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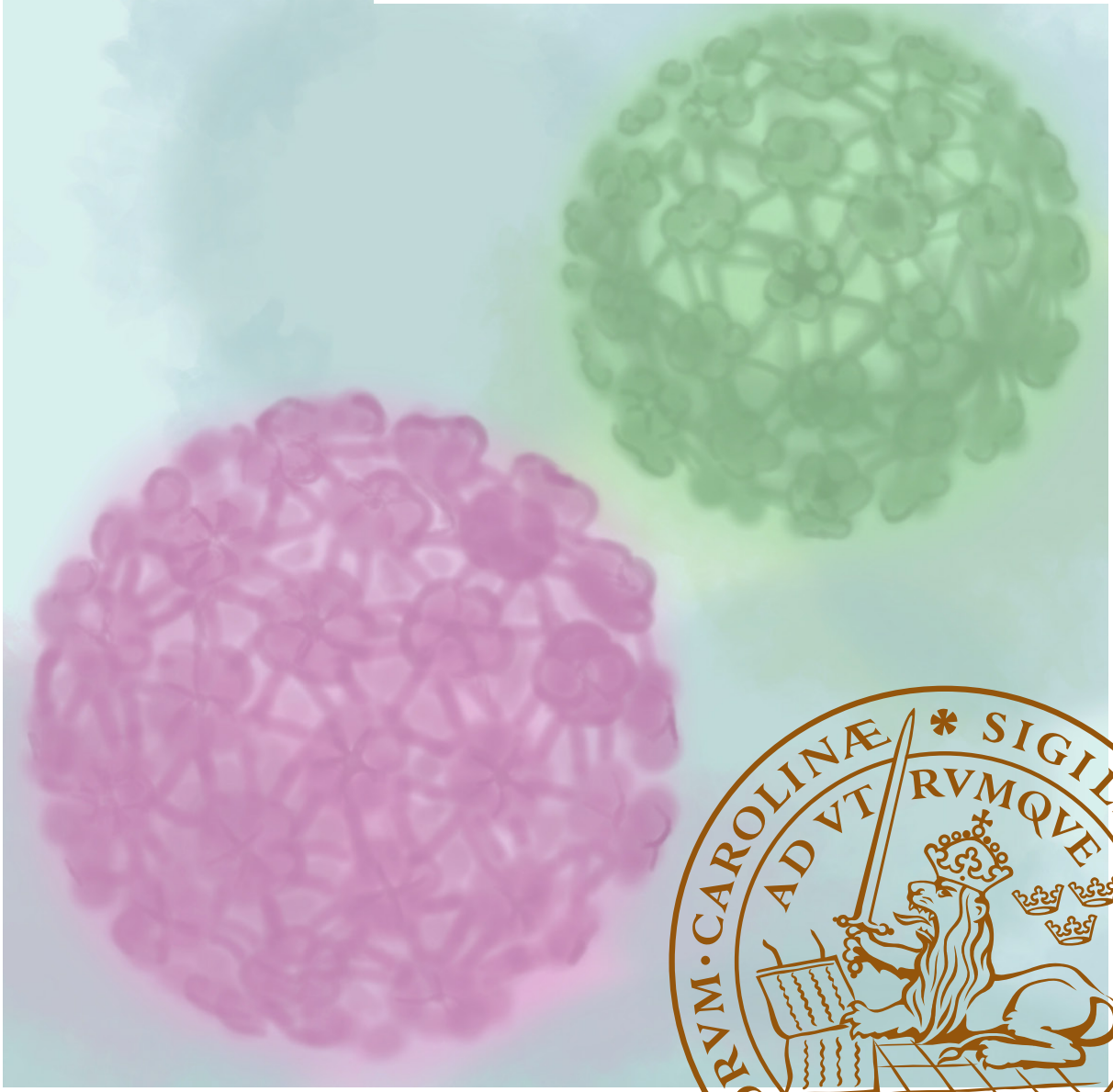

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Health economic aspects of head and neck cancer

Maria Silfverschiöld

LUND UNIVERSITY

DOCTORAL DISSERTATION

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Background
The incidence of head and neck cancer (HNC) is increasing, particularly for oropharyngeal cancer (OPC). Historically, HNC is associated with tobacco smoking and alcohol abuse, but high-risk human papillomavirus (HPV) is now a dominating risk factor for OPC. Treatment protocols for HNC often recommend surgery and radiotherapy (RT), frequently in combination, such as for advanced oral cavity cancer (OCC). In addition, relevant to OPC associated with high-risk HPV, preventive vaccination is a possible intervention. This thesis aims to provide comprehensive cost data for aspects of HNC from a societal perspective, including a specific focus on OPC associated with high-risk HPV and the cost-effectiveness of two treatment schemes for OCC.

