The Human Papillomaviruses Vaccines Era –
Cervical Cancer Prophylaxis

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ABSTRACT

Cervical cancer continues to be the leading cause of cancer mortality among women worldwide and responsible for a significant annual morbidity, despite the increased knowledge and the substantial efforts made to prevent the disease by early detection. The Human Papillomaviruses 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 (16 and 18) and one of them also includes the two types involved in virtually all genital warts (6 and 11). Preliminary clinical trials of HPV vaccines demonstrate immunogenicity and (short-term) safety. Cost-effectiveness of the vaccination programs plays an important role, particularly in the developing countries. In addition, HPV vaccination holds great promise to further reduce the disease burden of cervical cancer, even in countries where organized screening programs are effectively implemented.

Key words: Human Papillomaviruses (HPV), cervical cancer, HPV vaccine, screening, trial

BACKGROUND

Cervical cancer is the second most frequent cancer worldwide, representing about 10% of all female cancers. In 2002, there were an estimated 493.000 new cases of invasive cervical cancer, of which 83% were diagnosed in developing countries (1). Each year, there are an estimated 273,000 deaths from cervical cancer, over three quarters of which occur in developing countries (2). Less than 50% of women diagnosed with cervical cancer in developing countries survive beyond 5 years, and most victims are multiparous women at child-bearing age. In contrast, the 5-year survival rate in industrialised countries is about 66%. In Europe, the estimated average incidence is 15.7/100,000, and 80 women die from cervical cancer each day. There is a wide variation in the incidence rates among European countries, from an estimated high of 27.4 per 100,000 in Serbia and Montenegro and Romania to 4.3 per 100,000 in Finland (Figure 1).
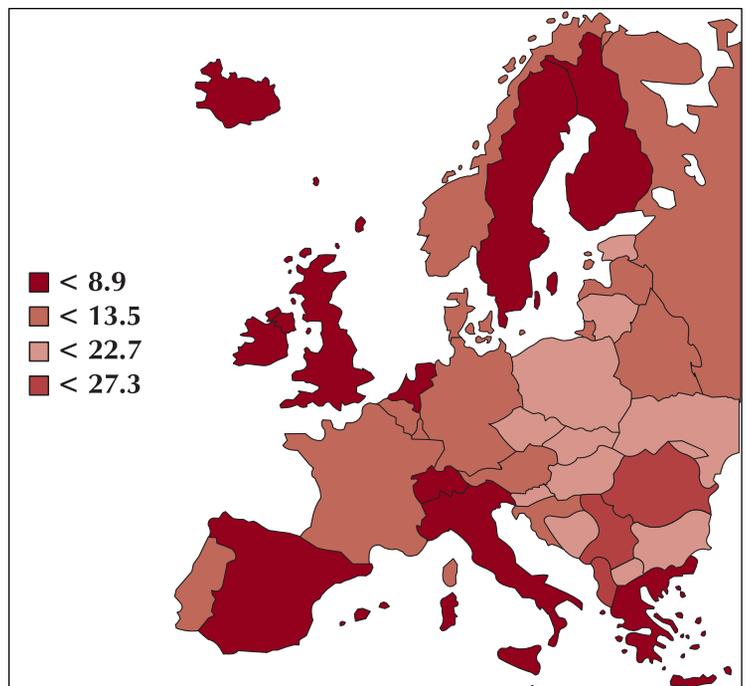

FIGURE 1. Incidence of cervix uteri cancer. Age-standardised rates (modified after 1)

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Infection with some mucosal types of human papillomavirus (HPV) is known to precede cervical cancer development by several years. Many studies have shown unequivocally that HPV DNA can be detected in =99,7% or adequate cervical cancer specimens, compared with 5-20% of cervical specimens from women identified as suitable epidemiological controls (3). Certain types of HPV have now been designated as the first ever identified necessary cause of a human cancer. ❑

CONTENT

General data about HPVs

Human papillomaviruses (HPVs) belong to the family Papovaviridae. They consist of a 72-capsomere capsid containing the viral genome. The capsomeres are made of two structural proteins: the 57 kD late protein L1, which accounts for 80% of the viral particle, and the 43-53 kD minor capsid L2. HPVs are relatively stable and, because they have no envelope, remain infectious in a moist enviroment for months (4). In general, they cause local epithelial infections. A viremia with viral spread to distant body sites does not occur.

