Human papillomavirus (HPV) and cervical cancer

Study of multiple infection, virus quantification, expression of oncogenic mRNA and detection of viral recombination.

The project has five major aims:
- To develop and validate diagnostic methods for detection and quantification of HPV, based on duplex real-time PCR, in order to complement cytological evaluations.
- To study co-infection with multiple HPV-types and amount of viral DNA in cervical samples from women with different grades of dysplasia.
- To study the relationship between expression of viral mRNA coding for oncogenic proteins (E6/E7) and development of severe dysplasia and cancer.
- To identify and study any vaccine-resistant HPV mutants and recombinant variants significant for vaccination outcome.
- To evaluate whether analysis of biomarkers for cancer development (such as p16$^{INK4a}$) can improve cytological evaluations.

Globally, the second most prevalent form of female cancer is cervical cancer. In the industrial world, most countries have introduced screening programs in order to detect cellular abnormalities in the cervix. But there is a need to improve the cytological evaluation. Cervical cancer is exclusively dependent on HPV-infection. Within two years, an HPV-infection is usually cleared by the immune system, but for 3-5% the infection becomes persistent with risk for development of malignancy. There are several commercial HPV-tests available today, but none of them is optimal for detecting or quantifying minor HPV-types in a sample with a mixed population. We have developed a real-time PCR that detects and quantifies 14 HPV-types.

Since 2006, HPV-vaccine is available that will protect against the most common oncogenic HPV-types (16 and 18). Maximum protection by vaccination in young women might however be hampered by one of the following scenarios: i) HPV-types not included in the vaccine may become more prevalent after eradication of HPV16 and 18 ii) a selection of point mutations in the capsid protein of HPV might occur, with the consequence that the immune system no longer recognize the virus which the vaccine is targeted against iii) recombination events leads to virus variants with intact oncogenic proteins but with another capsid that will not be neutralized by the immune system despite vaccination.

The proposed project could help to answer whether any of the above scenarios might be likely to happen, and a clinical trial was started in 2008. Analysis of 500 selected cervical samples with different grades of dysplasia will be performed with the in house real-time PCR, to evaluate multiple infections as well as to quantify “viral load”. Recombination and point mutations will be studied after genotyping based on different regions of the viral genome, and the whole genome will be phylogenetically analyzed after sequencing. Expression of viral oncogenic mRNA will be analyzed and quantified with real-time PCR, and splicing patterns will also be studied. HPV-positive women will be followed up after a year, to try to evaluate whether multiple infection might correlate with immunological inability to clear HPV-infection. Any correlation between amount of HPV (DNA and mRNA) and development of cancer will also be studied.
References


Co-workers

Magnus Lindh, Dept of Clinical Virology, Gothenburg University
Elin Andersson, Dept of Clinical Virology, Gothenburg University
Walter Ryd, Dept of Clinical Pathology, Gothenburg University
Thomas Rådberg, Dept of Obstetrics and Gynecology, Gothenburg University
Cecilia Kärrberg, Dept of Obstetrics and Gynecology, Gothenburg University
Björn Strander, Cervical Screening Oncology Centre, Sahlgren’s University Hospital