# S21. Perspectives in Prevention of HPV-Induced Cervical Cancer

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Infections with 15 types of the human papillomaviruses are associated with malignant transformation of epithelial cells of the lower genital tract. These viruses are referred to as high risk human papillomaviruses (HR-HPV) and encode two viral genes that confer numerous oncogenic features to normal replicating cells through interaction with various host cell proteins among them the p53 and pRB tumor suppressor proteins. These viral genes (E6 and E7) also induce severe disturbances of the mitotic spindle apparatus and chromosome segregation during mitosis of infected host cells. During the normal papillomavirus life cycle these genes are not expressed in replicating cells of the basal or parabasal cell layers. Their expression requires a certain degree of epithelial differentiation of the infected host cells in the intermediate and superficial cell layers. Here, their expression is not harmful since these cells have already lost their mitotic activity and are determined to be desquamated as exfoliated cell debris at the surface of the epithelium. In contrast to the normal life cycle of the papillomaviruses, may the aberrant and deregulated expression of the E6 and E7 genes in the basal or parabasal cells of the epithelium provoke chromosomal instability, significantly enhanced recombination of chromosome fragments and eventually integration of fragments of the viral genomes. The deregulated expression of the E6 and E7 genes in basal and parabasal cells results in strong over-expression of the cyclin dependent kinase inhibitor p16INK4a, that can thus be used as a very specific and sensitive biomarker for HPV-transformed cells or tissues in histological sections, cytological or biochemical samples(von Knebel Doeberitz, 2002). Since integration of the viral genomes creates specific molecular fingerprints for each individual HPV-transformed cell clone, analysis of the integration sites allows to monitor the clonal origin of individual dysplastic lesions (Wentzensen et al., 2004). This research revealed, that the vast majority of HPV-induced dysplastic lesions or cancers in the lower female genital tract were derived from initially transformed reserve cells of the transformation zone that subsequently spread to more distant sites in the cervix, vagina or vulva (Vinokurova et al., 2005). Taken together, these data strongly suggest, that HPV-related carcinogenesis in the female lower genital tract is the rare consequence of aberrant, deregulated HR-HPV infections of reserve cells of the cervical transformation zone. Biomarkers as p16INK4a, that could be delineated by the analysis of the molecular pathways involved in HPV-induced carcinogenesis permit the design of novel preventive, diagnostic and eventually also therapeutic strategies to combat this widespread disease.

## References

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