Persisting infections with about 13 different high-risk HPV types are the initial prerequisite to induce most cervical cancers (5). However, infections with these viruses are very widespread also among healthy women. The infection is usually self-limited and transient without causing cellular transformation or displasia, and therefore, HPV infections represent an important and necessary but far not sufficient risk factor. Very few of the infected women will ever develop a persistent infection that may last longer than 6-12 months and may pose a significantly increased risk of the subsequent development of cervical lesions.

The HPV way of action

To establish an infection, HPVs apparently require access to the basal and parabasal cell layers of the epithelium, or in case of the cervix, to cells located in the transformation zone. The virus infection gets access through scratches, scars or at the transformation zone, even directly to epithelial cells within the basal and parabasal layers (Figure 2). Here, it establishes a latent infection, i.e. the viral genome replicates along with the host cell. To replicate their genomes and successfully produce new infectious virions, the host cells require a certain degree of terminal differentiation. It appears that in the replication-competent basal and parabasal cells, only very little if any gene expression activity of the virus can be observed (6). This strategy to avoid viral gene expression and replication in epithelial stem cells but to permit it in differentiated cells that are determined to die because of their differentiation processes is very a elaborate strategy to permit maximal production of new infectious viral capsids causing almost no damage to the infected host.

If infected epithelial cells reach terminal differentiation, i.e. the stage where the capacity to proliferate is irreversibly lost, the viral genes may be strongly expressed and the replication cycle of the virus is initiated until finally mature viral capsids are release at the surface of the epithelium.

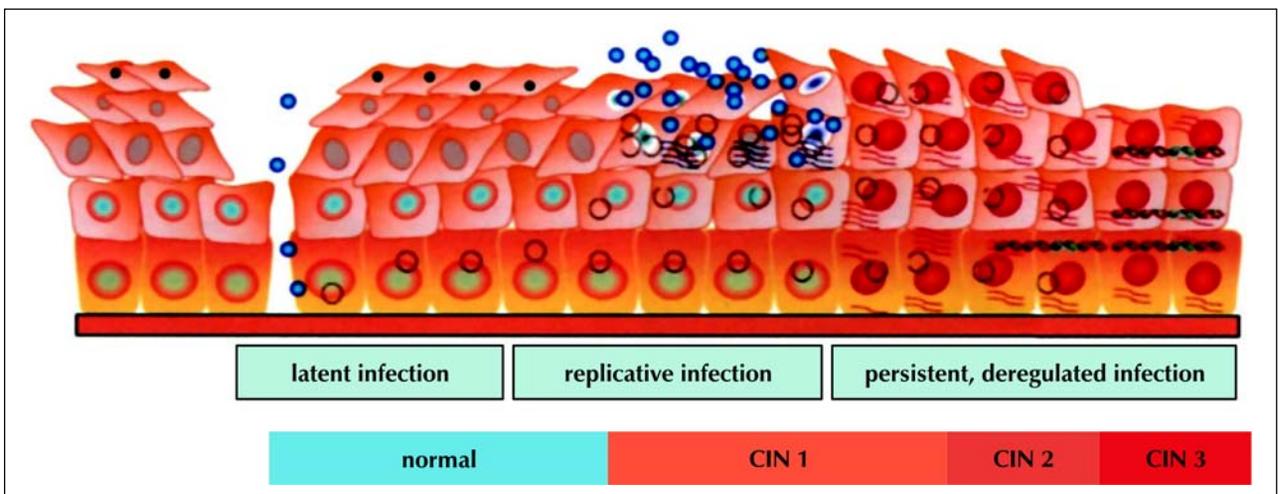Transformation of the epithelial cell may only occur in persisting infections in that the

FIGURE 2. Schematic representation of the natural history of HR-HPV infections (modified after 6)

molecular mechanism that prevents expression of viral genes in the immature basal and parabasal cells is lost. If the regulatory intracellular features that control the fine-tuned expression control of the viral genes along with the differentiation processes of the epithelium are disturbed and deregulated uncontrolled expression of genes involved in the replication of the viral genome suddenly occur in epithelial cells that have not yet reached the irreversible status of terminal differentiation. In this situation, interference of viral genes with those pathways that control replication of the epithelial cell and life cycle may result in the initiation of chromosomal instability.

The genetic functions of the virus that contribute to the induction of chromosomal instability have been very well documented by a long series of very detailed molecular and biochemical studies.

Three major aspects are involved:

1. The E6 protein of the oncogenic HPV types supports premature degradation of the p53 tumor suppresor gene and thus interferes with apoptotic functions (7)
2. The E7 protein induces destabilisation of the retinoblastoma protein complex and thus allows the cell to evade cell cycle control through the pRB pathway (8)
3. Both genes induce substantial disturbances of the mitotic functions by interfering with centrosome synthesis and function that results in desegregation of the chromosomes during mitosis and numerical and structural chromosomal aberrations (9).

