HPV Today

Newsletter on Human Papillomavirus

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THE TRUE IMPACT OF THE VACCINES IN DEVELOPED COUNTRIES WILL BE THE REDUCTION OF THE TOTAL COST OF THE SCREENING PROGRAMS

INTERVIEW WITH DIANE HARPER

You recently published[1] the result of a major vaccination trial showing high protection of women against persistent HPV-16 and -18 infections. What is your impression of this effort and of its implications?

The effort has involved many hundreds of scientists from all fields, as well as many clinicians and statisticians to design and evaluate the trials. The practically perfect efficacy against the two most common cancer-causing types of HPV means that cervical cancer may be drastically reduced worldwide, and potentially even eliminated, as the vaccines are further developed and screening methods become more precise.

A vaccine against HPV-16 and -18 targets the two most frequent types, involved in some 70% of cervical cancer. Why not include other high-risk types to increase protection against the 30% cancers induced by these other types?

Before we add other types to the current HPV vaccination formulation, we need to understand and monitor how the current bivalent cancer prevention vaccines fare in the larger phase-III trials. Questions that we will be able to answer include whether there is protection against any other related HPV types from the 16/18 vaccine that might come "free" without the need to alter the vaccine production; whether other, unrelated, cancer-causing HPV types become more prevalent in any population; whether screening practices can be refined to target the more rare cancer-causing HPV types; and whether the engineering processing of adding more types is economically feasible.

What other studies are underway and when do you expect further results?

There are several HPV vaccine studies underway, all with their own specific aims. The two most applicable

(continues on page 3)

Nº 07 October 2005

EDITORIAL

HPV VACCINES: THE LIKELY KEY PLAYERS IN A NEW CERVICAL CANCER PREVENTION MODEL

The HPV and cervical cancer prevention fields have reached a major turning point. The leading HPV vaccines under trial both include the two most frequent HPV types involved in cervical cancer (HPV-16 and -18) and one of them also includes the two types involved in virtually all genital warts (HPV-6 and -11). The results discussed by Dr. Harper in the cover interview are largely consistent with all other published trials. The evidence is so far consistent in showing that all women receiving three doses of either vaccine develop high antibody responses related to a nearly 100% efficacy in preventing both the type-specific HPV infections and the persistency of HPV DNA in the cervix. Viral persistency is considered a necessary intermediate endpoint for neoplastic progression.

The data are still too preliminary to be able to properly assess protection against cervical intraepithelial neoplasia 3 (CIN3), but the expectation is that these results should become available, and hopefully confirmatory, in 2005/2006.

While the scientific community is expectant, several key issues are still undetermined and will keep researchers occupied for some time. These include evaluations of long-term safety, duration of protection, number of doses required, age groups to be targeted, correlation between antibody titers and protection, cross-protection against other HPV types, male response to vaccines, and vaccine response under general population conditions, amongst others. In preparation, however, public-health institutions and other stakeholders are beginning to actively discuss logistics, delivery schemes, manufacturing requirements, and the costs involved in what may be the beginning of a massive vaccination effort to prevent the second most common cancer in women.

In developed countries with important screening efforts in place and (relatively) low rates of cervical cancer, HPV vaccines delivered to adolescent cohorts are not likely to visibly impact cervical cancer rates in the short and medium term. In contrast, the major impact is expected in the reduction of a substantial fraction (in the range of 40 to 50%) of pre-neoplastic lesions and their consequences. This in itself should represent a major reduction in costs and in the anxiety load associated with screening programs. Simplification of screening protocols as well as increasing their efficacy may indeed be a desirable outcome among vaccinated cohorts.

Developing countries, where conventional screening has had, at best, an inconsistent impact in mortality reduction may perceive these vaccines as the long-awaited option to confront cervical cancer. The implication of the major charities and vaccine support institutions will be needed to ensure prompt distribution of HPV vaccines to women in the poorest areas of the world.

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(from page 1) to public-health are the phase-III trials sponsored by both Merck and GlaxoSmithKline. Each trial has over 15,000 women randomized to receive the active HPV-16/18 (or 6/11/16/18) vaccine or a placebo/different vaccine. These strictly randomized controlled trials will be used to provide the data necessary for regulatory approval for the vaccines throughout the world. The US National Cancer Institute is conducting a natural history community based study using the bivalent 16/18 vaccine in Costa Rica. This study will provide a great deal of knowledge about the mechanism of immunity, in addition to detailing the effect of the vaccine in a population over time.

What is the expected impact of these vaccines on the pre-neoplastic conditions diagnosed in screening programs? What could be the implications for current screening protocols?

For developed countries with screening programs in place, the decrease in absolute numbers of cervical cancer cases will be small. The true impact of the vaccines in these countries will be in the ability to reduce by about half the number of abnormal cytology screens that are responsible for about one third of the total cost of these nations' screening programs. This will reduce the need for repeat cytology screens, for colposcopies, for HPV tests, for biopsies, for minimally invasive treatments, and, maybe most importantly, they will reduce the negative psychological impact that abnormal cytology and pre-neoplastic lesions have on women's lives. Screening will remain a mainstay of the prevention program as women will still be susceptible to the remaining oncogenic HPV types not related to those in the vaccine.

As these types are probabilistically uncommon, the recommendation for annual screening may be limited to 21-30-years-old women, with triennial screening for all vaccinated normal women thereafter.

What would be the target population in the introductory phases of this vaccine?

This is the most interesting question. First, the regulatory bodies must have supporting data in both the age and gender groups for which the vaccine is intended. Therefore, the most evident coverage will be for HPV-naïve women 15–25-years-old, as all phase-II studies support the tremendous efficacy seen in the trials designed to show this effect. Extending the vaccine recommendation to younger women and older women may occur with bridging studies of smaller numbers of women followed for less time, showing similar HPV immunogenicity levels. Second, which gender? In my opinion, the regulatory agencies will ask for data showing efficacy in reducing HPV transmissibility from men to women prior to licensing the vaccine for men.

I do think, however, that men will be vaccinated along with women eventually, but we have to show scientifically that the vaccine is safe, tolerable and effective in preventing HPV transmission from men to women, even if it has no clinical effect in men themselves.

Finally, we must remember that HPV not only causes cervical cancer, but also causes other anogenital organ cancers as well as cancers of the conjunctiva and upper aerodigestive tract. In addition, the benign types of HPV cause mass-producing lesions that replace the normal physiological functioning of the normal tissue, such as in juvenile laryngeal papillomatosis or esophageal warts. These new HPV vaccines look set to protect against many, if not all, HPV-associated diseases.

The HPV vaccine trial team lead by Dr. Diane Harper. Back row: Jorge Gonzalez, MD, Elizabeth Hirsh, PA, Greg Tsongalis, PhD. Middle Row: Ako Takakura, Tracy Gershengorn, Danielle Ligett, Marie Yeager, Catherine Dale, Karen Jacobi. Seated: Dorothy Belloni, MaiThao Tonnu, Diane Harper, Sarah Blanchard (with Olivia in her lap), Bernard Beaulieu, Lisa Matthews.

In your view, what will be the acceptability of these vaccines?

As we keep our focus on the prevention of cancer, I believe that there will be both physician and public clamor for this protection. The educational messages that we develop for each specific population must emphasize that this virus lives in the top 400 nanometers of our skin; not in our blood stream, nor in our spinal cord, nor any other internal organs. We must emphasize that this virus infects every single human being, usually in the form of hand or feet warts in childhood, so there is nothing extraordinary about having an HPV infection. We must emphasize that this virus can only move from one human to another (not through our pets or our towels or our linen) through skin-to-skin contact where the receiving skin already has an abrasion. We must emphasize that humans are meant to live in communities and must have skin-to-skin contact to survive. Cancer-causing HPV infections happen. Having a vaccine to protect ourselves from the infection only makes public-health sense!

