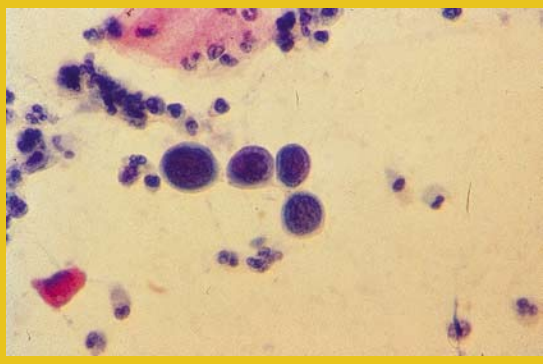

Figure 1:
This figure shows 4 cells with the features of squamous carcinoma in situ (type 3 graham cells). A very altered nucleus cytoplasmic ratio is seen with typical neoplastic nuclei.

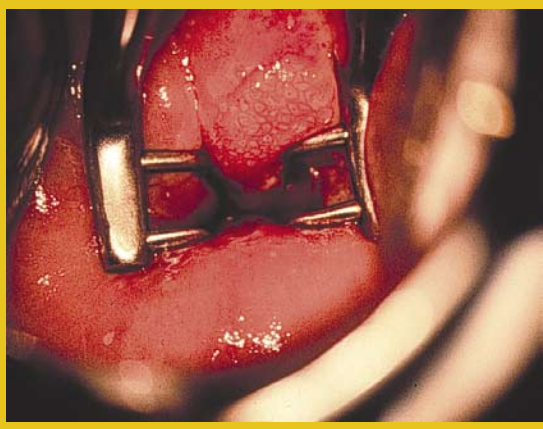

Figure 2:
Colposcopy of the lesion shows a mosaic clearly visible between 12 and 2 o'clock that, with the use of Kogan's endocervical speculum, is seen advancing into the canal. The histologic diagnosis of this sample was CIN 3/*carcinoma in situ.*

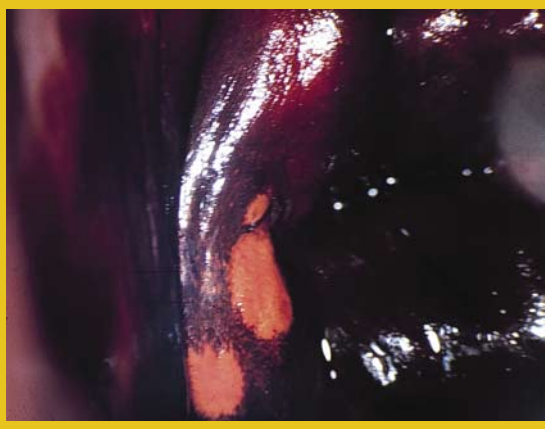

Figure 3:
Colposcopy of the vagina after application of Schiller's solution shows 2 larger areas and one small 1 on the lateral wall of the vagina close to the fornix which on histologic diagnosis was reported as vaginal intraepithelial neoplasia grade 2.

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CASE STUDY

FIELD HPV INFECTIONS, A CLINICAL DILEMMA

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A 53 year old patient, Gravida 5 Para 4 Spontaneous Abortion 1 with 2 living children, was referred to us in March 1994 with a Pap smear diagnosed as squamous carcinoma cells present.

At her first visit to our Colposcopy Clinic the patient was entered into a study where all cervical and vaginal microbiology was performed. Pap smear was repeated and showed cells suggestive of squamous carcinoma in situ/high grade intraepithelial lesion (Figure 1). Colposcopic examination was performed and after application of acetic acid a mosaic was found that had some extension into the endocervical canal (Figure 2). The biopsy and endocervical curettage (ECC) done at this visit were both positive for high-grade intraepithelial lesion (CIN 3/carcinoma in situ). Microbiology of the cervix was negative for Neisseria Gonorrhoeae, Chlamydia Trachomatis, Herpes Virus, and Cytomegalovirus. Vaginal flora examination revealed 3+ presence of Gardnerella Vaginalis, Bacteroides species 3+. Peptostreptococci were also present as were diphtheroids. Human Papillomavirus (HPV) DNA was tested using the Polymerase Chain Reaction (PCR) technique and was reported as positive for HPV type 16. Bacterial vaginosis was treated with Metronidazole. The patient was booked for a cone biopsy that was done the following month. The cone biopsy confirmed the presence of cervical intraepithelial neoplasia grade 3 (CIN 3), with glandular extension and (query) involvement of the margins.

A year after this cone biopsy the Pap smear was again abnormal showing high grade intraepithelial lesion. An endocervical curettage performed at this same visit was negative for dysplastic cells. A hanging drop revealed the presence of Trichomoniasis and the patient and her partner were treated with Metronidazole.

2 years after the cone biopsy there was still a positive Pap smear for high grade dysplasia. A small area was present in the cervix and biopsy was reported as CIN 2 (high-grade intraepithelial lesion). The patient was very reluctant to have definitive treatment in the form of hysterectomy.

Pap smear taken in April 1996 again showed carcinoma in situ cells. The patient finally agreed with the hysterectomy that was performed in May 1996. Squamous cells, carcinoma in situ, glandular involvement in the endocervical canal was found on pathology. The margins of the lesion were free of disease. On her follow-up after the hysterectomy a year later the patient again had Trichomoniasis that was treated. She was now on estrogen replacement therapy.

Over a year after the hysterectomy a small lesion was present in the vaginal fornix and the histologic diagnosis was of a vaginal intraepithelial neoplasia grade 1 (VAIN 1). This was treated with 5-Fluorouracil 5% cream and the patient remained free of disease for the following 2 years.

In August 1999 the Pap smear was again suggestive of high-grade intraepithelial lesion and colposcopic examination of the vagina revealed several areas of abnormality that were diagnosed as a VAIN 2 (Figure 3). This lesion was treated with laser vaporization on January 2000.