These cells may consequently undergo mitotic defects and, due to accumulation of further genomic alterations, finally progress to invasive carcinomas. The initiation of the deregulated type of the viral gene expression pattern can be regarded as the initial event in cervical carcinogenesis. For still unknon reasons, the cells of the transformation zone of the uterine cervix appear to be particularly sensitive to these events.

Natural history of HPV infection

Since the early 1980s attention was focused on HPV, based on rapidly accumulating evidence from molecular biological studies. The relative risk of the association of HPV and cervical cancer was two or three times higher than that of other potent risk factors for cancer. In 1995, the International Agency for Research on Cancer finally pronounced HPV16 and HPV18 as carcinogenic in human beings (10).

HPV infections are very common among general population, about 7 out of 10 women are exposed at least once to HPV during their lifetime. Without treatment, about 1 in 5 women exposed to HPV can develop cervical cancer. Exposure to these viruses occurs during sexual intercourse, often with the first partner (11). The estimated prevalence of HPV infection is about 30% before the age of 30 years, and it falls gradually to about 10% between 30 and 50 years, and to 5% beyond 50 years of age (Figure 3). In Europe, HPV16 and HPV18 are the most
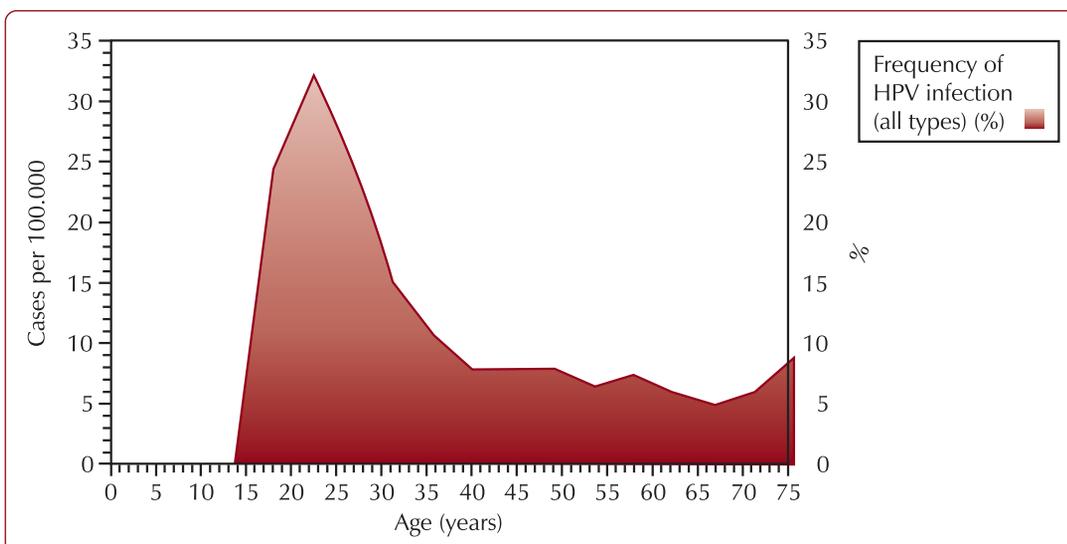

FIGURE 3. HPV infections in adolescents and adults. Hypothetical distribution of HPV prevalence in EU modelled after data available in the US and Canada (modified after 1)

prevalent types in women with a normal Pap test. While type 16 accounts for only 26,3% of low-grade squamous intraepithelial lesions (LSIL) and 45% of high grade squamous intraepithelial lesions (HSIL), a recent meta-analysis showed an HPV16/LSIL ratio about 2, compared with 1.21 for cancer/HSIL (12,13). Recently, it was reported that the risk of developing CIN3 or cancer 10 years after HPV infection was 17.2% for HPV16 and 13.6% for HPV18 (14). Exposure and persistence are more frequent with HPV16 than with other oncogenic HPV types. All these data substantiate the development and implementation of preventive vaccination against HPV16 and HPV18. Most women exposed to HPV develop a limited immunity, generally clearing HPV within 9-12 months. In contrast, HPV remains persistent for months or even years in 20% of women who may go on develop CIN and cancer, unless diagnosed and promptly treated (15). The onset of CIN lesions thus reflects the failure of the immune system to control HPV, a situation most common with HPV types 16 and 18. The simplified model of cervical carcinogenesis is shown in figure 4.