References: 1. Harper D *et al.* The Lancet 2004;364:1757-65

HPV IN SCREENING AND TRIAGE

AVAILA

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New innovative genetic technologies are evolving for the detection of HPV that can assist the clinician in the care and management of their patients. This is especially useful in the triage of patients reported with atypical cells from the Pap tests, as well as determining viral clearance after treatment. More importantly, HPV DNA analysis has proven to be extremely useful to pathologists in adjudicating discrepancies between cytologic and histologic findings.

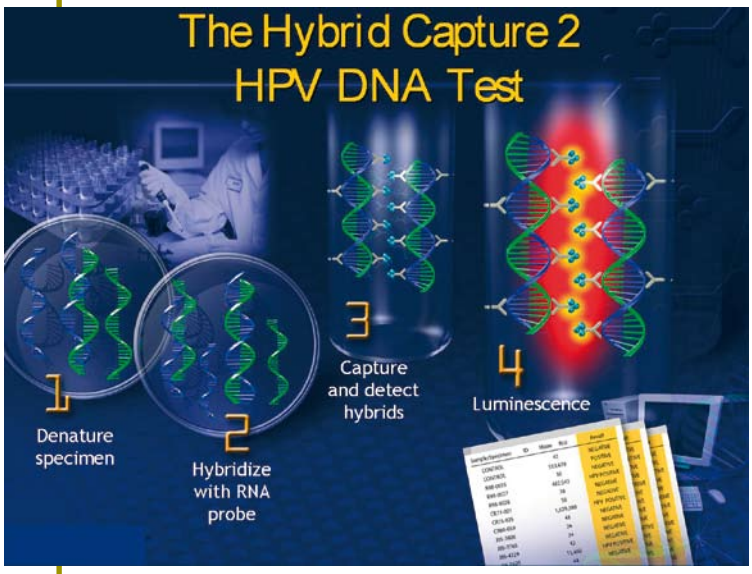


Figure 1
Molecular model of the HC2 DNA *test.*

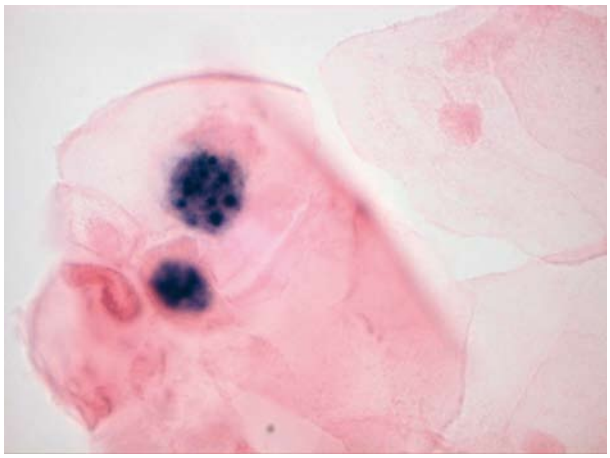


Figure 2
In situ hybridization staining of HPV*-infected cells taken from a Pap smear sample.*

Current HPV detection techniques include Hybrid Capture 2 (HC2), *in situ* hybridization (ISH), Invader technology, and polymerase chain reaction (PCR). Although these technologies have different methodologies, they share a strategy of hybridizing their probe to the common viral DNA target.

The Digene Hybrid Capture® 2 test is currently the only technology that is fully validated and approved by the Food and Drug Administration (FDA). This molecular ELISA-based assay (Figure 1) relies on the hybridization of an RNA probe to the single-stranded HPV DNA and subsequent chemiluminescent detection of the RNA/DNA hybrids. The clinical sensitivity of this test is very high (85 to 100%) with most publications reporting sensitivities of greater than 95%.[1] HC2 is a simple, high-throughput procedure with very good reproducibility.[2] However, several authors have reported false-positive reactions due to the cross-reactivity with low-risk HPV sub-types,[3] and the moderate analytical sensitivity of about 5,000 copies/test can result in a false negative in the case of few high squamous intraepithelial lesion (HSIL) cells or an overall low cellularity of the sample.

Ventana Medical Systems Inc. has a commercially available Inform® HPV automated *in situ* hybridization system, currently classified as an analyte specific reagent (ASR). It uses DNA probes to detect HPV in cytologic as well as tissue samples, while preserving the cellular morphology for histopathological analysis (Figure 2). This system is fully automated and requires only minimal technical intervention. It has greater than 95% specificity[4] and can localize individually infected cells.[5] Because of the differential staining patterns, integrated and episomal HPV DNA can be distinguished. This automated system is also capable of performing immunoperoxidase stains and is potentially profitable due to the available pathologist interpretation codes. The increased patient cost may be a limiting factor in its widespread deployment. Additionally, the ASR classification places additional responsibilities on the medical director to assure performance characteristics.

BLE HPV TESTS FOR CLINICAL PRACTICE

E. Blair Holladay, PhD, SCT (ASCP)

Vice President and Executive Director, Board of Registry American Society of Clinical Pathology. Chicago, Illinois. USA.

Third Wave Molecular Diagnostic have recently released their Invader® HPV test and have been approved for ASR status. This technology detects specific nucleic acid sequences directly with structure specific recognition (Figure 3).[6] The type-specific probe is enzymatically cleaved to release a 5'-flap oligonucleotide. This flap is then able to hybridize with a sequence-specific fluorescence resonance energy transfer (FRET) cassette. The resulting hybrid liberates a fluorescent molecule from the effects of a proximal quencher located in the FRET cassette, which can then be detected.[7] The benefits of this technology are that it is easy to use, relies on standard laboratory equipment, involves minimal start-up costs, and requires no specialized training. It is easy to automate and supports laboratory-developed test-menu expansion. However, because the test is relatively new, there are very limited data addressing the clinical sensitivity and specificity for cervical intraepithelial neoplasia (CIN)-2/3 and cervical cancer specimens. The ASR classification places an additional responsibility on the medical director to assure performance characteristics, and some molecular CPT codes may need to be negotiated with payers by the laboratory.

Roche Diagnostics has developed a PCR-based assay called the Amplicor® HR-HPV plate assay. This is the only assay discussed that actually creates more copies of the target sequence and is therefore the most sensitive at detecting the virus. Since it is used in conjunction with the HPV 37 Linear Array®, which provides genotyping information for 37 anogenital HPV types by dot blot, this test has a high degree of specificity and is able to determine viral loads.[8] Only a very small sample volume is required and intrinsic controls verify specimen adequacy. Other benefits include high-volume throughput and low direct cost. The instrument can be used for other assays as well as open the door for new emerging research-based management and treatment options. The limitations of this technology lie in the staff requirement of specialty-trained technologists and the expense of the equipment. There is limited data on each specific PCR method for a negative predictive value and its clinical use as a basis for atypical squamous cells of undeterminated significance (ASCUS) triage. Since this test does not have the ASR status, it can only be used for research purposes and is not billable as a clinical test.

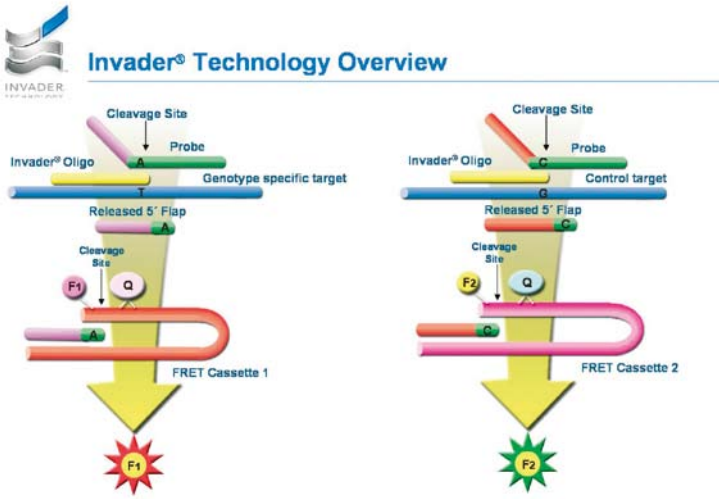


Figure 3
Third Wave Molecular Diagnostics Invader Technology

Currently, Hybrid Capture 2 is the conservative FDA-approved choice for ASCUS triage and/or cytology co-testing. *In situ* hybridization and Invader technology are competitive ASRs which would benefit from FDA approval and/or additional data establishing sensitivity equivalent to HC2. PCR is a promising research tool which will become more significant if data clearly establishes improved cost-effectiveness for increased analytic sensitivity, genotyping, and new management algorithms.