10 months later (October 2000) a Pap smear of the vaginal vault was again reported as high-grade dysplasia. Lesions were now present on the vaginal walls but in different areas than the ones previously treated. These were now multiple and another course of 5-Fluorouracil 5% cream was prescribed.

In July 2002 no lesions were seen in the vagina but the Pap smear was reported as atypical squamous cells present, high-grade dysplasia cannot be excluded.

In January 2003 examination was repeated revealing VAIN 1 on biopsy of some white areas. At this time the Pap smear was negative.

COMMENTS

This case shows some interesting clinical dilemmas. The first one is that this patient had, without any doubt, carcinoma in situ of the cervix that was mostly present in the exocervix but also re-occurred in the endocervical canal. Hysterectomy performed confirmed that diagnosis, but the hysterectomy was not, of course, the end of her problems. HPV-16 was present on her initial visit and again in a visit after the hysterectomy when VAIN 2 was diagnosed histologically in the vaginal vault. The carefully performed colposcopy of the vagina revealed the lesions to be re-occurring in different sites and this would be a good example of a multi-focal disease in the lower genital tract, due to the presence of an oncogenic HPV type (in this case 16). It may also be of interest that this patient has had initially bacterial vaginosis and on at least two occasions Trichomoniasis present.

We have demonstrated that the vaginal flora is quite different in patients with cervical intraepithelial neoplasia than in controls and that this altered vaginal flora, in particular anaerobic flora, may be a co-factor for HPV in the development of cervical or vaginal neoplasia.

HPV: THE ULTIMATE CANCER INITIATOR?

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The cumulative rate of HPV infection in a sexually active population by at least one of the 50+ anogenital HPV types probably approaches 100%. Contrasting the high rate of HPV exposure to the relatively low incidence of invasive cervical cancer (<1%) it is clear that while HPV may be a necessary cause of cervical cancer, it alone is not sufficient. What causes those few HPV infections to persist and progress to high-grade neoplasia and invasion?

To answer this question, consider what is known about the cellular pathogenesis of an HPV infection. HPVs are small viruses, encoding only 8–9 genes, and therefore are absolutely dependent on host-cell proteins to complete a productive life cycle. Most of these genes are non-structural (early) proteins involved in the regulation of viral replication and gene expression and host-cell interactions, but two early proteins, E6 and E7, are considered bona fide viral oncogenes, exerting pleiotropic effects on the cells in which they are expressed. The complete array of host protein interactions of E6 and E7 are too numerous and detailed for a brief review. However, in the context of effecting carcinogenesis, two classic interactions are notable.

The first of these interactions is the direct physical binding and sequestration of the retinoblastoma protein (pRB) by E7. Many cancers have been shown to have functionally inactivated pRB as a result of mutation, and pRB is a well-characterized tumor-suppressor protein which plays a crucial role in regulating progression of the cell cycle from G1 to S phase. Specifically, in its hypo-phosphorylated state, pRB is bound to the E2F transcription factor. Given exogenous signals for the cell to divide, pRB is phosphorylated and E2F is released to the nucleus, where it upregulates the transcription of the cyclins that allow for transition from G1 to S phase. Binding of pRB by HPV E7 results in release of E2F and therefore unregulated progression through the cell cycle.

Most cancer types have been associated with mutation or other forms of inactivation of another important tumor-suppressor protein, p53. p53 is activated in response to cellular stress and DNA damage, and serves to pause cell-cycle progression at the G2/M checkpoint. This suspension of the cell cycle allows time for DNA repair in the event of minimal damage to the genome, or signals a pro-apoptotic trigger if the genomic damage is extensive. The HPV E6 oncoprotein from high-risk types inactivates p53 by forming a stable bond with p53, and, with E6-AP (E6 associated protein), targets p53 for ubiquitin-dependent degradation. E6 has also been shown to activate telomerase, which must be expressed to allow cells to pass the "crisis" point after which they would normally stop dividing and become senescent.

Together, E6 and E7 expression from high-risk genotypes is sufficient to induce immortalization of human keratinocytes in cell culture, and can cooperate with cellular oncogenes to induce malignant transformation. In a multi-step model of carcinogenesis, E6 and E7 are efficient carcinogens whose expression results in a double-hit in the progression to carcinoma by inactivating RB and p53. Despite convincing *in vitro* evidence of the carcinogenic effect of E6/E7 (expressed in all HPV infections), few infections will develop into tumors.

This apparent paradox is likely explained by a change in the *regulation* of HPV gene expression, which is inextricably linked to the differentiation program of the keratinocyte. In a productive HPV infection, E6 and E7 are expressed at very low levels in the dividing cells of the basal epithelium. Oncogene expression is upregulated in the differentiating suprabasal cells, where it allows these non-dividing cells to activate the host replication machinery, facilitating high-copy viral DNA replication. Upon further differentiation, cells occupying the upper strata of the epithelium again downregulate E6/E7 expression. In contrast, high-grade squamous intraepithelial lesions (HSILs) and cancers are found to express high levels of E6 and E7 in actively dividing

