



**Karolinska  
Institutet**

**Institutionen för Laboratoriemedicin**

# STUDIES ON TUMOR VIRUS EPIDEMIOLOGY

AKADEMISK AVHANDLING

som för avläggande av medicine doktorsexamen vid Karolinska  
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## **ABSTRACT**

The causal relationship between several virus infections and human cancers are well established. However, it is also possible that additional cancers may be caused by known or yet unknown viruses. The present thesis has sought to both further elucidate known relationships between virus and cancer as well as to provide a basis for further exploration in the area of infections and cancer.

Infections during pregnancy have been suspected to be involved in the etiology of childhood leukemias. However, no specific infectious agent is yet linked to the etiology of these diseases. As a basis for further studies in this area, we applied high-throughput next generation sequencing (NGS) technology to describe the viruses most readily detectable in serum samples of mothers to leukemic children. The most common viruses found were TT viruses, including several previously not described TT viruses.

Merkel cell polyomavirus (MCV) is found in Merkel cell carcinoma (MCC), a rare and aggressive neuroendocrine tumor of the skin. To explore whether MCV infection might be associated with additional cancers, we investigated whether MCC patients are at excess risk of other cancers, using population-based Nordic cancer registries. Bidirectional evaluation of excess risk of other diseases among MCC patients revealed that they are at increased risk of other skin cancers as a second cancer, compared to the general Nordic population. Shared causative factors, such as exposure to ultraviolet light and/or MCV infection are among the possible explanations. Also, impact of increased surveillance of the skin should be noted as an explanation of the excess risk.

Cutaneous human papillomaviruses (HPV) are suspected to be involved in the etiology of non-melanoma skin cancer (NMSC). To evaluate whether there are any consistent association between cutaneous HPV infections and skin cancer, we conducted a systematic review and meta-analysis of studies that investigated HPV prevalences among cases of skin lesions and their healthy controls. We found that HPV species Beta-1, Beta-2, Beta-3 and Gamma-1 were more frequently detected in squamous cell carcinoma (SCC) compared to healthy controls.

To provide clues about possible carcinogenicity of 47 mucosal HPV types, out of which 12 are established as causes of cervical cancer, we also investigated the prevalence of 47 mucosal HPV types across the entire range of cervical diagnoses from normal to cervical cancer.

To investigate diversity of HPVs in skin lesions with increased sensitivity, different sample types from different skin lesion were subjected to high-throughput NGS after PCR amplification. Conventional molecular detection methods such as PCR are biased towards the primers used. Thus they might miss viruses that are divergent from the primer sequences. We also investigated whether NGS technology can be used to assess

presence of virus DNA in an unbiased manner, both in skin lesions as well as in condylomas that were classified as “HPV negative” by conventional PCR methods.

Unbiased sequencing identified two putatively new HPV types that were missed by NGS after PCR amplification. The advantage of unbiased sequencing over conventional molecular detection methods was further demonstrated in the study of “HPV negative” condylomas. We found several known as well as several putatively novel HPV types in condylomas that were previously found to be HPV negative by PCR.

In conclusion, we have used registry linkage studies, systematic reviews and meta-analyses and modern NGS technology applied to biobanked specimens to extend our knowledge of the epidemiology of cancer-associated viruses and to provide a basis for further exploration in this area.