Methods
In the present studies (**I-IV**), with top-down and bottom-up methods, direct costs (i.e., for outpatient and inpatient care) and indirect costs (i.e., for productivity loss due to morbidity and mortality) for aspects of HNC are estimated. The human capital approach is used when estimating productivity loss. A particular focus is on HPV^+-associated cancers, notably OPC and its subsets tonsillar and base of tongue cancer, respectively (**I**, **II**). Furthermore, using data from the ARTSCAN 2 randomised clinical trial, direct and indirect costs are detailed for two treatment schemes for OCC, and a cost-effectiveness analysis is performed with overall survival as effect measure (**III**). Finally, the cost of illness, including for informal care, is assessed for HNC for Sweden in 2019 (**IV**).

Results
The total societal cost of all precancers and cancers attributable to HPV in 2006 was €93.7 million (**I**). OPC was the most costly among cancers affecting both genders: €11.9 million per year. The mean cost per patient diagnosed between 2011-2014 was €103 386 for HPV^+ OPC and €120 244 for HPV^- OPC (**II**). Post-operative RT dominated pre-operative RT for OCC, and the difference in direct costs reached statistical significance (**III**). The total societal cost of HNC (all sites) in 2019 was €92.4 million. Productivity loss comprised 64% of these costs (**IV**).

Conclusions
HNC imposes a substantial economic burden on the healthcare sector and society. The results of the present studies may, together with data on morbidity and survival, lend support for preventive measures against OPC associated with HPV and a specific treatment scheme for OCC. Furthermore, they underscore the importance of early detection and rehabilitation of HNC. Finally, they may be an essential reference point for future economic assessments.

Key words: Head and neck cancer, human papillomavirus, cost-of-illness, cost-effectiveness.

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“Who (gets) what, when, where, and why”
(The Manhattan Transfer)

To Otto, Eric, and Sophie

My everything…

Table of contents

Abbreviations

BoT	Base of tongue
CA	Cost analysis
CBA	Cost-benefit analysis
CE	Cost-effectiveness
CEA	Cost-effectiveness analysis
COI	Cost of illness
CPP	Cost per patient
CUA	Cost-utility analysis
CUP	Cancer with unknown primary
DHT	Dental healthcare treatment
DRG	Diagnosis-related groups
FCA	Friction cost approach
GDP	Gross domestic product
HCA	Human capital approach
HNC	Head and neck cancer
HPV	Human papillomavirus
ICD-10	International Classification of Diseases 10th revision
ICER	Incremental cost-effectiveness ratio
OCC	Oral cavity cancer
OPC	Oropharyngeal cancer
OS	Overall survival
PIN	Personal identity number
PPP	Purchasing power parity
QALY	Quality-adjusted life years
QR	Quality registry
RT	Radiotherapy
RCT	Randomized clinical trial
RSR	Relative survival rate
SALAR	The Swedish Association of Local Authorities
SSIA	Swedish Social Insurance Agency
SweHNCR	Swedish Head and Neck Cancer Register
TC	Tonsillar cancer
W/wo	With or without

List of articles

Articles included in the thesis

This thesis is based on the following publications, referred to in the text by their Roman numerals.

I. Östensson E, **Silfverschiöld M**, Greiff L, Asciutto C, Wennerberg J, Lydrup M-L, Håkansson U, Sparén P, Borgfeldt C (2017). The economic burden of human papillomavirus-related precancers and cancers in Sweden. PLoS ONE 12: e0179520.

II. **Silfverschiöld M**, Sjövall J, Wennerberg J, Östensson E, Greiff L (2019). Societal cost of oropharyngeal cancer by human papillomavirus status, cancer stage, and subsite. PLoS ONE 14: e0220534.

III. **Silfverschiöld M**, Carlwig K, Jarl J, Greiff L, Nilsson P, Wennerberg J, Zackrisson B, Östensson E, Sjövall J (2023). Cost-effectiveness analysis of (accelerated) pre-operative *versus* (conventional) post-operative radiotherapy for patients with oral cavity cancer in Sweden. Eur J Health Econ. In Press.

IV. **Silfverschiöld M**, Jarl J, Hafström A, Greiff L, Sjövall J (2023). Cost of illness analysis of head and neck cancer in Sweden. Manuscript.

Additional article

Hafström A, **Silfverschiöld M**, Persson SS, Kanne M, Ingvar C, Wahlberg P, Romell A, Greiff L (2017). Benefits of initial CT staging before sentinel lymph node biopsy in patients with head and neck cutaneous melanoma. Head Neck 39: 2301-2310.

Thesis at a glance

Aim	Design	Principal finding
Paper I		
To estimate the cost of HPV-associated pre-cancers and cancers in Sweden, including OPC.	A prevalence-based top-down COI analysis.	Costs for HPV-associated cancer were €93.7 million per year. For males, OPC represented 56% of the cost.
Paper II		
To estimate the total societal cost of OPC by HPV status, cancer-stage, and site.	A population-based bottom-up COI analysis.	The mean cost of OPC was €106 590. The costs for HPV^{-} cases were 16% higher than for HPV^{+} cases.
Paper III		
To compare the cost and cost-effectiveness of two treatment regimens for OCC.	A bottom-up CEA of the ARTSCAN 2 RCT.	Post-operative RT for patients with resectable OCC was the dominant strategy when compared to pre-operative RT.
Paper IV		
To assess the total societal costs of HNC (all sites) for Sweden in 2019.	A population and registry-based top-down COI analysis.	The annual cost for HNC was €92.4 million, of which productivity loss represented 64%.

