HUMAN PAPILLOMAVIRUS-MEDIATED TRANSFORMATION OF THE ANOGENITAL TRACT


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Summary

Infection with high-risk human papillomavirus (HR-HPV) has been associated with intraepithelial neoplasia and carcinomas at various sites of the anogenital tract, including the cervix, vulva, vagina, penis and anus. Although HR-HPV is a necessary cause for cervical cancer, the majority of anal cancers and a subset of cancers at other genital sites, additional (epi)genetic events are required for malignant transformation. HPV-mediated transformation of human epithelial cells has been recognized as a multistep process resulting from deregulated transcription of the viral oncogenes E6 and E7 in the proliferating cells. Interference of E6 and E7 with cell cycle regulators induces genetic instability which drives the continuous selection of oncogenic alterations providing cells with a malignant phenotype. Early genetic events during cervical carcinogenesis associated with immortalization, include deletions at chromosomes 3p, 6 and 10p, whereas amongst others gain of chromosome 3q, loss of chromosome11, and epigenetic alterations such as inactivation of the TSLC1 tumor suppressor gene represent later events associated with tumor invasion.
1. HPV in anogenital cancers

Different areas of the lower anogenital tract share common risk factors for cancer development, such as sexual behaviour, exposure to HPV and smoking. For cervical cancer infection with HR-HPV has been recognized as a necessary cause. A causative role of HPV is also suggested for the majority of anal cancers as well as for a subset of vulvar, vaginal and penile cancers. Besides the anogenital cancers, a subset of head and neck cancers have been associated with HR-HPV infection. The causal relationship between HR-HPV infection and cervical cancer has become evident from epidemiological and functional studies, and hr-HPV has been detected in up to 99.7% of cervical squamous cell carcinomas (SCCs) and 94% to 100% of cervical adeno- and adenosquamous carcinomas.

In anal cancer the HPV detection rates range from 70% to 100%, dependent on gender, localization, sexual orientation and HIV positivity. Although the overall hr-HPV frequency is markedly lower in vulvar carcinomas, specific histological subtypes of vulvar carcinomas, i.e. basaloid and warty carcinomas, display relatively high HPV prevalence rates of 75-100%. In contrast, HPV is only detected in <= 23% of keratinizing carcinomas of the vulva. In vaginal and penile carcinomas the HPV prevalence is about 60% and 30-42%, respectively. As in vulvar carcinomas, penile carcinomas with basaloid features and those of the warty subtype display the strongest association with HPV.

The detection of HPV in only a subset of vulvar, vaginal and penile cancers points to multiple pathways of carcinogenesis for these sites. A heterogeneous etiology of vulvar cancers is supported by the observation of distinct genetic alterations in HPV- positive versus HPV-negative counterparts. Recent genetic analysis of head-and-neck cancers also revealed distinct patterns of genetic alterations in tumours with hr-HPV oncoprotein activity, compared to those without. Evidence for penile carcinomas being etiologically heterogeneous is supported by a study of Ferreux and coworkers in 2003 showing at least three alternative carcinogenic routes based on different mechanisms of interference with the p16INK4a/cyclin D/Rb pathway, one of which could be attributed to hr-HPV E7 oncoprotein activity.

Although HPV infections at different sites of the anogenital tract are common in the general population, a large difference in carcinoma frequency is found at the different sites. Cervical cancer is the second most common cancer amongst women world wide, with a mean age standardized incidence rate varying from 11.3 per 100,000 women in more developed countries to 18.7 per 100,000 women in less developed countries, and a peak incidence of 44.3 per 100,000 women in Middle Africa. The incidence of anal cancer among men having sex with men is similar to that for cervical cancer (35 per 100,000 men) and is even higher in HIV infected men. On the contrary, vaginal, vulvar and penile cancers are very rare, with incidence rates of about one per 100,000 per year. This suggests that the risk of progression is site dependent. A possible explanation for the relatively high incidence of cervical and anal cancer could be the presence of a transformation zone in both the cervix and the anus, which is suggested to be more susceptible to HPV-mediated transformation.
To date considerable data has been collected on the role of HPV in cervical carcinogenesis. Although likely, extrapolation to HPV infections at other anogenital sites needs further confirmation.

