HPV Today

Newsletter on Human Papillomavirus

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THE HART STUDY: GENESIS, RESULTS AND FUTURE

INTERVIEW WITH JACK CUZICK

The HPV in Addition to Routine Testing (HART) Study is having an impact on the screening scenario. What can you tell us about the study and its origins?

The HART study arose out of a long-standing interest in the use of the knowledge of HPV as the causative agent in cervical cancer. Back in 1983, in the same year as the discovery of HPV-16 by Durst & zur Hausen,[1] we initiated our first triage study with Michael Campion and Albert Singer.[2] That study examined 100 women with low-grade smears, and even with the relatively poor HPV-testing technology available then, we were able to show a clear difference in the progressive potential of HPV-16-like viruses compared to HPV-6. This led to a desire to investigate triage more systematically, and Tony Hollingworth joined us to do a thesis on the subject, initially using the old Filter In-situ Technology (FISH) for HPV testing. Results with FISH were not overly convincing. However, George Terry and Linda Ho soon joined us and set up a Polymerase Chain Reaction (PCR)-based HPV laboratory at University College, London. With this methodology we were again able to show that HPV-16 (and other high-risk types) were strongly associated with concurrent high-grade lesions, and this made it clear to us that there would be a clinical role for HPV testing.[3,4]

What were the first results on the sensitivity of HPV testing as a screening test?

By now we were ready to take the bold step of evaluating HPV in the context of a routine primary screening test. Now Anne Szarewski joined us, and as part of her PhD thesis activities, took on the clinical responsibility for conducting the first study, which was performed on 2000 younger women at the Margaret Pyke Centre in London. For this study we only tested for HPVs-16,-18,-

(continues on page 3)

Nº 05 September 2004

EDITORIAL

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HPV Today is rapidly becoming a significant communication vehicle between the HPV research community and the professionals involved in the prevention diagnostics and treatment of HPV. The newsletter now has a print run of 20,000 copies and is expanding remarkably in the form of electronic distribution, both as direct subscriptions and via scientific societies. We are pleased to announce, as of this issue, an enhanced collaboration with the editors of Papillomavirus Report and with the International Papillomavirus Society.

The cover interview with Jack Cuzick refers to the publication of the results of the HPV in Addition to Routine Testing (HART) Study, an investigation on management strategies of women with normal or borderline cytology and positive for high-risk HPV types. The study reiterates the increased sensitivity of HPV tests to detect prevalent or short-term incident cases of CIN2+ and concludes that a management strategy advising yearly follow-up in the context of screening programs is safe and efficient.

The International Agency for Research on Cancer (IARC) is now editing a new monograph on Screening for Cervical Cancer based upon the work of an international group of scientists that gathered in Lyon early in 2004. The monograph updates the previous publication of 1986 on the same subject, and concluded that there is sufficient evidence to consider HPV testing as a primary screening test with expected results at least as good as the ones achieved with conventional cytology. The same evaluation was reached by liquid-based cytology and computer-read cytology. These qualifications open the way for large demonstration projects comparing HPV tests and cytology directly, as well as for considering protocols of HPV screening as the primary test (with cytology as a triage option) in some populations.

The growing use of HPV tests in some countries has prompted studies on the emotional consequences generated among women (and their physicians) when faced with a diagnosis of HPV with normalcy or ambiguity in the cytology. Educational efforts at the clinical and population levels will be increasingly required, and some guidance is provided by the contribution of Barbara Moscicki based upon her work with adolescent women in the San Francisco area.

Finally, our colleagues from Australia announce the creation of the Asian Oceania Research on Genital Infections and Neoplasia (AOGIN), a novel and very active consortium devoted to stimulate HPV research and education in the Asia Oceania Region.

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JACK CUZICK

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(from page 1) 31 and -33 by type-specific PCR. We were astounded by the results.[5] Even with only four HPV types, the relative sensitivity of HPV for Cervical Intraepithelial Neoplasia (CIN)2+ lesions was 75%, compared to 56% for cytology. At that time the poor sensitivity of cytology was revolutionary news and was not readily accepted. It provoked an outcry from the cytologists, but these findings have since been confirmed in many studies.

What technology did you use in your early studies?

A weakness of this and most of the other early HPV studies was that they were based mostly on younger women, because they were a more convenient source of patients. However, the main failings of conventional screening were in older women, where most of the cancers occur. This time we linked up with Elisabeth Beverley to do a screening study in 3,000 women over the age of 35 at the Hammersmith Hospital under the supervision of Pat Soutter. This was the prototype for General Practitioner-based HPV testing and Elisabeth was kept very busy managing the 40 General Practitioner (GP) practices which contributed to this study. Again, the results were encouraging and reinforced the greater sensitivity of HPV testing.[6] This study also highlighted problems with specificity in the Sexual Health Responsability Program (SHARP) PCR system and especially the early Hybrid Capture I assay; subsequent testing with Hybrid Capture II greatly improved the performance characteristics.

The HART *team. Front row left to right: Janet Austin, Anne Szarewski, Linda Ho. Back row: Louise Cadman, Rob Edwards, Peter Sasieni, Jack Cuzick, George Terry, Philip Londesborough.*

When an HPV test is introduced, there will be a certain number of women with HPV-DNA who are normal on cytology. Does the HART Study contribute new information on the management guidelines for such women?

The stage was now set for a much larger multi-centre trial of HPV testing in routine practice. By now, the greater sensitivity of HPV was pretty well established, and a key question was how best to manage women who were HPV-positive but cytology-negative. In addition, we wanted to explore further the role of HPV testing for women with borderline cytological abnormalities and build on the ASCUS/LSIL Triage Study (ALTS) results. We took on this challenge in the HART study in which these women were randomised to immediate colposcopy vs follow-up with HPV testing and cytology. By examining cross-sectional detection rates, we would also make a substantial contribution to the rapidly increasing literature on sensitivity and specificity of HPV testing in routine screening. The study was conducted in five referral centres in London, Birmingham, Mansfield, Manchester and Edinburgh, with smears being taken in 161 GP practices. We now had the Hybrid Capture II assay and aimed at recruiting 12,000 women. The trial outline is shown in Figure 1.

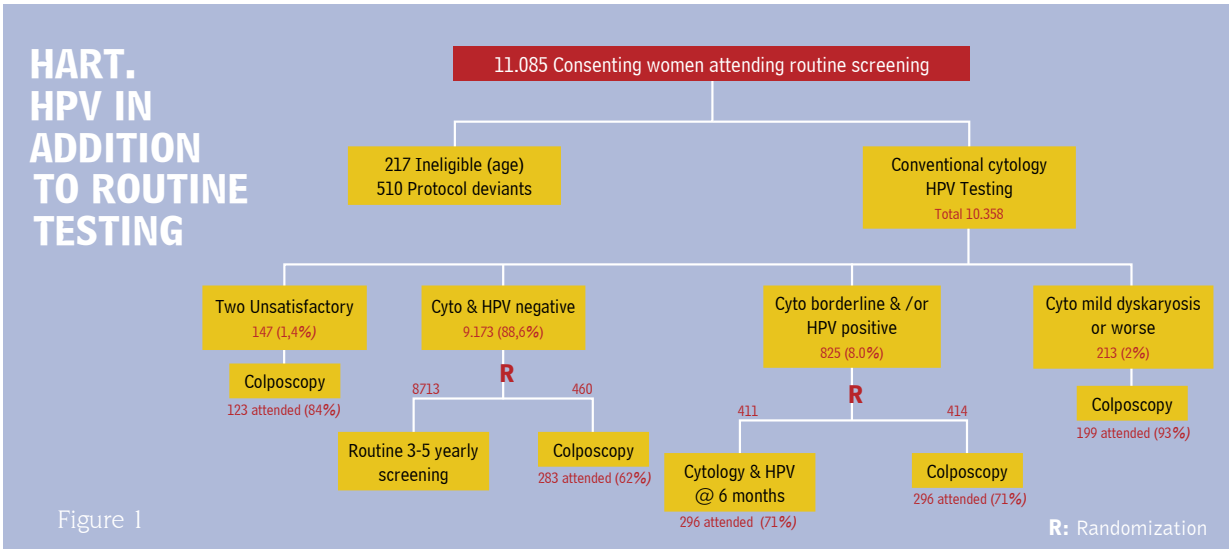

Figure 1

Was it easy to conduct such a complex trial using the GP clinics as your recruitment?

