HPV Today

Newsletter on Human Papillomavirus

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NEW OPPORTUNITIES FOR CERVICAL CANCER IN LATIN AMERICA

INTERVIEW WITH NUBIA MUÑOZ

by Dr. G. Pérez in Colombia

How do you see the problem of cervical cancer in Latin America?

Cervical cancer is an important problem in Latin America and Caribbean countries. It is the most common cancer in women in Bolivia, Ecuador, Paraguay, Peru, Guatemala, El Salvador, Honduras, Mexico, Nicaragua, Venezuela, and Haiti and the second most-common after breast cancer in Argentina, Brazil, Colombia, Costa Rica, Panama and in the Caribbean countries other than Haiti. In addition, while cervical cancer in developed countries has been declining steadily over the past 40 years, the rates in most Latin American countries have remained unchanged or have increased slightly.

What are the reasons for these high rates?

There are multiple reasons, but probably the most important ones are the lack of organized screening programmes and the high prevalence of cervical human papillomavirus (HPV) infections. Although there are screening programmes in some countries, they have been largely unsuccessful and the reasons for this are well known: a) lack of the political will to maintain an organized screening programme; b) lack of education for women at risk and for health care professionals about the importance of screening; and c) inadequate health care structures for screening, diagnosing and treating the cervical lesions detected. However, the positive impact of cytology screening has been documented in a few places in Latin America, such as Cali, Colombia,[1] where a 40 year old cancer registry has shown a decline in the incidence rate of cervical cancer from 70 per 100.000 in the 1960's to 30 per 100.000 in the 1990's.

What is known about cervical HPV infection in Latin America?

We have reported high prevalence (15-20%) in women without cervical cancer serving as controls in case-control

(continues on page 3)

Nº 04 February 2004

EDITORIAL

LATIN AMERICA AND CERVICAL CANCER: NEW HOPE AHEAD IN A LONG AND TORTUOUS ROAD

In spite of being a largely preventable disease, cervical cancer remains a leading cause of death to cancer among women in most Latin American countries. It has been alike for decades, in dramatic contrast with the efforts deployed to put screening into operation. Most countries so far, have seen limited success in following the screening models developed in many industrialized countries, with better developed and financed health systems. Better screening and human papillomavirus (HPV) vaccination, may result into a brighter future now available at a defined distance. Better screening strategies will benefit from recognizing the disparity across populations and allow a multiplicity of screening schemes, including high and low technology, even within a given country. Better screening has to benefit, as well of the arrival of better technology wherever it is available. The current cost limitations of technology such as HPV testing, should be addressed by the relevant bodies and the major sponsors and donors, to ensure rapid introduction towards universal coverage.

HPV vaccination with prophylactic products may well represent the solution for the generations that are now being born, while unlikely to protect the current adult female populations. However, universal vaccination will also require understanding and acceptance of the issues as well as affordability and availability of the vaccine. Thus massive immunization will require a definite and sustained effort by the Public Health institutions and systems. It will not be easy, neither fast but the field is moving and full of renewed hope.

Scotland first, and the rest of the United Kingdom soon after, decided to change their screening protocols and to adopt liquid-based cytology as the recommended procedure. The evaluation recognized the advantages of the liquid-based procedure in reducing the Atypical Squamous Cells of Undetermined Significance (ASCUS) fraction and increasing the detection rate of lesions. There is also a sense of general satisfaction among readers in terms of the shorter time required for smear reading and on the comfort of the method. In the Spring, the final evaluation of this group on HPV testing as a screening procedure will be available.

Meanwhile the HPV in addition to routine testing study (HART study), a randomized screening trial also in the United Kingdom, concluded that HPV screening could be used efficiently as the primary screening test, with cytology being the triage method of choice. Screening for cervical lesions is thus in a state of flux and a growing field of interest for pathologists, virologists, insurance companies and Public Health authorities.

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(from page 1) studies conducted in Brazil, Colombia, Paraguay, Peru,[2] as well as in prevalence surveys involving samples from the general population in Argentina, Colombia, Brazil, Costa Rica and Mexico. We have observed that, in most Latin American countries the curve showed two peaks: the first peak in young women and the second in middle aged. It is currently unknown whether the second peak represents reactivation of a latent infection, a cohort effect or whether it is associated with male sexual behavior. In some low-risk countries for cervical cancer, such as the US and certain European countries, the age-specific prevalence curve of HPV DNA shows a peak in women under 25 years of age followed by a sharp decline to reach very low levels in older women.

How do you envision the perspectives for the prevention of cervical cancer in Latin America?

Our studies demonstrating that HPV DNA was present in virtually all cases of invasive cervical cancer[3] had enormous implications in prevention strategies. First of all, as a primary prevention through vaccination. A recent report showing that a prophylactic HPV-16 vaccine was safe and highly efficacious in preventing persistent HPV-16 infection and HPV-related CIN[4] has raised hope for the prevention of this cancer.

Secondly, the integration of HPV testing into cytology screening programmes has been shown to be of great value in the management of women with borderline abnormal smears and also to have a great potential to increase the effectiveness of screening programmes by identifying those women who could benefit from a more intense follow-up and those who may need to be followed less frequently.

These substantial advances in our understanding of the central role of HPV in cervical cancer, provide a solid basis for developing new strategies to combat cervical cancer in Latin America.

What, in your opinion, will have the greatest impact on the prevention of cervical cancer in Latin America, HPV vaccines or screening?

It depends on the type of country or region within a country. Although more data is needed before formulating public-health policies on the use of new screening tests, I would suggest the following, based on currently available information:

- Latin American countries, or regions, with very limited resources, where cytological screening is not available either as an opportunistic or an organized programme, may consider introducing a screening programme using a simple and low-cost test such as visual inspection with acetic acid (VIA) or VIA with magnification (VIAM). A major advantage of this low-tech approach is the possibility of treatment in the same session (screen and treat approach), avoiding the major logistical difficulty of bringing women back for diagnosis and treatment. A disadvantage of this method is the low specificity, which can lead to overtreatment of women with false-positive results.
- Another alternative in these countries or regions could be to implement a screening programme based on HPV testing alone. However, the major disadvantages of the currently available commercial HPV test are its high cost and technology requirements. In this context, it is of interest to take into account a recent cost-effectiveness analysis of different screening strategies carried out in South Africa. This suggested that a lifetime screen between the ages of 35 and 50 would reduce the incidence of cervical cancer by 25-30%. The most cost-effective strategy was to use a single lifetime HPV test followed by cryotherapy for HPV-positive women (assuming that the HPV test had a sensitivity to detect dysplasia higher than 75% and a cost of USD 6 or less).[5] Although in the long run, a safe, affordable and efficacious prophylactic HPV vaccine will probably be the ideal solution for these countries or regions, a wait-and-see attitude must be strongly discouraged, since one or more decades may pass before such a vaccine becomes available. Low to middle income Latin American countries or regions with inefficient cytology-based screening programmes may want to improve such programmes by introducing HPV testing. Combined testing has been shown to have a higher sensitivity and negative predictive value than cytology alone. Thus, major savings to the health systems of these regions, may result from increasing the duration of the interval between screening tests 5-10 years in HPV-negative women.