Preface

My first encounter with the field of head and neck cancer was as Financial Controller of the Department of Specialized Surgery at Skåne University Hospital, Lund/Malmö, Sweden. An important part of my job was to allocate the annual financial budget, and a great challenge after that was to ensure that we stayed within it (potentially to the despair of the clinicians). Unfortunately, however, the costs were seldom put in relation to what we got for the money.

As an economist, I was concerned that our way of work left no room for a broader perspective, i.e., considering society's perspective and weighing costs against health gains. What if a treatment, which may be more expensive, enables a patient to recover faster and return to work sooner? Yes, it might cause higher treatment costs initially and threaten an already strained budget, but it may benefit society in the long run. A broadened view from society's perspective is needed to answer these questions, e.g., data on the cost of illness and cost-effectiveness.

Therefore, when Professor Lennart Greiff, Director of the Head and Neck Unit at the Department of ORL, Head & Neck Surgery, Skåne University Hospital, asked me to join his team and, with key collaborators, introduce health economic evaluations in clinical research, I was very excited. A literature review soon showed a knowledge gap concerning the burden of societal costs in the field of head and neck cancer, which comprised aspects of association with human papillomavirus, treatment schemes, and overall cost evaluations.

This was when my PhD-studies began…

Introduction

Head and neck cancer (HNC) is the 6th most common form of cancer worldwide (1). In Sweden, 1 695 new cases (2) and 449 deaths were recorded in 2019 (3). HNC can arise in the lips, the sinonasal cavities, the oral cavity, the nasopharynx, the oropharynx, the hypopharynx, the larynx, and the salivary glands, or may present as a neck node metastasis with an unknown primary lesion (CUP) (4, 5).

Tobacco smoking and alcohol abuse are established risk factors for HNC (6-8), but over the last decades, high-risk human papillomavirus (HPV) has emerged as an additional risk factor, notably for oropharyngeal cancer (OPC) with its subsets tonsillar cancer (TC) and cancer of the base of tongue (BoT) (9-13). Accordingly, the incidence of HPV^+ OPC is increasing (14-18). In the last decades the incidence of OPC, regardless of HPV status, has increased by approximately 5% per year in Sweden (2).

The treatment of HNC comprises surgery and radiotherapy (RT) with or without (w/wo) chemotherapy. They may be administered as stand-alone measures or in combination. For example, surgery and RT are often combined for oral cavity cancer (OCC) of cancer stage II-IV. Yet, there is limited information on by which order these measures are best administered, and there are no data on whether one scheme is more cost-effective than another. The recent ARTSCAN 2 randomized controlled trial (RCT) (19) may be used for such a comparison.

HNC affects healthcare systems in terms of increased healthcare consumption and society in terms of increased production loss due to sick leaves, granted early retirement and premature deaths. In addition, it affects the family and close friends in terms of providing informal care for the patient. The economic burden can be expressed as direct costs (i.e., for outpatient and inpatient healthcare), indirect costs (i.e., productivity loss due to sick leave, early retirement, and premature mortality), and informal costs (i.e., the informal care from the next of kin).

While direct costs have been assessed for various populations of HNC patients, information on indirect costs is often missing (20-32) or is only partly described (33-36). Accordingly, few estimates are available for the total economic burden of HNC from society's perspective. In addition, no studies have assessed the cost-effectiveness (CE) of different treatment regimens of OCC, i.e., the most common site of HNC.

With this knowledge gap, the purpose of this thesis is to provide, from a societal perspective, updated information on the economic burden of HNC and its sites, with a particular focus on OPC associated with high-risk HPV, as well as to evaluate the CE of different treatment regimens of OCC.

Background

Head and neck cancer

Sites and histology

HNC includes several types of cancers of the upper aerodigestive tract. These are categorized by the sites in which they originate: the lips, the oral cavity, the pharynx (i.e., the nasopharynx, oropharynx, and hypopharynx), the larynx, the sinonasal cavities, and the salivary glands (**Figure 1**) (1). As for many of these sites, the oropharynx is divided into subsites, e.g., tonsillar and BoT, which are the focus of papers **I** and **II**. HNC may also present as a neck node metastasis from a cancer with an unknown primary lesion (CUP). The most common histology of HNC, e.g., for OPC (paper **I** and **II**) and OCC (paper **III**), is squamous cell carcinoma (4, 5).