Recruitment proved more difficult than expected, mostly due to the time required to obtain fully informed consent for randomisation. GPs and nurses in busy surgeries often did not have time to spend 30-60 minutes describing the study, when the procedure itself took only five minutes and waiting rooms were full. If screening modalities are to be evaluated on this scale, it will be necessary to make clear policy statements and abbreviate consent procedures for tests which have enough prior data to indicate they are at least as good as the conventional test. This should be a major priority for screening research, and the recent International Agency for Research on Cancer (IARC) statement on HPV testing should help enormously in this respect (www.iarc.fr/).

Can you summarize the key findings of the study?

The results of the HART study have recently been published[7] and have further stimulated interest in HPV testing. As expected, HPV testing was substantially more sensitive than cytology (97% *vs* 76%), but less specific. The randomisation gave useful directions for managing HPV-positive, cytology-negative women. The results supported a policy of re-screening them at a one-year interval. This led to regression of HPV in about 42% of cases, and the HPV test remained positive in all cases that had CIN2/3 lesions. When combined with borderline smears, the same conclusions were reached, and about one-half of the low-grade lesions regressed on follow-up. No high-grade lesions were found in HPV-negative women with normal, borderline or even mild cytological lesions, suggesting they could be safely returned to routine screening.

Where do we go from here?

HPV testing has been clearly shown to be more sensitive but less specific than cytology. The vastly greater sensitivity suggests that HPV might reasonably be the sole primary screening testing, and that cytology could be reserved for the triage of HPV-positive women. The HART study has indicated that HPV-positive, cytology-negative women can be managed by repeat testing at one year. A possible algorithm for this is shown in Figure 2.[8] IARC has recently concluded that there is sufficient evidence that HPV testing alone can reduce the incidence and mortality from cervical cancer. However, a number of implementation issues still need elucidation, such as the appropriate ages for starting and stopping screening, the screening interval, the value of new markers of persistent infections, and the cost-effectiveness of HPV-based programmes. Ideally, they should be addressed by randomised demonstration projects, but they need to be of a large size (up to one million women or more) to show effects on cancer incidence. Streamlined 'public health' study designs are needed if full evaluation is to take place. This will keep us all busy for the next decade!!

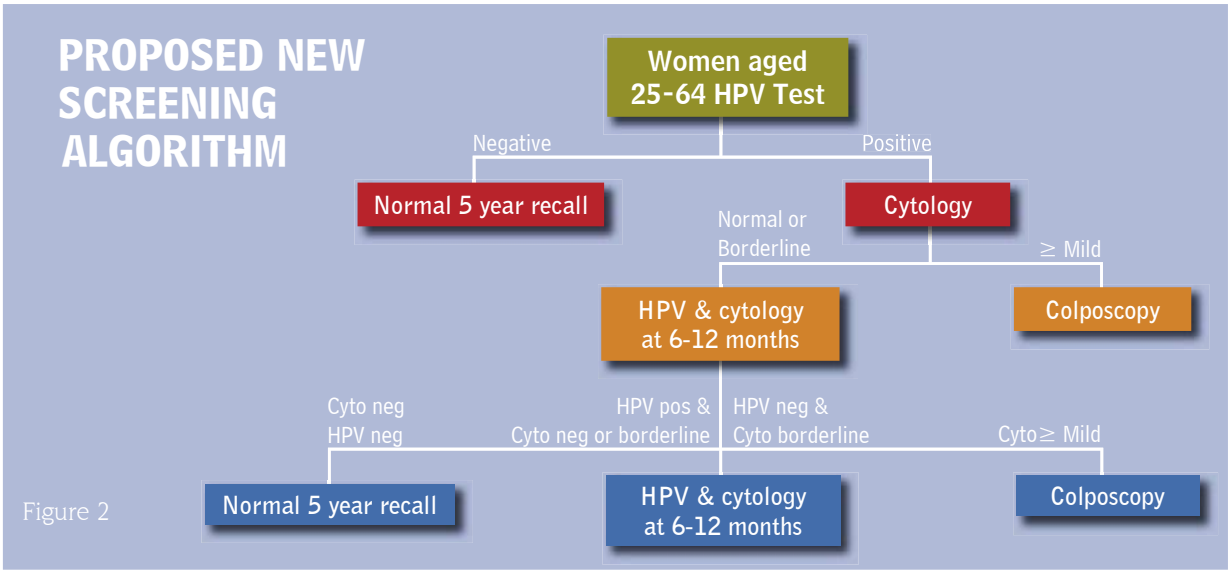

Figure 2

References: **1.** Durst M et al. A papillomavirus DNA from a cervical carcinoma and its prevalence in cancer biopsy samples from different geographic regions. Proc Natl Acad Sci 1983; 80: 3812-3815. **2.** Campion MJ et al. Progressive potential of mild cervical atypia: prospective cytological, colposcopic, and virological study. Lancet 1986; ii: 237-240. **3.** Cuzick J et al. Human papillomavirus type 16 DNA in cervical smears as predictor of high-grade cervical intraepithelial neoplasia. Lancet 1992; 339: 959-960. **4.** Cuzick J et al. Type-specific human papillomavirus DNA in abnormal smears as a predictor of high-grade cervical intraepithelial neoplasia. Br J Cancer 1994; 69: 167-171. **5.** Cuzick J et al. Human papillomavirus testing in primary cervical screening. Lancet 1995; 345: 1533-1536. **6.** Cuzick J et al. HPV testing in primary screening of older women. Br J Cancer 1999; 81: 554-558. **7.** Cuzick J et al. Management of women who test positive for high-risk types of human papillomavirus: the HART study. Lancet 2003; 362:1871-1876. **8.** Sasieni P et al. Could HPV testing become the sole primary cervical screening test? J Med Screen 2002; 9: 49-51.

HPV IN SCREENING AND TRIAGE

THE ASCUS AND LSIL TRIAGE STUDY (ALTS)

Diane Solomon

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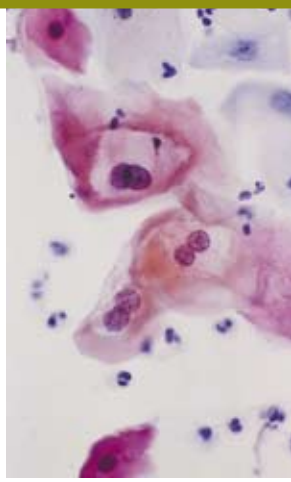


Figure: *Cytologic* LSIL *showing enlarged nuclei, binucleation and perinuclear cytoplasmic clearing (koilocytosis).*

What was the purpose of ALTS and how was it designed?

ALTS was a multicenter, randomized clinical trial sponsored by the National Cancer Institute (NCI) to compare three management strategies for women with equivocal and low-grade cytology results: (1) immediate colposcopy for all women; (2) HPV triage (referral to colposcopy if the enrollment HPV test was positive); and (3) repeat cytology with referral to colposcopy if the findings showed High-Grade Squamous Intraepithelial Lesions (HSIL). Four demographically diverse centers in the U.S. participated: University of Washington, Seattle; University of Oklahoma, Oklahoma City; University of Alabama, Birmingham; and Magee Womens Hospital of the University of Pittsburgh Medical Center Health System.

What were the conclusions in relation to the management of ASCUS?

ALTS found that HPV triage was at least as sensitive as immediate colposcopy in the detection of CIN3 or cancer (CIN3+) and would spare approximately half of the women (who are HPV negative) the emotional and financial burden of colposcopy. Follow-up by repeat cytology at the referral threshold of repeat ASCUS was also a safe triage option; however this strategy required more visits, and approximately two-thirds of women would be sent to colposcopy.[1]

The finding that about 50% of ASCUS were high-risk HPV positive underscores the biologic heterogeneity of this cytological interpretation. ASCUS is not a single entity, but rather the category encompasses HPV-related cell changes and findings that mimic these changes but are unrelated to HPV infection. HPV testing stratifies this heterogeneity by risk of CIN3+. In fact, HPV+ ASCUS is associated with the same risk of CIN3+ as LSIL (see Table).