We should keep in mind that a screening program, irrespective of the test chosen, should fulfill the following basic requirements to have an impact on the prevention of cervical cancer: to be able to motivate women at risk to seek screening services, to have sufficient availability of health care facilities in order to be able to screen the majority of women at risk, to be able to diagnose and treat the cervical lesions detected and to be

Drs. G. Pérez, J. Noguera, C. Reyes y N. Muñoz with one of the teams that evaluates HPV vaccine in Colombia.

able to collect the necessary information to facilitate ongoing monitoring and evaluation of the programme.
The introduction of a prophylactic HPV vaccine in these countries will reinforce the gains derived from effective screening programmes using combined testing. The degree of protection conferred by the HPV vaccine will depend on its composition. An HPV 16-18 vaccine, like the ones currently being tested, would theoretically prevent 65-70% of cervical cancer, while one against the eight most common high-risk types in cervical cancer (HPV-16, -18, -45, -31, -33, -52, -58 and -35) would prevent about 90% of cervical cancer. Thus, effective screening programmes will continue to be needed even after the introduction of an HPV vaccine because women already infected with the types against which the vaccine is directed, as well as women infected with high-risk HPV types that are not prevented by the vaccine, will remain at risk from cervical cancer.

Where do you see the major impact of your research work on HPV and cervical cancer?

Our epidemiological studies carried out in 25 countries around the world have been instrumental in demonstrating that HPV is not only the central cause of cervical cancer, but also a necessary cause.[3] They also provide the basis for an epidemiological classification of genital HPV types into low- and high-risk types.[2] The above information has been shown to be essential for planning new preventive strategies to combat cervical cancer.

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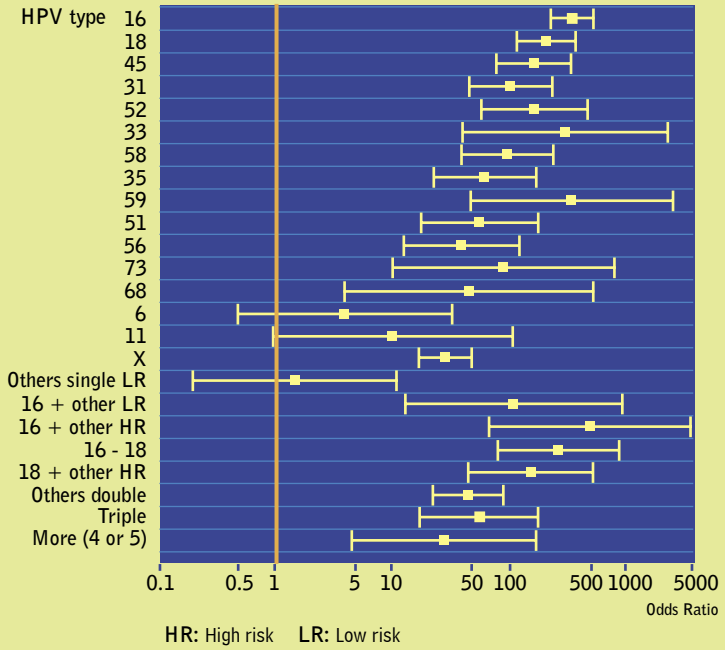
HPV IN 100 SLIDES

The graph shows that the point estimates of the Odds Ratio for HPV-16 and -18 are in the several hundreds range and displays the shortest confidence intervals (CI), reflecting also the higher prevalence of these types. The graph also shows that there are no statistically different risk estimates for any of the individual high-risk types (as shown by the overlap of their 95% CI). This observation, shown now for the first time, has been interpreted as a strong justification for the use of a high-risk cocktail including all major types whenever HPV testing is employed in screening or triage programs. On very rare occasions, HPV-6 or -11 appear as the only types detectable in a specimen of cervical cancer. This observation requires further documentation to confirm the absence of other high-risk types that remained undetectable in this study. Alternatively, some still poorly understood host factors, translating into an unusually high susceptibility of the host to the carcinogenic effects of HPV, could explain the finding. Multiple infections do not add to the risk above the risk linked to single infections.

HPV TYPE-SPECIFIC RISK ESTIMATES FOR CERVICAL CANCER



HR: High risk **LR:** Low risk

Source: Muñoz N et al. Epidemiologic classification of Human Papillomavirus types associated with cervical cancer. New Eng J Med 2003, 348(6): 518-527.

SKIN CANCER IN ORGAN TRANSPLANTATION: A MULTIDISCIPLINARY CHALLENGE

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The transplantation of solid organs has benefited more than one million patients worldwide. The vast majority of organ-transplant recipients, however, still require lifelong immunosuppressive treatment, which is associated with an increased risk of developing bacterial, fungal and viral infections as well as neoplasms. With almost 50% of all malignancies in transplant patients, non-melanoma skin cancer, especially squamous-cell carcinomas (SCC) and their precursors actinic keratoses (AK), represents the majority of neoplasm diagnosed in this special group of patients. Data from the Dermatological Outpatient department of the Charité Hospital indicates that 40% of the organ-grafted patients show pre-malignant or malignant lesions on their first visit. A further 22% go on to develop SCC, 17% basal-cell carcinomas (BCC), 12% Bowen's disease and nearly 5% malignant melanoma. Actinic keratoses are found in 43% of these patients. Almost 75% of the lesions are located on sun-exposed areas of the skin.

Aftercare in organ-grafted patients still focuses on the prevention and treatment of organ rejection, although in the face of increasing survival times of grafted patients nowadays regular dermatological check-ups become more important. Preventive strategies based on a conscientious analysis of individual risk-factors should be able to reduce the high incidence of skin cancer in this group of patients. The effects of immunosuppressive agents, ultraviolet (UV) radiation and oncogenic viruses (human papillomavirus,HPV) are the key risk-factors for developing skin cancer. Early treatment of precancerous lesions would be able to lower the high burden of skin cancer in this group of patients. Specialized dermatological outpatient departments, either as part of an interdisciplinary clinic for organ-transplant recipients or integrated into existing dermatological departments are needed to optimize care in this field. The SCOP Network (SCOP, Skin Care in Organtransplant Patients) was founded in December 2000 as an interdisciplinary network of dermatologists, transplant physicians, patient-support groups and basic researchers. The SCOP Network was expanded in June 2002 to include known European experts in the field (www.scopnetwork.org). In 2001, its sister organization, International Transplant-Skin Cancer Collaborative (ITSCC), was established for North America and Australia.

The objectives of these networks are:

1. standardized aftercare of transplanted patients including research on new therapeutic approaches,
2. collection of epidemiological data, and
3. basic research.

However, new opportunities to advance patient care, education and research, with the final objective of easing the burden of cutaneous malignancies in these patients, remain an assignment for dermatologists world-wide.

• *The structure of the* SCOP *Network*

INVASIVE CERVICAL CANCER IN WOMEN WITH HUMAN IMMUNODEFICIENCY VIRUS (HIV) INFECTIONS AND ACQUIRED IMMNUNODEFICIENCY SYNDROME (AIDS)

Cervical cancer is an AIDS-defining disease

Cervical cancer is caused by certain genotypes of sexually transmitted human papillomaviruses (HPV). Because cervical cancer is more common in women with AIDS, invasive cervical cancer was classified as an AIDS-defining condition in women with HIV infection in 1993. In western countries about 2–3% of women with AIDS have cervical cancer as their AIDS-defining condition. Notably, anal cancers, also HPV-related, occur excessively in persons with AIDS, particularly in homosexual men.