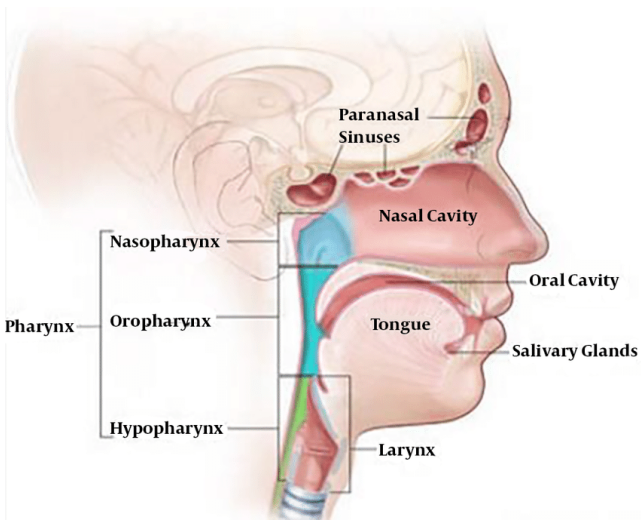

Figure 1. The upper aerodigestive system. Illustration of locations of paranasal sinuses, nasal cavity, oral cavity, tongue, salivary glands, larynx, and pharynx (including the nasopharynx, oropharynx, and hypopharynx). © (2012) Terese Winslow LLC, U.S. Govt. has certain rights.

Incidence and risk factors

Globally, over 930 000 new HNC cases are diagnosed annually, making it the 6th most common form of cancer (1). In Sweden, 1 695 individuals were diagnosed in 2019 (**Figure 2**) (2, 37).

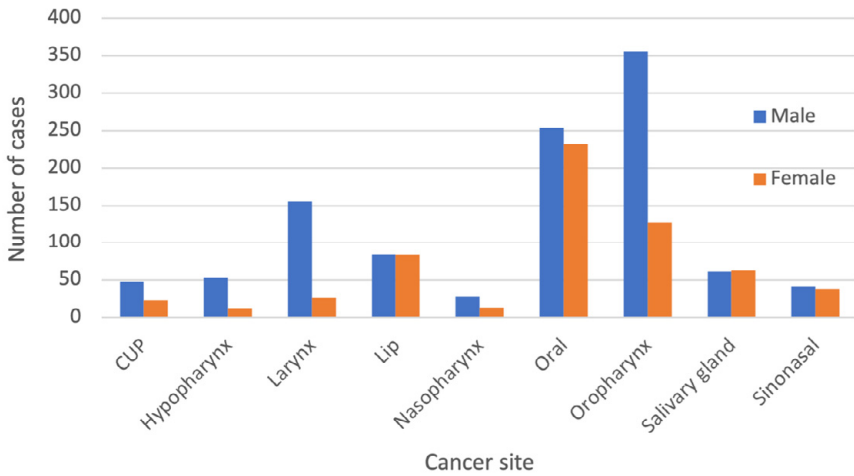

Figure 2. Number of new head and neck cancer cases per site in Sweden in 2019. Source: The Swedish Cancer Registry and Swedish Head and Neck Cancer Register (accessed January 16, 2023). Abbreviation: CUP, cancer with unknown primary.

Traditional risk factors of HNC are tobacco smoking and alcohol abuse (6-8). Furthermore, poor dental hygiene contributes to a 5-fold increase in risk for OCC and OPC (38). In recent years, high-risk HPV infections have emerged as an additional risk factor for TC and BoT-cancer (9-13). In the United States, HPV^+ OPC increased by 225% between 1988 and 2004, while HPV^- disease declined by 50% (14).

In Sweden, the incidence of OPC between 1990 and 2021 rose by 293% for males and 191% for females (**Figure 3**). In a study by Louie *et al.*, the incidence of OPC in England is projected to increase significantly and, by 2025, pass OCC and become the most frequent HNC, representing about 35% of all HNCs (39). For OPC (w/wo association with HPV), there is a 3:1 ratio between males and females, and the most common localization is the tonsils (**Figure 4**).

HPV is the most common sexually transmitted virus (40), and the number of lifetime sex partners positively correlates with high-risk HPV^+ OPC (11, 38, 41, 42). However, most people exposed to HPV do not develop HNC, suggesting that there are other components to the risk as well (43).