What were the conclusions in relation to LSIL?

We found that cytological LSIL was associated with high HPV positivity of over 80% (range 79–86% at all four clinical centers). While the narrow range of HPV positivity indicates that the interpretation of LSIL is fairly reproducible (see Figure), the high HPV positivity also limits the clinical triage utility of the test to identify women who do **not** need colposcopy. Follow-up by cytology at a threshold that would provide at least 90% sensitivity for CIN3+ would refer more than two-thirds of women for colposcopy. These data suggest that there is currently no efficient triage for LSIL, but the cumulative risk for CIN3+ (16%) and CIN2 or above (28%) warrants colposcopic evaluation for U.S. practice.[2] Therefore, the Consensus Guidelines developed under the aegis of the American Society for Colposcopy and Cervical Pathology recommend colposcopy for LSIL.[3]

How generalizable are these findings?

A recent meta-analysis[4] compared the performance of HPV testing and repeat cytology following an ASCUS result. The findings, based on studies from several countries, reached the same conclusions as ALTS. At this point, we do not need additional large studies of different populations to compare international variation in HPV triage of equivocal cytology. Instead, different regions will need to explore the meanings of their laboratories' cytology terminology and its correlation with HPV positivity to determine the utility of HPV triage in their setting. We are in the process of developing an online library of cytological, histological, and colposcopic images linked to HPV and demographic information from ALTS to facilitate international correlative studies.

TABLE: TWO-YEAR CUMULATIVE DIAGNOSIS OF CIN2+ AND CIN3+ BY ORIGINAL CYTOLOGY AND HPV TEST

Original Diagnosis		Histologic Diagnosis after 2 years of follow-up	
Cytology	HPV test	CIN 2&3 Clinical center	CIN 3+ Pathology quality control expert group
ASCUS	HPV (-)	3.1%	1.7%
ASCUS	HPV (+)	27%	15%
LSIL	All	28%	16%

Immediate colposcopy and HPV Arms of ALTS TRIAL (N = 3,110)

The two year risk for CIN3+ *of an* ASCUS HPV(-) *is* 1.7% *as compared to* 15% *for an* ASCUS HPV(+). *The* CIN3 *risk of a* LSIL *is* 16%, *equivalent to the* ASCUS HPV(+). *In the* ALTS *trial, over* 80% *of the* LSIL *cases were* HPV-DNA (+).

ABBREVIATIONS
ASCUS: Atypical Squamous Cells of Undetermined Significance.
LSIL: Low-grade Squamous Intraepithelial Lesions.
CIN: Cervical Intraepithelial Neoplasia.

What are some future clinical HPV testing research questions?

HPV testing is not recommended as a triage test following an LSIL cytology result. However, the use of HPV testing as an adjunct to cytology for primary screening of women 30 and older will yield some cases of women with a combination of LSIL cytology and HPV-negative test results. Current interim guidance suggests colposcopy for such women.[5] We may need to reconsider management of HPV-negative LSIL as we collect data from this older age-group. We must also consider management strategies for women 30 and older who have negative cytology but a positive HPV test result on screening. Strategies that focus on identifying HPV persistence may provide greater specificity without compromising sensitivity.

References: 1. ALTS Group. Results of a randomized trial on the management of cytology interpretations of atypical squamous cells of undermined significance. Am J Obstet Gynecol 2003; 188:1383-1392. **2.** ALTS Group. Randomized trial on the management of low-grade squamous intraepithelial lesion cytology interpretations. Am J Obstet Gynecol 2003; 188:1393-1400. **3.** Wright TC Jr et al. 2001 Consensus Guidelines for the management of women with cervical cytological abnormalities. JAMA 2002; 287: 2120-2129. **4.** Arbyn M et al, Virological versus cytology triage of women with equivocal Pap smears: a meta-analysis of the accuracy to detect high-grade intraepithelial neoplasia. J Natl Cancer Inst 2004; 96:280-293. **5.** Wright TC Jr et al. Interim Guidance for the use of human papillomavirus DNA testing as an adjunct to cervical cytology for screening. Obstet Gynecol 2004; 103:304-309.

DEVELOPMENT OF HPV VACCINES

Professor Ian Frazer
Director of Centre for Immunology and Cancer Research - Brisbane, Queensland, Australia.

The Centre for Immunology and Cancer Research, a research centre of the University of Queensland at the Princess Alexandra Hospital in Brisbane, Australia, has been pursuing over many years, under the leadership of Dr Ian Frazer, vaccines to prevent and treat cervical cancer.

Therapeutic Vaccines

Initial research efforts in the 1980s were focused on understanding the immunobiology of the E7 protein of HPV-16, which at that time had only recently been recognised as a potential target for immunotherapy for cervical cancer. Preclinical studies by Dr Robert Tindle, now Director of the Sakzewski Virus Research Centre in Brisbane, used locally developed animal models to establish the immunogenicity of this protein,[1] and its potential as a vaccine to treat established transplantable tumours expressing E7 protein.[2] Subsequent clinical studies established the safety and immunogenicity of HPV-16 E7 protein in patients with cervical cancer,[3] and, in collaboration with Commonwealth Serum Laboratories (CSL Ltd, Melbourne, Victoria, Australia) of a combination of an E6E7 fusion protein with Iscomatrix adjuvant in patients with Cervical Intraepitelial Neoplasia (CIN)2/3.[4] Recognition that there were a wide range of potential therapeutic vaccines for cervical cancer and precancer, and no effective surrogate markers of vaccine efficacy that could be used to rank potential vaccines in preclinical studies, led to a collaboration between Dr Frazer's research group and Dr Paul Lambert at the McArdle institute in Madison Wisconsin, USA, to develop better models of cervical cancer immunology. A skin-grafting model was developed in which skin transgenic for the E7 protein could be grafted to normal mice,[5] and vaccines tested for their ability to promote graft rejection. This model is being used to understand the requirements for a successful vaccine[6] - recent data suggest that no simple protein or peptide vaccine alone is sufficient to promote rejection of the E7-expressing keratinocytes. Rather, high frequencies of specific CD8 T-cells are required, which can be achieved by passive transfer and immunisation. Resistance to killing appears to be local to the graft, and current studies are focussed on understanding the local mechanisms of resistance to immunotherapeutic responses.

Prophylactic Vaccines

Interaction in 1990 between Dr Ian Frazer's interests in immunology and Dr Jian Zhou's interests in papillomavirus structural biology, following a sabbatical spent by Dr Frazer in Cambridge, England, led to development of a method for production of papillomavirus virus-like particles (VLPs) where the major capsid protein of HPV-16 was expressed using recombinant vaccinia virus from the second initiation codon in the L1 open reading frame.[7] Alternate VLP production methods were developed, including *Baculovirus* systems, and *E. coli*. VLPs were shown to be highly immunogenic, generating strong antibody responses[8] without additional adjuvants.

References: **1.** Tindle, RW et al. A "public" T-helper epitope of the E7 transforming protein of human papillomavirus 16 provides cognate help for several E7 B- cell epitopes from cervical cancer-associated human papillomavirus genotypes. Proc Natl Acad Sci USA 1991;88:5887–5891. **2.** Tindle, RW et al. Immune response to human papillomaviruses and the prospects for human papillomavirus-specific immunisation. Curr Top Microbiol Immunol 1994;186:217–253. **3.** Frazer, IH et al. Vaccines for Human Papillomavirus infection and anogenital disease. Tindle,R.W. (ed.), pp. 91–104 (Landes Bioscience, Austin, Texas,1999). **4.** Frazer, IH et al. Immunotherapy for HPV associated pre-cancer. Cancer Immunity 2003;3 Suppl 1:25. **5.** Dunn, LA et al. Presentation of the HPV16E7 protein by skin grafts is insufficient to allow graft rejection in an E7-primed animal. Virology 1997;235:94–103. **6.** Frazer, IH et al. Tolerance or immunity to a tumor antigen expressed in somatic cells can be determined by systemic proinflammatory signals at the time of first antigen exposure. J Immunol 2001;167:6180–6187. **7.** Zhou, J et al. Expression of vaccinia recombinant HPV-16 L1 and L2 ORF proteins in epithelial cells is sufficient for assembly of HPV virion-like particles. Virology 1991;185:251–257. **8.** Zhou, J et al. Definition of linear antigenic regions of the HPV-16 L1 capsid protein using synthetic virion-like particles. Virology 1992;189:592–599. **9.** Zhang, LF et al. HPV-6b virus-like particles are potent immunogens without adjuvant in man. Vaccine 2000;18:1051–1058. **10.** Liu, WJ et al. Papillomavirus virus-like particles for the delivery of multiple cytotoxic T-cell epitopes. Virology 2000;273:374–382. **11.** Zhou, J et al. Papillomavirus capsid protein expression level depends on the match between codon usage and tRNA availability. J Virol 1999;73:4972–4982. **12.** Liu, WJ et al. Polynucleotide viral vaccines: codon optimisation and ubiquitin conjugation enhances prophylactic and therapeutic efficacy. Vaccine 2001;20:862–869.