2. HPV and cervical cancer development

Cervical cancer evolves from preexisting noninvasive premalignant lesions, referred to as cervical intraepithelial neoplasias (CINs) or squamous intraepithelial lesions (SILs). These premalignant lesions are classified histologically on the basis of progressive atypia of epithelial cells: CIN I corresponds to mild dysplasia, CIN II to moderate dysplasia and CIN III to both severe dysplasia and carcinoma in situ. CIN I is also classified as low-grade SIL (LSIL) and CIN II/III as high-grade SIL (HSIL). It is still a matter of debate whether cervical cancer generally develops from infected normal cervical epithelium via a sequence of well recognizable CIN I-CIN II-CIN III lesions, or directly via a rapidly induced CIN III lesion. It is of note that CIN I and II lesions often display a viral oncoprotein expression pattern suggestive of a productive viral infection (see below), whereas CIN III lesions exhibit an expression pattern indicative of HPV-induced transformation. Moreover, there are indications that some CIN III lesions may develop rather fast (within 2 years following normal cytology), whereas it would take another 10 to 12 years for most CIN III lesions to develop into invasive cervical carcinoma. This suggests that CIN III represents a heterogeneous disease of which only the advanced stages are likely to have invasive potential and is supported by studies on molecular markers.

HPV infections are very common in young women and frequently resolve spontaneously. The lifetime risk to ever contract HPV is estimated to be 80%. Despite relatively high HPV prevalence, the ultimate development of cervical cancer is a rare event occurring after a long period of viral persistence. The majority of infected women appear to clear the virus by an effective immune response. Clearance of an high-risk HPV infection has been linked to cytological regression. On the other hand, a persistent HR-HPV infection appears a prerequisite for clinical progression and the development of CIN III and cervical cancer.

3. HPV-mediated transformation: additive events

The long time period between hr-HPV infection and cervical cancer appearance as well as the low frequency of progression of hr-HPV associated premalignant lesions to invasive cancer reflect the multi-step nature of HPV-induced cervical cancer. For the latter, additional genetic and epigenetic events are required. Recent in vivo and in vitro data have provided more insight into the steps that may contribute to malignant transformation following HPV infection. These steps include deregulated expression of the viral oncogenes E6 and E7, leading to genetic instability and alterations in regulatory host cell genes by which HPV-transformed cells gain an immortal phenotype and subsequent invasive growth properties.

4. Deregulation of E6 and E7 transcription

Active viral replication and virion production is specifically seen in low-grade CIN lesions and benign wart-like lesions, such as condyloma acuminata. In these lesions the
viral genome is maintained as monomeric episomes in basal cell nuclei, and vegetative DNA amplification occurs only in squamous epithelia undergoing terminal differentiation. Usually, low levels of viral mRNA can be detected in the infected basal cells, but viral transcription, including that of the E6 and E7 genes, is markedly increased in the differentiated layers. Other than providing the E1 and E2 proteins necessary for viral DNA replication, HPVs rely entirely on the host cell DNA replication machinery for viral DNA synthesis. By retrovirus-mediated gene transfer it has been demonstrated that HPV E7 alone is necessary and sufficient to induce cellular DNA replication in a differentiation-dependent manner in organotypic raft cultures of primary human keratinocytes. Reactivation of cellular DNA replication has also been shown in the differentiating spinous cells of condylomata and low grade cervical intraepithelial neoplasias. The fact that differentiated cells have already lost the ability to divide explains why expression of E6 and E7 in differentiated layers does not result in cellular transformation. However, when oncogenes become active in the dividing basal cells, as seen in high grade lesions, interference of hr-HPV E6 and E7 with cell cycle regulators can result in transformation.