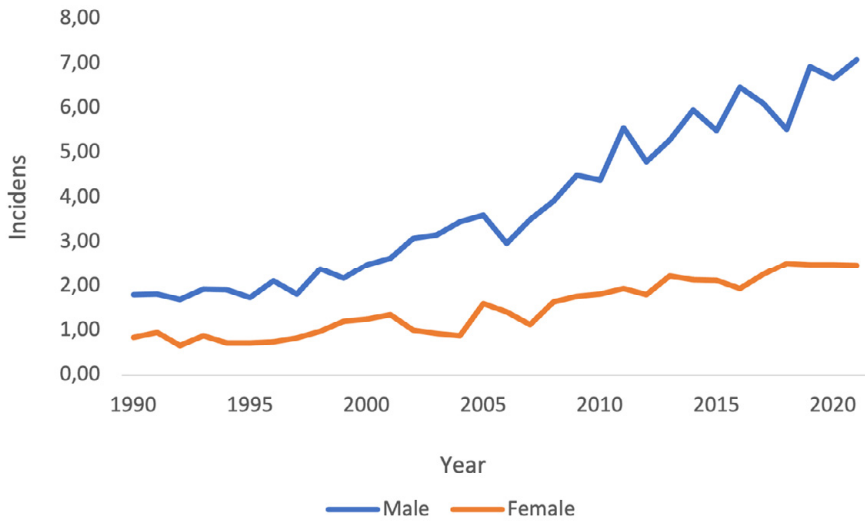

Figure 3. Incidence of oropharyngeal cancer per 100 000 inhabitants between 1990 and 2021. Source: the Swedish Cancer Registry (accessed April 16, 2023).

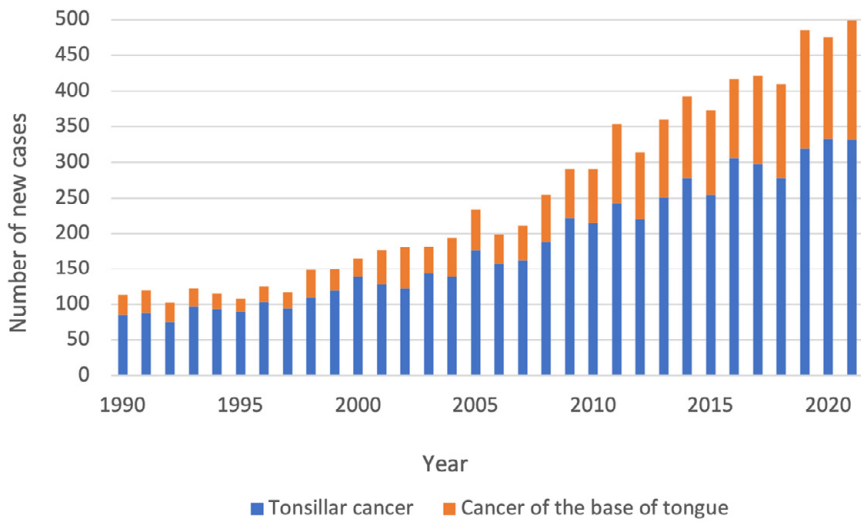

Figure 4. Number of new cases in Sweden per year of tonsillar cancer and cancer of the base of tongue between 1990 and 2021. Source: the Swedish Cancer Registry (accessed April 16, 2023).

Symptoms

Depending on where the cancer originates, patients with HNC can present with various signs/symptoms, comprising nasal blockage and epistaxis, ulcers (e.g., of the lip or oral cavity) w/wo pain, sore throat, swallowing or breathing difficulties, hoarseness, or with a lump in the neck (4). The symptoms can be vague and experienced long before the patient seeks medical advice, resulting in a late diagnosis, more extensive treatment, and a worsened prognosis. More than 50% of the individuals diagnosed with HNC are diagnosed in an advanced stage (44-46).

Work-up and treatment

About 90% of patients diagnosed with HNC receive treatment with curative intention (37). Work-up and treatment follow a "standardized care plan", often requiring a multidisciplinary team of head and neck surgeons, oncologists, plastic surgeons, maxillofacial surgeons, radiation therapists, contact nurses, dentists, nutritionists, speech therapists, physiotherapists etc. The work-up includes a thorough clinical examination with endoscopy (under general anaesthesia if needed), diagnostic biopsies and/or cytologies, and imaging, e.g., CT, CT-PET, or MRI scans) (**Figure 5**) (47).

Patients diagnosed with early-stage HNC, i.e., approx. a third of the cases (48, 49) receive uni-modality treatment, i.e., radiotherapy (RT) or surgery (49). In contrast, patients with advanced HNC typically receive combinations of modalities, including surgery and RT w/wo chemotherapy (49), which is the focus of paper **III**. Chemotherapy is offered concomitantly with RT to some advanced-stage HNCs and as unimodality palliative treatment (49). Immunotherapy, which takes advantage of a person's immune system to help kill cancer cells, is currently offered to selective patients as a second line of palliation.

Taken together, the treatments are extensive with life-long side effects, e.g., dry mouth, taste alterations, trismus, dysphagia, neck/shoulder impairment, lymphedema, and, occasionally, hearing impairment. These side effects have a significantly negative impact on quality of life (50, 51).

Prognosis and survival

The 5-year relative survival rate for all sites of HNC is 67%, although it varies greatly, e.g., from 29% to 92%, between sites (37). Age, clinical stage at diagnosis, and comorbidities are important prognostic factors (46, 52-54). The 5-year survival rate for patients with early-stage HNC is favourable (86%) (48). The prognosis for HPV^+ OPC is better than for the HPV^- disease (9, 14), with a 5-year overall survival (OS) of 81% *vs*. 40%, respectively (55).