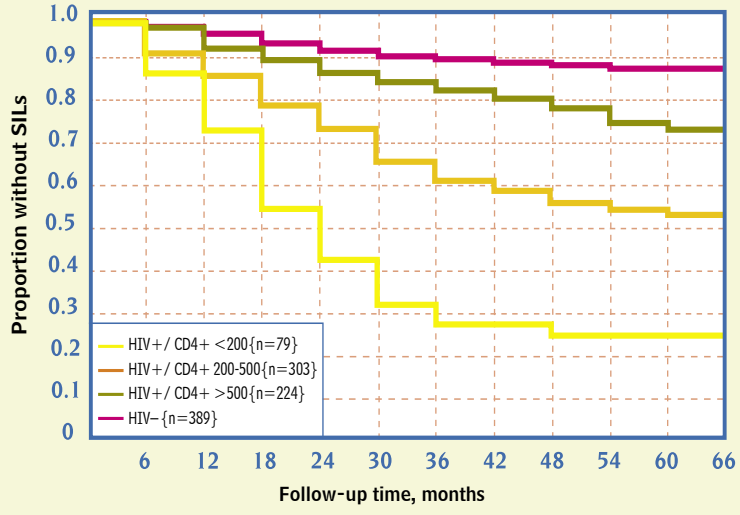
Is the increase in invasive cervical cancer related to HIV infection?

While cervical cancer is more common in women with AIDS, it could still occur because of shared risk-factors for HPV infection. Women infected with HIV by sexual partners will also be a group highly exposed to anogenital HPV genotypes.

In European women with AIDS, the risks of cervical cancer are between four and fifteen times greater than normal women. The upper range of these risk estimates was found in Southern European studies. However, European women who get AIDS are not typical of women in the general population. Many have used intravenous drugs, have had male sexual partners who used intravenous drugs, or have been commercial sex workers. As a group, they, or their sexual partners, have been sexually active to a greater extent than the general population. This sexual behaviour puts them at high risk of HPV infection; women in the USA have similar risk factors. However, among those who went on to develop AIDS, there was a four- to fivefold higher risk of cervical cancer several years before being diagnosed with AIDS, presumably at a time when their immune system was still relatively intact. The risk did not increase as they progressed to AIDS, or in the years after AIDS onset.

The data about cervical cancer are difficult to interpret because screening through pap smears reduces the risk of progression. Less-aggressive screening policies among HIV-infected people in Southern Europe could explain the observed discrepancy within Europe. Similarly, in the USA, HIV-infected, but still healthy, women may receive less-frequent care than those with AIDS. In Africa, where HIV and HPV infection are both endemic, there is little or no screening for cervical cancer. However, despite this lack of screening, most studies have not found any increase in cervical cancer, and in one study, HIV-2 was found to be a greater risk-factor for cervical cancer than HIV-1, even though the latter is more immunosuppressive.

Figure 1 ***Proportion of women without squamous intraepitelial lesions* (SIL) *by* HIV *status and* CD4⁺ *cell counts.***



How could HIV affect the chances of developing invasive cervical cancer?

Although evidence of an increased risk is debatable, it remains plausible that HIV-related immunosuppression could affect the risk of cervical cancer in HPV-infected women. Infection with HIV initiates a progressive destruction of the cellular immunity, as measured by CD4-positive cell counts, possibly leading to poor HPV control. There is evidence that HPV levels in the anal canal increase with immunosuppression. The higher risks and poor control may both contribute to the increased incidence of HPV-related tumors.

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Furthermore, women with HIV infection have a higher prevalence of HPV DNA and squamous intraepithelial lesions (SIL) in cervical and anal mucosa. Several reports show a relationship between SIL and low CD4+ cell counts. Figure 1 illustrates how the proportion of women with SIL increases with decreasing number of CD4+ cell counts among HIV-infected and -uninfected subjects.[1]

In contrast, HIV-induced immunosuppression has a weaker effect on the progression from advanced cervical epithelial neoplasia/high grade SIL to invasive cervical cancer. Figure 2 shows how the risk of invasive cervical cancer or in situ cervical cancer (measured using standardized incidence ratios) among US HIV-infected women was not clearly related to the levels of CD4+ cell counts.[2] The reasons for the lack of association could be biological, but progression is also affected by interventions introduced by screening, making interpretation difficult.

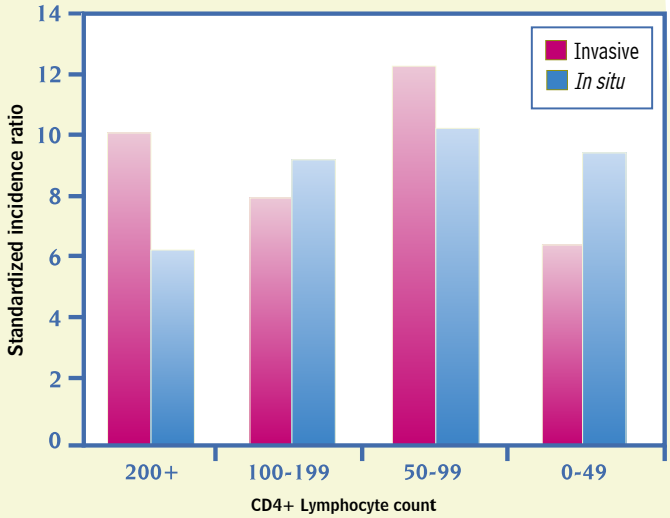
How should one manage cervical-cancer risk in an HIV-infected woman?

In recent years, the great improvements in HIV management with antiretroviral drugs has resulted in good HIV control, allowing prolonged survival with only modest immunosuppression. While better immunity could help to control HPV in infected women, these women are members of a high HPV-risk group that will still need regular monitoring to prevent progression from HPV infection to cervical cancer. In some countries it is recommended that women receive two cervical cytology smears within the first 12 months of being diagnosed with HIV infection. If both results are normal, screening tests should be repeated at annual intervals. In addition, adding recently available tests for HPV presence may be a cost-effective modification of this policy. Although most will be positive, it would provide reassurance to those who are not infected.

Some clinical reports have described a poor prognosis for women with AIDS who develop cervical cancers. Their cancers are said to be large and likely to have metastases and progress rapidly. This poor prognosis is often attributed to HIV-related immunosuppression, but it could also be due to a poorer quality screening care prior to detection. The number of such cases is too low to permit a critical evaluation.

All persons with HIV infection should receive the highest quality of HIV management available. When immunity is not compromised, standard care for cervical cancer can be offered, although it will be appropriate to monitor CD4 status. Clinicians face difficult choices in the management of any cancer when the patient already has severe immunosuppression from HIV infection. Here, non-operative management may be preferred as the initial course, pending improvement in the immunosuppression. However, even in those patients with severe immunosuppression, appropriate antiretroviral drugs will often improve levels of immunity to a level that permits optimal operative care of the cervical cancer. Clinicians should also note that HPV is etiologically associated with anal cancer and infection is common in persons who have anal sex. There are techniques to screen anal mucosa for dysplastic cells, but the very low incidence makes general screening

Figure 2 ***Standardized incidence ratios for invasive cervical cancer and in situ cervical cancer by*** **CD4+** ***cell counts among women with*** **AIDS.**



Based on linked records from AIDS *and cancer registries in* 11 USA *regions* 1990-96.[2]

unwarranted, unless there are clinical reasons to be concerned.

Unfortunately, for women coinfected with HIV and HPV who live in less-developed areas, therapies for HIV and even cervical cancer may not be readily available. When there are no signs of severe immunosuppression, operative management of the cervical cancer should be tried unless there is already evidence of metastases. Chemotherapy adjuvant regimens can be added, but the patient needs careful clinical and, if possible, laboratory monitoring for the development of immunosuppression. If that happens, such therapies must be stopped. If the patient is already severely immunosuppressed when she presents with cervical cancer and no HIV care is available, the prognosis of end-stage AIDS must be weighed against the prospects for controlling the cervical cancer.]