HPV infection is usually transient in women under 30, but tends to be more persistent and problematic after this age. Types 16 and 18 are more persistent than other types. Thus, the presence of HPV within the cervix may or may not be associated with clinical lesions. In contrast, the persistence of viral DNA beyond 12 to 18 months is predictive of current or future lesions, especially in the case of HPV16 or HPV18 infection (16). HPV persistence is associated with expression of certain viral genes, especially E6 and E7 (high-risk HPV types only), whose role in host cell imortalization involves an action on proteins that regulate the normal cell cycle (17). Specific binding of E7 protein to products of the cell cycle inhibitory gene pRb is responsible for cell proliferation. E6 protein binding degrades p53 protein, thereby disrupting apoptotic mechanisms.

Prevention of cervical cancer: HPV prophylactic vaccines

Cervical cancer is one of the few avoidable human cancers. Its prevention is currently based on early diagnosis and treatment of benign and precancer lesions. This approach, form screening to effective prevention, is unique to cervical cancer.

The fact that cervical cancer is caused by a viral infection raises the possibility of preventing the disease by vaccination against this known etiological agent. Campaigns against sexually transmitted diseases had a limited impact on the incidence of HPV infection, particularly those due to high-risk types.

The role of the immune response in limiting cervical cancer development is unproven, but is supported indirectly by the higher incidence of HPV infection, CIN and disease recurrence after treatment in immunocompromised patients. HPV infection and cervical neoplasia are associated with impaired cell-mediated immunity, not disorders of humoral immunity, which implies that cellular immune effectors are more important than antibodies in these diseases. Further evidence of immunity against
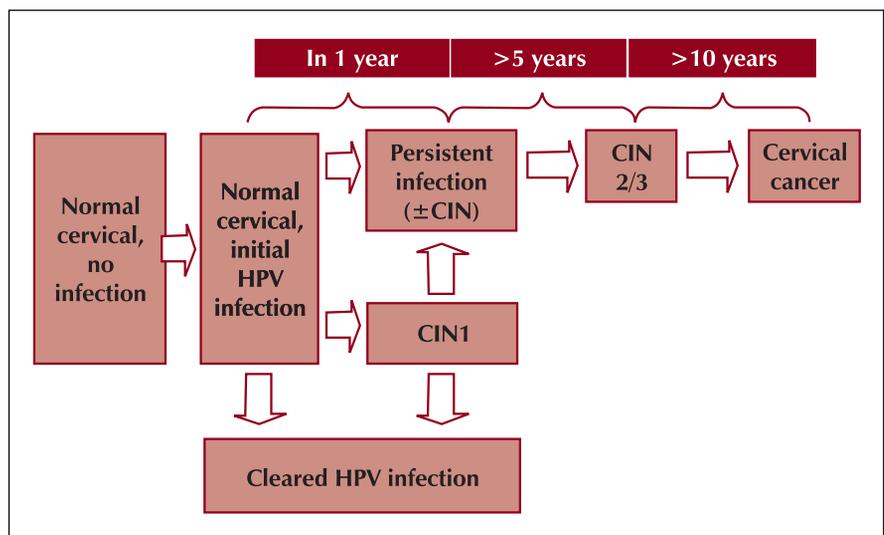

FIGURE 4. Natural history of high risk HPV infection (modified after 15)

HPV disease derives from established and experimental treatments for HPV lesions that appear to work by modifying local immune response.

HPV infection is limited to the epithelium; the viral lifecycle depends on infection of basal cells that normally differentiate into mature squamous cells as they progress towards the epithelial surface. HPV viral particles consist of the viral DNA genome surrounded by the protein capsid, which is composed of HPV L1 and L2 proteins. Thus, it is possible that antibodies against L1 and L2 could be virus neutralizing, and prevent or attenuate infection. Once HPV infects, early viral proteins are expressed within lower epithelial layers and viral replication occurs. As infected cells reach the surface, the L1 and L2 proteins are produced and allow shedding of mature virions with exfoliated cells. During infection, HPV DNA is generally found in the cytoplasm. However, the majority of cervical tumours show integration of high-risk (HR) HPV DNA into the host genome, with loss of virion production (L1 and L2 are not expressesd). Integration commonly disrupts the HPV virus in the E2 open reading frame; loss of E2 increases expression of E6 and E7, conveying a selective growth advantage to these cells. The net effect of integration is the transformation of infected cells into a malignant phenotype. The constant presence of E6 and E7 in cervical cancers renders them tumour-specific antigens, and raises the possibility that vaccination against E6 and E7 HPV types could produce a therapeutic immune response.