References: 1. Solomon D *et al.* J Nat Cancer Inst 2001;92(12): 293-299. **2.** Castle P *et al.* J Clin Microbiol 2002;4(3):1088-1090. **3.** Poljak M *et al.* J Clin Virol 2002; 25 (Suppl 3):S89-97. **4.** Qureshi MN *et al.* Diagnostic Cytopathology 2003; 29(3):149-155. **5.** Bewtra C *et al.* Acta Cytologica 2005; 49(2):127-131. **6.** Hjertner B *et al.* J Virol Methods 2005;124(1-2):1-10. **7.** Hessner MJ *et al.* Clin Chem 2005;46(8 Pt 1):1051-1056. **8.** van Ham MA *et al.* J Clin Microbiol 2005; 43(6):2662-2667.

PREVENTIVE VACCINATION AGAINST HPV DISEASES: POLICY DRIVERS FOR MAXIMUM EUROPEAN PUBLIC-HEALTH BENEFIT

Mathematical models of the impact of HPV vaccination were presented and discussed in an interactive expert meeting hosted by Sanofi Pasteur MSD during the European Research Organization on Genital Infection and Neoplasia (EUROGIN) 2004 International Expert Meeting (October 21–23, 2004, Nice, France). The audience was asked a series of questions concerning HPV vaccination policy. The answers were collected and then discussed. The panel experts were N. Muñoz/chair and epidemiology (France), F.X. Bosch/epidemiology (Spain), G. Garnett/mathematical modeling (UK), J. Patnick/screening (UK), C. Sultan/pediatrics endocrinology (France), M. Watson/vaccinology (France).

How should prophylactic HPV vaccination (types 6, 11, 16, 18) be targeted?

84% of the audience gave a "universal" recommendation and that it should be based, for example, on age and/or gender and 16% gave an "at risk" recommendation, i.e., based on lifestyle criteria. Prof. Garnett explained that target vaccination of the higher-risk population defined by the number of sexual partners is not as effective as vaccinating the entire population at risk. The distribution of infections within the population indicates that a large fraction of infections are of those who have a moderate level of risk and the easiest to protect with a vaccine. Protecting those at moderate risk would have a big impact on reducing HPV infection by interrupting the transmission of infection within the population. Since it's difficult to predict who may or may not be infected, and most sexually active people are likely to be infected at some time in their lives, no a priori high-risk group could be identified.

Should HPV vaccination (type 6, 11, 16, 18) be recommended for women only or for both sexes?

66% of the audience answered "both men and women" and 34% answered "women only". The modeling results were illustrated as shown in figure 1.

What age groups should be the primary population for which routine vaccination against HPV (types 6, 11, 16, 18) should be universally recommended?

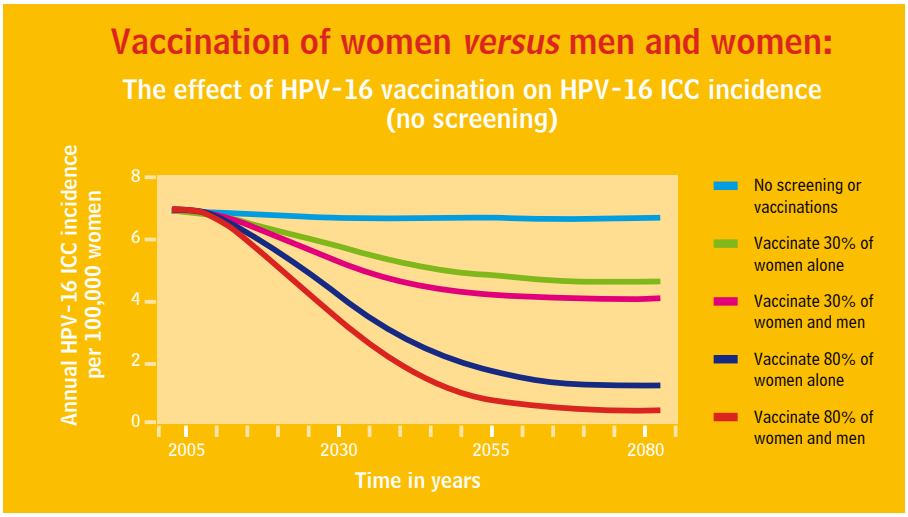
90% of the audience answered "before onset of sexual activity", i.e. pre-adolescent (approximately 9–13 years of age), 40% answered "around the onset of sexual activity", i.e. adolescent (approximately 14–17 years of age) and 14% answered "after the onset of sexual activity", i.e. young adult (>18 years of age).

The value of disease and prevention models.

Modeling the HPV-16 vaccination impact on invasive cervical cancer (ICC) incidence at different ages predicts that vaccination impact would be greatly reduced if vaccinating after sexual debut, assuming the vaccine has no therapeutic effect. Prof. Garnett commented that vaccinating too early would delay the vaccination benefit if there was no catch-up in an older cohort. The duration of protection has therefore to be considered when selecting vaccination age groups.

Vaccine Acceptability

Prof. Sultan expressed concern about the acceptability by parents of vaccinating girls before puberty, and suggested vaccinating around puberty and menarche as basic prevention while including sexually active adolescents as advance prevention.



The synopsis of the discussion was edited by the members of the panel. The model depicted was presented by Prof. G. Garnett.

Figure 1:
The incidence of ICC is modeled as a function of vaccination coverage and gender. Results suggest that vaccinating 80% of both women and men has a slightly greater impact than vaccinating 80% of women alone. Model developed by Ruanne Barnabas using data from the population of Finland.

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HOW TO EXPLAIN HPV TO YOUR PATIENT

Counseling the patient with HPV generally involves explaining one or more of the following issues: viral infection, sexual transmission, cancer development, and risk quantification.

The meaning of these terms for the patient is different from the clinical meaning, and explaining HPV implies the translation of medical terminology into concepts that are understandable by the patient.

Viral infection

The detection of a virus in humans clearly means a viral infection, as the virus cannot live outside human cells; however, for the patient a viral infection is an obvious synonym of disease. On the contrary, it is well known that HPV can cause only two diseases in the genital tract: genital warts and squamous intraepithelial lesion (SIL); the latter is easily detected by cytology screening and eliminated through a simple office procedure under local anesthesia. So, detection of HPV is not disease detection, and infection does not mean disease, it is simply the only way the virus can stay in the body. This is a key communication point that is very simple but necessary: viral infection and viral disease are unanimously intended as synonyms but are clearly two very different biological events.

The oral cavity is one of the many examples of other similar conditions that can easily describe this situation: it is common knowledge that the oral cavity contains bacteria, and nobody believes themselves to be sick simply because they have bacteria in the mouth; however, a dental abscess is clearly recognized as a bacterial-related disease. This will exemplify what is the difference between a viral infection and a viral disease.

Sexual transmission

Having intercourse is one of the most exciting activities in life. The possibility of contracting cancer through sexual intercourse is a very difficult communication issue to handle. In most instances, mucosal oncogenic HPVs at the genital level are sexually acquired, and patients link the presence of HPV to a specific sexual partner or contact. The key point to understand is that transmission of microorganisms, whether virus or bacteria, occurs normally during intercourse, whereas disease development is a host-dependent phenomenon. In the case of HPV-related neoplasia, virus persistence, not the presence of the virus, is the factor that relates to disease development, therefore the cause of the disease is not to be found in the person who transmitted the agent. Rather, disease development is to be found in those factors which affect the "normal" process of viral clearance in the host. In this way the key message is not "try to avoid HPV", but "know if there is a persistent viral infection", so the message is not "don't have intercourse", but "if having intercourse, test for the presence of persistent, high-risk viral infection".