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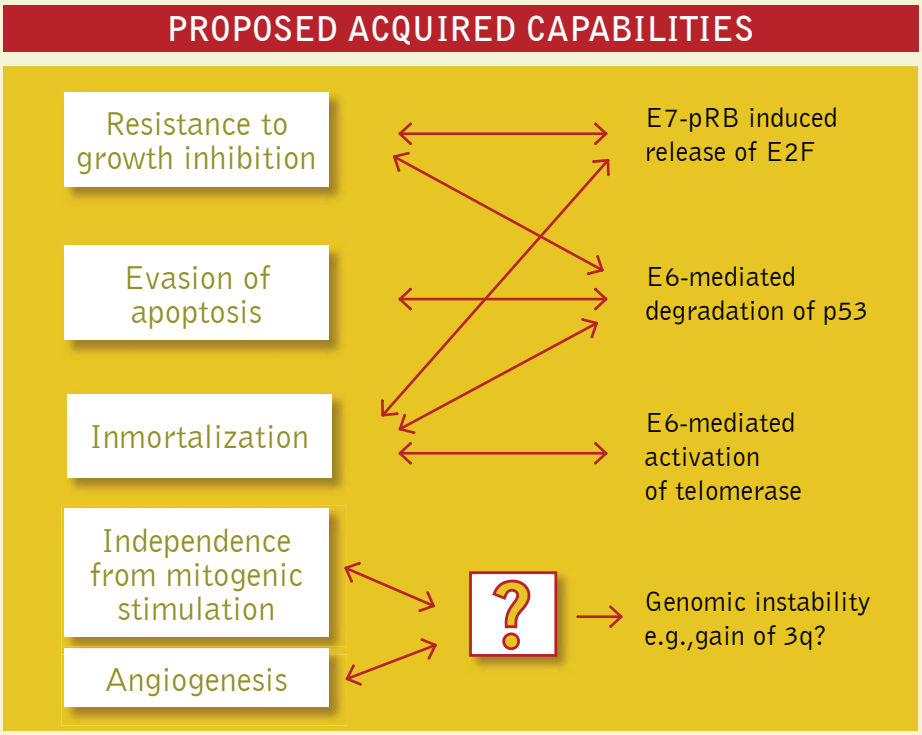
Further reading

•Stanley MA. Human papillomavirus and cervical carcinogenesis. Best Pract Res Clin Obstet Gynaecol 2001;15:663-76. •Bernard H-U. Gene expression of genital human papillomaviruses and considerations on potential antiviral approaches. Antiviral Ther 2002;7:1-19. •Bosch FX et al. The causal relation between human papillomavirus and cervical cancer. J Clin Pathol 2002;55: 244-265.

cells. Normally, it appears that E6/E7 expression is tightly regulated by the viral E2 protein as well as by several host regulatory proteins. The regulatory region of the HPV genome contains silencer elements that bind differentiation-specific cellular proteins (e.g., AP1 and progesterone) which can repress gene expression in the basal layers of the epithelium. To prevent progression to neoplasia, it is critical that E6/E7 expression levels remain low in mitotically active cells. Thus, changes in expression (particularly differentiation-specific expression) of these host regulatory proteins in the dividing basal cells could induce transcription of E6/E7 in a cellular environment that would favor malignant transformation. Maintenance of the genome in episomal form is necessary to carry out the full viral lifecycle. However, in most invasive cancers the HPV genome is found to be integrated into the host DNA, and E2 expression is often lost as a result of integration. The loss of E2-dependent HPV transcriptional repression in these cells results in a constitutive activation of E6/E7 expression that could feasibly lead to inappropriate expression of viral oncoproteins in mitotically active cells, giving these cells a selective survival advantage and supporting a causal role for integration in cervical carcinogenesis.

Hahn and Weinberg[1] have proposed that most (if not all) human tumors are governed by a distinct set of genetic and biochemical principles. Under their model, disruption of a limited number of cellular pathways would be sufficient to induce a tumorigenic phenotype in a variety of human cells. They propose five "acquired capabilities", outlined in Figure 1. The function of HPV as a carcinogen can be easily recognized in this model, as E6/E7 expression can confer at least 3 of these acquired capabilities to the infected cell, as shown in Figure 1. The elevated risk of cervical cancer resulting from persistent infections could thus be potentially explained by: (a) the longer cells contain HPV genomes, the greater the likelihood of unregulated E6/E7 expression, (b) persistence is a result of loss of differentiation-dependent viral gene expression, and/or (c) persistent infection increases the opportunity for acquisition of the remaining "acquired capabilities" of a transformed cell.



Two final questions remain:

(1) what causes a minute fraction of HPV infections to lose differentiation dependence and gain these three acquired characteristics as a result of viral oncogene expression, and (2) how do these cells acquire the remaining properties that define malignant transformation?

It seems logical that future investigations should attempt to answer these questions by reconciling the molecular insights into the cellular pathogenesis of HPV and the epidemiologically identified factors associated with HPV-induced cervical cancer.

For example, case-control studies consistently report an association of long duration oral contraceptive use, multiparity, and smoking, with cervical cancer.

These exposures suggest a role for reproductive hormones and redox changes in the cervical microenvironment in the molecular pathogenesis of cervical cancer. Progesterone and redox-responsive transcription factors (e.g., AP-1) have been shown to influence HPV gene expression. Alternatively, exposure to estrogen metabolites and reactive nitrogen/oxygen species can also induce direct genotoxicity. It will be of great interest in the coming years to determine the precise biological mechanisms by which these exposures increase the risk of cervical cancer.

An effective prophylactic HPV vaccine holds the greatest promise for the next quantum leap in cervical cancer prevention. However, currently planned vaccines do not target the full spectrum of carcinogenic genotypes and do not address the cancer risk of those already infected. Therefore, progress in our understanding of HPV-associated carcinogenesis must remain a top priority.

Figure 1
Cervical carcinogenesis according to Hahn and Weinberg's acquired capabilities model.[2]

MEN'S CONTRIBUTION TO CERVICAL CANCER RISK

Men as carriers and vectors of oncogenic HPVs

Human Papillomaviruses (HPVs) are sexually transmitted and, as with any sexually transmitted infection, men are implicated in the epidemiological chain. Acting both as "carriers" and "vectors" of oncogenic HPVs, male partners may be important contributors to the risk of developing cervical cancer in their female partners. Although more rarely than women, men may also become the "victims" of HPV infections, as a substantial fraction of penile and anal cancers are strongly related to infection by the same oncogenic genotypes that cause cervical cancer.

Sexual behavior patterns and cervical cancer risk: a hypothesis

The extent to which males contribute to the risk of HPV-related cancers in a particular population depends mainly on 2 factors: (1) the overall pattern of sexual behavior in the society as a whole, and (2) on the background HPV prevalence.