A rational approach to the stimulation of anti-HPV immunity requires knowledge of what immune response, if any, occurs in natural HPV infection. HPV causes no viraemia or systemic manifestations, is not cytolytic and does not activate the inflammatory response. Such chronic infection is more likely to result in immunological tolerance than in T-cell activation. The ability of HPV to persist is consistent with the concept of the virus having low immunogenicity. However, there is almost certainly a role for the immune system in limiting and eradicating HPV infection, and it is this immunity which vaccination seeks to induce or augument.

Humoral immunity

Binding of a receptor Ig molecule to an HPV antigen activates the B-cell, stimulating rapid proliferation, and creates a clone of plasma cells that secrete antibody to the viral antigen. Neutralising antibodies bind to sites that inactivate the virus. The development of HPV antibodies in association with disease progression implies that antibodies are secondary to prolonged antigen exposure and incresing viral load, rather than a mechanism for tumour clearance (18). This is consistent with the concept that cellular, not humoral, immunity has the critical role of destroying virally infected cells. However, there remains the possibility that antibodies against HPV capsid proteins could neutralize viral particles, preventing or controlling infection. Whilst there are several studies that have associated HPV 16 capsid antibodies with cervical infection by HPV 16 (19), the available data continue to support the view that this is a consequence of persistent exposure to the antigen. There are no lon-gitudinal studies of seropositivity in HPV-negative women, to establish whether capsid antibodies reduce re-infection.

Cellular immunity

Once virus particles have entered host cells, infection is dealt with cell-mediated immunity, not by antibody. Cytotoxic T-lymphocytes(CTLs) recognize foreign peptide antigens presented on the infected target cell surface by molecules of major histocompatibility complex (MHC), where, in the presence of co-stimulatory molecules, binding to a CTL may induce an immune response. Infiltrating T-cells are seen in regressing warts caused by low-risk (LR) HPVs. Cervical cancer show tumour-infiltrating lymphocytes that are predominantly CTLs. Even high-grade CIN lesions may spontaneously regress in what is, presumably, an immunologically mediated manner. Specific CTLs also infiltrate cervical tumours and are retained in higher numbers at the disease site than in peripheral blood. There is no definite relationship between immune responsiveness and disease clearance, nor has it been established whether proliferation to HPV 16 E7 is associated with persistent infection, or clearance of HPV and CIN regression. Nevertheless, T-helper 1 proliferation may generate specific CTLs that could eliminate HPV lesions (20).

Principles of HPV Vaccination

Two types of HPV vaccine are under development: (1) prophylactic vaccines to

prevent HPV infection and associated lesions, and (2) therapeutic vaccines to induce regression or remission of established precancer lesions or cervical cancer.

Current prophylactic HPV vaccines are based on purified virus-like particles (VLPs), i.e. the viral capsid, without the viral DNA, composed of the main envelope protein L1 of the oncogenic HPV types. VLPs are indistinguishable from the complete virions under electron microscope. At present, two pharmaceutical companise, GlaxoSmithKline (GSK) and Merck and Co. are actively developing prophylactic vaccines. VLPs are produced in baculovirus-infected insect cells (Cervarix®, GSK) or yeast (Saccharomyces cerevisiae) cells (Gardasil®, Merck). They are neither infectious or oncogenic. They induce a high titer of specific neutralizing antibodies, which protect the cervix by transudating into the cervical mucus. The antibodies bind to the viral capsids and thereby prevent the host cell infection. Vaccination with VLPs of nonhuman papillomavirus types with mucosal tropism confers type-specific protection, but no regression of the existing lesions. This suggest that propylactic vaccination will not act on clinically established lesions.

According to the three randomised trials of candidate HPV vaccines published so far, HPV vaccination can prevent not only precancer lesions associated with these viral types but also both persistent and incident infection, with almost total efficacy (21,22,24). Vaccination prevents clinical onset and also eliminates the virus from the genital tract, thus avoiding infection of new partners. In the three studies, vaccination was most effective in preventing the aquisition and persistence of the relevant HPV types and CIN related types.

HPV Types in the vaccines

The number of viral types used as immunogenes is an important issue. A recent review of case-control studies indicates that a pentavalent vaccine composed of VLPs of HPV16, HPV18, HPV45, HPV31 and HPV33 could potentially prevent 83% of all cases of cervical cancer. A heptavalent vaccine, also including HPV52 and HPV58, could prevent 87% of the cases (23). The maximum gain is obtained with four viral types, beyond which one comes up against the law of diminishing returns.