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THERAPEUTIC HUMAN PAPILLOMAVIRUS (HPV) VACCINES

Numerous preclinical studies in mice using transplantable tumor models have shown that vaccines containing E6 and E7 nonstructural papillomavirus proteins cure early-stage established tumors. Despite the fact that this model is of limited predictive value for persistent cervical infection, E7 and E6/E7 therapeutic vaccines have moved from research to a development phase during the last decade. These vaccines are composed of peptides, fusion proteins, chimeric virus-like particles (VLPs), encapsidated plasmid DNA and recombinant vaccinia virus.

Early-phase human trials using such therapeutic vaccines have shown that they are safe, since no serious adverse effects have been reported. Initially, most of the clinical studies were performed in women with advanced cervical cancer and evidence of clinical efficacy was not obtained. This might have been due to the fact that E7 is a poor immunogen in humans, that immunotolerance to E7 might have been induced during the early phase of viral infection, and also to the fact that a decrease in the expression of the Major Histocompatibility Complex (MHC) molecules at the surface of the tumor cells is observed in most patients with invasive cervical cancer.

Due to these limitations, therapeutic vaccines have more recently been evaluated in patients with precancerous cervical lesions, anogenital intraepithelial neoplasia or anogenital warts. The results obtained are more encouraging than with advanced cancer lesions. Evidence of a possible therapeutic effect is based either on a decrease in the viral load or viral persistence and/or a reduction in the size of the lesions. In spite of the lack of correlation generally reported between immune response to the vaccine antigens and clinical efficacy, the reality of the virological and clinical response is indicated by the fact that the effect is dose-dependent. Such a "therapeutic effect" was observed in 30–60% of the vaccinated patients. The reduction in viral load was demonstrated in only one placebo-controlled trial, but no changes in colposcopic appearance or cervical histology were observed in these patients. Although anogenital warts and low-grade squamous

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NEWS

NATIONAL HEALTH SERVICE (NHS) CERVICAL SCREENING PROGRAMME TO INTRODUCE LIQUID-BASED CYTOLOGY

Susan Mayor. Br. Med. J. 2003;327: 948 (25 October).

The NHS cervical screening programme in England and Wales is switching to liquid-based cytology to minimise the number of smear tests that are unsuitable for testing. It is also going to change the frequency of screening to intervals based on age. The change follows pilot studies of liquid-based cytology showing that it is associated with fewer "inadequate" cervical smear tests, so reducing the number of women recalled for repeat testing. Use of liquid-based cytology is also associated with quicker reporting times.

The pilot studies, carried out at three sites in England (Bristol, Newcastle, and Norwich), showed that the technique reduces the number of false-negative

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Company/Institution	Antigen	Type	HPV Type
Xenova/Cantab	E6 + E7	Live rVaccinia virus (TA-HPV)	16,18
Transgene	E6, E7, IL2	Live rVaccinia virus (MVA-HPV-IL2)	16
Xenova/Cantab	L2 / E6 / E7	Fusion protein (TA - CIN)	16
Cantab	L2 / E7	Fusion protein (TA - GW)	6
Stressgen	E7	Fusion protein: mycobacterial heat shock protein / E7 (HspE7)	16
CSL	E6 / E7	Fusion protein (CerVax 16 ™)	16
Cytel	E7	Peptide	16
University of Leiden	E7	Peptide	16
Zycos	E7	Microparticle-delivered DNA (Zyc 101)	16
MediGene	L1, E7	Chimeric VLPs	16
NCI	L1 / L2 / E7	Chimeric VLPs	16

intraepithelial lesions (LSIL) can regress naturally, it is probable that cases of regression were due to the vaccine since the rate of regression was particularly high in vaccine recipients. Regression of lesions is less frequently observed in patients with high-grade squamous intraepithelial lesions (HSIL), and complete regression in some vaccinees with HSIL is encouraging. However, in the absence of placebo-controlled randomized clinical trials comparing the regression of the lesions, it is only possible to speculate on the clinical efficacy of the therapeutic vaccines.

The development of therapeutic vaccines is thus moving away from a vaccine that aims to eradicate tumor cells to a vaccine that aims to prevent the LSIL and HSIL from progressing to in situ and invasive cancer. If only a limited virological and clinical response is foreseeable with these therapeutic vaccines, it could be expected that a reduction in the viral load in infected cells might result in a significant slowdown in the evolution of the disease. However, if LSIL and HSIL become the target of therapeutic vaccination, the addition of other viral components, such as non-structural proteins E2 and E4 and perhaps structural proteins L1 and L2, to the vaccine must be investigated for their possible therapeutic effects. Larger placebo-controlled studies are necessary to demonstrate that the virological and clinical efficacy observed is a consequence of the immunization and not due to spontaneous regression of the lesions. However, such an investigation is hampered by the fact that evidence must be obtained through ethically acceptable trial designs. Although clinical vaccine studies are continuing, it is unlikely that an effective therapeutic vaccine will be available and recommended for widespread use within the next five years.

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test results. Results from the Bristol pilot study, showed that the rate of inadequate smears fell from 9–10% to 1.5% and reduced the average waiting time for test results from eight to two weeks.

The NHS cancer-screening programme also announced that the frequency of cervical screening is being changed from the current interval of every three to five years for women aged 20–64 years. Women will be invited for a first test at the age of 25 years and will be offered screening every three years until the age of 50. Cervical screening will then be offered every five years for women aged 50–64 years.

Julietta Patnick, director of the NHS cancer-screening programmes, said: "The introduction of liquid-based cytology offers a major improvement to the cervical cancer screening programme."

She added: "I am also pleased that we are standardising the interval for screening based on good evidence from our own programme. These changes, in our view, mean that English women will have access to the best cervical screening programme in the world."

The NHS programme has been associated with a 42% drop in the incidence of cervical cancer in England and Wales between 1988 and 1997. Up to 300.000 women a year, however, are estimated to need repeat testing because their smears cannot be read properly.

HPV TESTING AFTER CIN TREATMENT

Summary

Human papillomavirus (HPV) DNA is regularly cleared after treatment of cervical intraepithelial neoplasia (CIN) because the transformation zone -the feeding ground for the causal agent- is removed. The negative predictive value (NPV) of HPV testing is very high, indicating that a negative HPV test almost excludes CIN persistence or recurrence after CIN treatment. This is also true after incomplete conization with positive margins. The sensitivity of an HPV test with regard to the detection of CIN recurrence, is high. The combination of cytology and HPV testing increases the safety of follow-up after CIN therapy. HPV testing helps to avoid over- or undertreatment after CIN therapy.

After therapy of CIN, recurrence rates of 3 to 15% are observed. After incomplete resection showing positive cone margins, the recurrence rate reaches 22% on average.[1] The incidence of invasive cervical cancer in women after conization due to CIN-3 is reported to be at 1 per 1000 per year, which gives a cumulative incidence of 1% after 10 years.[2]

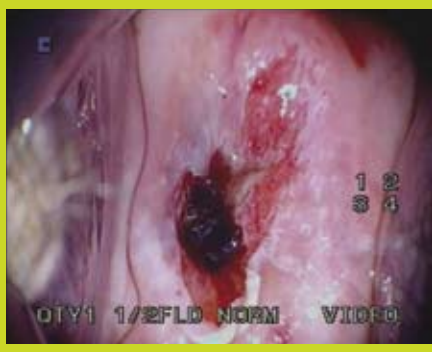
Repeat follow-up after treatment has so far consisted of repeat cytology and possibly colposcopy. A drawback of close follow-ups with repeat cytology is the relatively high rate of postoperative positive cytology results. However, a histologically proven CIN lesion, has been found in only 40 to 60% of the positive Pap smears after conization.[3] Reparative cytological changes seem to be responsible for this phenomenon of reduced specificity. On the other hand, lots of data have been accumulated that the sensitivity of cytology in screening for cervical cancer and its precursors is inferior compared to HPV DNA testing.