Cancer development

Explaining the relation between HPV and cancer development is another critical issue as, generally, HPV detection is equated with cancer development. There are three key facts to be considered here: 1) the process of cancer development necessarily passes through the development of cancer precursor lesions, which can easily be identified and cured; 2) only a very small number of persistently infected women will develop cancer precursor lesions, and only a very small portion of these lesions will become malignant tumors; and 3) the time for cancer development is long, sometimes as long as ten years.

Risk quantification

One of the most difficult issues to be explained in medicine is risk. Traveling by car carries the risk of dying from a car accident; in comparison, the risk of a cancer developing in a patient found to be HPV positive is negligible. However, starting the car engine is not generally associated with fear. In addition, in the process of cervical cancer development, the long time-interval and the opportunities for screening act as a net that is capable of preventing the very rare event of cancer occurrence.

CONCLUSIONS

HPV counseling is a critical issue to implement the new knowledge in this field. Patients need to be informed in simple and logical terms to be both reassured and well-informed on their health status. The issue is challenging, almost as challenging as the task addressed by scientists in the last twenty years that has led to the discovery of the causal relationship between HPV and cervical cancer. They succeeded in that difficult task. Why should we fail now?

THE ESSENTIAL TRANSFORMING PROTEINS OF HPV: E5, E6 AND E7

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The genome of HPV encodes several proteins. The proteins expressed during the early stages of the virus life-cycle (E1–E7) are responsible for the pathogenicity of the virus, while the proteins expressed at later stages (L1 and L2) are structural proteins that make up the mature virion (Table 1). This brief monograph will review the most salient characteristics of E5, E6 and E7, the viral transforming proteins of HPV-16, which is the virus most often associated with cervical cancer.

The papillomavirus genome does not encode the enzymes necessary for DNA replication and transcription, therefore papillomavirus has to sustain cell proliferation to replicate itself and it does so via its three transforming proteins: E5, E6 and E7. It is important to stress that the role of these proteins is to favour viral replication and generation of mature progeny virus. Neoplastic transformation of pre-malignant infections is an accident: it is a dead-end process for the virus, as a transformed, non-differentiating cell cannot sustain virion production.

E5[1,2]

The biological activities of HPV E5 are not fully characterized. HPV-16 E5 is 83 amino acids long and is characterised by a very high content of hydrophobic amino acids. E5 is localised in the endomembrane compartments of the cell, primarily the endoplasmic reticulum and the Golgi apparatus (GA). It stimulates EGF-dependent activation of the EGF receptor (EGF-R) and cell proliferation, interacts with the 16K subunit c of the V-ATPase proton pump and interferes with the acidification of the GA and endosomes. Endosome acidification is necessary for ligand dissociation and receptor proteolysis, and its inhibition by E5 would lead to the extended lifespan of activated EGF/EGF-R complexes in endosomes. However, other studies have found that E5 supports cell-cycle progression with little effect on either the levels or activation of the EGF-R.[3,4]

Expression of E5 is often lost during malignant progression, and, compared to E6 and E7, whose expression is continuous throughout infection and malignant progression, E5 appears to have a lesser role in the neoplastic process. Rather, the functions of E5 are consistent with the activity of the protein taking place early in the viral life-cycle, aimed at the establishment of a transformed cell clone by favouring both cell proliferation and escape from immunosurveillance. E5-associated down-regulation of MHC class I in naturally occurring papillomas is the first example of a defined action of E5 during natural infection.[5]

FUNCTIONS OF HPV PROTEINS

Protein	Function
E1	ATPase and DNA helicase; recognizes and binds to the viral origin of DNA replication as a hexameric complex; necessary for viral DNA replication.
E2	Main regulator of viral gene transcription; binds the viral transcriptional promoter as a dimer; involved in viral DNA replication; interacts with and recruits E1 to the origin.
E4	Acts late in the viral life cycle; interacts with the keratin cytoskeleton and intermediate filaments; localises to ND10; induces G2 arrest; believed to facilitate virus assembly and release.
E5	Induces unscheduled cell proliferation; interacts with 16k subunit c of vacuolar ATPase; activates growth-factor receptors and other protein kinases; inhibits apoptosis; inhibits traffic of MHC complexes to the cell surface.
E6	Induces DNA synthesis; induces telomerase; prevents cell differentiation; interacts with four classes of cellular proteins: transcriptional co-activators, proteins involved in cell polarity and motility, tumour suppressors and inducers of apoptosis, primarily p53, and DNA replication and repair factors.
E7	Induces unscheduled cell proliferation; interacts with transcription factors and chromatin remodelling enzymes; activates positive regulators of the cell cycle and inhibits negative regulators and tumour suppressors, primarily p105Rb; destabilises centrosomes and causes mitotic defects.
L1	Major viral structural protein; self-assembles in capsomeres and capsids; interacts with L2; interacts with cell receptor(s); encodes neutralizing epitopes.
L2	Minor viral structural protein; interacts with DNA; interacts with ND10s; believed to facilitate virion assembly; may interact with cell receptor(s); encodes linear virus neutralizing epitopes.

GRAPH

E6[6,7]

E6 is approximately 150 amino acids long. It is characterised by four CXXC motifs, which permit the formation of two zinc-binding fingers. E6 interacts with, and interferes with the function of, numerous cellular proteins. These proteins can be divided into four broad classes: transcription factors/co-activators and signal transducers; pro-apoptotic proteins; proteins involved in cell architecture, polarity and adhesion; and DNA replication and repair factors. Given that several proteins can belong to more than one class, E6 is capable of affecting and subverting many cell functions. Some of the interactions between E6 and its cellular partners are direct, while some are mediated by another protein, E6-AP, an ubiquitin ligase that flags proteins destined to degradation through the proteasome.

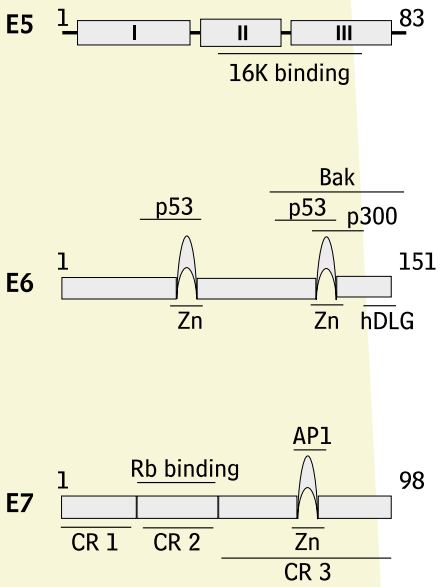
Among the class of transcription factors/co-activators are the tumour suppressor p53, the oncoprotein c-myc, the interferon-responsive factor IRF1 and the co-activators p300/CBP and AMF-1, and among the signal transducers are E6TP-1 (putative GAP proteins) and E6BP/ERC-55 (a Ca2+ binding protein). Binding of E6 to p53 leads to degradation of p53. In the absence of p53, negative regulators of the cell cycle are not expressed and cell proliferation continues even in conditions in which cell division is deleterious, leading to mutations and chromosomal abnormalities. Interaction of E6 with c-myc results in improper control of the levels of this cellular proto-oncogene. p300/CBP and AMF-1 are transcription co-activators that are required for chromatin re-modelling and are therefore important in the control of transcription. The interaction with IRF1 blocks the interferon-induced transcriptional activation of genes that encode immune molecules, thus potentially contributing to viral immune escape.[8]

p53 is the first and foremost among the pro-apoptotic proteins inhibited by E6. p53 induces apoptosis when the cell DNA is too damaged to be repaired. Its interaction with, and degradation by, E6 counteracts apoptosis mechanisms activated by improper cell proliferation signals induced by E7 (see below), thus allowing the infected cell to continue dividing. Other pro-apoptotic proteins, such as the Bcl2 family member Bak and the FADD protein, are also targeted for degradation. Additionally, E6 interacts with members of the MAGI family, which are proteins that are believed to act as, or to interact with, tumour suppressors.