Requirements for an HPV Vaccine

The ongoing and published randomised studies have focused on a monovalent vaccine (HPV16), a bivalent vaccine (HPV16 and HPV18), and a quadrivalent vaccine (HPV16, HPV18, HPV6 and HPV11). Vaccine efficacy is assessed by using viral and lesional markers such as persistent HPV infection, CIN (especially high-grade CIN) and cancer, although follow-up is currently too short for this latter endpoint. The analyses focus on specific efficacy against the vaccine types, but also on potential cross-immunity to other HPV types and their associated lesions. It must be determined the duration of protection and the possible need for booster injections. Ongoing studies are examining the correlation between antibody titers and clinical protection. Two candidate vaccines are currently being tested in phase III trials. The GSK vaccine (Cervarix®) is bivalent, containing HPV16 and HPV18 VLP L1, while Merck vaccine (Gardasil®) is quadrivalent and contains HPV16, HPV18, HPV6 and HPV11 L1. The first vaccine is designed to prevent CIN and cervical cancer due to HPV16 and HPV18, while the second vaccine is designed to prevent not only these lesions but also condyloma acuminatum, a frequent disease in external genitalia of young women.

Results of the GSK Bivalent (HPV16 and HPV18) Vaccine

A phase II multi-center, randomized, double blind, placebo-controlled trial (HPV 001) was conducted in Brasil, Canada and United States (24). Each shot dispensed 40 ìg of HPV16 and HPV18 VLP L1. The adjuvant was ASO4, for the maintenance of the sustained immune response. Three injections were given, at 0, 1 and 6 months. About 1,100 women aged 15-25 years have been enrolled. The inclusion criteria were HPV16 and HPV18 seronegativity (Elisa), HPV16 and HPV18 PCR negativity and a normal Pap smear (liquid-based citology).

Compared with placebo, efficacy against incident infections ranged from 91,5 (types 16 and 18) to 100% (type16). Efficacy on persistent infections was 100% (types 16 and 18). Efficacy on cytologic abnormalities related to these two viral types was 93%. The vaccine induced strong seroconversion: 7 months after vaccination, titers of neutralising antibodies to HPV16 and HPV18 reached levels 1,000 times higher than

at baseline and 80-100 times higher than after natural infection. Recent results were obtained regarding possible cross-imunization by the bivalent vaccine against virus types phylogenetically related to HPV16 and HPV18.

The results of a follow-up study (HPV 007) after multicentre double-blind, randomised placebo-controlled trial reported in 2004 were published in april 2006 (25). This study included 776 women who originally received all three doses of bivalent HPV-16/18 virus-like particle ASO4 vaccine or placebo. More than 98% seropositivity was maintained for HPV-16/18 antibodies during the extended follow-up phase. It was noted a significant vaccine efficacy against HPV-16 and HPV-18 endpoints: incident infection 96,9%; persistent infection: 6 months definition, 94,3%; 12 months definition, 100%. In a combined analysis of the initial efficacy and extended follow-up studies, vaccine efficacy of 100% against cervical intraepithelial neoplasia (CIN) lesions associated with vaccine types. Investigators also noted broad protection against cytohistological outcomes beyond that anticipated for HPV 16/18 and protection against incident infection with HPV 45 and HPV 31 (cross protection). The vaccine has a good long-term safety profile. Up to 4-5 years, the HPV-16/18 L1 virus-like particle ASO4 vaccine is highly immunogenic and safe, and induces a high degree of protection against HPV-16/18 infection and associated cervical lesions.

A phase III trial started in 2003 involves 30,000 female volunteers aged from 10 to 25 years and over 25 years. The aim is to determine the best age for vaccination, as well as safety and long term efficacy.

Merck Trials

Phase I Trial involved 300 subjects and assessed the immunogenicity and tolerability of a range of monovalent VLP L1 vaccine doses. 82 subjects received the monovalent HPV16 vaccine, while the control group consisted of 167 subjects, some of whom were vaccinated with an HPV11 vaccine while others received a placebo. No cases of persistent HPV16 infection were detected by PCR in the active vaccination group, while 15 cases occured among the controls, indicating that there was no cross-immunization between the HPV11 vaccine and HPV16. The titer of neutralizing

antibodies was 1,000 times higher than at baseline 8 months after the first injection. The antibody titer fell slightly with time but remained 100 times higher than at baseline after 36 months. The antibody titer did not vary significantly with the vaccine dose used, and it was decided to use the lowest doses for phase II trials.

