Epidemiological Characteristics of Oral and Oropharyngeal Squamous Cell Carcinoma

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Summary

The epidemiology of head and neck cancer has shown remarkable changes in past decades (**chapter 1**). Worldwide, the incidence is still increasing, with high incidence rates in Southeast Asia and parts of Central and Western Europe, and low incidence rates in Japan and China. However, the incidence of head and neck squamous cell carcinoma (HNSCC) in the US has declined in recent years, consistent with the decrease in tobacco use and alcohol intake. However, the incidence of oropharyngeal squamous cell carcinoma (OPSCC) is rising in the US and this trend is also observed in Northern Europe, Australia and Canada.
Human papillomavirus (HPV) is thought to be responsible for 30-70% of OPSCC, with reported high incidence rates in the US and Scandinavia. HPV mainly affects the tonsils and base of tongue. Great variation in incidence and fraction of HPV-induced cancers between countries can be explained by many factors, such as the variety of methods used to assess HPV positivity, the tumor sites included, sexual habits, smoking and alcohol consumption. The clinical behavior of HPV-positive OPSCC in terms of response to treatment and prognosis appears to be superior compared to HPV-negative OPSCC, regardless of treatment strategy.

Within the head and neck cancer spectrum another, smaller, subgroup of patients comprises the young onset oral and oropharyngeal SCC (OSCC) patients, aged 25-45 years at cancer diagnosis (**chapter 2**). Besides alcohol, tobacco and HPV, various etiological factors may play a role within this group; for example, inherited syndromes and increased mutagen sensitivity. Although an increase in incidence was noticed in some Western countries, in The Netherlands incidence decreased for all head and neck subsites in this age group except for tongue carcinoma in young men[(1)]. Development of HNSCC at a young age (<45 years old) is uncommon, accounting for approximately 6% of all HNSCC patients.

Several reports from Western countries show increasing incidence trends of HNSCC in young patients, which are disproportional to trends in HNSCC patients above 45 years old, and reflect primarily oral cavity and oropharyngeal cancers.

A study from the US noted that carcinoma of the tonsil, tongue and base of tongue increased in young white patients from 1973-2001[(2)]. A Scandinavian study noted an increase of 5 to 6-fold in tongue carcinoma in patients under the age of 40, compared to a 2-fold increase in the HNSCC population above 40 years old, from 1960-1994[(3)]. The cause for this increase in incidence remains ill defined, as tobacco use appears to have stabilized over recent decades and regular alcohol intake in Western youth has decreased. Increasing rates of HPV positivity in OPSCC might explain a part of the increased incidence of young onset OPSCC, as HPV-positive OPSCC is characterized by lower rates of self-reported tobacco/alcohol exposure and higher rates of sexual promiscuity and marijuana use. Some of these young onset OSCCs result from genetic predisposition to inherited HNSCC-susceptibility syndromes such as Fanconi Anemia and Bloom's syndrome, or as a result of subtle forms of HNSCC susceptibility such as increased mutagen sensitivity.

Chapter 3 focuses on the increase in incidence of OPSCC over the last 25 years in several Western countries. The pathogenesis of HPV and the clinical behavior of HPV-related oropharyngeal carcinomas are examined in this chapter, in keeping with the recent literature, which attributes the increase in incidence of OPSCC in part to the association of HPV infection. The profile of HPV-positive OPSCC differs from HPV-negative OPSCC in several aspects, including unique molecular biological tumor characteristics and better survival rates. The increase of HPV-positive OPSCC may have implications for treatment, for the organization of follow-up programs and for prevention strategies. Closer collaboration with sexologists may be necessary to improve awareness among the population at risk for OPSCC and anogenital cancer and to improve doctor− patient communication about the risks of sexual behavior.

In **chapter 4**, a multivariable survival analysis was performed of 54 young onset (<40 years) and 1708 older patients with oral and oropharyngeal SCC treated at the Netherlands Cancer Institute during 1977-2008.
Younger patients may have genetically distinct cancers, given that they have a lower prevalence of carcinogen exposure and a higher prevalence of HPV infection.