VLPs as developed by Dr Frazer's group have been pivotal in their subsequent successful use in clinical trials as potential prophylactic vaccines against the cancer-associated papillomaviruses

The centre has also pursued trials of VLPs as immunotherapy for genital warts. Encouraging safety and immunogenicity results from an initial phase Ib study in man, in collaboration with colleagues at Wenzhou Medical College in China,[9] have led to an ongoing and expanded clinical testing program funded by the National Health and Medical Research Council (NHMRC) of Australia, the Wellcome Foundation and the Cancer Research Institute in New York.

Combined Prophylaxis and Therapy

Chimeric VLPs incorporating epitopes from various papillomavirus non-structural proteins were produced in the mid 90's by modifying the L1 gene sequence.[10] Such chimeric proteins were shown in pre-clinical studies to engender immune responses against the incorporated epitopes, which could be therapeutic with transplantable tumours. Concerns about stability and ease of use of chimeric VLPs led to exploration of better formulations for such vaccines. Oral delivery proved unreliable. Polynucleotide vaccines encoding chimeric papillomavirus L1 proteins were initially rather poorly immunogenic, until it was recognised that immunogenicity could be increased by codon modifying the L1 sequence to give better expression.[11] Combining codon modification with ubiquitin incorporation led to a polynucleotide vaccine which gave strong humoral immune responses against conformational neutralising determinants on PV virions, and equally strong cell-mediated immune responses against both the L1 protein and the incorporated epitopes.[11,12] These proved efficacious for both prophylaxis and therapy in pre-clinical trials, and novel delivery systems designed to improve immune responses in primates to such modified polynucleotide vaccines are now being developed in collaboration with colleagues at the University of Queensland.

HPV IN 100 SLIDES

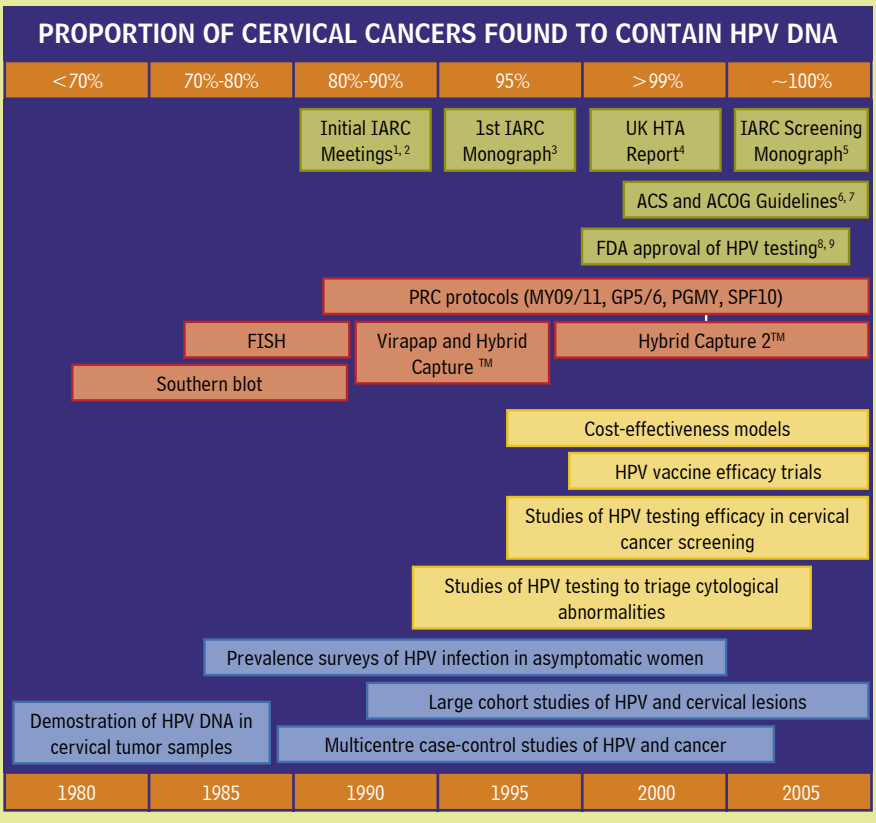
A TIMELINE OF RESEARCH AND POLICY TOPICS ON THE EPIDEMIOLOGY AND PREVENTION OF HPV INFECTION AND CERVICAL CANCER

LEGEND:

Green: Key policy milestones concerning HPV testing in cervical cancer screening.
Red: Successive HPV testing systems based on DNA hybridization.
Yellow: Domains of prevention and public health research on HPV and cervical cancer.
Blue: Predominant type of epidemiologic and clinical studies providing the evidence for an etiologic role for HPV in cervical cancer.

ABBREVIATIONS:

IARC: International Agency for Research on Cancer.
HTA: Health Technology Assessment.
ACS: American Cancer Society.
ACOG: American College of Obstetrics and Gynecology.
FDA: Food and Drug Administration.
FISH: Filter In-situ Hybridization.
PCR: Polymerase Chain Reaction.



Courtesy E. L. Franco

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HPV AND THE ADOLESCENT WOMEN

Are adolescents in the US aware of the existence of HPV?

Adolescents are aware of HPV as a disease "entity", mostly in the context of acquiring genital warts or developing cervical cancer. On the other hand, the medical term "human papillomavirus" remains relatively unfamiliar to most youths and the connection between warts, cancer and the virus is quite vague for most adolescents, if it exists at all.[1]

The association between Pap-smear diagnosis and HPV is also confusing for most adolescents (as it is for adults). Most sexually active adolescents who have had a pelvic examination are aware that a Pap smear was taken, but most do not know what the Pap smear detects or why they had the test.

Adolescents also frequently confuse the "H" viruses (Herpes Simplex Virus (HSV), Human Immunodeficiency Virus (HIV) and HPV). Care must be given to distinguish these in conversations with adolescents who have HPV infections, making sure they understand that they do not have HIV or HSV.

Do you think it is important to increase awareness of the virus and its implications?

Offering reproductive educational information, if it is accurate, can never be wrong. This question, however, becomes more complex, since for adult women, HPV screening and education is becoming a priority given that HPV testing is now routine for Atypical Squamous Cells of Undetermined Significance (ASCUS) triage and is being offered as a primary screening test for women over 35 years of age in some areas.[2] In contrast, because of the high prevalence of HPV in sexually active teenagers, HPV testing for teenagers is probably not appropriate and leads to confusion regarding triage and treatment.

How frequent are these infections in young women?

Up to 50% of adolescents and young adults acquire HPV within four to five years of first experiencing sexual intercourse (Figure 1) and up to 25% of adolescents who acquire HPV will develop Low-Grade Squamous Intraepithelial Lesions (LSILs) (Figure 2).[3] The confusing point is that 90–95% of these HPV infections regress, and 95% of LSILs also regress in these young women.[4,5] In addition, new infections are constant, creating overlapping waves of acquisition and regression. Consequently, a single HPV test is not helpful in determining the natural history of the virus in a teenager.

How do you envisage the implications for screening recommendations?