An increase in E6/E7 expression in proliferating basal-like cells might be due to integration of the viral DNA in the host cell genome, which is observed in most invasive cancers and a subset of high-grade lesions. Conversely, viral integration may be the result of a genetically unstable environment created by deregulated E6/E7 expression in (para)basal cells. HPV integration has been suggested to promote carcinogenesis by a targeted deregulation of critical cellular genes by means of insertional mutagenesis. However, no firm evidence for such an event has yet been found and HPV integration sites appear randomly distributed over the whole genome with a preference for fragile sites. Nevertheless, integration of hr-HPV genomes and the expression of integrate-derived papillomavirus oncogene transcripts (iPOTs) has emerged as a strong progression factor. In vitro studies, using epithelial raft cultures, have shown that altered histone deacetylation may contribute to deregulated E6/E7 expression in proliferating cells.

In summary, it seems that uncontrolled E6/E7 expression in proliferating basal and parabasal epithelial cells is a phenomenon that distinguishes the process of cell transformation from productive viral infection.

5. E6 and E7, the viral oncogenes

Both viral genes E6 and E7 are needed for induction as well as maintenance of a transformed phenotype, particularly by interference with cell cycle control and apoptosis.

High-risk HPV E6 complexes via a cellular protein, E6-associating protein (E6-AP), with the tumor suppressor gene product p53, resulting in rapid ubiquitin-dependent proteolytic degradation of p53. E6-mediated interference with p53 function together with inactivation of the pro-apoptotic protein Bak by E6 prevent cells from undergoing apoptosis, resulting in a state of genetic instability and enhancing the risk of malignant conversion. Over the past years a growing list of other proteins has been identified
which may contribute to the transforming activity. Another interesting p53-independent target of E6 is telomerase.

The E7 gene product of high-risk HPV is the second major transforming protein. HR-HPV E7 interacts with the retinoblastoma tumor suppressor gene product, pRb, and its family members, p107 and p130, thereby interfering with their control on the G1/S transition of the cell cycle. Inactivation of Rb by HR-HPV E7 can be identified by a permanent upregulation of its upstream inhibitor p16\(^\text{INK4A}\). Since p16\(^\text{INK4A}\) expression is regulated by a Rb-dependent negative feed-back loop, continuous inactivation of Rb by hr-HPV E7 results in increased p16\(^\text{INK4A}\) levels as can be detected in HPV-infected CIN lesions and cervical carcinomas. Hence, the detection of increased p16\(^\text{INK4A}\) expression in liquid based cytology specimens may provide a promising marker for the detection of HPV-induced dysplasia with deregulated E7 expression.

In addition to the Rb-family members, E7 has been shown to interact with other host cell factors. It still remains to be determined whether and by what mechanism these interactions relate to E7-mediated transformation.

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Biographical Sketches

Renske D.M. Steenbergen, PhD, received her MSc degree in Biomedical Sciences at the University of Leiden, The Netherlands in 1991. In 1997 she received her PhD degree at the VU university in Amsterdam The Netherlands. In 1999 she was awarded a fellowship of the Royal Netherlands Academy of Sciences, which resulted in a faculty position at the Dept. of Pathology at the VU Medical Center in Amsterdam, the Netherlands.

She is a PI on a number of research project related to HPV-induced transformation using both in vitro model system and clinical material. The research of Renske Steenbergen and colleagues focuses on the elucidation of the multistep process of cervical carcinogenesis aiming at the identification of novel biomarkers and therapeutic targets for cervical cancer.

Jillian de Wilde, received her MSc degree in Biomedical Sciences at the VU University in Amsterdam, The Netherlands, in 2003. From 2002 till present she has been working as a PhD student at the Dept. of Pathology at the VU University Medical Center in Amsterdam, the Netherlands. The research of Jillian de Wilde and co-workers focuses on the identification of the mechanism(s) underlying telomerase/hTERT deregulation during HPV-mediated transformation and cervical carcinogenesis.

Saskia M. Wilting, received her MSc degree in Biomedical Sciences at the University of Leiden, The Netherlands in 2002. From 2003 till present she has been working as a PhD student at the Dept. of Pathology at the VU University Medical Center in Amsterdam, the Netherlands. The research of Saskia Wilting and co-workers focuses on the genetic profiling of human papillomavirus induced cervical carcinomas and precursor lesions, ultimately aiming at the identification of novel biomarkers for the early detection of cervical cancer.