Disease-specific survival and overall survival was calculated with and without control for tobacco and alcohol exposure. Younger patients were significantly more often treated with chemoradiation with or without surgery and less often with RT alone, compared with older patients. The percentage of “never smokers” and “never drinkers” was higher in the younger group (24%) compared to the older group (18%). We found that DSS was not significantly different between oral and oropharyngeal SCC patients who were younger or older than 40 years, even when adjusted for tobacco and alcohol consumption.

Most data on the rising proportion of human papillomavirus-related HNSCCs has been generated during the last decade; however, still little is known about the relationship between young onset HNSCC and HPV. The purpose of the study reported in **chapter 5**, therefore, was to determine in what proportion of patients HPV infection was associated with HNSCC in young patients and whether this was related to the presence or absence of tobacco and alcohol. A second aim was to investigate the potential surrogate immunohistochemical markers p16 and p53 for HPV positivity.
Paraffin-embedded, archival biopsy materials from 45 HNSCC patients <40 years were analysed. HPV subtypes were identified by PCR followed by genotyping. $p16^{INK4a}$ and p53 expression were determined by immunohistochemistry.
We identified HPV16 positivity in 31% of all HNSCC patients aged <40 years, and in 60% of all oropharyngeal SCCs. The presence of $p16^{INK4a}$ accumulation and the absence of p53 overexpression were found to be good surrogate markers for HPV-associated HNSCC in young patients.

Although several studies from different countries report a rising incidence of HPV - related OPSCC, the incidence of HPV- related OPSCC varies widely throughout the world. In **chapter 6** we determined the incidence of HPV DNA and survival of three consecutive cohorts of patients with OPSCC treated in the NKI-AVL in the period 1980-2009.

The incidence of HPV positivity in oropharyngeal SCC in the Netherlands Cancer Institute cohort was 28% for the time period '80-'89, to 38% and 38% for periods '90-'99 and '00-'09, respectively**.** This stable incidence is low compared to most other studies and is in contrast with the ongoing rises in most Western countries, possibly as a result of differences in sexual habits, smoking and drinking habits and demographic differences. HPV-positive tumors in these cohorts were found to have better overall and disease-free survival.

The question remains whether the rising incidence of OPSCC is specifically due to an increase in HPV-associated OPSCC or whether there are other explanations for this upward trend. This issue is addressed in **chapter 7**, evaluating incidence, development of second primary tumors and survival of all 16,480 patients with oral tongue (OTSCC), oral cavity excluding oral tongue (OCSCC) and oropharyngeal SCC diagnosed from 1989 through 2008 in The Netherlands.
We observed similar increases in incidence of OPSCC, OTSCC and OCSCC in females. In males, however, the incidence of OTSCC and OPSCC increased and the incidence of OCSCC remained stable. Survival increased for all three subsites. Patients with OPSCC showed the poorest prognosis with a relative survival of 41.6% after 5 years and 29.4% after 10 years ($p<0.001$) over the entire period 1989-2008. However survival increased substantially for OPSCC patients over time (5-year RS of 37.2% in 1989-1993 to 47.6% in 2004-2008, $p<0.001$). The mean age at diagnoses gradually increased reflecting the aging of the post-World War II generation. The 'baby-boom' resulted in a profound increase in the number of men and women in the 50-64 age group. In this age group, excessive intake of alcoholic drinks and current or past use of tobacco is substantially more prevalent than in younger adults. Our findings suggest that exposure to the traditional risk factors of tobacco and alcohol as well as increasing average age still explain most of the trends in head and neck squamous cell carcinoma epidemiology rather than a more prominent role of HPV in recent years.

Knowing the patterns and trends in causes of death in a population is critical to understand how to target interventions to maximize the population's health.

Patients with oral cavity (OCSCC) and oropharyngeal squamous cell carcinoma (OPSCC) are known for their risky behavior that includes excessive alcohol consumption and heavy smoking. In **chapter 8** we analyzed causes of death of 94.7% of 9,620 patients who died in the study period. Data were obtained for patients who were diagnosed from 1989 through 2006 and who died up until January 1, 2009 and analyzed for cause-specific cumulative mortality.