> a woman's risk of cervical cancer will depend less on her own sexual behavior than on that of her husband or other male partners

This concept is not new, and it was first formally proposed by Skegg et al.[1] back in 1982. These investigators hypothesized that, in some populations,
a woman's risk of cervical cancer will depend less on her own sexual behavior than on that of her husband or other male partners.
They put forward the idea that cervical cancer incidence rates in an unscreened population will vary according to 3 different sexual behavior patterns, as shown below:

	Women	Men	Where?	Predicted cervical cancer incidence
Pattern A	Mostly monogamous	Mostly monogamous	Certain religious communities	Lowest
Pattern B	Mostly monogamous	Many sex partners Frequent contact with sex workers	Some Male Dominant societies	Highest
Pattern C	Several sex partners	Several sex partners	Permissive societies	Intermediate

According to this model the highest cervical cancer incidence rates would be observed in "Pattern B" communities, in which many men have intercourse with a small number of highly promiscuous women, frequently sex workers, who constitute a reservoir of HPV infection.

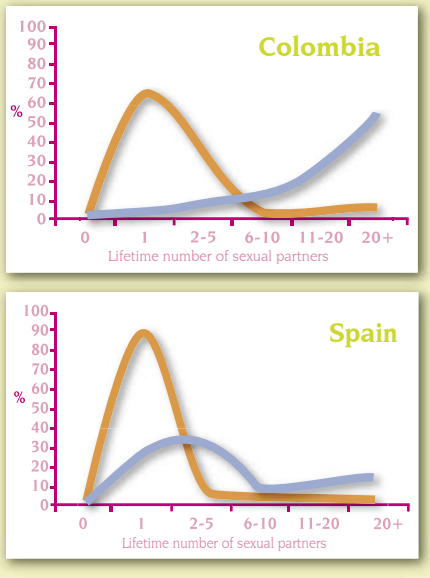
Evidence from the IARC studies on the male role

Between 1985 and 1993 the International Agency for Research on Cancer (IARC) conducted a series of case-control studies in countries with low, intermediate and high incidence rates of cervical cancer to assess the role of HPV and other sexually transmited infections (STIs) in the etiology of this cancer. Husbands or current stable sexual partners of the women recruited in these studies were also invited, interviewed, and penile exfolliated cells tested for HPV DNA by state-of-the-art PCR techniques. This was accomplished in 1,925 men enrolled in 7 case-control studies carried out in Colombia, Brazil, Thailand, The Philippines, and Spain.
This design, allowed, 20 years later, the testing of Skegg's hypothesis by actual, individually collected data on HPV infection and sexual practices in adult men and women in populations with contrasting incidence rates of cervical cancer.

Number of sexual partners

The figure below plots the distribution of the lifetime number of sexual partners in men and women for 2 selected countries that have a fivefold difference in the ratio of cervical cancer incidence rates: Colombia, (age-adjusted incidence rate (AAIR) of 34.4 per 100,000 women), and Spain (AAIR of 7.1).

Distribution of lifetime number of sexual partners in adult men and women in Colombia and Spain



The curve for Colombia closely resembles that hypothesized in Skegg's "Pattern B" society, with women being mostly monogamous (around 70%), and men highly promiscuous (55% of men had 20 or more sexual partners). In contrast, the corresponding distribution in Spain, although not identical, is consistent with Skegg's "Pattern A" society, with the vast majority of women being monogamous (around 90%), and a small fraction of men highly promiscuous (15% of men had 20 or more sexual partners). Clearly, the male-to-female disparity in terms of number of sexual partners is more marked in high-risk Colombia than in low-risk Spain, thus confirming the contrasting cervical cancer incidence rates predicted by Skegg's model.

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Institut Català d'Oncologia. Barcelona, Spain.

Age at first sexual intercourse

Distribution of age at first sexual intercourse in adult men and women in Colombia and Spain

Early sexual debut in women is an indicator consistently associated with an increased risk of cervical cancer. As shown in the figure below the pattern of the distribution of age at first regular intercourse shown by both sexes differs greatly between high-risk Colombia and low-risk Spain: 68% versus 24% men initiated sex at age 16 or younger in Colombia and Spain, respectively, and 26% versus 6% women initiated sex at age 16 or younger in Colombia and Spain respectively.

Contacts with sex workers

Prevalence of reported contacts with prostitutes (79% in Colombia versus 52% in Spain) also correlated with cervical cancer, as did the fraction of men's sexual partners that were prostitutes: 28% versus 10% men had more than 50 partners that were prostitutes in Colombia and Spain, respectively.

Penile HPV

Concerning HPV infections in men and women the results from these studies showed that penile and cervical HPV correlated strongly with cervical cancer incidence rates. In high-risk Colombia men had a higher HPV prevalence than women (19% versus 15%, respectively). In low-risk Spain, HPV prevalences for both men and women were five- to sixfold lower than those in Colombia, although men had a somewhat lower HPV prevalence than women (3% versus 5%, respectively).

Male circumcision

Mediated by HPV, male circumcision is also a factor that may modulate the risk of cervical cancer. Pooled analyses of IARC data showed that circumcised men not only had a substantially lower risk of penile HPV infection than uncircumcised men, but also that their partners had a lower risk of HPV infections and a lower risk of developing cervical cancer. These associations were particularly strong in men that had engaged in high-risk sexual behavior.

Conclusion

The findings from the IARC studies underline the importance of the sexual background of each male partner in a woman's risk of developing cervical cancer, supporting the role of men as vectors of oncogenic HPVs. In populations in which the number of partners of men differs greatly from that of women, prostitution is likely, and a woman's risk of cervical cancer is more dependent on the sexual behavior of her partner than on that of her own.