Phase II Trials. In this trials 1,193 subjects were injected intramuscularly at 0, after 2 months and 6 months with HPV16 VLP L1 vaccine and compared with 1,198 controls. The interim assessment after 17 months showed that HPV16 vaccine was 100% effective against persistent HPV infection and against HPV16-associated CIN and CIN3 (21). Results at 3.5 years showed the same 100% efficacy. Whatever the viral type, efficacy was 30% on CIN1, 40% on CIN2, 52% on high-grade lesions and 73% on CIN3. At 36 months, the neutralizing antibody titer was 100 times higher than at baseline and 10 times higher than after natural infection.

Phase IIb Trials examined the performance of a quadrivalent vaccine against HPV16, HPV18, HPV6 and HPV11 (Gardasil®) during a 36-month period (22). Efficacy reached 90% on persistent infections associated with all four viral types, 90% on associated lesions, 100% on HPV6 and HPV11 condylomata, 86% on lesions associated with HPV16 and 89% on lesions associated with HPV18. The titers of neutralizing antibodies against HPV18, HPV6 and HPV11 fell significantly at 36 months. Correlation between antibody titers and clinical protection must be further studied.

Phase III Trial. A cohort of 25,000 women are participating in this study of vaccine tolerability, imunogenicity, public health benefit and efficacy on high grade CIN, CIN1 and condyloma acuminatum. The results for more than 10,000 patients at 17 months post-vaccination follow-up showed 100% efficacy on HPV16 and HPV18 infection and at 26 months follow-up associated CIN2-3. The FUTURE I study of the quadrivalent vaccine showed 100% efficacy on HPV6, HPV11, HPV16 and HPV18 infection and on associated CIN in situ squamous carcinoma of all stages. Efficacy on HPV6, HPV11, HPV16 and HPV18 infection and on associated vaginal and external genital lesions was also 100%. The full results of these randomised studies should become available before the end of 2006. ❏

COMMENTS

The results of ongoing phase III trials will be necessary to answer to some outstanding questions: who will be the ideal target population, should girls alone be vaccinated, or both boys and girls, the duration of protection, does cross-protection occur, which groups are at risk and if vaccination should be optional or recommended, cancer prevention by HPV vaccination, vaccination of adult women, including those with prevalent HPV infection, how to vaccinate people in developing countries, how to incorporate vaccination programs into current screening strategies for cervical cancer? Ongoing phase III trials are expected to provide new information on the natural history of HPV infections (26). More than 30% of the population seems to have multiple HPV infections, and the natural history of such infections is not known. It remains to be shown whether cervical cancer is due to latent or persistent infection or rather to infection acquired at a more advanced age? Similarly, we do not yet known whether current vaccines might lead to the selection of viral genotypes that are currently rarely associated with cervical cancer.

Therapeutic vaccines

Therapeutic vaccine candidates also have been developed, several of which have undergone Phase I/II clinical evaluation.

A live recombinant vaccine virus expressing modified versions of the E6 and E7 genes from HPV-16 and -18 (TA-HPV) has been tested by Xenova in two open-label Phase IIa trials in women with high grade vulvar intraepithelial neoplasias (VIN). A single immunization with TA-HPV induced at least 50% reduction in lesion size in 44% of the vaccinated patients. An additional study evaluated the combination of TA-HPV with TA-CIN, a recombinant fusion protein made up of the L2, E6 and E7 proteins of HPV-16, produced in E. coli. Three immunizations with TA-CIN followed by a single immunization with TA-HPV resulted in 23% of the patients experiencing a >50% reduction in VIN lesion size.

Another recombinant bacterial fusion protein of HPV-16 E6 and E7 formulated with the ISCOMATRIX adjuvant has been made by CSL and shown to elicit good immune responses in a Phase I study.

Transgene is developing a MVA-based vaccine that expresses modified HPV-16 E6 and E7 proteins, as well as the IL-2 cytokine. The vaccine is aimed at treating cervical as well as ano-genital dysplasias. In an initial Phase II clinical trial in women with CIN2/3, 43% of the patients receiving the highest dose of the vaccine showed clinical improvement within 6 weeks. A second trial is now under way, using this high dose in 18 women with CIN2/3 who will be followed for a 6-month period.

Stressgen has conducted a number of Phase II clinical trials with a fusion protein made of E7 and heat shock protein (HspE7). In a Phase II study on 133 patients with anal dysplasia, there was no difference in adjudicated pathological response between vaccine and placebo recipients, although a significant effect was noted by the treating physician in "global assessment" scoring. The HspE7 vaccine was also shown to induce a 40% response rate within 8 weeks in a trial in 21 women with high grade dysplasia. Elucidation of the full extent and duration of the clinical benefit will require additional long-term follow-up.