The main cause of death was due to the primary tumor (58% of all deaths, 71% of the excess mortality). We observed that, compared with the general population, patients with OCSCC/OPSCC experienced excess mortality from cancers of the esophagus and lung, from death due to ischemic heart disease and myocardial infarction, pneumonia, diseases of the digestive tract, accidents and suicide. The effects of tobacco and alcohol abuse appear to dominate the excess mortality in these patients. Excess mortality due to cancer of the esophagus and lung was significantly greater in patients with OPSCC, possibly as a result of an increased latency time between tumor development and diagnosis. Risk of death due to pneumonia was over two times higher for OPSCC patients than for OCSCC patients, therefore special attention for dysphagia should be paid to these patients. Achieving a reduction in cause-specific excess mortality in those patients alive after five years of follow-up, by extending the duration of clinical follow-up visits, appears difficult since most mortality occurs during the first three years after diagnosis. The diseases that affect long-term cause-specific mortality are frequently not amenable to screening and often have a poor prognosis. Education on a more healthy lifestyle, including smoking cessation and alcohol abstinence programs, should remain a part of the follow-up program at all times.

Conclusions and future perspectives

This thesis analyzed the epidemiological characteristics of patients with oral cavity and oropharyngeal squamous cell carcinoma over the past decades, and the changes in those characteristics.
Within the spectrum of head and neck cancer, young-onset head and neck cancer and HPV-associated oropharyngeal squamous cell carcinoma have received special attention since a proportion of these patients have a different clinical and etiological phenotype compared to the typical carcinogen related head and neck cancer patients and a proportion of these patients show an increasing incidence. In the following chapter, conclusions and future perspectives on these subgroups will be discussed.

Young patients

Approximately 6% of oral cavity and oropharyngeal squamous cell carcinomas are diagnosed in individuals younger than 45 years of age. Combining the data presented in chapter 4 with data from previous studies strongly suggests that the survival difference between young- and late- onset head and neck cancer is unlikely to be large. Exceptions are patients with genetic syndromes who are prone to develop multiple primary tumors who have a poor prognosis and patients with HPV-related oropharyngeal SCC who have a better survival[4, 5].

Whereas several European countries and the USA report an increasing incidence of young onset head and neck cancer, Dutch incidence data show a significant decrease. The etiology of the development of young- onset head and neck cancer is diverse and can be divided roughly into patients with excessive tobacco or alcohol abuse, genetic predisposition and infection with high-risk human papillomavirus, or a combination of these factors.

Because of the relative rarity of young-onset head and neck cancer it remains difficult to achieve sufficient numbers of patients to adequately study the survival differences between young and older patients.

The true impact of young age on HNSCC clinical behaviour will remain difficult to determine unless multi-institutional databases can be combined. The International Fanconi Anemia Registry can function as an example, where a number of international research groups combine their datasets for research. More detailed analysis of clinical factors and tumor biology can be studied when sample pooling on an international level will be organised. Therefore, within a consortium of head and neck biology research labs, special attention must go to this subgroup of young-onset HNSCC patients simultaneous to the increasing research on HPV-related OPSCC.

HPV

Worldwide, there is agreement about the carcinogenic role of oncogenic human papillomavirus in oropharyngeal cancer. Studies from the US, Australia, Scandinavia and the UK appear to suggest a rise in the proportion of HPV-associated OPSCC[6-10]. Recent figures suggest that around 65% of all OPSCC tumors are HPV positive, whereas this proportion was around 23% in the 1970s[6]. Part of the high variability in the proportion of HPV positivity in OPSCC patients reported worldwide may be due to varying exposure to HPV in different geographical regions, different oropharyngeal subsites that were taken into account and differences in HPV detection methods among studies. Other possible explanations for the high variability in the proportion of HPV positive OPSCC's are the influence of anti-smoking campaigns, which have been more successful in some countries and as a result the relative frequency of HPV associated tumors may have risen. In contrary, the ageing population in several countries is a strong factor in age-related OPSCC, which is seldom HPV related, resulting in an absolute rise in OPSCC incidence.
The hypothesis that increasing incidence of OPSCC in The Netherlands is not specifically due to increasing incidence of HPV DNA positive OPSCC is supported by recent molecular epidemiological evidence of HPV DNA positive OPSCC from The Netherlands, which documented an HPV-positive incidence of around 30-40% over the last decade[11-13].
There are clinical and biological differences between HPV-positive and HPV-negative OPSCC patients.