This concept of repeated rapid sets of acquisition and elimination is born out in the low rates of High-Grade Squamous Intraepithelial Lesions (HSILs) (<1%) and extremely low rates of invasive cancer (<0.001%) in adolescents.[6,7] Consequently, most health-care providers are becoming less enthusiastic about screening adolescents for HSILs, and less so for HPV testing. These associations led to new screening guidelines in the US. The American Cancer Society suggests that a health-care provider can safely delay Pap-smear screening in adolescents until three years after the initiation of sexual intercourse.[8] These new guidelines are quite bold since they base the "risk" not on chronological age but on years of risk behavior. The fear of using chronological age is that young women who initiate intercourse at 12 or 13 years of age would have their Pap-smear screening delayed by between 9 and 13 years if an age of 21 or 25 years were used as a chronological indicator.

How would you place HPV in the context of reproductive and sexual health education?

It is important to incorporate HPV and cancer screening into health and reproductive education where all Sexually Transmitted Infections (STIs) are discussed in context of their importance. *C. trachomatis* infections have the most

immediate morbidity among adolescents, with infertility and ectopic pregnancies reflecting devastating outcomes if untreated. HPV must be put into context: it can cause genital warts, but warts are a nuisance and cannot, and will not, turn into cancer. HPV types other than those associated with genital warts are important if they are not controlled by the body. They must understand the importance of cancer screening and when to initiate it. So education regarding STI and Pap-smear testing is important and must be given accurately and repetitively. The concept of screening should be incorporated into all early education prior to the onset of sexual activity and continued throughout.

How do you explain to an adolescent with an ASCUS the presence of HPV?

ASCUS in young women is more often than not a non-specific change not associated with HPV; with rare cases of HSILs and extremely rare cases of invasive cancer uncovered. Consequently, any triage for ASCUS is welcomed. HPV tests will frequently be positive, since it is quite common in adolescents with normal or abnormal cytology.[9]

It should be emphasized to the healthcare provider that other infections such as *C. trachomatis* infections are much more common in sexually active teens than HSILs, and infections in adolescents with ASCUS should be looked-for.[10]

If HPV testing is performed on an adolescent with ASCUS, it can be explained to them that HPV infections are very common. It can then be explained that, currently, medical practice is to refer a woman with ASCUS, since some of the women with HPV who have an abnormal smear have the precancerous HSILs. If this were true, then they would need to have some treatment. It is important not to emphasize HPV as a sexually transmitted disease. Rather, HPV should be treated as a very common infection, much like a cold. If they kiss their boyfriend who has a cold, they most likely will get the virus that caused the cold. But it should also be explained that their body usually will get over the cold; the same happens with HPV.

Which are the most common clinical manifestations leading to a medical visit?

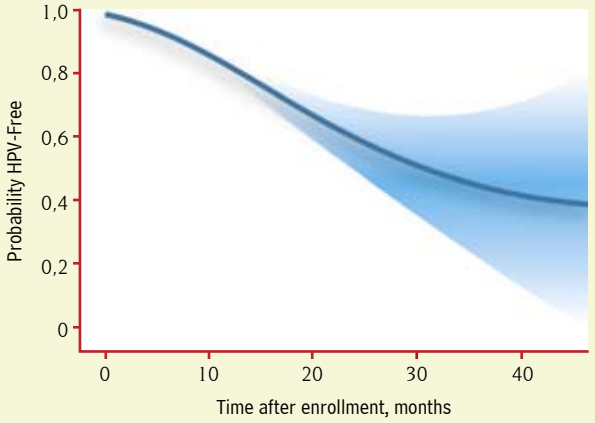
The most common reason adolescents come to the clinic for sexually related advice is a pregnancy scare or wanting birth control. Consequently, screening for STIs like *C. trachomatis* and *N. gonorrhea* is of utmost priority in young adolescents. With urine testing available for *C. trachomatis* and *N. gonorrhea*, pelvic examinations are no longer required and now reflect higher rates of acceptability for screening. Also, going over sexual risk behavior and screening for HIV is also important. Adolescents, on occasion, will state that they are here for their annual Pap, the understanding of which is quite vague for an adolescent. With the new recommendations to delay Pap smears until three years after starting sexual intercourse, it remains critical that annual reproductive screening is offered. For the first three years after intercourse is initiated this will include STI screening, and thereafter Pap smear and STI screening.

In the case of genital warts, what are your current recommendations?

Genital warts are fairly devastating to most adolescents. They consider themselves unclean and, once treated, they are reluctant to return because of the pain. Self-applied treatments are well accepted among older adolescents; however, younger adolescent girls are often hesitant to look "down" there or to touch themselves. Consequently, office therapy is best. Compliance is best

Figure 1

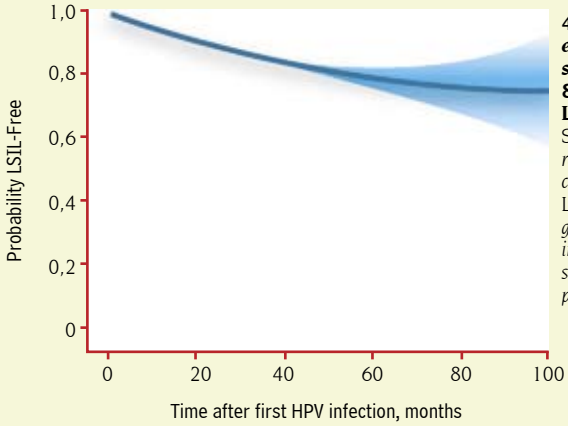
Estimated distribution of time after enrollment that the participants remained free of HPV



40 months after entering the study close to 40% remain HPV-DNA free. *Shaded area represents the 95% confidence interval. HPV indicates human papillomavirus.*

Figure 2

Estimated distribution of time after enrollment that the participants remained free of LSIL



40 months after entering the study close to 80% remain LSIL free. *Shaded area represents the 95% confidence interval. LSIL indicates low-grade squamous intraepithelial lesion; HPV: human papillomavirus.*

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Moscicki AB *et al. Risks for incident human papillomavirus infection and low-grade squamous intraepithelial lesion development in young females.* JAMA; 2001; 285(23): 2995-3002.

if a topical anesthetic such as Eutectic Mixture of Local Anesthetics (EMLA) is applied first.

What is your advise concerning the use of condoms?

There are many important reasons to emphasize why condoms are important. First, we know they are important in pregnancy and STI prevention. Although most studies suggest that condoms give little protection from acquiring HPV, condoms do prevent other STIs, including HSV, HIV, *C. trachomatis* and *N. gonorrhea*. STIs most likely play a role in cervical cancer development. Both *C.* trachomatis and HSV have been implicated as important cofactors. Also, rates of SILs are dramatically increased in HIV-infected women. Although CD4 immunosuppression plays a role in accelerating the progression, HIV status also appears to play an independent role. I currently counsel adolescents to continue using condoms for all the above reasons.

What are the most important lessons from your extensive studies among adolescent women?

These can be relatively easily summarized and are referred to above in more detail. First, HPV and LSILs are common but regression of HPV and LSILs are even more common. HSILs are more rare and invasive cancer extremely rare. Screening for Pap smears can be delayed safely until at least three years after initiating vaginal intercourse, since invasive cancer during this period is not at all likely to occur and the waves of HPV and LSIL acquisition/development and regression are overlapping, resulting in confusing clinical information that, in general, leads to overaggressive treatment. We have also been involved in numerous immunology studies and our findings suggest that cell-mediated immune responses measured both systemically and locally are critical in maintaining HPV control.[11] Studies of early acquisition must be performed in young women since first infections are likely to occur in this age group. Regarding attitudes toward HPV testing, some of our earlier work also suggests that adolescents are not interested in HPV testing if there is no cure.