Prof. Peter Snijders received his degree in biology (with main focus on molecular biology) at the Catholic University in Nijmegen in 1987 and his doctoral degree at the VU University in Amsterdam in 1992 (cum laude). From 1992 he is staff member of the department of Pathology, VU University medical center, Amsterdam, and since 2000 head of the unit of Molecular Pathology within this department.

He is PI of a number of studies in the field of HPV in relation to particularly anogenital and head and neck cancers. He was involved in the development of the HPV GP5+/6+ consensus PCR method that is amongst the most widely used HPV PCR assays today. In addition, he was amongst the first to establish a plausible etiological role of mucosal HPV in tonsillar cancer. In current research lines HPV-induced oncogenic progression is investigated using both in vitro models and clinically well-defined patient material, aiming at the identification and characterization of genes involved in this process and candidate markers for risk assessment. Viral and host markers are already being tested in screening and clinical trials for their capability to assess the risk of cervical cancer and high-grade precursor stages, and newly identified markers will be investigated likewise. Part of his work is funded by the Dutch Cancer Society (NKB) and the Netherlands Organization for Health and Development (ZonMW).

He is (co)author of over 120 international (peer reviewed) papers in his area of expertise.

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Prof. Chris Meijer is a pathologist who received his medical doctor degree at the state University in Leiden in 1972. During his medical study he worked on experimental models, investigating the cellular and (immuno)histochemical changes in lymph nodes draining skin areas of rodents with contact hypersensitivity and received for this work in 1971 his PhD at the Vrije Universiteit in Amsterdam. He is certified as surgical Pathologist and as a medical immunologist. He worked at the Central laboratory of the Blood transfusion service in Amsterdam (1972-1973) on in vitro models of cell mediated immune reactions and received his training in Pathology at the State University Leiden under the guidance of Prof Th.G van Rijssel and Prof. A.Schaberg(1973-1977). He was staff member and head of the Laboratory for Experimental Pathology at the Dept of Pathology, State University Leiden (1977-1980). He moved to Delft where he became staff member and head of the Laboratory for immunopathology in the SSDZ in Delft (1980-1982). In 1983 he was appointed as Prof of Pathology and became head and director of the Department of Pathology at the Vrije Universiteit medical center, Amsterdam. In this position he integrated the results of basic and translational research on cancer and immunology in new diagnostic assays for pathology labs and restructured and implemented three successful research lines in his department. He is in the board of several (Bio)medical Journals and presently member of the research council of the Dutch society for the fight against cancer (KWF/NKB) He has chaired and served on many committees with focus on research or policy making in oncology, immunology and pathology. His research interests are in the field of oncology pathology and immunology and more specifically concern haematopathology, especially non Hodgkins lymphoma and the relationship between viruses and cancer. Chris Meijer has published more than 730 scientific articles in international peer reviewed journals, is the (co-)inventor of several patents in the field of cervical cancer, including new HPV detection methods and received the Marie Parijs Prize for clinical research (1981), the van Vlissingen prize for excellent research on cutaneous lymphomas (1999) and the Eurogin service award for excellent clinical research in the field of cervical cancer (2003). Since 1986 he is heading a group of scientists working on basic and translational aspects of HPV in cervical cancer. He is currently involved in implementing new preventive strategies for cervical cancer in The Netherlands and developing countries, including prophylactic HPV vaccination and HPV testing as primary tool in cervical screening, using cost-effectiveness calculations based on data sampled in randomised clinical trials of which he was/is the principal investigator.

Antoinette A.T.P. Brink, PhD, received a MSc degree in Medical Biology at the Radboud University of Nijmegen, The Netherlands in 1994. In 2000 she received her PhD at the VU University in Amsterdam, The Netherlands. Between 2000 and 2003 she worked as a postdoc in the laboratory of Molecular Cell Biology at the University of Leiden, The Netherlands, studying human papillomavirus integration. In 2003, she was appointed at the VU University again to work on the development of improved HPV detection methods and as a technical supervisor for molecular diagnostics.