Patients with HPV-positive OPSCC are found to have significant differences in sexual history in terms of higher number of lifetime genital sex partners and oral sex partners[14, 15]. Biologically, HPV-positive tumors have only occasional chromosomal losses, allelic imbalances and a lower number of chromosomal alterations than HPV-negative tumors[16]. In combination with an increased sensitivity to radiotherapy and chemoradiation, HPV-positive tumors have a better prognosis compared to HPV-negative tumors. The mode of HPV transmission and the reason why not all infected patients develop HPV-induced OPSCC remains to be clarified.

With respect to further studies we would like to emphasize the importance of stratification for HPV status, not only in young patients but in all oropharyngeal cancer patients. In order to routinely imply HPV determination without expensive time-consuming methods, clinicians can perform $p16^{INK4a}$ immunohistochemical staining that has proven to be a good surrogate marker for HPV positivity (**chapters 5,6**). A national population-wide registry that screens for scientifically relevant prognostic parameters (including HPV) could be helpful to determine guidelines for OCSCC and OPSCC patients to optimize risk assessment and screening programs.

Currently, as noticed in **chapter 9**, the cause of death registry for HNSCC patients in The Netherlands does not provide accurate information regarding the specific cause of death. Inaccuracies could be reduced by direct personal communication with the treating physician, but this would be difficult to organize. However, better education for registering physicians on the importance of improving the quality of death certification and detailed documentation and instructions for complex or difficult cases will be accomplishable in the near future.

At the moment great efforts are made to customize optimal treatment schedules based on tumor- HPV status that do not compromise survival outcomes but lower treatment-related toxicity and morbidity. Several ongoing clinical trials are investigating different ways to de-escalate treatment[17]. Several trials testing the replacement of cisplatin by cetuximab to reduce toxicity have shown no benefit so far[9, 10].

Moreover, EGFR (epidermal growth factor receptor), the target of cetuximab, seems to be a relevant oncogenic factor only in HPV-negative disease.
However, data are still controversial. Other trials (ECOG 1308 and Mayo Clinic) study the reduction of the total dose of radiotherapy in patients pre-treated with induction chemotherapy. Preliminary results suggest that induction chemotherapy appears to identify a group of patients with low 1-year failures rates after reduced dose radiation. De-escalation may be less appropriate for high staged disease or patients with a significant smoking history. Longer follow-up and more trials are required to confirm these results. Apart from de-escalation, a more promising strategy is to combine current treatment with immunotherapy, either by therapeutic vaccination or immunostimulation [18, 19].
Another therapeutic option is transoral robotic surgery (TORS). TORS permits resection of selected pharyngeal tumors transorally without the morbidity and functional deficit of more extensive surgery or (chemo)radiation[17, 20]. Although the data for TORS are still in their early phase, results appear promising [17, 21].

Clinical trials to determine the efficacy of HPV vaccines for prevention of oral HPV infection have not been conducted yet, but should be seriously contemplated. The current bivalent and quadrivalent HPV vaccines have shown to significantly reduce the rate of lesions in the cervix, vulva, vagina, and anogenital region [22]. However, vaccination coverage among girls must be sufficiently high (>80%) to prevent transmission of oral HPV16 infection to boys (i.e., through herd immunity) as well. Populations with vaccination rates sufficient for herd immunity might observe reductions in OPSCC incidence as a consequence of reduced rates of anogenital to oral HPV transmission, provided that these transmission routes play a role in the origination of OPSCC. In practice, the unvaccinated birth cohorts do not benefit from vaccination. Even many decades after the start of vaccination program, only unvaccinated cohorts with ages close to the vaccinated ones experience a minor reduction in HPV prevalence [23]. In contrast, the prevalence of oncogenic-HPV among the vaccinated birth cohorts (with 80% vaccination coverage among women) will be close to the eventual steady- state (when all women are fully vaccinated) already after 10 years of starting the vaccinations.