Numerous proteins involved in adhesion, cell architecture and polarity are targeted by E6. hDlg, hScrib and MUPP control cell polarity and cellular scaffolds, and their interaction with E6 would lead to deregulation of cytoskeletal organisation and cell–cell interactions.

Among DNA replication and repair factors are mcm7, XRCC1[9] and O^6-methylguanine-DNA methyltransferase.[10] These interactions may contribute to genomic instability and the acceleration of the neoplastic process.

In addition, E6 induces the activity of telomerase, leading to cell immortalisation, and alters the function of p105Rb, leading to deregulation of the G1/S transition.[11]



Diagrammatic structure of HPV-16 *transforming proteins. E5 has three hydrophobic domains separated by short, non-hydrophobic stretches. The three domains are believed to form three transmembrane α-helices, although other configurations are possible. The region binding the 16k subunit c is indicated.*
E6 has two zinc-binding fingers, which interact with p53. The domains interacting with p300, Bak and hDLG are indicated. The C-terminus also binds MAGI *and* MUPP *proteins.*
E7 has three conserved regions (CR), *shared with transforming proteins of other viruses, and one zinc-binding finger which interacts with* AP1. *The p105Rb binding domain in the second* CR *is indicated.*
For references, see text.

E7[12–14]

E7 is a protein approximately 100 amino acids long. It has two CXXC motifs that form a single zinc-binding finger. E7 can immortalise primary human keratinocytes by itself, although the immortalisation process is more efficient in the presence of E6. Like E6, E7 interacts with numerous cellular proteins, including the tumour suppressor protein p105Rb and other pocket proteins, transcription factors and chromatin remodelling proteins, negative regulators of the cell cycle and components of the innate immune response.

Association of E7 with p105Rb causes degradation of p105Rb, leading to loss of control over E2F transcription factors and consequent activation of cellular genes involved in DNA replication. The interactions with pocket proteins underlie the ability of E7 to immortalise cells and to abrogate normal DNA damage responses.[15]

E7 interacts with members of the AP-1 family of transcription factors. These associations are both p105Rb-dependent and -independent, and through them E7 can modulate cell-cycle progression and cell differentiation. E7 also interacts with members of the basal transcription machinery such as the TATA-binding protein (TBP) and the TBP-associated factor TAF(II)110, thus potentially affecting gene transcription in a generalised way. Furthermore, E7 can deregulate gene

transcription in a general way by interacting indirectly with histone deacetylase (HDAC), a chromatin remodelling factor. E7 activates G1/S cyclins and inactivates the cyclin-associated kinase inhibitors $p21^{cip1}$ and $p27^{kip1}$. These interactions, direct or indirect, lead to entry into S phase. The unscheduled entry of a normal cell into S phase induces apoptosis. HPV-transformed cells evade apoptosis induced by E7-mediated unscheduled proliferation thanks to the inhibition of the apoptotic pathways by E6.

Two other aspects of the biology of E7 deserve mention: destabilization of centrosomes, independent from p105Rb binding,[16] and interaction with components of the interferon pathways, such as ISGF-3 and IRF-1. The former causes mitotic defects and genome instability,[17] and the latter inhibition of the interferon signal transduction with possible crucial evasion by the HPV-infected cell of the host innate immune response.[8]

CONCLUSION

A picture is emerging in which the three transforming proteins of HPV act in concert to promote cell proliferation, inhibit apoptosis and evade the host innate and adaptive immune response.

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THE 22ND INTERNATIONAL PAPILLOMAVIRUS CONFERENCE AND CLINICAL WORKSHOP

Joel Palefsky[1]
Anna-Barbara Moscicki[2]

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The 22nd International Papillomavirus Conference and Clinical Workshop were held in Vancouver, Canada from April 30 to May 6, 2005. This meeting saw record breaking attendance with nearly 1,300 people attending the clinical workshop and/or main conference and nearly 800 abstracts submitted.

Much excitement was generated by ongoing studies of preventive HPV vaccines and preparations for their possible implementation in the near future, and a great deal of attention was paid to the impact of these vaccines in the developing world, along with recent assessments of screening and treatment methods suitable to those settings.

The invited speakers for the conference included some true luminaries. Dr. Nobutaka Hirokawa gave the conference's opening talk with his compelling story about the role of kinesins in directing protein trafficking in cells, data with clear relevance for the biology of HPV. Dr. Max Parkin gave a startling overview of the attributable

CONSORTIUM

The World Health Organization (WHO) recently announced a joint international effort with the International Agency for Research on Cancer (IARC), the Harvard University, the Program for Appropriate Technology in Health (PATH), and the Institut Catala d'Oncologia (ICO), which have all received new grants from the Bill & Melinda Gates Foundation. The grants announced total $12.9 million.

Cervical cancer is the leading cause of death from cancer among women in developing countries, killing about a quarter of a million women a year. The disease affects about half a million women every year, and represents a major health inequity, as 80% of cervical cancer victims live in low- or middle-income countries.

Currently, the best way to prevent cervical cancer is through regular gynecological screening and, when necessary, treatment of associated pre-cancerous lesions. However, due to the cost and complexity of regular screening and treatment, this method has had only a limited impact in the countries where it is most needed.

The Bill & Melinda Gates Foundation has previously supported activities to evaluate and implement low-cost screening methods in developing countries through a $50 million grant to the Alliance for Cervical Cancer Prevention (ACCP). Additional grants from the Gates Foundation to the Alliance totaling $6.4 million were awarded this year.

The Foundation is also supporting development of low-cost methods for HPV screening through a $13 million grant to PATH.

Vaccines to prevent HPV infections have the potential to be cost-effective and to reduce the incidence of cervical cancer and related pre-cancerous lesions, particularly in low-resource settings. Modeling studies suggest that combining HPV vaccination and screening programmes may have the most impact on disease control.

With promising HPV candidate vaccines on the horizon, there are complex challenges ahead that must be overcome before the vaccine can be successfully introduced in

MEETING REPORT

fraction of cancer cases due to infectious agents, specifically HPV, Hepatitis B and C and Helicobacter pylori. Dr. Rafi Ahmed gave important insights into memory CD8+ T-cells and their function in chronic infections, and Dr. Elizabeth Blackburn presented her latest data on telomerase with its implications for HPV-induced immortalization.

Other invited lectures sparked much conversation and dialogue. Dr. Eleftherios Diamandis presented his recent data on the applications (and current limitations!) of proteomics to understand cancer biology. Lessons learned from breast cancer and cancer genomics were elegantly presented by Dr. Joe Gray. Dr. Robert Hendricks gave some insightful parallels to Herpes Simplex Virus (HSV) latency and the role of functionally distinct memory CD8+ T-cells.

The topics of sessions ranged from the epidemiology of male HPV infection to molecular markers to factors driving DNA replication. The functions of the early-region HPV proteins continue to be uncovered. The immunology sessions highlighted recent advances in basic HPV immunology and provided new insights into the science behind the vaccines under development and novel vectors for delivery. Some of the clinical highlights included animated dialogues around HPV testing for specific HPV types, such as HPV-16, for clinical triage. Discussion on vaccines ranged from estimates of their impact to cost-effective methods for their distribution. New molecular methods to diagnose cervical disease were also discussed. Although cytology is not yet "driftwood", molecular markers appear to be increasingly promising to improve the diagnosis of cervical high squamous intraepithelial lesion (HSIL).

