

# New opportunities to decrease the impact of head and neck cancer

Citation for published version (APA):

Demers, I. (2024). *New opportunities to decrease the impact of head and neck cancer: uncovering HPV awareness, viral integration, and treatment options in preclinical models*. [Doctoral Thesis, Maastricht University]. Maastricht University. <https://doi.org/10.26481/dis.20240327id>

## Document status and date:

Published: 01/01/2024

## DOI:

[10.26481/dis.20240327id](https://doi.org/10.26481/dis.20240327id)

## Document Version:

Publisher's PDF, also known as Version of record

## Please check the document version of this publication:

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## Impact paragraph

Head and neck squamous cell carcinoma (HNSCC) covers a heterogeneous group of tumors, leading to clinical challenges in the prevention and management of this disease.<sup>1-3</sup> The studies in this thesis have added to our understanding of HPV awareness in The Netherlands, HPV genome integration and its detection, the efficacy and underlying mechanisms of novel targeted therapies, and the application of ex-vivo tumor culture models for the prediction of therapy response. In this impact paragraph, we will place our findings into a scientific and societal perspective.

### Awareness is key: implications for primary and secondary prevention

The increasing incidence of HPV-related head and neck cancers highlights the importance of HPV awareness and efforts for effective prevention. The results of this thesis show that the public awareness of HPV and the association of HPV with oropharyngeal cancer is still suboptimal (**Chapter 2**).<sup>4</sup> The identification of these knowledge gaps illustrates the necessity for improvement of HPV awareness, e.g., in the form of (public) education programs and interventions, aiming to increase HPV vaccination coverage and ultimately the elimination of HPV-related malignancies. To raise awareness for HPV-related oropharyngeal cancer in the population, the results of this thesis have been used for the national ‘Make Sense Campaign’ by the Dutch Working Group on Head and Neck Tumors (NWHHT). In addition, an informative quiz was shared on social media of the Maastricht University Medical Center on International HPV Awareness Day. In November 2023, our study on the lack of HPV awareness in the population has been recognized by the media and results were published in more than 10 regional and national newspapers online and on paper. Amongst others, *NOS Nieuws* published an article entitled “Te weinig mensen weten dat HPV-virus keelkanker kan veroorzaken”, describing the results of our study. Similar studies in other European countries and the USA underscore the general lack of HPV awareness and further discussions are currently ongoing to organize cross-border collaborations to increase HPV awareness and reduce global cancer burden.

Well-informed healthcare providers, such as general practitioners (GPs), also play an important role in the stimulation of vaccine uptake for both boys and girls. Our results in **Chapter 3** demonstrate that the knowledge of the link between HPV and oropharyngeal cancer as well as patient characteristics among GPs in The Netherlands offer room for improvement.<sup>5</sup> Awareness of HPV-related head and neck cancer and corresponding patient characteristics among GPs would lead to early detection of these tumors, timely treatment, and improved patient outcome. Therefore, GPs that participated in our study

received a fact sheet on HPV and its role in oropharyngeal cancer and our findings on HPV awareness among GPs has been shared with this occupational group via the Dutch Journal for GPs 'Huisarts & Wetenschap' (**Chapter 4**).

## Methodological development: implications for future studies into HPV integration

Besides new discoveries, progress in science also relies on the development, refinement, and validation of methodologies. Although HPV genome integration is a common genetic event in HPV-related oropharyngeal tumors, its biological consequences for disease progression and patient prognosis are still unclear. Importantly, limitations of current HPV integration detection methods have hampered research into the clinical relevance of HPV integration (**Chapter 5**).<sup>6</sup> This thesis describes a novel sequencing-based approach that enables sequencing of longer DNA sequences, which is especially valuable for formalin-fixed, paraffin-embedded tumor tissue. The proposed method will enable the assessment of HPV integration in a large study cohort of readily available tumor material, without the need for the collection of fresh frozen tumor tissue. Together with mRNA expression profiling, application of this method will lead to a better understanding of the causes and consequences of HPV integration and the identification of prognostic and/or predictive biomarkers for patients with HPV-related oropharyngeal cancer. Once validated, such biomarkers may play a significant role in patient stratification and the choice for treatment modality. In addition, the presence of HPV integration, including exact integration number and integration location, could guide clonality assessment of multiple tumors with HPV-involvement in one patient, with therapeutic implications. Lastly, the proposed sequencing approach may be applied for integration detection of other (oncogenic) virus types, or additional indications in which the sequencing of long DNA sequences is required, such as the identification of chromosomal rearrangements or gene fusions in multiple cancer types.

## Turning knowledge into personal benefit: implications for therapeutic strategies

The general aim of the studies performed in this thesis is to turn knowledge into a benefit for society but also for the individual patient. Over recent decades, survival rates for HNSCC patients have hardly increased and current treatment-related side effects are still substantial. The identification of novel targeted therapies offers a promising direction towards an improved, more personalized treatment approach. In **Chapter 7** and **Chapter 8**, we show that the antiviral agent cidofovir and multiple CDK4/6 and PI3K/Akt/mTOR pathway inhibitors effectively reduce HNSCC cell proliferation. The

obtained knowledge on their efficacy and underlying molecular mechanisms serves as a foundation for future (pre)clinical studies, investigating the value of these agents, as monotherapy or in combination with existing treatment modalities, in the targeted treatment of HNSCC patients.

The use of ex-vivo tumor-derived culture models for treatment response prediction has gained much attention over recent years. In this thesis, we aimed to summarize the variety of proposed culture models to provide a comprehensive and structured overview of advantages, disadvantages, nomenclature, and possible applications as a reference point for (new) investigations into the predictive value of these model systems (**Chapter 9**). In addition, we developed and validated a histoculture model for the evaluation of radiosensitivity and observed varying response rates between individual patients (**Chapter 10**). Once validated in a large study with adequate comparison to clinical patient data, this assay could be a valuable tool for the personalized selection of existing treatment modalities as well as testing of novel therapeutic options. Next to head and neck cancer, this application could easily be adopted for other tumor types and (DNA damaging) therapies.

The results in this thesis present new opportunities to decrease the impact of head and neck cancer by serving as a basis for (pre)clinical research and by contributing to new developments in prevention and personalized treatment of head and neck cancer patients. Our findings have been communicated on various (inter)national conferences and are published or will be published in peer-reviewed, preferably open access journals. Thereby, the created knowledge is made available to experts in the field and serves as a new starting point for future research.

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