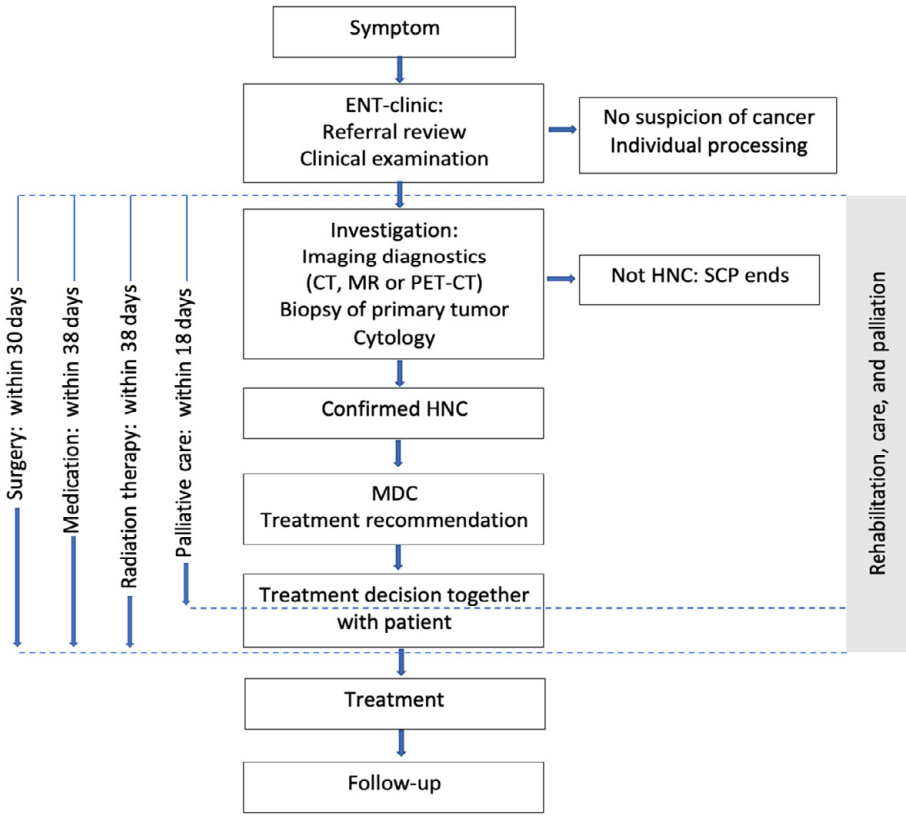

Figure 5. Standardized care plan for head and neck cancer. Abbreviations: MDC, multi-disciplinary conference; HNC, head and neck cancer; ENT, ear, nose, and throat; SCP, standardized care plan. Adopted and revised from the Swedish Head and Neck Cancer Register.

Notably, a Chinese report with data obtained from the American Surveillance Epidemiology and End Results (SEER) database indicates major improvement in survival over time for HNC, with 5-year relative survival rates (RSR) increasing over 10-year periods from 1975-1984 (54%) to 1985-1994 (56%) to 1995-2004 (61%), and 2005-2014 (67%) (56). Additionally, a study from Denmark, utilizing the Danish Cancer Registry, shows a significant increase in 5-year RSR for HNC from 49.0% to 62.4%, respectively, between 1980-1984 and 2010-2014 (57). As for Sweden and Finland, similar trends have been identified for several subgroups of HNC (58).

History of human papillomavirus

HPV was first discovered in skin cells in the 1950s by scientists searching for clues to what might trigger cervical cancer (59). In 1976, the German virologist Harald zur Hausen recognized its role in the carcinogenesis of *cervix uteri*, for which he received the Nobel Prize in medicine in 2008. Later, Brandsma & Abramson (1989), and Ishibashi (1990), suggested the role of HPV infections in the development of some cancers of the upper aerodigestive tract (60, 61). Syrjänen *et al*. suggested HPV involvement in different subsets of HNC in the early 1980s (62).

The papillomaviruses and the polyomaviruses were originally considered to belong to the same virus family termed *Papillomaviridae*. However, it was later established that the two groups had very different characteristics and, consequently, were divided into two separate families, i.e., *Papillomaviridae* and *Polyomaviridae* (63). HPV is a double-stranded DNA virus (63), and over 200 papillomaviruses have been identified together with an even higher number of subtypes (64).

Human papillomavirus and related diseases

Globally, over 630 million people are infected with HPV, with an even distribution between men and women (65). HPV is the most common sexually transmitted virus in Sweden (40) and worldwide (66), and the second leading cause of cancer caused by infectious agents (67). Chesson *et al.* estimate the average lifetime probability of acquiring HPV for individuals with at least one opposite sex partner to 85% for women and 91% for men (68). Identifying HPV's role in the development and progression of various benign and malignant conditions is considered one of the most significant events in medicine and global healthcare (69, 70).

HPVs are divided into low-risk and high-risk types based on their ability to cause cancer. Low-risk HPV causes benign tumours (warts, papillomas), whereas high-risk HPV (e.g., type 16) is associated with cancer in the cervix, vulva, vagina, penis, oropharynx, and anus. High-risk HPV causes about 5% of all cancers (71).