References

1. Skegg DC et al. Importance of the male factor in cancer of the cervix. Lancet 1982;2:581-583

Further reading

•Kjaer SK et al. Case-control study of risk factors for cervical neoplasia in Denmark. I: Role of the "male factor" in women with one lifetime sexual partner. Int J Cancer 1991;48: 39-44 •Muñoz N et al. Difficulty in elucidating the male role in Colombia, a high risk area for cervical cancer. J Natl Cancer Inst 1996;88:1068-1075 •Bosch FX et al. Male sexual behavior and HPV DNA, key risk factors for cervical cancer in Spain. J Natl Cancer Inst 1996;88:1060-1067 •Castellsagué X et al. Prevalence of penile human papillomavirus DNA in husbands of women with and without cervical neoplasia: A study in Spain and Colombia. J Infect Dis 1997;176:353-361 •Castellsagué X et al. Male circumcision, penile human papillomavirus infection, and cervical cancer in female partners. N Engl J Med 2002;346:1105-1112

NEWS

FDA APPROVES EXPANDED USE OF HPV TEST

The Food and Drug Administration (FDA) recently approved expanded use of a laboratory test to detect the presence of human papillomavirus (HPV), one of the most common sexually transmitted infections in women.

FDA initially approved the HPV DNA test in March 2000 for testing women who had abnormal Pap test results to determine whether they needed to be referred for further examination. The new indication allows the test to be used for screening, in conjunction with the Pap test, of women over 30 years of age for HPV infection. It should be used along with the Pap test, a complete medical history and an evaluation of other risk factors to help physicians determine what kind of follow-up is necessary.

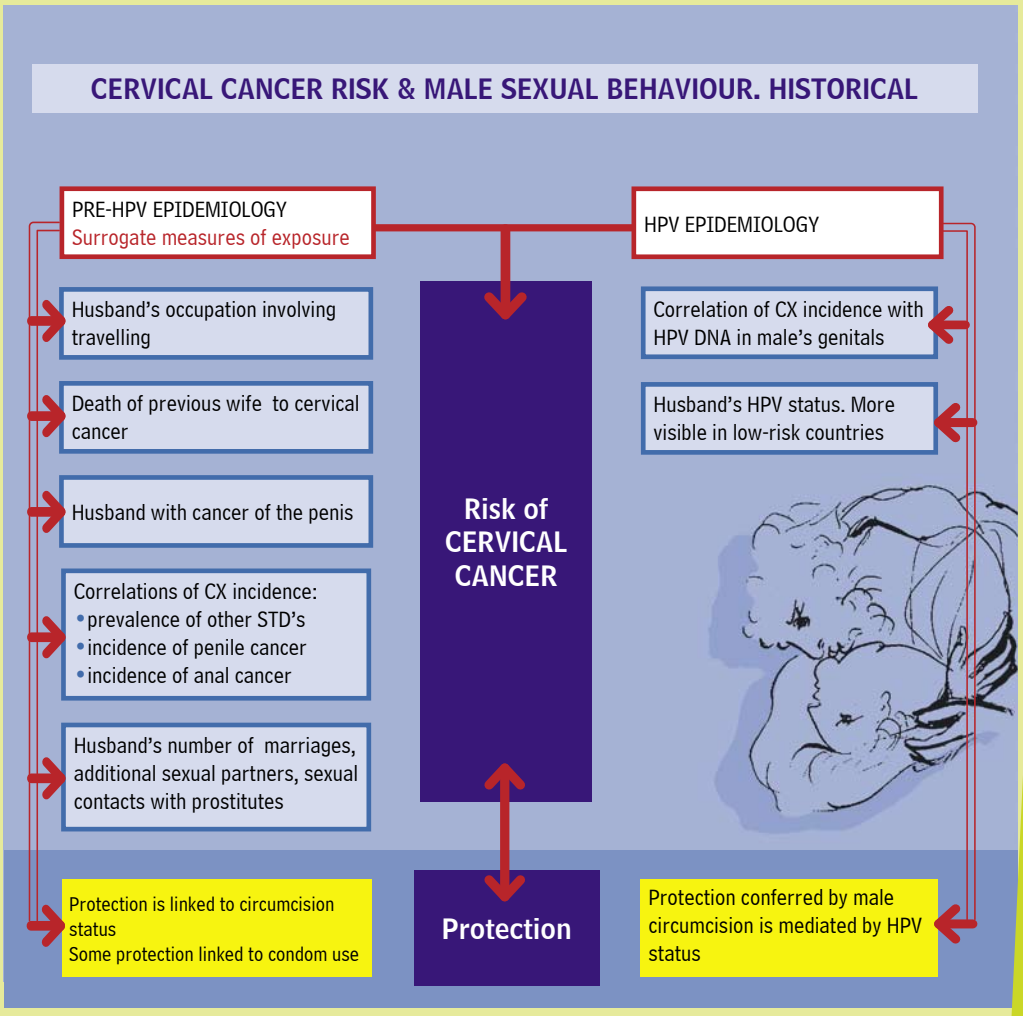
The HPV DNA test, like the Pap test, is performed by collecting cells from the cervix and then sending them to a laboratory for analysis. The test detects high-risk types of HPV in cell DNA even before there are any conclusive visible changes to the cervical cells.

Women who have normal Pap test results and no HPV infection are at very low risk (0.2%) of developing cervical cancer. Women who have an abnormal Pap test and a positive HPV test are at higher risk (6-7% or greater) of developing cervical cancer if not treated.

The HPV DNA test is not intended as a substitute for regular Pap screening. Nor is it intended to screen women under 30 who have normal Pap tests. Although the rate of HPV infection in this group is high, most infections are short-lived and not associated with cervical cancer.

HPV IN 100 SLIDES

The evidence that male sexual behavior is a determinant of the risk of cervical cancer is historically consistent. Early studies showed correlation between the incidence rates of cervical cancer and measures of male's sexual behavior, the background prevalence of sexually transmitted diseases or the circumcision status of the male population. After a diagnosis of cervical cancer, women and their husbands are at increased risk of secondary cancers of the genital tract. More recent studies, which included HPV DNA testing, have confirmed that all previous epidemiological observations are indeed explained by the presence of HPV DNA in the penis or the distal urethra.



