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Institutet**

Institutionen för Onkologi-Patologi

**Occurrence of human papillomaviruses (HPV)
types in HPV related cancer and in the genital
and oral tracts of young adults**

AKADEMISK AVHANDLING

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Abstract

Human papillomavirus (HPV) is associated to cancer of the uterine cervix, the third most common cancer among women, but also to head and neck squamous cell carcinoma (HNSCC), the sixth most common type of cancer in the world. HPV occurs in most cervical cancer (CC). In HNSCC, HPV is most frequently observed in oropharyngeal squamous cell carcinoma (OSCC) where tonsillar squamous cell carcinoma (TSCC) and the base of tongue account for 70-80% of the cases. It has also been shown that OSCC has increased in many Western Countries and we have shown HPV to be responsible for the increase of TSCC in Stockholm. In recent years, two vaccines were introduced against HPV, Gardasil (Merck) and Cevarix (GSK), both efficient against infection with HPV type 16 and 18 and Gardasil against HPV 6 and 11 as well, and these will change the prevalence of HPV types at different sites.

The aim of this thesis was to investigate the role of HPV in the increase of tongue base cancer in the Stockholm. In addition, we wanted to obtain different base lines for the prevalence of different HPV types for cervical cancer and in the genital and oral tracts in young adults in the Stockholm region. Finally we wanted to compare different HPV E6 variants in TSCC and CC as well as in cervical samples (CS) from healthy young women.

The first paper showed that the prevalence of HPV in base of tongue cancer in Stockholm increased from 58% in 1998-1999 to 84% 2006-2007 with HPV 16 dominating (86%). The parallel increase in incidence and proportion of HPV positive base of tongue cancer suggests HPV may contribute to this increase similar to that previously shown for TSCC.

The second paper showed a very high prevalence of HPV with 92.9% in all uterine cervix cancer cases, with 93.3% and 91.4 % in SCC and ADC, respectively. All HPV positive cases harbored HR types, either alone or as multiple infections. HPV 16 and 18 dominated, followed by HPV 33, 31, 45 and 56, in cervical cancer in the Stockholm region. Public HPV vaccination should inhibit a large proportion of HPV 16 and 18 positive tumors.

The third paper revealed a high HPV prevalence in 544 analyzed cervical samples from non-vaccinated young women aged 16-23 years of age and 70% were positive for HPV and 62% were positive for HR-HPV types. Over a third (34.7%) of the women was infected with HPV 16 followed by HR-HPV types 51, 18, 52 and 73. The prevalence of HPV, as well as HR-HPV infection appeared to increase with age in women aged 17 – 21y, and then decrease. The data indicates that HPV vaccination in an early age can prevent HPV 16 and 18 infections and demonstrates the need for further monitoring of the prevalence of HR-HPV types.

The fourth paper showed that 9.3% (9.2% for women and 9.8% for men) of the 483 oral samples from young adults were HPV-positive, with 7.2% being positive for HR-HPV types. HPV 16 was the most common (31%) followed by HPV 59 and HPV 51. Among these 174 women that were tested both for genital and oral HPV infection, oral infection was more frequent in women with (17.1%) as compared to those without (4.4%) genital infection ($p=0.043$) and there was a high HPV type concordance between the oral and genital locations.

The fifth paper showed several patterns of HPV 16 E6 with the HPV E6 variant R10G was relatively common (19%) in TSCC, absent in CC and infrequent (4%) in CS, indicating significant differences of HPV 16 variants in TSCC compared to CC and CS which has not been observed before. Furthermore, the well-known L83V variant was very common in TSCC (40%) as it was in CC (31%) and CS (29%). The majority of HPV 16 (>90%) belonged to the European phylogenetic lineage and its derivatives. No significant relation between R10G variant and survival of TSCC patients was observed.

In conclusion, we have demonstrated that HPV infection may play a role for the increase in base of tongue cancer, and HPV 16 and 18 are highly prevalent in CC and CS. HPV 16 is frequently found in oral samples indicates that HPV vaccination will potentially be useful to combat some of these tumors. Finally, we have shown differences in HPV 16 E6 variants between the TSCC and CC sites.