Repeat follow-up by colposcopy requires a gynaecologist trained in that method. It is time-consuming and expensive. Furthermore, colposcopic examination after conization, is quite often unsatisfactory, because of the endocervically dislocated squamocolumnar junction.[4] Therefore, an improvement in the follow-up after CIN treatment, seems desirable to avoid unnecessary anxiety of the patient, as well as to not overlook a CIN recurrence.

Infection with HPV is a prerequisite for the development and maintenance of the vast majority of cervical intraepithelial neoplasia and cervical cancer.[5,6] In previous studies it has been reported that HPV DNA is usually no longer present two years after effective treatment for CIN.[7] In recurrent CIN high-risk HPV DNA could be detected.[8] These data suggest that strategies for follow-up after treatment of CIN based on monitoring HPV persistence, may be feasible.

A positive HPV DNA test result after CIN treatment can be found in 0-92%,[8] although in many studies detailed reports about the rate of positive resection margins, CIN persistence or recurrence are missing. Furthermore, a significant variation in the type of CIN treatment modality can be noted within one study as well as between the studies. This allows only a reduced comparability between the studies. However, we tried to answer the following questions in the context of the evaluation of HPV DNA testing as a follow-up method after CIN treatment.

Picture 1



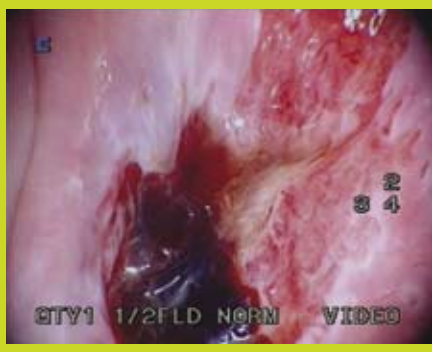
Colposcopy 6 month after LEEP *with 3% acetic acid: fragile epithelium, atypical transformation zone with erosion and repair between 1 and 4 o´clock.*

Cytology: repair and inflammation, can not rule out CIN (*Pap* III).

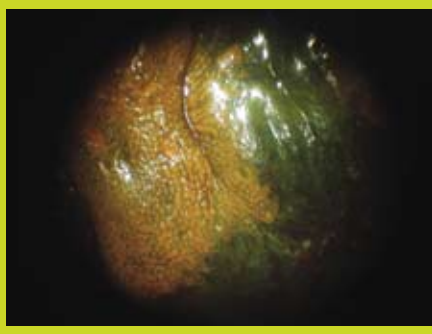
HPV HC 2: *high-risk* HPV *positive.*

Histology (punch biopsy after 9 months): CIN 3.

*Re-*LEEP: CIN 3 *with clear margins.*



Picture 2

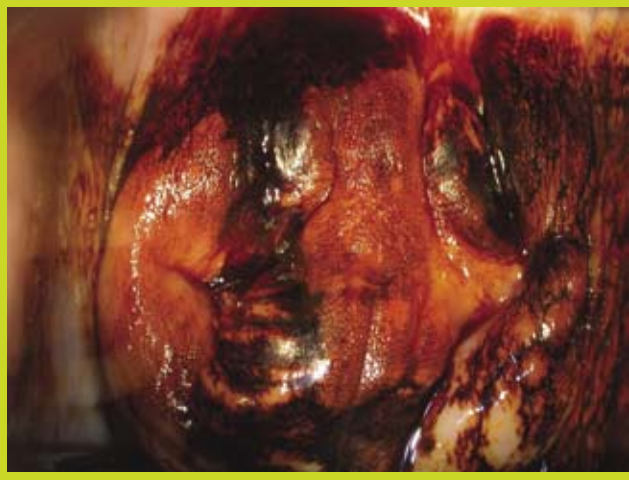


44 year old patient with a history of CIN 3 *cold knife conization 4 years ago and hysterectomy 2 years ago because of* HSIL/CIN 1-2.

Referred to colpo clinic because of ASCUS *and* HR HPV *positive.*

Colposcopy: VAIN 2-3; *cytology* HSIL; *biopsy* VAIN 3.

Treatment: CO_2*-laser vaporization.*



Peter Hillemanns, Christian Dannecker
Department of Obstetrics and Gynecology. Klinikum der Universität München, Germany

What is the rate of HPV DNA clearance after CIN treatment? Are there any differences between ablative methods such as cold-knife conization or loop diathermy (LEEP/LLETZ) and destructive methods such as cryotherapy? How long do we have to wait for HPV clearance?

A successful CIN treatment usually results in HPV clearance. Most studies have reported a very low HPV persistence after successful CIN therapy (no detectable persistent or recurrent CIN). The case-control study by Cruickshank et al. showed a positive HPV test six months after therapy, in only 12% of patients without CIN recurrence, compared to 29% in the group with recurrent CIN.[9] This gives an odds ratio of 2,9 for a CIN recurrence based on the presence of a positive HPV test. In another case-control study of Acladious et al., 47% of the patients with recurrent CIN were HPV positive, whereas only 6% of the cured patients harboured HPV DNA.[10] Kjelberg et al. reported that only three (2,7%) out of 108 women tested HR-HPV positive 35 months after conization, and the type-specific clearance rate even reached 100%.[11] In the same study, 37 of the untreated women presented had high HPV persistence rates during the same observation period. Obviously, HPV clearance correlates with successful CIN therapy.

A study published by Nobbenhuis et al. gives us some information about the time intervals of HPV clearance after CIN therapy.[12] Three months after successful conization without recurrence, 86% of the patients were already HPV negative, reaching 99% after 24 months. On average, HPV was negative after eight months in patients without recurrence (range 4–18 months). Clearance rates of high-risk HPV DNA decreased with increased severity of the lesion ($p = 0,02$). HPV clearance occurred, on average, 3 months before cytological regression.

A relatively fast HPV clearance of 91% after 3 months was demonstrated in the study of Kucera et al.[13] Elfgren et al. compared the postoperative HPV persistence rate in patients undergoing different treatment modalities.[14] 6 months after needle conization, HPV DNA could be detected less often than after cryotherapy (7% versus 36%). An incomplete resection showed a high HPV persistence rate of 69%.

Are there any differences in the HPV persistence rates after complete versus incomplete resections?

A negative HPV test after treatment has a very high negative predictive value. In the majority of the studies a very high NPV for HPV testing after CIN treatment was demonstrated: between 92% and 100%. This also holds true for conizations of CIN3 lesions with positive resection margins. Jain et al. analyzed a collective with 42% positive resection margins and 18% positive endocervical curettages.[15] No patient with a postoperative negative HR-HPV test had residual CIN in the hysterectomy specimen. The NPV of HPV detection after conization is superior to cytology. Nobbenhuis et al. had an NPV for HPV of 98% after 6 months compared to cytology with 93%.[12] The 3-month interval for HPV testing still has a high percentage of HPV-positive patients.[16] The combination of a negative HPV test and a negative pap smear further improves the predictive value.

What is the sensitivity of HPV DNA for the detection of persistent or recurrent CIN? Is there an additional benefit using combined cytology and HPV testing after CIN treatment?