HPV ON THE INTERNET

WWW

www.dermnetnz.org/index.html
Official website of the New Zealand Dermatological Society. It includes information for patients, general practitioners and dermatologists, publications, events and a directory of dermatologists.

www.nccc-online.org
Official website of the National Cervical Cancer Coalition. It includes information for patients - including a section with accounts from women who have fought the physical and emotional battle of cervical cancer - and professionals. It also contains an area that provides important information regarding Human Papillomavirus, including some of the latest cancer trials and information on upcoming vaccines.

www.sccps.org
Official website of the Singapore Society of Colposcopy and Cervical Pathology. It includes information for physicians, events, news and updates, and links of interest.

www.cytopathology.org
Official website of the American Society of Cytopathology (ASC). It includes information for patients and physicians, the guidelines of the ASC, events, news and updates, and links of interest. The first version of the Nongynecological Cytology Practice Guidelines is also available here. This first version contains information that is applicable for all nongyn specimens and the respiratory tract.

www.ebcog.org
Official website of the European Board And College Of Obstetrics And Gynaecology (EBCOG). It includes information for physicians, meetings and links of interest.

www.escmid.org/sites/index.asp
Official website of the European Society of Clinical Microbiology and Infectious Diseases. It includes information for physicians, meetings, awards and grants, job opportunities, publications, information about study groups, courses and workshops, affiliated societies and links of interest.

www.igcs.org
Official website of the International Gynecologic Cancer Society (IGCS). It includes information about meetings and congresses, a calendar of events, access to different publications, and special areas for IGCS members.

PREPARING THE HEALTH DECISION-MAKERS, PARENTS AND ADOLESCENTS FOR THE ULTIMATE FIGHT AGAINST CERVICAL CANCER!

Marc Steben
Public Health Infectious Disease Unit, National Public Health Institute of Quebec, Vulvar Disease Clinic. Gyne-Oncology Department University of Montreal Hospital Center. Canada.

First introduced by Jenner in 1796, immunisation has been a very potent weapon in the fight against naturally occurring infections. However, parents who are influenced by fear-inducing media messages may hesitate or refuse to have their children vaccinated against a sexually transmitted infection.

How serious is HPV infection?

It is a leading cause of cancer world-wide. Some HPV types cause genital warts, and others cause cervical and other genital neoplastic lesions, including cancer. They also cause important physical and psychosexual suffering.

Why are vaccines urgently needed to control HPV infection?

The usual public health measures for control of bacterial Sexually Transmitted Infections (STIs) are not working for viruses such as HPV:

- Condom protection is more imperfect
- No screening is generally available to detect the carriers, either for men or women
- No effective tracing of contacts and treatment by antiviral agents is available.

Why should we bother eliminating this infection if it is so common?

There is no other reservoir for HPV infection than the human being. HPV infection can theoretically be eliminated like smallpox was. The way to transmit the infection is sexual contact, thus better living conditions do not tend to reduce HPV infections. However cervical screening does protect against cervical cancer.

Isn't the natural immunity produced by getting the infection better than the one produced by the vaccine?

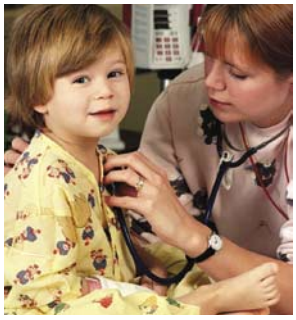
1. An immune response to HPV may appear long after the infection has been acquired thus permitting transmission to other partners, and
2. there is no natural immune response against the HPV oncogenic strains for a segment of the population.

If other children are vaccinated, why does my child need to be vaccinated?

There is always a small proportion of the people vaccinated who do not develop immunity and will develop or carry the virus if exposed. There are also a few children who cannot be immunised because of immunity problem or allergy concerns. If unvaccinated people come into contact with unprotected carriers transmission will result.

But vaccines are not 100% effective ...

It is more likely than for other vaccine preventable infections that HPV vaccines will not carry all the genotypes necessary to protect against all HPV infections. However, because the burden of these infections is so important, public health programs with even imperfect coverage will result in immense health gains for individuals and the community.



...and they are so new that we do not even know if booster doses will be needed

Most vaccines induce both short-term protection and also a long-term immune memory that can last for a lifetime, but we have to realise that the most critical period for HPV infections is probably during the first few years of sexual activity when the number of partners and susceptibility to cancer may be highest.

Are HPV vaccines safe?

Many thousands of patients have been immunised with HPV vaccines. Serious effects have been very limited. There is no risk to acquisition or transmission of HPV since the vaccine contains only one surface antigen, no genetic material and obviously no complete HPV.

Will providing protection against STI make my children promiscuous?

Although immunisation against HPV infection may be made available, the possibility of contracting other STIs will remain so high as to warrant continuation of condom use and other prevention activity. There is no sign that hepatitis-B vaccination has rendered adolescents more promiscuous.

The final word

With the limited information available at the moment, we can say that the benefits of immunisation greatly prevail over the risks that are, in fact, very low or even hypothetical at the moment.

References

Montreal public health direction. www.santepub-mtl.qc.ca
A parent's guide to vaccination published by the Canadian paediatric society, 2003. www.cps.ca
Canadian immunization awareness program. www.immunize.cpha.ca
World health organization. www.who.int
immunization action coalition (USA). www.immunize.org

KEY PUBLICATIONS

INCLUSION OF HPV TESTING IN ROUTINE CERVICAL CANCER SCREENING FOR WOMEN ABOVE 29 YEARS IN GERMANY: RESULTS FOR 8,466 PATIENTS

Petry KU, Menton S, Menton M, Loenen-Frosch F, De Carvalho GH, Holz B, Schopp B, Garbrecht-Buettner S, Davies P, Boehmer G, Van Den AE, Iftner T. Br J Cancer 2003;88:1570-1577.

Data from a prospective cohort study of 8,466 women attending routine cervical cancer screening showed that a negative HPV-test result, even in combination with a positive Papanicolaou result, virtually excluded any risk of underlying high-grade disease, but this was not the case for a negative Pap result. This study shows that HPV testing is of value for the detection or exclusion of prevalent CIN in a routine cervical cancer-screening setting and could be used for further risk classification of women for follow-up management.