HPV is the cause of more than 90% of anal and cervical cancers, about 70% of vaginal and vulvar cancers, and more than 60% of penile cancers. The link between HPV and OPC has gradually been established over the past decades through numerous scientific studies and clinical observations, and the incidence is increasing (14-18). More than 70% of OPC in Sweden are linked to HPV (72, 73).

As discussed by Rodrigues *et al*., most HPV infections are asymptomatic, and the human body clears most of them spontaneously (74). The study also demonstrates that approx. 60% of uterine cervical HPV infections may be cleared within the first year, and 90% within three years. Similarly, Plummer *et al.* shows that 91% are cleared within 24 months (75). However, persistent high-risk HPV infections not cleared represent an increased risk of developing cancer (75, 76).

HPV vaccine and its consequences

Vaccination against HPV is the only vaccination that prevents cancer (77). For example, the incidence of cervical cancer has been significantly reduced following the introduction of such vaccinations. Initial data on the vaccine's effect on OPC is also encouraging (65). There is evidence of substantial herd protection when vaccine coverage exceeds 50% (78). In addition, a recent study has shown a strong impact of herd immunity on oral infection rates in unvaccinated individuals: from 2009 to 2016, the oncogenic HPV prevalence in unvaccinated men decreased by 38% (79).

According to WHO, the primary target group in most countries for HPV vaccinations as a preventive measure for cervical cancer are 9-14-year-old girls (80). There are three types of efficient prophylactic HPV vaccines available: a bivalent, a quadrivalent and a nonavalent (80).

As of 2022, 125 countries have introduced the HPV vaccine in their national immunization programme for girls, and 47 countries also include boys (80). In Sweden, vaccination against HPV began in 2010 for girls aged 12 (40). Not until 2019, after several cost analyses (CAs) and cost-effectiveness analyses (CEAs) had been made, showing economic and medical gains with a gender-neutral vaccination program, it was decided to include the young boys in the program starting in 2020 (40).

By including boys in the program, it was estimated that 120-130 HPV-caused cancer cases per year could be prevented (81). The predicted annual cost for including boys, i.e., 56 million SEK, was financed by government grants (81). According to the Swedish Cancer Foundation, if 70% of all children are vaccinated against high-risk HPV, HPV-driven cancers may be eradicated (82).

For optimal protection, the vaccine should be administered before sexual debut. It provides over 90% protection against the HPV types included in the vaccine if the individual has not been infected with the virus before the vaccination. However, the vaccine cannot cure an ongoing infection, nor can it halt incipient cell changes (40).

The Swedish healthcare system

In Sweden, healthcare is largely a public service financed through taxation. Of the gross domestic product (GDP) of Sweden, 10.9% is allocated to the healthcare sector. This spending aligns well with the rest of the EU, whereas, in comparison, the US spent 16.8% of its GDP on the healthcare sector in 2019 (**Figure 6**) (83). The Swedish healthcare service is decentralized to regions and municipalities, and providers are reimbursed according to Diagnosis-Related Group (DRG) tariffs. However, certain care, e.g., HNC care, is decentralized to the seven university hospitals. Only a negligible part is financed by patient fees (84).

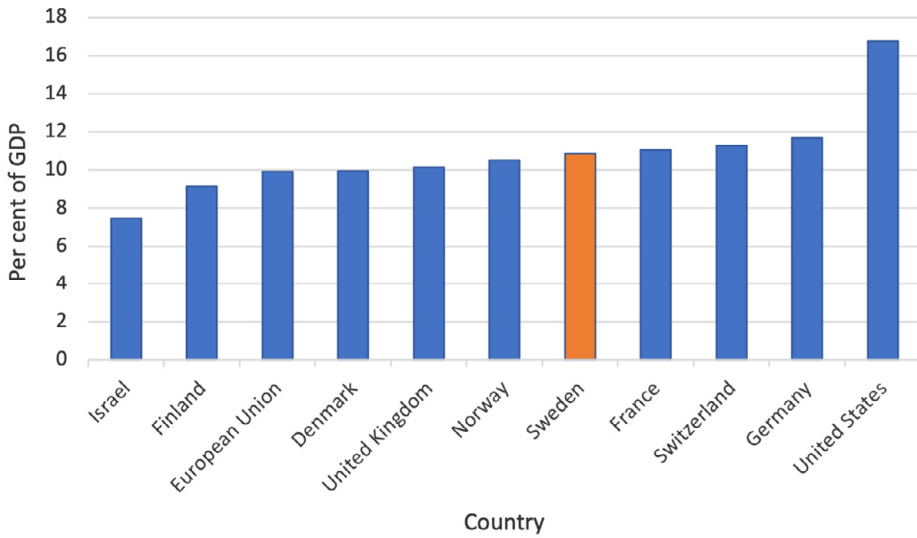

Figure 6. Percentage of gross domestic product spent on the healthcare sector by country in 2019. Source: Worldbank.com (accessed February 15, 2023).