The sensitivity of a positive HPV test after CIN treatment for the detection of a CIN persistence or recurrence is high in most studies. However, there is a significant variation, between 47 and 100%. Compared to cytology, HPV DNA testing is equivalent or, in most studies, shows even better results.[8,10,12,15] Chua et al. achieved only 50% sensitivity of cytology three to four months after CIN treatment, whereas HPV testing yielded 92%,[8] which is very similar to the Dutch study (62% versus 92% after 6 months).[12] Furthermore, both test methods have similar specificity (91% and 92%). However, two studies reported less-favourable results for HPV testing. Combined cytology with colposcopy had a higher sensitivity (100%) than HPV DNA testing alone (50%) and could improve the sensitivity of combined HPV testing and cytology up to 72% compared to HPV testing alone.[10,17]

The HPV approach required fewer colposcopic and reconization procedures to detect one case of residual CIN 2-3. Its higher positive predictive value than that of cytology provided a significant decrease in false-positive rates and a reduction of US$88 per detected case.[18]

What are the take-home messages? What can be implemented into routine?

Despite the growing number of studies published, recommendations concerning the accuracy of HPV testing in the follow-up of patients with CIN treatment are limited because of missing prospective randomized studies with long follow-up of HPV testing. However, based on current evidence it can be stated that a successful CIN treatment usually leads to HPV clearance. This has significant implications since HPV persistence is known to be a prerequisite for the progression and persistence of CIN.[5,19] Therefore, destruction or excision of the CIN epithelium may represent an effective therapy in the removal not only of neoplastic tissue but also of an HPV infection. This information has significance in preoperative counselling. Different methods such as cold-knife conization versus LEEP/LLETZ did not show different HPV clearance rates. Cryotherapy, however, had a lower HPV clearance rate.[14]
A negative HPV test nearly excludes a recurrent or persistent CIN after treatment. This is important in patients with positive resection margins in their conization

specimens because it allows a conservative follow-up of these patients without the necessity of immediate reconization or even hysterectomy. HPV testing alone seems to require fewer colposcopic and reconization procedures, and costs less than cytology to detect residual CIN.

However, one has to keep in mind that HPV clearance after CIN treatment may need a couple of months. About 10% of patients without recurrence still have a positive HPV test 6 months after CIN therapy. This time interval seems appropriate for the first follow-up HPV DNA testing.

Based on current data, additional HPV testing leads to a significant improvement in the detection rate of recurrent or persistent CIN and should be implemented in the routine follow up procedure. Postoperative cytology cannot be omitted in the follow-up at the moment.

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1. Reich O et al. Cervical intraepithelial neoplasia III: long-term follow-up after cold-knife conization with involved margins. Obstet Gynecol 2002;99(2):193–196. **2.** Soutter WP et al. Invasive cervical cancer after conservative therapy for cervical intraepithelial neoplasia. Lancet 1997;349(9057):978–980. **3.** Bollen LJ et al. Prediction of recurrent and residual cervical dysplasia by human papillomavirus detection among patients with abnormal cytology. Gynecol Oncol 1999;72(2):199–201. **4.** Bigrigg A et al. Efficacy and safety of large-loop excision of the transformation zone. Lance. 1994;343:32–34. **5.** Nobbenhuis MA et al. Relation of human papillomavirus status to cervical lesions and consequences for cervical-cancer screening: a prospective study (In Process Citation). Lancet 1999;354(9172):20–25. **6.** Ho GYF et al. Natural history of cervicovaginal papillomavirus infection in young women. New Engl J Med 1998;338:423–428. **7.** Elfgren K et al. Conization for cervical intraepithelial neoplasia is followed by disappearance of human papillomavirus deoxyribonucleic acid and a decline in serum and cervical mucus antibodies against human papillomavirus antigens. Am J Obstet Gynecol 1996;174(3):937–942. **8.** Chua KL et al. Human papillomavirus analysis as a prognostic marker following conization of the cervix uteri. Gynecol Oncol 1997;66(1):108–113. **9.** Cruickshank ME et al. Persistent infection with human papillomavirus following the successful treatment of high grade cervical intraepithelial neoplasia. Brit J Obstet Gyn 2002;109(5):579–581. **10.** Acladious NN et al. Persistent human papillomavirus infection and smoking increase risk of failure of treatment of cervical intraepithelial neoplasia (CIN). Int J Cancer 2002;98(3):435–439. **11.** Kjellberg L et al. Regular disappearance of the human papillomavirus genome after conization of cervical dysplasia by carbon dioxide laser. Am J Obstet Gynecol 2000;183(5):1238–1242. **12.** Nobbenhuis MA et al. Cytological regression and clearance of high-risk human papillomavirus in women with an abnormal cervical smear. Lancet 2001;358(9295):1782–1783. **13.** Kucera E et al. Is high-risk human papillomavirus infection associated with cervical intraepithelial neoplasia eliminated after conization by large-loop excision of the transformation zone? Eur J Obstet Gynecol Reprod Biol 2001;100(1):72–76. **14.** Elfgren K et al. Rate of human papillomavirus clearance after treatment of cervical intraepithelial neoplasia. Obstet Gynecol 2002;100(5 Pt 1):965–971. **15.** Jain S et al. Negative predictive value of human papillomavirus test following conization of the cervix uteri. Gynecol Oncol 2001;82(1):177–180. **16.** Costa S et al. Factors predicting human papillomavirus clearance in cervical intraepithelial neoplasia lesions treated by conization. Gynecol Oncol 2003;90(2):358–365. **17.** Bekkers RL et al. The role of genotype-specific human papillomavirus detection in diagnosing residual cervical intraepithelial neoplasia. Int J Cancer 2002;102(2):148–151. **18.** Almog B et al. Clinical and economic benefit of HPV-load testing in follow-up and management of women postcone biopsy for CIN2-3. Br J Cancer 2003;89(1):109–112. **19.** Remmink AJ et al. The presence of persistent high-risk HPV genotypes in dysplastic cervical lesions is associated with progressive disease: Natural history up to 36 months. Int J Cancer 1995;61:306–311.

WORLD CONGRESS FIGO 2003

The FIGO 2003 World Congress was one of the most important scientific events to take place in the field of Obstetrics and Gynaecology in recent years. This conference successfully brought together 9.000 participants. The event was organized around 140 monographic sessions covering the hottest topics in the field, both from the point of view of basic, innovative science and from a clinical and therapeutic point of view. There was a constant effort to ensure that the scientific presentations were attractive enough so that the interests of all participants would be met.

Some sessions covered very innovative topics (leptins, inhibins, metalloproteinases, Sports and Women, Organisation of Oncology Units, etc.) and others clinical topics (Myomas, Policystic Ovarian Syndrome, Pelvic Floor, Adolescent Pathologies, etc.). A great number of social health topics were discussed, and many groups organised their own specific sessions (World Health Organization, International Federation of Fertility Societies, etc.). There were also sessions on secondary topics of unquestionable interest to the professional, such as the use of robotics or a session which discussed the procedures involved in scientific journal publication. Interest was also centered on the important topics of maternal health throughout the world. To this end, various sessions were organised to cover topics related to maternal mortality and how to prevent it.

FIGO 2003 was one of the most important scientific events to take place in the field of Obstetrics and Gynaecology in recent years

Many national and international scientific societies organised sessions (International Urogynecological Association, World Association of Perinatal Medicine, Spanish Society of Gynaecology and Obstetric, European Board and College of Obstetrics and Gynaecology, American College of Obstetrician and Gynaecologist, Brazilian Federation of Gynaecology and Obstetrics Societies, Argentinian Federation of Gynaecology and Obstetrics Societies, Latino American Federation of Obstetrics and Gynaecology Societies, etc.) presenting their most significant work and research.