References:

1. Ramirez JE et al. Genital HPV infections: Knowledge, perception of risk, and actual risk in a nonclinic population of young women. J Women's Health 1997; 6: 113–121. **2.** Wright TC Jr et al. Interim guidance for the use of human papillomavirus DNA testing as an adjunct to cervical cytology for screening. Obstet Gynecol 2004; 103(2): 304–309. **3.** Moscicki AB et al. Risks for Incident Human Papillomavirus Infection and Low-Grade Squamous Intra-Epithelial Lesion Development in a Longitudinal Cohort of Adolescent and Young Women. JAMA 2001; 285(23): 2995–3002. **4.** Moscicki AB et al. High rate of regression of Low-grade squamous intra-epithelial Lesions (LSIL) among adolescents and young women. Lancet, in press. **5.** Schlecht NF et al. Human papillomavirus infection and time to progression and regression of cervical intraepithelial neoplasia. J Natl Cancer Inst 2003; 95:1336–1343. **6.** Mount S et al. A study of 10,296 pediatric and adolescent Papanicolaou smear diagnoses in northern New England. Pediatrics 1999; 103: 539–545. **7.** Ries LAG et al. SEER Cancer Statistics Review, 1973–1999. Bethesda, MD: National Cancer Institute. 2002. **8.** Saslow D et al. American Cancer Society guideline for the early detection of cervical neoplasia and cancer. CA Cancer J Clin 2002; 52(6): 342–362. **9.** Moscicki AB et al. Prevalence and risks for cervical human papillomavirus infection and squamous intraeptihelial lesions in adolescent women: Impact of infection with human immunodeficiency virus. Archives of Pediatrics and Adolescents 2000; 154(2):127–134. **10.** Lehmann M et al. Detection of Chlamydia trachomatis DNA in cervical samples with regard to infection by human papillomavirus. J Infect 1999; 38(1): 12–17. **11.** Scott M et al. Cell-mediated immune response to human papillomavirus infection. Clin Diagn Lab Immunol 2001; 8(2): 209–220.

NEWS

LIQUID-BASED CYTOLOGY (LCB) AND HPV TESTING IN CERVICAL CANCER SCREENING

CANADA, DECEMBER 2003

Dr Marc Steben
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Direction de la Sante Publique. Unite Maladies Infectieuses. Montreal, Quebec, Canada.

The Canadian Coordinating Office for Health-Technology Assessment (CCOHTA) has issued a technology report on "HPV Testing and Liquid-Based Techniques for Cervical Cancer Screening". The medical literature was searched between January 1997 and July 2003 for comparative trials on: • The diagnostic accuracy of LBC, HPV testing and Pap smears. • The economic evaluations or cost studies of LBC and HPV testing.

Conclusions: • For women with an ordinary risk of cervical cancer, but not for women at high-risk of cervical cancer, LBC is more sensitive than the Pap smear. • LBC produces a lower rate of unusable samples of cervical cells. • HPV testing, either on its own or combined with cytology, is more sensitive than the Pap smear but less specific for primary screening and triage. • LBC screening every three years or longer may be as cost-effective as the Pap smear. • Economic modelling based on the use of LBC in a Canadian context is needed before conclusions can be made about the cost-effectiveness of HPV testing.

IARC PREPARES A NEW MONOGRAPH ON CERVICAL CANCER SCREENING

On April 20–27, 2004, the International Agency for Research on Cancer (IARC) convened a working group including over 50 international scientists. The Monograph concluded that there was sufficient evidence that both liquid-based cytology and automated cytology can reduce cervical cancer incidence and mortality. It also found sufficient evidence that testing for HPV can achieve reductions in cervical cancer incidence and mortality. The overall evaluation on HPV testing states that: "the efficacy of HPV testing, using a validated system, as the primary screening modality can be expected to be at least as good as that of conventional cytology". The Monograph will be published later in 2004.

www.iarc.fr/pageroot/PRELEASES/pr151a.html

THE 21ST INTERNATIONAL PAPILLOMAVIRUS CONFERENCE AND CLINICAL WORKSHOP

MEXICO CITY, FEBRUARY 20–26 2004

EPIDEMIOLOGY AND PREVENTION RESEARCH ON HPV

Having left behind the growing pains endured during its childhood and teenage years, the international PV conference series has now reached adulthood. It keeps on gaining in stature, and the delegates that arrived in the historical Mexican capital last February 20 helped to make the event the largest yet, with over 1.300 participants and nearly 650 abstracts. The conference venue's stately architecture was within a short walk of sites that have witnessed so many portentous moments in the 3.000-year history of the Mesoamerican civilizations. Oblivious to the historical grandeur outside the Sheraton Hotel, the delegates served and were served an eclectic blend of innovative science and ambitious Public Health agenda that reflected the much shorter, but no less exciting, history of the HPV research field.

The Mexico conference's many outstanding contributions in the areas of epidemiology, prevention, and Public-Health research indicated an unparalleled level of interdisciplinary activity. Over the past 20 years, the community of scientists working in these domains has painstakingly produced a solid body of research that fills a continuum spanning from etiology to prevention. It is probably fair to say that few areas in cancer research have benefited from progress this fast. We now have a deeper understanding of the causal role that HPVs play in cervical carcinogenesis than can be claimed by researchers in most other areas in cancer prevention. This knowledge has spawned vigorous research fronts in the area of prevention of HPV infection and, ultimately, of cervical cancer via vaccination. The many sessions devoted to HPV vaccines and immunization topics were among the most well attended in the conference. The Mexico meeting also showcased the highlights of a growing body of research on issues related to societal questions about the importance of HPV infection.

Public-Health scientists presented a rich and diverse mix of papers on psychosocial research on matters related to HPV detection, screening, and vaccination. Because of its robust epidemiological and Public-Health research on HPVs, Mexico is unique among developing countries. Befittingly, the conference brought to light some of the best papers on international health topics, which included long-term cohort studies, trials of HPV screening and vaccination, and studies of cost-effectiveness of health interventions aimed at HPV infection control. Prominent in the scientific program were the preliminary results from the ongoing randomized controlled trials of HPV testing in cervical-cancer screening. These high-profile studies will provide the evidence that will eventually replace that which was obtained in previous clinical studies without randomization. Such studies will ultimately form the basis for future policy in cervical-cancer prevention by screening.

It is impossible to give justice here to the many worthwhile research contributions in the areas of epidemiology and Public-Health that caught the attention of delegates to the 21st International Papillomavirus Conference in Mexico City. There was no indication that research in these areas has begun to plateau in volume or become less innovative; on the contrary, there was a clear sense that the field is as vast and dynamic as ever. Well-grounded knowledge on etiology and disease mechanisms is leading to prevention initiatives, as it should. It has also fueled new, exciting research on HPVs and the diseases that they cause. The Mexico conference served as an excellent high ground to examine on the road ahead.

www.insp.mx/hpv2004/index.php

Eduardo L. Franco

Professor of Epidemiology and Oncology
Director, Division of Cancer Epidemiology, McGill University. Montreal. Canada.

BASIC RESEARCH ON HPV

This Papillomavirus meeting provided an exciting and productive forum for both clinical and basic studies on Papillomavirus and related disorders. Major aspects of the viral life-cycle discussed included replication, transcription, and functions of viral proteins. A central role for E1-E4 is expected due to its interactions with almost all other viral products. New binding partners for E6, E7 and E2 were described, although their exact role in the viral cycle is still unclear, as well as the precise molecular events necessary for viral persistence and clinical manifestations. Reports indicate that both E6 & E7 have multiple effects on cytokine expression and immune recognition, as well as on several adhesion molecules.

Alejandro García Carrancá, PhD

Unidad de Investigación Biomédica en Cáncer.
Instituto de Investigaciones Biomédicas, UNAM.
Instituto Nacional de Cancerología, Mexico.

Sequences important for nuclear-cytoplasm distribution of major viral products were described, together with the effects of some modifications in their functions. The meeting was attended by more than 1.300 scientists, medical doctors and students from around 45 different countries and represented also an important opportunity for the general public to learn about these viruses and to better combat cervical cancer.

SELF – SAMPLING FOR HPV: WHICH METHOD TO USE ?

Diane M. Harper, MD, MPH, MS

Director. Gynecologic Cancer Prevention Research Group. Norris Cotton Cancer Center. Associate Professor. Departments of Community and Family Medicine; Obstetrics and Gynecology. Dartmouth Medical School. Associate Professor. Department of Women's and Gender Studies. Dartmouth College. New Hampshire, USA.

HPV testing in public health populations of women has become increasingly more important as the epidemiological evidence linking specific types of HPV to cervical cancer has become well established. Plans for large population screenings for HPV, as a surrogate marker for abnormal cytology, are underway in countries that have no cytopathology infrastructure or organized Health Plans. This article is intended to assist those planning self-sampling Public-Health projects in their choice of a self-sampling technique.

