

Chapter 13

HPV Detection: Current Status and Future Goals for Personalized Prevention

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ABSTRACT

Human papilloma viruses (HPVs) have been acknowledged to be the leading risk factor of cervical intra-epithelial lesion creation (CIN) and cervical cancer development (CxCa), while recently, a vaccine protecting from the most commonly HPV types found in CxCa has been produced and introduced in vaccination schemes across the globe. Many different techniques have been created and utilized in HPV detection and monitoring with a vast amount of them being commercialized and few of them integrated in screening strategies. However, there has been no effort in combining data from all the different techniques and provide efficient patient triaging schemes, since, apart from the obvious increase of patient cost, the amount of data and its interpretation in patient management has been impossible.

INTRODUCTION

Human papilloma viruses (HPV) are members of the papillomaviridae family. HPVs are small (7,000-8,500bp) double stranded DNA viruses with no RNA phase in their life cycle that can only be reproduced in keratinocytes. Over 100 different types have been identified and isolated,

both in humans and animals (de Villiers, 2004). Around 40 types have been isolated from human cervical specimens and HPVs have been classified, according to their epidemiology in cervical lesions, as low risk and high risk (Dunne, 2007; Muñoz, 2003; Trottier, 2006). Although HPVs have been mostly isolated from cervical samples they have also been identified from samples from the anus, vulva, vagina, skin and even head and neck cancers.

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HPV Detection

HPVs are small double-stranded DNA viruses encoding ten proteins in total, out of which two (E6 and E7) are considered oncoproteins (Mantovani, 2001; Münger, 2001) and two (L1 and L2) are the structural proteins of the viral capsid. The rest proteins include one helicase (E1), one transcription factor (E2), two proteins that induce host proliferation (E5) and viral replication (E4) and a short protein that is expressed only in few papillomavirus types that may substitute for the E6 open reading frame. E6 has been shown to interact with the p53 tumor suppressor protein leading to its degradation, while E7 inactivates members of the pRB family of tumor suppressor proteins and activates telomerases. Both proteins enhance cell proliferation and down regulate apoptosis.

HPVs proteins are named after the stage of the viral infection cycle; E proteins are early expressed proteins and are responsible for the replication of the virus, while L proteins are late expressed proteins after the virus has replicated. HPVs infect cells of the basal epithelium of the cervix via minor abrasions of the squamous epithelium. At first the virus reproduces as an extra-chromosomal plasmid during cell division and these infections are sub-clinical. Later on and after the expression of viral oncogenes, the virus reproduces by thousands and infection spreads in more cells (activated infection). After a long lasting infection, the virus is proposed to be integrated in the host genome leading to deregulation of gene expression, disruption of tumor suppressor genes and the accumulation of genetic changes that ultimately result in malignant transformation of epithelial cells (Andersson, 2005). A persistent infection by HPV aided by other parameters results in HPV integration in host DNA leading to progression to high grade lesions (Wallin, 1999). Most HPV infections are cleared by the host's immune system before they progress in the creation of intra-epithelial lesions. Only persistent infection with high risk HPV types has been acknowledged as the most important risk factor for cervical cancer development (Walboomers, 1999).

First connection of HPVs with cancer was proposed by Stefania Jablonska in Poland in 1972 in epidermodysplasia verruciformis (Jabłońska, 1978). Initial evidence supporting that theory emerged in 1978, when Jablonska and Gerard Orth discovered HPV-5 in skin cancer. In 1976 Harald zur Hausen published the hypothesis that human papillomavirus plays an important role in the cause of cervical cancer, and finally in 1983 and 1984 zur Hausen and his collaborators identified HPV16 and HPV18 in cervical cancer (zur Hausen, 1976). HPVs' linking to cervical carcinogenesis has led to the award of the 2008 Nobel Prize of medicine to Dr. Harald zur Hausen for his pioneering work (zur Hausen, 1976; zur Hausen, 1991).

HPV infection prevalence can vary substantially across different age groups, study populations and countries (Revzina, 2005). Although the prevalence of HPV is about the same worldwide and Cervical Intraepithelial Neoplasias (CIN) develop gradually resulting in progression to CxCa within a time frame between 10-20 years, the worldwide incidence of CxCa differs. This reflects different strategies countries have developed, mainly due to the adaptation of organized screening programs that are based on periodical cytological examination of cervical smears. This examination was invented by a Greek medical doctor, George Papanicolaou and is performed via microscopic morphological evaluation of cervical cell alterations according to a grading system. The most commonly used system is the Bethesda 2001 (Solomon, 2002). Abnormal findings during the microscopic inspection of cells results, depending of the severity of the findings, in either repeated testing after 6-12 months or immediate referral to colposcopy. Should a visible lesion be identified a biopsy is taken followed by a therapeutic surgical intervention after histological verification (Wright, 2007). Organized screening programs have reduced substantially CxCa incidence and fatality rates (Peto, 2004). However, CxCa remains a serious problem of public health worldwide,

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