Among the culminant events in the conference were the Keynotes and New Perspective Lectures, which were delivered by world-renowned authors. For example, Markus Sépala, gave The De Watteville Lecture discussed the role of certain endometrial and myometrial proteins as regulators of reproductive processes such as implantation as well as certain regulatory elements involved in the growth of cancer cells. Another speaker was Dr. F. Xavier Bosch, who discussed that cervical cancer is essentially the result of a viral infection with some types of papillomavirus leading to two courses of action: preventive and therapeutic. For example, methods exist for the prevention of sexually-transmitted infections, such as papillomavirus. Furthermore, antiviral therapy may be used in the future to treat genital cancer. Along these same lines, vaccines are currently being developed to prevent HPV infection.

the recognition that cervical cancer is a result of a viral infection with some types of papillomavirus, paves the way for preventive and therapeutic actions

Prof. Petraglia presented one of the leading-edge topics, discussing the role of certain neurohormones of placental origin in the control of foetal growth and development, as well as their role in development of the pregnancy. Dr. Croxato reviewed the current situation of contraception throughout the world and analysed various methods, particularly the newest methods, and the different tendencies currently observed in different parts of the world. He placed particular emphasis on contraception in third world countries, where it is a definite problem due to the general population's lack of access to health services.

vaccines are currently being developed to prevent cervical cancer, which is one of the most important cancers worldwide

FIGO is an institution whose objective is to increase awareness among all those who are involved in feminine health

Dr. Visser presented a critical analysis of the different technologies used in modern-day perinatal care. In recent years there have truly been great advances in technology available for use in monitoring pregnancy. However, technological advances do not always translate into improvements in perinatal outcomes, and on occasions technology has been put into practice more due to commercial pressure than to any true benefit it may provide. Dr. Leodolter reviewed the surgical Wertheim procedure, which is used to treat cervical cancer. He actually reviewed how surgical procedures have become less aggressive and less invasive, yet more effective than the traditional procedures and with less deformities and side effects.

Lastly, Dr. Belizán reviewed one of the most urgent problems in Latin America: maternal mortality. It should be noted that worldwide, one woman dies every minute due to problems related to childbirth, and another 30 are left with a significant deformity or lesion (such as a fistula). These numbers alone are disturbing, but in terms of infant mortality, approximately 3,4 million babies die in the immediate neonatal period every year. The conference presented the different attempts that have been made to alleviate this problem, indicating that the solution does not depend solely on medical treatment, but on a social organisation, in which various health care and social policies will play a fundamental role.

FIGO is an institution whose objective is to increase awareness among all those who are directly or indirectly involved in the problems of feminine health. Reality shows us each day that this objective sometimes becomes unachievable. For this reason, we need everyone's help.

Prof. Lluis Cabero Roura
Vice-president of FIGO

KEY PUBLICATIONS

SEGO 2002 CONSENSUS DOCUMENTS

Having been in preparation since 2002, the Consensus Documents of the Spanish Society of Gynecology and Obstetrics (SEGO) have recently been published. This publication dedicates an extensive chapter to papillomavirus infection, which provides complete, up-to-date information on aetiology, pathogenesis, and oncogenesis; epidemiology and natural history; pathology and clinical characteristics; screening and diagnosis; treatment and follow-up; special situations; and prevention and health care education.

Schering Corporation has assumed sponsorship and distribution of this Consensus Manual.

DIETARY INTAKE AND RISK OF PERSISTENT HUMAN PAPILLOMAVIRUS (HPV) INFECTION: THE LUDWIG-MCGILL HPV NATURAL HISTORY STUDY

J Infect Dis 2003;188:1508-1516.
Giuliano AR, Siegel EM, Roe DJ, Ferreira S, Baggio ML, Galan L, Duarte-Franco E, Villa LL, Rohan TE, Marshall JR, Franco EL.

This nested case-control study evaluated the association between dietary intake and persistence of type-specific HPV infection, during a 12-month period, among 433 HPV-positive women participating in an on-going longitudinal natural history study in Brazil. High dietary consumption of β-cryptoxanthin, lutein/zeaxanthin, and vitamin C, and consumption of papaya at least once a week, were all inversely associated with persistent HPV infection, a strong biomarker of risk of cervical cancer.

CERVICAL CANCER: FROM ETIOLOGY TO PREVENTION

Thomas Rohan and Keerti V. Shah, editors.
Kluwer Academic Publishers, 2003.

Written by a team of leading cervical cancer scientists, this book reviews the accumulated evidence related to the biology, etiology, and prevention of cervical cancer. Two chapters are devoted to the biological basis of cervical cancer. Four chapters review the biology, molecular pathogenesis, exposure measurement, and epidemiology of HPV. Two chapters deal with the etiology and epidemiology of squamous-cell cervical cancer and cervical adenocarcinoma. Six chapters update the main preventive strategies to fight cervical cancer, including educational strategies, screening, chemoprevention, preventive and therapeutic HPV vaccines as well as policies for implementing cervical cancer prevention and control strategies.

MANAGEMENT OF WOMEN WHO TEST POSITIVE FOR HIGH-RISK TYPES OF HUMAN PAPILLOMAVIRUS (HPV): THE HART STUDY

Lancet 2003;362:1871-1876.
Cuzick J, Szarewski A, Cubie H, Hulman G, Kitchener H, Luesley D, McGoogan E, Menon U, Terry G, Edwards R, Brooks C, Desai M, Gie C, Ho L, Jacobs I, Pickles C, Sasieni P.

The HART study, a multicentre screening trial of 11.085 women aged 30-60 years, shows that HPV testing is significantly more sensitive than borderline or worse cytology (97,1% vs. 76,6%), but less specific (93,3% vs. 95,8%) for detecting CIN2+. HPV testing with cytological triage of HPV-positive women could be used for primary screening in women older than 30 years. HPV-positive women with normal or borderline cytology could be managed by repeat testing after 12 months. This approach could potentially improve detection rates of CIN2+ without increasing colposcopy referral rates.

CONDOM USE PROMOTES REGRESSION OF CERVICAL INTRAEPITHELIAL NEOPLASIA AND CLEARANCE OF HUMAN PAPILLOMAVIRUS (HPV): A RANDOMIZED CLINICAL TRIAL

Int J Cancer 2003 Dec 10;107(5):811-816.
Hogewoning CJ, Bleeker MC, van den Brule AJ, Voorhorst FJ, Snijders PJ, Berkhof J, Westenend PJ, Meijer CJ.

A clinical trial that included 148 women with cervical intraepithelial neoplasia (CIN) and their male sexual partners, who were randomized for condom use. The results showed that condom use significantly promoted regression of CIN and clearance of cervical HPV. Moreover, in a related paper, the trial also showed that condoms shortened the median time to regression of flat penile lesions (Bleeker et al, Int J Cancer 2003, 107: 804-810).

HIGH FREQUENCY OF DETECTION OF HUMAN PAPILLOMAVIRUSES (HPV) ASSOCIATED WITH EPIDERMODYSPLASIA VERRUCIFORMIS IN CHILDREN WITH PSORIASIS

Br J Dermatol 2003;149:819-825
Mahe E, Bodemer C, Descamps V, Mahe I, Crickx B, De Prost Y, Favre M.