The HPV field has proven itself to be particularly dynamic and exciting in the last several years, and this was reflected in the Vancouver Conference, a conference that will be fondly remembered for years to come.

BILL & MELINDA GATES *foundation*

developing countries. A broad strategy to address these challenges aims to support the additional studies that are needed in key high-disease-burden areas.

The Gates Foundation announced recently that it will support the following projects:

• The WHO Initiative for Vaccine Research will work with partners to create an HPV Laboratory Network to facilitate vaccine licensing and monitoring in developing countries, to harmonize and standardize laboratory procedures and create an international, multi-disciplinary policy platform, and set guidelines for future HPV vaccine introduction, in consultation with regions and countries.

• The WHO HPV and Cervical Cancer Information Centre, to be based at the ICO in Barcelona, will facilitate global, regional, and country-specific decisions on current and new options for cervical cancer prevention.

• The IARC will collect new epidemiological data on HPV in low-resource countries in Asia, Africa, and Eastern Europe. These studies will focus on worldwide differences in age at first HPV infection and in the distribution of HPV types other than those included in currently available HPV vaccines.

• Harvard University will develop a series of models for different epidemiologic settings that will be used to evaluate both the population impact and cost-effectiveness of different HPV vaccination strategies.

• PATH will work to develop partnerships with the private sector to facilitate early introduction of HPV vaccine in selected developing countries, develop a case for investing in HPV vaccine, address country- and region-specific programmatic issues, and identify information needs.

The Bill & Melinda Gates Foundation is taking major steps forward towards the use of the novel HPV vaccines in the prevention of cervical cancer worldwide.

KEY PUBLICATIONS

PROPHYLACTIC QUADRIVALENT HUMAN PAPILLOMAVIRUS (TYPES 6, 11, 16, AND 18) L1 VIRUS-LIKE PARTICLE VACCINE IN YOUNG WOMEN: A RANDOMISED DOUBLE-BLIND PLACEBO-CONTROLLED MULTICENTRE PHASE-II EFFICACY TRIAL

Villa LL, Costa RL, Petta CA, et al. Lancet Oncol 2005;6(5):271-278.

This randomised, double-blind, placebo-controlled phase-II study was done to assess the efficacy of a prophylactic quadrivalent vaccine targeting HPV types 6, 11, 16, and 18. A total of 277 young women were randomly assigned to quadrivalent HPV L1 virus like particles (VLP) vaccine and 275 to placebo at day 1, month 2, and month 6, and followed for 36 months by regular gynaecological examinations, cervicovaginal sampling for HPV DNA testing, serum antibodies to HPV, and Pap testing. Combined incidence of persistent infection or disease with HPV vaccine types fell by 90% (95% confidence interval, CI, 71-97) in those assigned vaccine compared with those assigned placebo. A vaccine targeting these four types could substantially reduce the acquisition of infection and clinical disease caused by common HPV types.

COST-EFFECTIVENESS OF HUMAN PAPILLOMAVIRUS DNA TESTING IN THE UNITED KINGDOM, THE NETHERLANDS, FRANCE, AND ITALY

Kim JJ, Wright TC, Goldie SJ. J Natl Cancer Inst 2005;97(12):888–895.

The cost-effectiveness of each country's current screening policy was compared, with the use of a computer-based model of the natural history of cervical carcinogenesis, with two new strategies: 1) cytology using HPV DNA testing as a triage strategy for equivocal results, and 2) cytology until age 30 years and HPV DNA testing in combination with cytology in women above 30 ("combination testing"). It was found that both "HPV triage" and "combination testing" are more effective than each country's screening policy. HPV DNA testing has the potential to improve health benefits at a reasonable cost compared with current screening policies in these countries.

ATLAS DIGITAL DE ENFERMEDADES DE LA VULVA. CORRELACIÓN CLÍNICO-PATOLÓGICA Y TERAPÉUTICA (DIGITAL ATLAS OF VULVAR DISEASES)

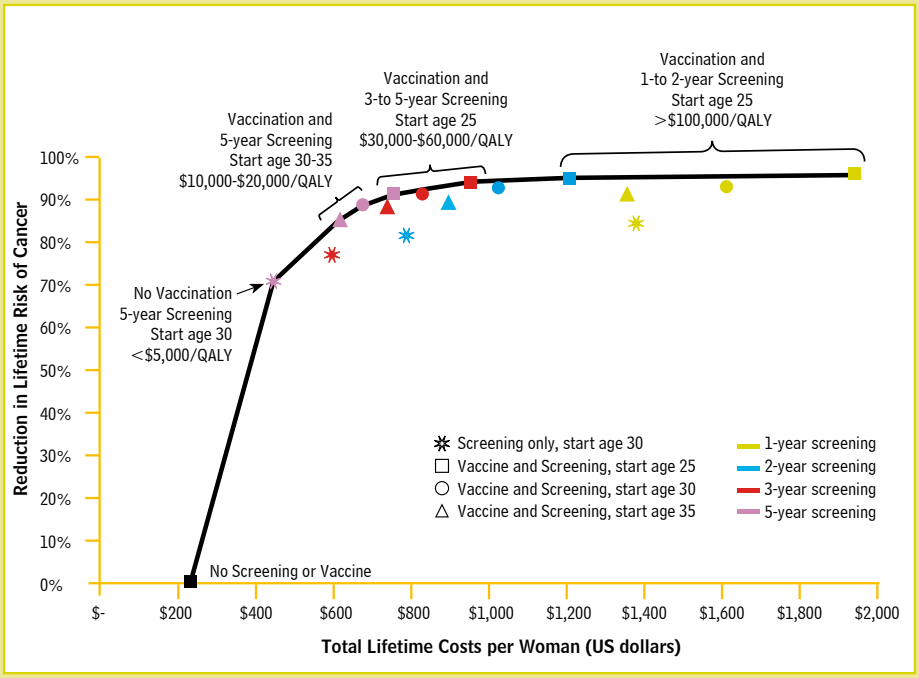
Puig-Tintoré LM, Ordi J, Torné A, Cararach M, Palou Aymerich J. CD-ROM [Text in Spanish]. Edited by the "Asociación Española de Patología Cervical y Colposcopia". Barcelona 2005.

THE ELEVATED 10-YEAR RISK OF CERVICAL PRECANCER AND CANCER IN WOMEN WITH HUMAN PAPILLOMAVIRUS (HPV) TYPE 16 OR 18 AND THE POSSIBLE UTILITY OF TYPE-SPECIFIC HPV TESTING IN CLINICAL PRACTICE

Khan MJ, Castle PE, Lorincz AT, et al. J Natl Cancer Inst 2005;97(14):1072–1079.

This study shows that the identification of HPV-16 and -18 from other oncogenic types may identify women at the greatest risk of ≥ cervical intraepithelial neoplasia (CIN) 3. Women (n=20810) in the Kaiser Permanente health plan (USA) enrolled in a cohort study of cervical neoplasia were tested for 13 oncogenic HPV types by Hybrid Capture 2 (HC2), and those found positive were tested for HPV-16 and -18. Enrolment Pap smear interpretation and HPV test results were linked to histologically confirmed CIN3 and cervical cancer occurring during 10 years of follow-up. The authors found that the 10-year cumulative incidence rates of ≥CIN3 were 17.2% among HPV-16+ women, 13.6% among HPV18+ (HPV-16 negative) women, but only 3.0% among HC2+ women negative for HPV-16 or -18, and 0.8% among HC2-negative women.