Methods for detection of HPV have been primarily developed for longitudinal research studies and not tested for their applicability to general populations of women. Cervico-vaginal lavage has proved unacceptable to women and unwieldy in large populations.[1-4] Cytobrushes and Hybrid Capture™ samplers are not a preferred method of self-sampling for Western European women due to the stiffness of the brushes, despite their clinical efficacy.[3,5] Cotton swabs trap the cervico-vaginal cells leading to false-negative clinical results. One Dacron swab has been the most frequently used self-collection method[6–8] because it provides easy laboratory processing for detection of HPV, but at lower sensitivity levels than clinician-directed cervical sampling.

We found that two Dacron swabs used consecutively provide an equivalent detection of high-risk HPV types to the clinician-directed cervical sampling; this technique is more sensitive and specific than a single Dacron swab or a tampon left in the vagina for less than 10 seconds.[9] A tampon left in the vagina between one and four hours, though, produces an equivalent rate of HPV detection as two Dacron swabs.[10] Tampons have proven effective for the detection of Chlamydia, Gonorrhea and Trichomoniasis as well as HPV in screening large public populations for sexually transmitted infections. Longer duration of exposure to the vaginal walls appears to be necessary to improve the detection rate of HPV, though.

From left to right:
MaïThao Tonnu, BA, *Dorie Belloni*, BS, *Meghan Raymond Longacre*, PhD, *Jean Reichert*, MS, *Polly Goralski*, RN, *Jorge Gonzalez*, MD, *Diane Harper*, MD, MPH.

The timing of the sample collection does not affect HPV detection. We have shown that the phase of the menstrual cycle has no effect on HPV detection, the recency of sexual intercourse does not change the ability to detect HPV in the woman, and the number of days since the last self-sampling occurred does not affect the reproducibility of detecting HPV, making short-term repeat sampling (either daily or weekly) possible.[11] The ability to repeat sampling in a short time-interval is important for the practical aspects of public-health screening, as samples may be lost, invalidated, or otherwise not processable and need to be repeated quickly.

Younger age, increased parity, and oral contraceptive use are associated with increased detection of HPV by two consecutive Dacron swabs.

In addition to detecting HPV, two consecutive Dacron swabs are effective for detecting women with CIN 2/3 disease, using the presence of high-risk HPV as the surrogate marker. The sensitivity and specificity are 100% in a small study;[9] with Odds Ratios ranging from 13 to 60 for CIN 2/3 associated with the positive high-risk HPV types in large studies.[11]

The acceptability of self-sampling among women is culturally dependent. If the culture promotes a woman's understanding of her anatomy, such as adopting the use of tampons for menses, self-sampling will be a successful technique for mass cervical-cancer screening. **The work published in American and European populations indicates almost universal acceptance of self-sampling, and a preference for self-sampling over the yearly speculum examination.** Studies to determine acceptability of self-sampling for the intended population are paramount before starting any large-scale projects.

Self-sampling, by its very nature, will include both vaginal and cervical cells. The type distribution of HPV and number of types of HPV infection differ between vaginal and cervical samplings. There are more types, with higher viral loads and different distributions, for the cervico-vaginal collection technique than for the cervical technique alone. This additional information, collected by using two consecutive Dacron swabs may, in time, provide a method for monitoring the clearance of HPV to undetectable levels.

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AOGIN

A CONCEPT FOR THE FUTURE

From left to right:
Associate Professor Michael Quinn,
Associate Professor Suzanne Garland,
Dr Jeffrey Tan.

•**Dr Jeffrey Tan.** Consultant Gynaecologist. Oncology & Dysplasia Clinic. •**Associate Professor Suzanne Garland.** Director of Microbiological Research. Director of Clinical Microbiology & Infectious Diseases (RWH). Senior Consultant Microbiology & Infectious Diseases (WCH). •**Associate Professor Michael Quinn.** Director. Oncology/Dysplasia Unit. The Royal Women's Hospital. Carlton, Australia. •**Dr Isabelle Heard.** Service d'Immunologie Clinique, Hôpital Européen Georges Pompidou. Paris, France. •**Professor Jong Sup Park.** Department of Obstetrics and Gynaecology. The Catholic University of Korea, Seoul Korea.

Worldwide, carcinoma of the cervix is very common in women, being second only to breast cancer. Incident cases per annum are estimated to be nearly half a million (470,600 cases p.a.), with almost 80% occurring in the developing world (379,100).

More than 50% of the cervical cancer cases in the developing world occur in the Asia-Pacific region. In an effort to control cervical cancer in this region the setting up of Asian Oceania Research on Genital Infections and Neoplasia (AOGIN) has been proposed.

This organisation will be an expert multidisciplinary group within the region along the lines of the European Research Organization on Genital Infection and Neoplasia (EUROGIN)/European Course on HPV Associated Pathology (ECHPV), as developed for Europe and, more recently, Latin America. The proposed group would work with healthcare professionals (as well as the general public), particularly those in women's health, with the goals of collaboration and research, scientific exchanges, education and training, and providing information, surveys and audits. AOGIN would bring together clinicians and scientists whose work is related to genital infections and neoplasia.

It is proposed that AOGIN would have four main areas of activity:

1. Collaboration and Research

The scientific committee (a group comprising clinical and scientific experts) would develop and encourage collaboration on clinical and basic research projects, as well as seeking international collaboration (e.g. with EUROGIN).

2. Scientific Exchanges, Education and Training

The multi-disciplinary nature of this organisation would mean that AOGIN would be a forum for exchanging views and for cooperation between partners. It recognised that there are different levels of research capabilities in each country of the region and AOGIN would work to support the countries according to their requirements.

3. Information

AOGIN would be a genuine teaching and information platform for physicians, patients and public authorities.

This would be achieved by:

• Organising international congresses to provide a forum to present up-to-date information and to review progress in the understanding and treatment of genital infection and neoplasia.

• Promoting courses and workshops to review current clinical practice and technical developments in cervical cancer screening technology and management.

• Preparing training sessions to encourage specialised centres to develop screening programmes.

• Coordinating and supporting consensus meetings and expert panels on issues encountered in everyday practice. These would lead to recommendations for improvement of medical practices, while taking into account financial resources.

• Organising satellite symposia at major international conferences and encouraging the exchange of information with other specialist organisations in this field.

4. Surveys and Audits

AOGIN would commission medical practice surveys with the aim of assessing practice effectiveness. Follow-up support would be provided, and advice and recommendations made to enhance good medical practice and improve financial management.

Conclusion:

We look forward to collaborating with organisations within and beyond the Asia-Oceania regions to ensure the success of our aims.

Contact with AOGIN:
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Jeffrey Tan: **tanj@cryptic.rch.unimelb.edu.au**
Michael Quinn: **Michael.Quinn@affinityhealth.com.au**

KEY PUBLICATIONS

NO CONFIRMED CASE OF HUMAN PAPILLOMAVIRUS DNA–NEGATIVE CERVICAL INTRAEPITHELIAL NEO– PLASIA GRADE 3 OR INVASIVE PRIMARY CANCER OF THE UTER–INE CERVIX AMONG 511 PATIENTS

Bohmer G, van den Brule AJ, Brummer O, Meijer CL, Petry KU
Am J Obstet Gynecol 2003;189:118–120

After exclusion of inadequate samples and erroneous diagnoses, HPV DNA was associated with all confirmed cervical intraepithelial neoplasia grade 3 and primary cervical cancers. These findings confirm previous reports that found HPV to be a necessary cause of cervical cancer.

PSYCHOLOGICAL IMPACT OF HUMAN PAPILLOMAVIRUS TESTING IN WOMEN WITH BORDERLINE OR MILDLY DYSKARYOTIC CERVICAL SMEAR TEST RESULTS: CROSS SECTIONAL QUESTIONNAIRE STUDY

Maissi E, Marteau TM, Hankins M, Moss S, Legood R, Gray A. BMJ 2004;328 (7451):1293.