It has been suggested that HPVs associated with *Epidermodysplasia verruciformis* (EV), including the oncogenic HPV-5, may contribute to the pathogenesis of psoriasis. This study found high levels of EV-HPVs in 26 children and 28 adults with psoriasis (38,5% and 35,7%, respectively), and also of HPV-5 (46,2% and 46,4%) and HPV-36 (15,4% and 25,0%). In contrast, lower levels were observed in controls (6,7-10,1% in 15 children with atopic dermatitis and in 28 healthy adults). The early detection of several EV-HPV genotypes in children suggests a putative role for these viruses in the pathogenesis of psoriasis.

CASE STUDY


Figure 1


Figure 2

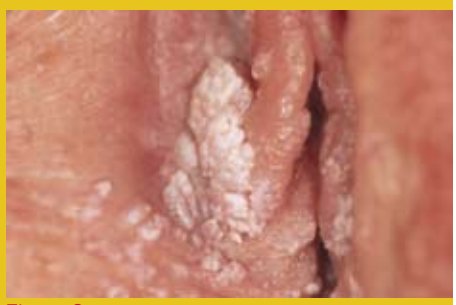
Figure 3


Figure 4


Figure 5

MANAGEMENT OF IMIQUIMOD INDUCED ERYTHEMA

Dr. Colm O'Mahony
Countess of Chester NHS Trust, Chester, England.

Imiquimod cream (Aldara®) is an excellent additional drug for the routine management of genital warts. Its two main attractive features for us in this clinic is that patients can treat themselves in the comfort and privacy of their own home, and the recurrence rates are low. There is a wide variation in the speed of response of patients to the cream. Some patients get an accelerated response with a lot of erythema, and this can alarm the patient and staff, and unfortunately, can result in cessation of therapy, bringing a sense of failure as the patient is returned to the other treatment protocols of podophyllotoxin, cryotherapy or electro-cautery, etc.

We have extensive experience in this department over seven years in the use of Imiquimod and managing any consequent erythema.

The following is a typical case showing extensive erythema, which simply required management - not cessation.

A 24-year-old female attended in October 2002 with extensive genital warts, which had been present for 2 months. There were some very large warts and these were treated with cryotherapy on that visit, and she was also given imiquimod to use 3 times a week. In mid-November, she attended with severe vulval erythema and still had extensive warts (Figures 1, 2 & 3). Note that the erythema spreads beyond the wart area in a "field effect", indicating that there is probably HPV in the whole area of the erythema rather than just in the wart area. She was advised to stop the imiquimod until the inflammation settled, i.e. 2-3 weeks, and then gradually re-start.

In January 2003, she gradually re-introduced the imiquimod once a week, and also had a session of cryotherapy to three of the larger warts. When seen in mid-February, the warts had completely cleared and there was no further erythema (Figures 4 & 5).

This case illustrates the typical inflammatory reaction that can develop when the immune response becomes activated. This erythema is usually painless and generally requires nothing more than washing and salt baths. Patients should be reassured that this indicates immune-system activity and is a good omen for wart clearance. It also has to be emphasised, of course, that erythema is not a pre-requisite for the imiquimod to be effective. Also, many clinics use a combination of physical (ablative) therapies and imiquimod to speed up the process, and some patients psychologically like to see some of the larger warts being de-bulked.

In summary, neither patient nor physician should get alarmed with the erythema of the immune response. Patience and reassurance is all that is required. If the patient wishes, cryotherapy can be performed during the resolution phase of the erythema.

INTERNATIONAL AGENDA

5th - 10th March 2004

American Academy of Dermatology Annual Meeting
City: Orlando, Florida, USA.
Secretariat: American Academy of Dermatology. 930 North Meacham rd PO Box 4 Schaumburg, IL - 60168-4014 .
Tel: +1 847-330-0230
Fax:+1 847-330-1090
E-mail: rescalante@aad.org

24th - 27th March 2004

Annual Meeting of the Society of Gynecologic Investigation
City: Houston, Texas, USA.
Venue: The Westin Galleria. 5060 West Alabama, Houston, Texas 77056.
Contact: Society for Gynecologic Investigation. 409 12th Street, SW. Washington, DC 20024.
Tel:+1 202 863-2544
Fax: +1 202 863-0739
E-mail: lgilders@acog.org
Web: www.sgionline.org

10th - 11st April 2004

XV International Congress Of Cytology
City: Santiago, Chile.
Venue: Campus Occidente. Universidad de Chile.
President: Matías Jiménez-Ayala FIAC.
Contact: Ms. Marta Moreno.
Tel: +1 56-23-368-216
Fax: +1 56-22-332-996
E-mail: mmoreno@tajamar.cl
Web: www.xvcongress.cl

29th April - 1st May 2004

2nd Congress of Clinical Microbiology and Infectious Diseases (ECCMID)
City: Budapest, Hungary.
Venue: Novotel Budapest Congreso. 1123 Budapest, Jagelló út 1-3.
President: JH Saurat.
Fax: +36 1 383 79 18
E-mail: info@ead-vbudapest2004.com
Web: www.eadvbudapest2004.com

14th - 19th May 2004

Joint Medical Society for the Study of Venereal Diseases (MSSVD) and IUSTI Spring Meeting
City: Bath, UK.
Venue: Victoria Hall, Leeds Town Hall.
President: Dr Angela Robinson.
Secretariat:Academic Department Royal Society of Medicine 1 Wimpole Street London W1G 0AE.
Tel: +44 20 7290 2968
Fax: +44 20 7290 2989
E-mail: mssvd@rsm.ac.uk
Web: www.mssvd.org.uk/bath04.htm

16th -19th May 2004

37th Annual Scientific Meeting and trade exhibition. Australasian College of Dermatologists
City: Sidney, Australia.
Venue: Sydney Convention & Exhibition Centre (Convention Centre South), Darling Harbour, Sydney.
Secretariat: Australasian College of Dermatologists. PO Box B65 Boronia Park - NSW 2111 Australia.
Tel: +61 (02) 9879 6177
Web: www.dermcoll.asn.au/asm37/asm37.html

22nd - 24th July 2004

The International Skin Cancer Congress
City: Zürich, Switzerland.
President:Günter Burg
Secretariat: Reinhard Dummer. University Hospital of Zürich Department of Dermatology. Gloriastrasse 31. Zurich - 8091. Switzerland
Tel: +41 1 255 88 37
Fax: +41 1 255 44 03
E-mail: nicole.brunner@usz.ch
Web: www.skincancer.ch

1st - 4th October 2004

International Congress of the Lower Genital Tract and Colposcopy XXXIII Annual Meeting
City: Buenos Aires, Argentina.
Secretariat: Argentine Society of the Lower Genital Tract and Colposcopy.
E-mail: sociedad@colpoweb.org

21st - 23rd October 2004

Eurogin 2004. International Expert Meeting. HPV Infection and Cervical Cancer Prevention Priorities and New Directions-physicians, Patients and Public Health Issues
City: Nice, France
Contact: EUROGIN France.
174, rue de Courcelles, 75017 Paris, France.
Tel: +33 1 44 40 01 20,
+33 1 47 66 05 29
Fax: +33 1 47 66 74 70
E-mail: admin@eurogin.com

10th - 13th November 2004

Portuguesse Society of Obstetrics and Gynaecology National Congress
City: Lisbon, Portugal.
Venue: Universidad Catolica.
Contact: Carlos Santos Jorge.
E-mail: csjorge@netcabo.pt

30th April - 6th May 2005

22nd International Papillomavirus Conference
City: Vancouver, Canada
Venue: Hyatt Regency
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E-mail: joelp@mediane.ucsf.edu
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