HPV IN 100 SLIDES



QALY: *Quality-Adjusted Life Expectancy. Courtesy of Jane Kim and Sue Goldie. Harvard School of Public Health.*

This is a figure depicting the potential cost-effectiveness of different cervical cancer control strategies involving HPV 16/18 vaccination with and without cytology screening conducted at different frequencies. In this stylized example, we assumed that the vaccine is administered to a single cohort of females at age 12 with a 90% effectiveness against preventing incident HPV-16 and -18 infection over their lifetime, and we varied screening with conventional cytology every one, two, three or five years, starting at either 25, 30, or 35 years of age. Selected data shown are from Goldie et al. (2004).[1]

The figure shown is referred to as an "efficiency frontier" and depicts the relationship between the total discounted per-woman lifetime costs and health benefits associated with the most efficient strategies. Strategies that fall to the right of the curve are referred to as "dominated" in that they are either more costly and less effective, or more costly and less cost-effective than strategies that are on the curve.

On the graph, costs (x-axis) are expressed in US dollars, and effectiveness (y-axis) is expressed as the percent reduction in lifetime risk of cancer, compared to no screening or vaccine. The cost-effectiveness of moving from one strategy to a more costly alternative is represented by the difference in cost divided by the difference in health benefit associated with the two strategies –or the incremental cost-effectiveness ratio– and is expressed here as cost per quality-adjusted life expectancy (QALY). Starting from the lower left and moving up the curve, the reader can see that screening alone every five years starting at age 30 costs less than $5,000 per QALY gained, compared to no screening or vaccine; this strategy is associated with a reduction in lifetime risk of cancer of approximately 70%. The next two most efficient strategies include vaccination combined with five-year screening beginning at the ages of 30 or 35, which range from $10,000 to $20,000 per QALY gained, with reductions in cancer risk ranging from 85% to 90%. Vaccination and 3- to 5-year screening starting at age 25 ranges from $30,000 to $60,000 per QALY gained. Vaccination and screening annually or biennially starting at age 25 costs more than $100,000 per QALY gained, while yielding less than one additional day of quality-adjusted life expectancy; reductions in cancer risk reach up to 97% with these strategies.

There is no universal criterion that defines a threshold cost-effectiveness ratio below which an intervention would be considered cost-effective; however, one proposed rule of thumb may be based on the Commission on Macroeconomics and Health, which defined interventions with a cost-effectiveness ratio under the per capita GDP as "very cost-effective".[2] Using this criterion in the U.S. ($40,100), vaccination at age 12 combined with cytologic screening every five years beginning at age 25 has the potential to be more effective than our current screening program and very cost-effective.

There are a number of limitations to the analysis upon which this stylized example is based. We refer the reader to the manuscript for more information on these limitations.[1]

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POINT OF VIEW

HPV IN SKIN CANCER. COMMENTS ON THE IARC INTERNATIONAL EVALUATION

Prof. Dr. Dr. h.c. Herbert Pfister
Institut für Virologie, University of Cologne.
Köln, Germany.

The carcinogenicity of HPV was evaluated in February 2005 by a Monograph Working Group at the International Agency for Research on Cancer (IARC), which acknowledged that there is compelling evidence for the carcinogenicity of HPV-5 and HPV-8 in the skin in patients with epidermodysplasia verruciformis (EV) and limited evidence for the carcinogenicity of HPV genus-beta types in the skin in general.[1]

The carcinogenic potential of beta-HPV, better known as EV-associated HPV, has been convincingly documented by experimental studies. We recently published the development of squamous cell skin carcinomas (SCSC) in 6% of transgenic FVB/n mice with the early genome region of HPV-8 under the control of the human keratin 14 promoter at an age of about one year without any further treatment with physical or chemical carcinogens (Figure).[2] Furthermore, expression of the HPV-8 E7 gene from a retroviral vector in adult human epidermal keratinocytes promoted overexpression of matrix metalloproteinases in a complex raft culture system, disruption of the basement membrane and keratinocyte invasion through the underlying dermis.[3]

In humans, the association between EV HPV and non-melanoma skin cancer is clearly less strong. EV HPV causes clinically unapparent, low-level infections in probably everyone early in, and throughout, their lives, whereas SCSC rarely arise before the age of 65. Nevertheless, (sero)epidemiological data provide some support for an association between EV HPV infection and an increased risk of precancerous actinic keratoses and skin cancer. In contrast to transgenic mice, EV HPV will rarely cause harm to humans because only a few keratinocytes are infected and oncogene expression from the viral promoter is very weak. Their carcinogenic potential becomes obvious, however, in the genetic background of EV, which allows replication of viral DNA to high copy numbers and expression of the oncogenes E6 and E7. EV HPV also appears to be more active in immunosuppressed patients, who experience a 100-fold increased risk of SCSC.

EV HPV DNA has been detected in up to 65% and up to 90% of SCSCs of immunocompetent and immunosuppressed patients, respectively. According to the low-levels of HPV DNA in skin cancers, ranging from one viral genome per 20 to more than 10,000 cells, the presence of HPV is not mandatory for maintenance of the malignant phenotype of skin cancer cells.[4] The small number of HPV-positive cells does not exclude, however, an initiating role of HPV in carcinogenesis, and may even have an impact on the growth and invasion of the tumor by secretion of cytokines or metalloproteinases.

A synergism between EV HPV and sunlight (UV) – the most notorious risk factor in skin carcinogenesis – is particularly intriguing. The antiapoptotic activities of E6 may favor accumulation of mutations, for example in the p53 gene. We found it striking that UV-irradiation of HPV-8 transgenic mice with a minimal erythemal dose induces massive tumor growth within two weeks, whereas the skin of their non-transgenic litter mates appeared completely normal.

In summary, it was formally correct to speak of limited evidence for the carcinogenicity of EV HPV in human skin because (sero)epidemiology was hampered by widespread infections in controls and assays for EV HPV are still in an early phase of development. However, recent experimental studies and the plausibility of clinical observations on EV HPV in immunosuppressed and genetically predisposed patients strongly support the epidemiological evidence and provide ample incentives to further our understanding of HPV in skin carcinogenesis and to develop targeted prevention and therapy.

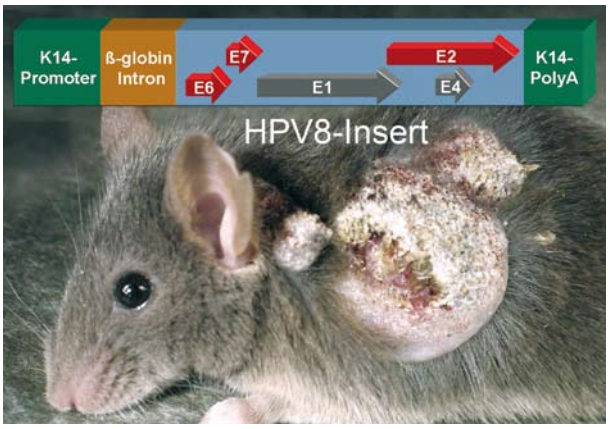

Figure:
Skin cancer in HPV-8 *transgenic mice. More than* 90% *of transgenic mice with the* HPV-8 *expression construct shown on top develop multifocal papillomas with varying degrees of dysplasia. Squamous cell carcinomas were diagnosed in* 6%.

References:
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THE COEXISTENCE OF HPV-16- AND -18-RELATED HIGH GRADE SQUAMOUS INTRAEPITHELIAL NEOPLASIA AND MICROINVASIVE ENDOCERVICAL ADENOCARCINOMA

CASE STUDY

Massimo Origoni MD, Luigi Caputo MD, Flavia Lillo MD

Vita-Salute San Raffaele University School of Medicine, Dept. of Obstetrics and Gynecology and Laboratory of Virology, IRCCS Hospital San Raffaele Milano, Italy.

We present the case of a concomitant diagnosis of cervical intraepithelial neoplasia, CIN3, and microinvasive endocervical adenocarcinoma (FIGO IA1) in a 39-years-old woman with a previous long-term negative cytological cervical screening.

The patient was referred to our Institution with a cytological evidence of high grade SIL (CIN3) suspicious for HPV morphological cellular alterations.