SEROREACTIVITY TO EPIDERMODYSPLASIA VERRUCIFORMIS–RELATED HUMAN PAPILLOMAVIRUS TYPES IS ASSOCIATED WITH NONMELANOMA SKIN CANCER

Feltkamp MCW, Broer R, di Summa FM, Struijk L, van der Meijden E, Verlaan BPJ, Westendorp RGJ, ter Schegget J, Spaan WJM, Bouwes Bavinck JN. Cancer Res 2003;63:2695-700.

DNA from epidermodysplasia verruciformis-related human papillomavirus (EV-HPV) types is frequently found in nonmelanoma skin cancer. Immunological data from subjects recruited in a case-control study of 540 cases with a history of skin cancer and 333 controls showed that EV-HPV serorecognition was associated with nonmelanoma skin cancer, in particular for HPV types 8 and 38. Further analyses suggest that EV-HPV-directed seroresponses would be included upon skin cancer formation rather than upon infection.

FUTURE DIRECTIONS IN EPIDEMIOLOGIC AND PREVENTIVE RESEARCH ON HUMAN PAPILLOMAVIRUSES AND CANCER

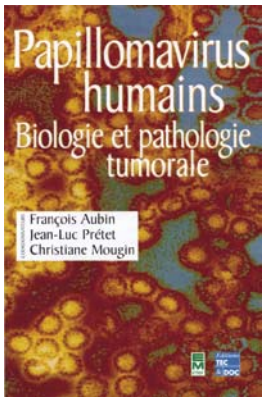
Bosch FX, Solomon D, Schiffman M, editors. Journal of the National Cancer Institute Monographs, No.31, Oxford University Press 2003.

This monograph is the results of a cooperative effort of a group of senior epidemiologists and interdisciplinary scientists who met in June 2002 at the National Cancer Institute, Bethesda, Maryland (USA). Rather than a review of evidence or a policy document this monograph offers suggestions and new ideas for useful work concerning epidemiologic and preventive research on HPV and cancer.

BASELINE CYTOLOGY, HUMAN PAPILLOMAVIRUS TESTING, AND RISK FOR CERVICAL NEOPLASIA: A 10-YEAR COHORT ANALYSIS

Sherman ME, Lorincz AT, Scott DR, Wacholder S, Castle PE, Glass AG, Mielzynska-Lohnas I, Rush BB, Schiffman M. J Natl Cancer Inst 2003;95:46-52.

In a 10-year cohort study involving 23,702 women it was found that negative baseline Pap and HPV tests were associated with a low risk for CIN 3 or cancer in the subsequent 45 months, largely because a negative HPV test was associated with a decreased risk of cervical neoplasia. Negative combined test results should provide added reassurance for lengthening the screening interval among low-risk women, whereas positive results identify a relatively small subgroup that requires more frequent surveillance.



PAPILLOMAVIRUS HUMAINS. BIOLOGIE ET PATHOLOGIE TUMORALE

Aubin F, Prétet JL, Mougin Ch, editors. Édictions Tec&Doc - EM Inter. Language: French

Written by a team of 89 authors, this book reviews and updates all aspects of the biology and pathology of Human Papillomaviruses including virology, biology, natural history, epidemiology, HPV detection, screening, as well as clinical, prophylactic and therapeutic aspects. A final chapter is devoted to HPV research discussing unanswered questions, current controversies, and future perspectives concerning HPV and HPV-related diseases.

THE ALLIANCE FOR CERVICAL CANCER PREVENTION (ACCP)

Jacqueline Sherris, Ph.D.
Strategic Program Leader, Reproductive Health Program for Appropriate Technology in Health (PATH). Coordinating Agency for the Alliance for Cervical Cancer Prevention (ACCP). USA.

How was The Alliance conceived? Who participated in the project? What was the role of the Bill & Melinda Gates Foundation?

In 1999, ACCP partners convened to discuss issues related to cervical-cancer prevention in developing countries and identified key activities that could accelerate access to effective screening and treatment approaches in these settings. They proposed working with developing-country partners to:

- assess innovative approaches to screening and treatment for precancer;
- improve service delivery systems;
- ensure that community perspectives and needs are incorporated into program design;
- heighten awareness of cervical cancer and effective prevention strategies.

Based on this proposal, the Bill & Melinda Gates Foundation (Seattle, USA) awarded a five-year, $50 million grant to the ACCP. Alliance partners are: Engender Health (a family planning and reproductive-health agency based in New York), International Agency for Research on Cancer (IARC), a reproductive health agency affiliated with Johns Hopkins University, (JHPIEGO), Pan American Health Organization (PAHO), and Program for Appropriate Technology in Health, based in Seattle (PATH), which serves as the Alliance coordinating agency.

Where is the Alliance concentrating its efforts?

Alliance-funded research and demonstration projects are currently underway in Bolivia, El Salvador, Ghana, India, Kenya, Peru, South Africa, and Thailand, among other countries.

What are some of the key findings of the Alliance to date?

The Alliance for Cervical Cancer Prevention is in the fourth year of its five-year project. During the first 3 years of the project, considerable progress has been made in the 4 ACCP focus areas. First, models for appropriate, affordable, and efficacious screening and treatment technologies have been developed. Altogether over 160,000 women had been screened through Alliance projects as of August 2002, and approximately 8,000 women had undergone treatment by cryotherapy, loop electrosurgical excision procedure (LEEP), or other methods. Second, the Alliance has developed a range of materials related to delivery of cervical-cancer prevention strategies in low-resource settings. Third, women's needs and concerns have been integrated into program design, implementation, and education. Fourth, appropriate and effective awareness-raising strategies are being implemented to gain broad-based support worldwide for cervical cancer prevention efforts.

What would you like to highlight as key achievements of some ACCP country projects?