Finally, Zycos Inc. (now MGI Pharma) is developing a DNA plasmid-based therapeutic vaccine which, in a Phase II study, provided resolution of 43% pre-cancerous lesions caused by HPV in vaccinated women as compared to 23% in placebo recipients.

Medigene, in partnership with Schering AG, has developed a "chimeric" VLP vaccine (CVLP) using L1 or L2 recombinant proteins fused to modified E7 or E2 oncogenic antigens. This technology allows the combination of both prophylactic and therapeutic components in the same immunogen. The safety of these vaccine candidates has been successfully tested by Medigene but their reported immuno-genicity and efficacy were unsatisfactory. ❑

CONCLUSION

HPV vaccines are well tolerated, immunogenic and effective on most common HPV infection and their associated diseases. The immunization is robust, but follow-up is currently limited to 4 years and the minimum protective antibody titer is not known. The most effective strategy for preventing cervical cancer by HPV vaccination is to ensure a high coverage of the program. Screening for cervical cancer should continue
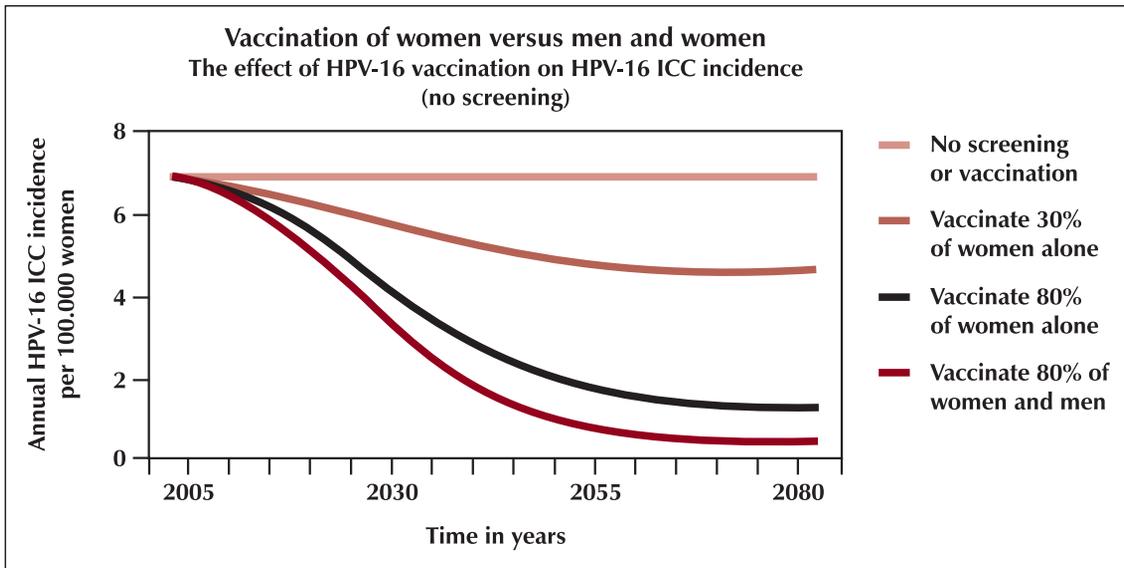
FIGURE 5. The incidence of invasive cervical cancer as an function of vaccination coverage and gender. Results suggest that vaccinating 80% of both women and men has a slightly greater impact than vaccinating 80% of women alone (modified after 26)

in the meantime. Strategies based on both screening and vaccination are being studied.

HPV vaccination would probably have a different impact on cervical cancer in different countries. In industrialised countries the vaccine will change the screening strategies and reduce the incidence of CIN 2/3. In developing countries, where 80% of cases of cervical cancer occur and where cytological screening is nonexistent or ineffective, vaccination against HPV16 and HPV18 would prevent 70% of cervical cancer cases. However, given the natural history of HPV infection, the impact on cervical cancer would only be measurable some 20 years after the beginning of vaccination campaign (Figure 5). In industrialized countries, the impact on screening results would be observed more rapidly, with likely reductions

of 90% in the incidence of HPV16 and HPV18 infection and with a estimated reduction of 50% in cytological abnormalities, 50% in CIN1 and 70% in CIN3. A significant reduction in the prevalence of cytological abnormalities would be perceptible after 3-5 years (22,24). Because most cases of cervical cancer are associated with HPV16 and HPV18, more than 95% of deaths due to this malignancy colud be prevented with an effective prophylactic HPV vaccination. The younger the target population, the longer the interval before an impact on HPV infection and cancer becomes noticeable.

Thus, the link between HPV and cervical cancer, discovered 30 years ago, is shortly to be broken, to the benefit of individual women and public health alike. ❑

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