



**Karolinska  
Institutet**

**Institutionen för Onkologi-Patologi**

# Studies on the influence of human papillomaviruses (HPV) and other biomarkers on the prevalence of oropharyngeal cancer and clinical outcome

AKADEMISK AVHANDLING

som för avläggande av medicine doktorsexamen vid Karolinska Institutet offentligen försvaras i föreläsningssalen, CCK, R8:01

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av

**Anders Näsman**

*Huvudhandledare:*

Professor Tina Dalianis  
Karolinska Institutet  
Institutionen för Onkologi-Patologi

*Bihandledare:*

Docent Torbjörn Ramqvist  
Karolinska Institutet  
Institutionen för Onkologi-Patologi

*Fakultetsopponent:*

Professor Peter Stern  
University of Manchester  
Paterson Institute for Cancer Research

*Betygsnämnd:*

Professor Sonia Andersson  
Karolinska Institutet  
Inst. för klinisk vetenskap, intervention och teknik  
Enheten för obstetrik och gynekologi

Professor Ulf Gyllensten  
Uppsala Universitet  
Inst. för immunologi, genetik och patologi

Professor Catharina Svensson  
Uppsala Universitet  
Inst. för biokemi och mikrobiologi

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## ABSTRACT

**Background.** Oropharyngeal squamous cell carcinoma (OSCC), where tonsillar (TSCC) and base of tongue squamous cell carcinoma (BOTSCC) dominate, is increasing and is now the most common head and neck squamous cell carcinoma (HNSCC) in Sweden. Smoking and alcohol are risk factors for HNSCC, but in 2007, human papillomavirus (HPV) infection was also recognized as a risk factor for OSCC. Notably, HPV positive OSCC has a much better clinical outcome than and HPV negative OSCC. The last decade treatment of HNSCC, including OSCC, has been intensified with chemoradiotherapy, due to the generally poor prognosis of HNSCC. Such treatment, with more side effects, is likely needless for most HPV positive OSCC, but since around 20% of the patients do not do well, additional markers are needed to single out patients with an expected favourable outcome before possible de-escalation of treatment.

**Aims.** To follow incidence and HPV prevalence in OSCC over time in order to understand why OSCC has increased. To search for additional predictive biomarkers in HPV positive OSCC, to more safely de-escalate treatment.

**Results:** *In papers I-II* we showed that the prevalence of HPV in TSCC had increased significantly in Stockholm from 23% (1970-1979); to 28% 1980-1989; to 57% 1990-1999; to 79% 2000-2007. Notably, also during the 2000s there was a significant increase in HPV prevalence, from 68% 2000-2002; to 77% 2003-2005; up to 93% 2006-2007. Likewise, HPV prevalence also increased in BOTSCC, from 58% 1998-2001 to 84% 2006-2007. The increase in HPV prevalence was paralleled by an increase in incidence of TSCC and BOTSCC, and when estimating the HPV incidence in TSCC, the incidence had increased 7-fold from 1970 to 2006. *In paper III* we found that HPV positive TSCC had significantly more CD8<sup>+</sup> and Foxp3<sup>+</sup> tumour infiltrating lymphocytes (TILs), and that a high CD8<sup>+</sup>TIL count was correlated with a favourable clinical outcome in both HPV positive and negative TSCC. In addition, a high CD8<sup>+</sup> count and a high CD8<sup>+</sup>/Foxp3<sup>+</sup> ratio were significantly correlated with a favourable 3- year disease-free survival in HPV positive and negative TSCC respectively. *In papers IV-V*, we show that absence of “classical” HLA class I intensity staining was correlated with a favourable disease-free survival, disease-specific survival, overall survival and progression-free survival in patients with HPV positive OSCC, and to a worse clinical outcome in patients with HPV negative OSCC. Moreover *in paper V*, patients with HPV positive OSCC with absence of /or weak “classical” HLA class I intensity staining presented a very high survival that was independent of treatment regime. HLA-E, -G was also analysed in TSCC, but without any outcome correlation. In addition, HLA class II expression was analysed and found to be more common in HPV positive than HPV negative OSCC, but correlated to better clinical outcome only in the latter group.

**Conclusion:** A parallel increase in incidence as well as HPV prevalence in TSCC and BOTSCC was demonstrated suggesting HPV infection being responsible for the epidemic increase in OSCC. Finally, HPV positive TSCC or OSCC with high CD8<sup>+</sup> TIL counts or with absent/weak HLA class I intensity staining presented a very good clinical outcome, suggesting that these markers could potentially be used to select patients for prospective randomised trials de-escalating oncological treatment.