Prevalence of oncogenic- HPV infection in females between 10 and 70 years would drop from 9.5% (before vaccination) to 4.3% after 20 years[23]. Although not proven, it is expected that the incidence of HPV related cancers will drop accordingly.

HPV screening

Although in most countries screening for cervical cancer is widely applied, there are no validated screening options for OPSCC yet. In cervical carcinogenesis, Pap smears are used which detect potentially pre-cancerous changes or cervical dysplasia through direct cell and tissue examination[24]. A recent study evaluated whether screening with an equivalent of the Pap test allowed identification of HPV-induced oropharyngeal pre-cancerous lesions; although a strong association was found between HPV16 and accessible oropharyngeal lesions, there was no association between HPV16 and cytologic evidence of dysplasia in the absence of oropharyngeal lesions[25]. An oropharyngeal Pap test equivalent may therefore not be feasible, most likely due to limitations in sampling the relevant tonsillar crypt epithelium[25]. Another screening option for HPV-related OPSCC could be detection of oral oncogenic HPV infection; however, presence of the HPV virus in the oral mucosa does not necessarily indicate the presence of dysplasia or OPSCC as reported in the anogenital regions. Studies reporting on prevalence and incidence of oral HPV infections confirm this finding. Kero et al., who studied young, sexually active, healthy men in stable heterosexual relationships, found a point prevalence of oral HPV infection fluctuating from 15.1% to 31.1% during 7-year follow- up in Finland [26]. Studies from the United States report prevalence ranging between 4% and 10.1%.[15, 27] To elucidate the clinical relevance of the HPV carriage detected in the study of Kero et al., these men received a thorough clinical examination of their oral mucosa and none of them developed dysplasia[26]. Prior studies have called for more longitudinal research in order to better understand oral HPV infection transmission, how likely infections are to be cleared, and factors associated with persistence of the infections.

Follow-up

Follow- up programs to decrease mortality due to second cancers outside the head and neck region, following five years of complete remission, have thus far not shown to reduce mortality [28] and do not appear to be cost-effective (**Chapter 9**). Taking into account the rather small number of patients surviving primary OSCC for five years or more, it becomes even harder to demonstrate any cost effectiveness of second cancer screening in this group. Even when SPTs such as lung and esophagus cancer are detected in a resectable stage, survival after resection of these cancers remains poor [22, 29]. To date, the implementation of lung cancer screening for primary lung cancer is currently the subject of a major policy decision within the USA. Findings of the US National Lung Screening Trial (NLST) showed a 20% reduction in lung cancer mortality in a high-risk cohort (age 55-74, smokers and former smokers)[30]. The European community awaits mortality and cost-effectiveness data from the Dutch-Belgian lung cancer screening trial (NELSON) in 2015-16 and from pooled trials thereafter. So far, results from the NELSON trial seems promising, with a proportion of 1.2% false-positive low-dose computed tomography (LDCT) scans out of all scans compared to 23.3% in the NLST[23, 30]. It is questionable whether a NELSON screening strategy with LDCT will have impact on decreasing mortality from second primary lung cancer following primary head and neck cancer. Nevertheless, a general practitioner should be aware of the high risk of other serious illnesses in surviving HNSCC patients such as second primary cancers, high cholesterol, diabetes mellitus, cardiovascular disease, CVA and hypertension. Moreover, in the follow-up of HNSCC survivors, emphasis should always remain on smoking cessation and alcohol abstinence, as studies have shown that continued tobacco and alcohol intake are responsible for 1/3 of second primary tumors and are the major cause of morbidity and mortality in HNSCC patients[31]. Additionally, we recommend the creation of educational programs for young people on the prevention of HNSCC, which will eventually lead to more progress in public health.

Annually, the International Federation of Head and Neck Oncologic Societies organizes the 'Head and Neck Cancer Day'[24] emphasizing that HNSCC is the leading cause of death and disability in many parts of the world while most of this mortality and morbidity are preventable.

Providing affordable facilities for prevention, early detection, diagnosis, treatment, rehabilitation, surveillance and palliative care should be a governmental concern.

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