HPV positivity in women with borderline or mildly dyskaryotic smear-test results was associated with greater anxiety, distress, and concern than that associated with an abnormal cytology result. Informing women more effectively about the meaning of borderline or mildly dyskaryotic smear-test results and HPV status, in particular about the absolute risks of cervical cancer, may avoid some anxiety for those who are HPV positive, while achieving some reassurance for those who test HPV negative

HUMAN PAPILLOMAVIRUS INFECTION IN MEN WHO HAVE SEX WITH MEN PARTICIPATING IN A DUTCH GAY–CO–HORT STUDY

van der Snoek EM, Niesters HG, Mulder PG, van Doornum GJ, Osterhaus AD, van der Meijden WI. Sex Transm Dis 2003;30: 639–644

This cross-sectional study of 241 HIV-negative and 17 HIV-positive men who have sex with men found that HPV DNA was detected more often at the anus than at the coronal sulcus. HIV positivity was associated with a higher prevalence of high-risk HPV types at the anus but not at the coronal sulcus. In the majority of steady couples, partners were infected with different HPV types.

PROJECTED CLINICAL BENEFITS AND COST–EFFECTIVE–NESS OF A HUMAN PAPILLOMAVIRUS 16/18 VACCINE

Goldie SJ, Kohli M, Grima D, Weinstein MC, Wright TC, Bosch FX, Franco E. J Natl Cancer Inst 2004;96:604–615

The strategy of combining introduction of a HPV16/18 vaccine given at age 12 years with triennial conventional cytological screening beginning at age 25 years was the most effective strategy as compared to the next most effective strategy of introducing the same vaccine but with cytological screening every five years beginning at age 21 years. This triennial strategy would reduce the absolute lifetime risk of cervical cancer by 94% compared with no intervention.

CASE STUDY

TREATMENT OF VIN III WITH IMIQUIMOD: A CASE REPORT

Michel Roy
CHUQ-Hôtel-Dieu de Québec, Canada.

Figure 1
Multifocal VIN III, *before treatment.*

Figure 2
Partial clearance after 6 weeks of imiquimod.

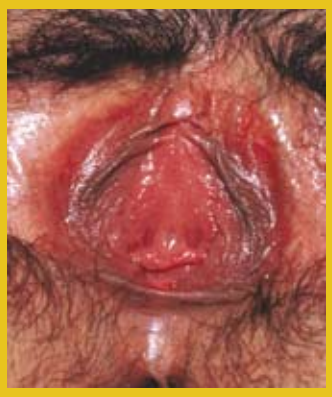

Figure 3
Complete clearance after 12 weeks and 4 weeks follow-up.

The incidence of vulvar intraepithelial neoplasia (VIN) is rising, especially in the young population. Risk factors include smoking, immunological deficiencies and the presence of intraepithelial neoplasia of the cervix and/or vagina. We now know that an oncogenic human papillomavirus (HPV-16) is an important etiological factor in the development of VIN III.

Management of VIN III must be conservative and individualized, and because the rate of progression to invasion is high, treatment is recommended for all cases except during pregnancy; spontaneous regression has been described in some pregnant patients.

The therapeutic choices for the clinician today range from local destructive methods to excision. In young patients, where lesions are usually multifocal, CO_2 laser vaporization has been used extensively. The success rate of this therapeutic modality is between 70 and 90%, with a high recurrence rate of between 30 and 40%. In most cases with widespread disease, however, general anesthesia is necessary. Furthermore, after laser vaporisation the healing time can be long and potent analgesics are needed for some weeks. Because of the side effects of laser vaporisation and the clinical trials showing good results of imiquimod 5% (Aldara®) for the treatment of genital warts, we started to use imiquimod instead of laser vaporisation in a selected group of patients.

Case Report

We proposed imiquimod 5% to a young 26-year-old patient with multifocal pigmented lesions of the vulva (Figure 1). She was advised to apply imiquimod in small amounts, using a mirror to direct the application. The cream was to be rubbed in, not necessarily on the visible lesions but on the affected area, twice a week. After 6 weeks of self-treatment the results were very good (Figure 2) with partial response, and without side effects except for local burning. She continued the treatment for 6 more weeks, twice a week. On examination four weeks after the last application of the cream, she had a complete clinical response (Figure 3). She has had no recurrence after 2 years of follow-up.

Since then, we have started to offer patients with VIN III imiquimod 5% as a therapeutic modality. Preliminary results presented at the 21st International Papillomavirus Conference and Clinical Workshop in Mexico City show that we can expect a complete clinical clearance in over 60% of patients and a partial response (of more than 75%) in another 35% of patients. We can expect a very good clinical response in over 90% of treated patients with very limited side-effects. So far no recurrences have been noted among 22 patients with complete clinical clearance with imiquimod 5% and followed for between 6 and 48 months.

Conclusions

Because of the high recurrence rate, the multifocality of VIN, and the side-effects of classical treatments, other possibilities have to be explored, especially in premenopausal patients. Self-applied imiquimod, an immune response modifier, seems to be successful for the treatment of VIN III. If further clinical studies confirm its efficacy, especially the low recurrence rate after treatment, it will be a significant addition to the treatment modalities of this affection.

INTERNATIONAL AGENDA

Buenos Aires, Argentina

1st-4th October 2004

International Congress of the lower genital tract and colposcopy. XXXIII Annual Meeting

Organizers: Argentine Society of the Lower Genital Tract and Colposcopy.
Tel: +30 2 108 047 709
E-mail: sociedad@colpoweb.org

Athens, Greece

12th-15th October 2004

30th European Congress of Cytology

President: Helen Koutselini.
Tel: +30 2 108 047 709
E-mail: nkakalis@zeincro.com
Web: www.zeincro.com/Congress/

Lisbon, Portugal

14th-16th October 2004

3rd International Symposium -HPV and Cancer-

Organizers: Alfredo Martins Barata, João Olias, Maria Clara Bicho, Rui Medeiros.
Tel: +351 21 412 95 00
E-mail: papiloma.3.virus@gsk.com
Web: www.sppv.org

Nice, France

21st-23th October 2004

2004 EUROGIN International Expert Meeting

Organizers: European Research Organization on Genital Infection and Neoplasia (EUROGIN).
Tel: +33 1 44 40 01 20
+33 1 48 88 96
E-mail: admin@eurogin.com
Web: www.eurogin.com/nice2004/

Indianapolis, USA

29th October 2004

2nd Annual Symposium on Women's Health Issues

Organizers: Indiana University School of Medicine Continuing Medical Education.
Tel: +1 317 274 8353
+1 888 615 8013
E-mail: cme@iupui.edu

Lisbon, Portugal

10th-13th November 2004

XVIII National Congress of Obstetrics and Gynaecology

President: Carlos Santos Jorge.
Tel: +351 21 926 99 00

Chicago, USA

13th-17th November 2004

52nd Annual Scientific Meeting of the American Society of Cytopathology

President: Edmund Cibas.
Tel: +1 302 429 8807
E-mail: asc@cytopathology.org
Web: www.cytopathology.org

Florence, Italy

17th-21st November 2004

13th Congress of the European Academy of Dermatology and Venereology

President: Torello Lotti.
Tel: +39 055 50 35 342 – 347
E-mail: president@eadv2004.org
Web: www.eadv2004.org

Larnaca, Cyprus

19th-21st November 2004

2nd International Educational Meeting of the European Academy of Gynaecological Cancer

President: Vasilios Tanos.
Tel: +35 722 71 37 60
Web: www.topkinisis.com/conference/gynaecological1.php

Bangkok, Thailand

25th-28th November 2004

The Asian Pacific Congress Controversies in Obsterics, Gynecology and Infertility

Organizers: The Royal Thai College of Obstetricians and Gynecologist.
Tel: +41 22 908 0488
E-mail: cogi@kenes.com
Web: www.kenes.com/asiancogi/

Paris, France

15th-18th December 2004

VIth Congress of the International College On Gynaecological Imaging

Chair: B. N. Blanc.
E-mail: acatois@jbbsante.fr
Web: www.33docpro.com/gynecologia

Aurangabad, India

6th-9th January 2005

AICOG 2005

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Tel: +91 240 234 87 31
E-mail: conference@aicog2005.com
Web: www.aicog2005.com

Vancouver, Canada

30th April- 6th May 2005

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