Colposcopy and multiple cervical biopsies were performed on the basis of a large, grade-2 atypical transformation zone (Grade 2 AnTZ) (Figure 1): colposcopical findings accounted for keratosis, thick aceto-whitening epithelium, and atypical vessels.

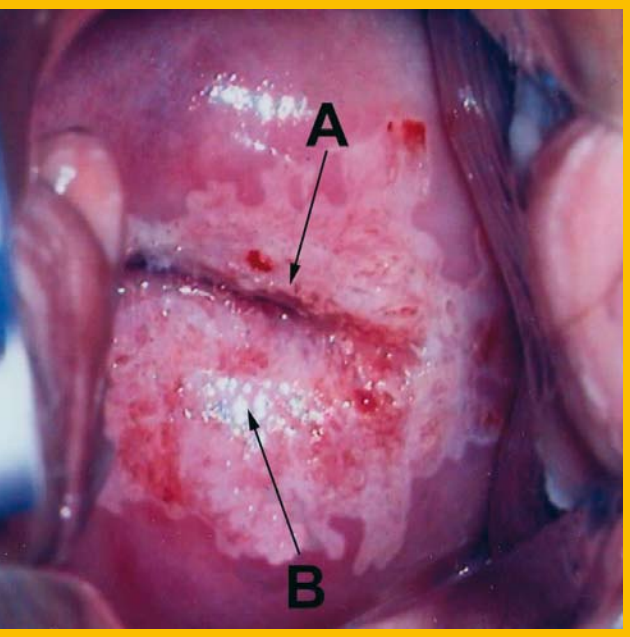

Figure 1
Colposcopic appearance of the lesion.
A: *atypical vessels*
B: *aceto-whitening epithelium*

Two biopsies were performed at the exocervix (aceto-whitening epithelium) (B) and close to the external os (atypical vessels) (A), with histological report of "CIN3, flat condyloma, and focal endocervical glandular atypical hyperplasia (GCIN)" at the exocervical site, while the external os biopsy accounted for "mucinous moderate-differentiated (G2) endocervical adenocarcinoma with a focal area of subepithelial microinvasion (<3 mm), and flat condyloma".

HPV-DNA testing (Hybrid Capture 2, Digene Corporation, Gathersburg, MD USA) proved positive for high-risk HPV genotypes, which was subsequently confirmed by positive polymerase chain reaction (PCR) typing of HPV-16 and -18 sub-types (Inno_Lipa HPV, Innogenetics, Ghent, Belgium).

The patient was treated with cold-knife cervical conization and diagnostic endocervical curettage. The final diagnosis was pT1a1 grade-2 mucinous cervical adenocarcinoma (FIGO IA1) in association with a squamous high-grade intraepithelial lesion (CIN3); endocervical curettage resulted in glandular hyperplasia with mild atypia. The surgical margins were free of disease.

At two months after treatment colposcopy, cytology, and HPV-DNA detection were negative.

The coexistence of a squamous and glandular preinvasive cervical lesion is quite a common finding in cervical preneoplastic pathology,[1] as already published by Brown J et al., who reported a 16% of coexistence of CIN3/endocervical glandular atypia and 1% of coexistence of CIN3/adenocarcinoma in situ. In particular, the author focused his attention on the presence of glandular atypia, stating that the natural history of this alteration is still uncertain; in our case, the concurrent presence of squamous intraepithelial lesions, glandular atypia and microinvasive adenocarcinoma, together with the evidence of HPV-16 and -18, seems to indicate a linear progression towards cervical cancer of both cellular lines.

Concerning the relative role of HPV, Tase T et al. have studied the presence of HPV-18 and -16 in microinvasive adenocarcinomas and CIN3, respectively:[2] their findings showed a preponderant presence of HPV-18 in glandular microinvasive lesions and of HPV-16 in pure squamous lesions. Using in situ hybridization in cases of coexistent CIN3 and microinvasive adenocarcinomas, a similar evidence of single HPV-18 positivity was reported; the author concluded that CIN coexisting with adenocarcinoma may be a result of a metaplastic process of adenocarcinoma or of bidirectional differentiation of the affected reserve cells.

According to our case and to our virological data, we favor this second hypothesis: we believe, in fact, that the contemporary presence of the two HPV types (16 and 18) could act as a double-oriented trigger upon deep basal reserve cells of the transformation zone.

Our hypothesis seems to be confirmed by data published by Leary J et al., who did not find any positivity for HPV-16, using in situ hybridization, in cases of adenocarcinomas in situ; on the contrary, all cases investigated were HPV-18 positive only.[3]

According to the results of previous studies,[4-6] which demonstrated clearance of HPV infection after surgical removal of cervical pre-invasive lesions, in our case the excision of the lesion resulted in the early clearance of HPV infection.

As it is well known that endocervical adenocarcinoma is an increasing reality, especially among younger women, and that traditional cytological cervical screening (Pap smear) seems to be less sensitive in these cases,[7] our case report suggests that HPV-DNA testing and typing may be particularly helpful both in the diagnosis and in the post-operative management of these patients.

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INTERNATIONAL AGENDA

Kuwait City, Kuwait

29th Nov - 1st Dec 2005

8th International Gcc Dermatology and Venerology Conference

Venue: Crowne Plaza-Kuwa
Contact: Kuwait Society of Dermatologist
Tel: +965 9718 109
E-mail: q8dvc@yahoo.com
Web: www.ksd-derma.org

Phoenix, Arizona, USA

1st – 4th December 2005

Advanced Colposcopy: The Complete Lower Genital Tract

Venue: Pointe Hilton Squaw Peak Resort
Contact: The American Society for Colposcopy and Cervical Pathology
Tel: +(301) 733 5775
E-mail: amason@asccp.org e-mail
Web: www.asccp.org

Bangkok, Thailand

4th -7th December 2005

Preventing Cancer in Low Resource Settings: From Research to Practice

Venue: Montien Riverside Hotel
Contact: JHPIEGO'S Cervical Cancer Prevention Program
Tel: +410 537 1874
E-mail: cervicalcancer@jhpiego.net
Web: www.jhpiego.org

Brussels, Belgium

26th – 28th January 2006

15th International Meeting FGOG: Endocrine Treatment & Prevention of Breast and Gynecological Cancer

Venue: KBC Building
Contact: Flemish Gynecology Oncologic Group - FGOG (VWOG)
Tel: +32 478 59 83 80/
+32 16 34 46 35
E-mail: vwog2006@yahoo.com
Web: www.kuleuven.be/fgog/

Noida, India

9th – 12th February 2006

24th Annual Convention of Indian Association for Cancer Research (IACR) and International Symposium on Human Papillomavirus and Cervical Cancer

Contact: Institute of Cytology & Preventive Oncology (ICMR)
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iacr2005@rediffmail.com
bcdas48@hotmail.com

Las Vegas, USA

13th - 17th March 2006

American Society of Colposcopy and Cervical Pathology's 2006 Biennial Meeting

Venue: JW Marriott Las Vegas Resort, Spa and Golf
Contact:American Society for Colposcopy and Cervical Pathology
Tel: + (800) 787-7227 or (301) 733-3640
E-mail: amason@asccp.org
Web: www.asccp.org/biennial.shtml

Paris, France

23rd - 26th April 2006

Eurogin 2006

Venue: Palais des Congrès
Contact: Eurogin
Tel: +33 1 44 40 01 20
E-mail: admin@eurogin.com
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Maratea, Italy

24th - 27th May 2006

VII European Course of Cervical Pathology and Colposcopy

Contact: Roberto Piccoli
Tel: +390 815 585 090
E-mail: rpiccoli@unina.it

Prague, Czech Republic

1st - 7th September 2006

The 23rd International Papillomavirus Conference and Clinical Workshop

Venue: Hilton Hotel Prague
Contact: International Papillomavirus Society
Tel: +1 319 339 7177/
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Web: www.ipvconference2006.org

Kuala Lumpur, Malaysia

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3rd - 10th November 2007

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