- In Thailand, JHPIEGO and its Thai partners have demonstrated the safety, acceptability, feasibility, and necessary programmatic effort of a cervical-cancer prevention strategy using a single -visit approach: visual inspection with acetic acid (VIA) followed by immediate cryotherapy for test-positive cases.
- In South Africa, EngenderHealth, in collaboration with Columbia University and the University of Cape Town, is completing a randomized clinical trial to determine the safety and efficacy of screening with VIA or HPV DNA testing followed by treatment with cryotherapy for positive cases.
- In the Osmanabad district in India, IARC and its Indian partners are carrying out a randomized clinical trial evaluating the comparative efficacy (with CIN and cancer mortality rates as endpoints) and cost effectiveness of screening programs using VIA, cytology, and HPV DNA testing (with approximately 40,000 women in each arm of the study).
- In collaboration with the respective Ministries of Health, PAHO has established demonstration sites in Peru and El Salvador to evaluate VIA as an alternative screening method and to monitor the safety of cryotherapy in these settings. PAHO as a regional office of the World Health Organization has also been working collaboratively with 8 member countries to strengthen cervical cancer prevention and control programs, while simultaneously advocating for its positioning as a priority on the public health agenda of Latin America and the Caribbean.
- In Western Kenya, PATH is working with several Kenyan partners to evaluate the potential sustainability of a service delivery model for cervical-cancer prevention using VIA, visual inspection with acetic acid and magnification (VIAM) for confirmation, and cryotherapy for treatment. PATH also is working with Kenyan NGOs to develop appropriate advocacy approaches for drawing attention to the need for cervical-cancer prevention programs.

What would you recommend to public health institutions in relation to cervical-cancer prevention?

Our recommendations would highlight the importance of an integrated view of cervical-cancer prevention. Clearly, selecting a screening strategy is a key step and, at the same time, strategies that ensure maximum program coverage of older women (in their 30s and 40s) and ensure appropriate follow-up are equally important for ultimately saving women's lives.

What are your current research plans and the future perspectives of the Alliance?

Overall, by the end of 2004, the Alliance expects to have defined the safety and effectiveness of alternative screening methods. It expects to have developed algorithms/tools to assist policy makers in assessing options for cervical-cancer prevention programs. The Alliance should have established models of services responsive to needs of women and ensured that the international health community recognizes and leverages ACCP findings and recommendations.

INTERNATIONAL AGENDA

2nd - 5th December 2003

8th World STI/AIDS Congress

City: Punta del Este, Uruguay.
Venue: Hotel Conrad Resort
President: Dr. Hilda Abreu
Secretariat: CONGREX SWEDEN AB. P.O. Box 5619. SE-114 86 Stockholm (Sweden).
Tel: +46 8 459 6600
Fax: +46 8 661 9125
E-mail:
stiaids.registration@congrex.se
stiaids.abstract@congrex.se
Web:
www.congresos-rohr.com/stiaids/

3th - 6th December 2003

XXIV Congreso Argentino de Obstetricia y Ginecología-FASGO 2003

City: Buenos Aires, Argentina
Venue: Sheraton Hotel Mar del Plata
President: Dr. Carlos Fayanás (SOGBA)
Contact with: Av. Córdoba 1646- 5º Piso Of. 201. (1055) Ciudad de Buenos Aires.
Tel: +54 (011) 4812-3656/8800
E-mail: fasgo@abaconet.com.ar
Web: www.fasgo.org.ar

23th - 24th January 2004

3rd European Congress for Colposcopy and Cervical Pathology

City: Paris, France.
Venue: Institute Pasteur
President: J-L Leroy
Secretariat: Alexandra Sebaoun
Tel: +33 1 45 23 96 05
Fax: +33 1 45 23 96 08
E-mail: alexandra.sebaoun@societeccc.fr
Web: www.europeancolposcopy.com

6th - 11st February 2004

62 Annual Meeting of the American Academy of Dermatology

City: Orlando, United States of America
Contact with: American Academy of Dermatology
Tel: +1 847-330-0230
Fax: +1 847-330-1090
E-mail: rescalante@aad.org
Web: www.aad.org/Meetings/AM04_intro.htm

20th - 26th February 2004

Twenty-First International Papillomavirus Conference

City: México City, México
Organizers: Alejandro M. García-Carrancá, Patricio Gariglio, Mauricio Hernández and Eduardo Lazcano
Secretariat: Julieta Tovar
Tel: +52 5 622-3830;
Fax: +52 5 622-3891
E-mail:hpvconference@insp.mx
Web: www.hpv2004.com

15th - 19th March 2004

2004 ASCCP Biennial Meeting

City: Orlando, Fl (USA)
Venue: Disney's Contemporary Resort
Contact: ASCCP Office Contact Information. 20 West Washington Street, Suit 1, Hagerstown, MD 21740
Tel: +1 301 733-3640
Fax: +1 301 733-5775
Web: www.asccp.org

11th -15th April 2004

XV International Congress of Cytology

City: Santiago de Chile, Chile
Venue: Sheraton Hotel and Convention Center Santiago.
President: Dr. Matias Jiménez-Ayala
Secretariat: Dr. Angelo Castiglione, Dr. Lucrecia Illescas
Web: www.xvcongress.cl/

27th - 29th April 2004

World Vaccine Congress Montreal 2004

City: Montreal, Canada
Venue: Fairmont Queen Elizabeth Hotel, Montreal.
Contact with: Noreen Meehan. Conference Manager
Tel: +44 0 207 827 5984
Fax: +44 0 207 242 1508
E-mail:
noreen.meehan@terrapinn.com

3th - 7th October 2004

10th Biennial Meeting of the International Gynecologic Cancer Society

City: Edinburgh, United Kingdom
Venue: Edinburgh International Conference Centre (EICC)
President: Ian V. Scott MB,ChB. FRCOG
Secretariat: Kenes International. 17 rue du Cendrier, P.O. Box 1726. Ch-1211 Geneva 1 Switzerland
Tel: +41 22 9080488
Fax: +41 22 7322850
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