The Swedish Parliament decided in 1997, following a government bill, that healthcare should be conducted according to three principles: (i) the principle of human value, which means that all people are equally valuable and have an equal right to healthcare regardless of age, gender, education, social, or economic status, (ii) the principle of need and solidarity, which means that those with the most severe illnesses must receive care first, and (iii) the CE principle, which means that there must be a reasonable relationship between the costs and the effect of a treatment. If two different treatments achieve the same effect, the less costly shall be given (85).

National registries

Sweden has a unique opportunity to conduct registry studies thanks to the Swedish personal identity number (PIN) system and a well-developed registry infrastructure (86). The Swedish PIN, unique to each person, is a useful tool for linkages between medical registers and allows for virtually 100% coverage of the Swedish healthcare system (86). It is used in large parts of society, including healthcare and employment status, which makes it possible to compile information about a person's health, illnesses, and treatments over time.

Sweden has several Quality registries (QRs) that are unique with respect to coverage and quality, including the Swedish Head and Neck Cancer Register (SweHNCR) (87). Most of them are initiated by health professionals, predominantly physicians,

and include disease-specific data, treatment, and survival aspects. Unlike mandatory government-administered national registries, such as the Swedish Cancer Registry (CR) (2), the Cause of Death Registry (3), and the cost-per-patient (CPP) registry, QRs are voluntary. Patients must receive information about the registry as well as be informed of their right to refuse participation and to have data erased from the registry. However, patients are not required to actively give their consent. Instead, they are included by default if they do not actively object (i.e., an "opt-out" mechanism) (87).

The registries in Sweden make it possible to carry out high-quality register studies in a way that may be impossible in many other countries. The registries in Sweden have led to a significant amount of research and have contributed to increased knowledge in many areas, including health, illness, and care. They have also helped to identify risk factors for disease, improve treatments, and reduce the burden of disease on the population.

In Sweden, sick leave is handled by the Swedish Social Insurance Agency (SSIA) and the employer. The employer pays “sick pay” to the employee for the first 14 days of sick leave. Thereafter, the responsibility passes over to the SSIA. Sick leaves shorter than 14 days are therefore not registered at SSIA.

Health economics

General definition

According to textbook definitions, economics concerns allocating scarce or limited resources between competing actors. An informal interpretation is that it is about “who (gets) what, when, where, and why”. Health economics applies this to healthcare and the medical sector. It deals with the allocation and use of resources in the production and delivery of healthcare services. It includes studies of the financing, organization, delivery, and consumption of health services and the economic and social consequences of these actions.

With ageing populations, a seemingly ever-increasing ability to develop new treatments and technologies, and the unlimited demand for healthcare services, costs strain our healthcare system. Health economics inform policy decisions by identifying efficient ways to improve health outcomes, allocate resources, and ensure equitable access to healthcare for all.

Economic evaluations

How does a society get the most value for money? We do not automatically want to select a less costly treatment option unless it, at the same time, generates an equal or better outcome. Accordingly, when comparing alternatives, both the cost and the effect of the treatment, as well as the incremental cost per unit of effect, must be considered. Economic evaluations are essential in health economics as they provide a systematic approach to assessing the value of healthcare interventions. They provide information relevant to unavoidable trade-off decisions within the healthcare sector. By comparing costs and benefits of different interventions, it is possible to identify the alternative that offers the best value for money and to allocate resources accordingly. This is necessary since resources are scarce, and we must therefore allocate them wisely. Drummond *et al*. define economic evaluations as: "the comparative analysis of alternative courses of action in terms of both their costs and consequences" (88). There are several different types of health economic evaluation methods (**Table 1**).

Table 1. Measurements of costs and consequences in economic evaluations.

Analysis	Evaluation of costs	Identification of consequences	Evaluation of consequences
Cost-effectiveness analysis	Monetary units	Single effect	LY gained, disability days saved, OS etc.
Cost-utility analysis	Monetary units	Single or multiple effects	Healthy years (quality-adjusted LY etc.)
Cost-benefit analysis	Monetary units	Single or multiple effects	Monetary units

Abbreviations: LY: Life-years; OS: overall survival.

Cost-effectiveness analysis (CEA), cost-utility analysis (CUA), and cost-benefit analysis (CBA)

CEA is useful when a decision-maker must choose between a limited range of options within a certain budget. It puts the costs and outcomes in relation to each other. Calculating an incremental cost-effectiveness ratio (ICER) produces a cost per unit of effect, which can be put against the willingness to pay for that extra effect.

$$ICER = \frac{Costs\ for\ treatment\ A\ (€) - Costs\ for\ treatment\ B\ (€)}{Effects\ of treatment\ A\ (\%) - Effects\ of\ treamment\ B\ (\%)}$$

CUA is a variant of CEA, the difference being that it uses utility as an outcome (88). This outcome is usually expressed as quality-adjusted life-years (QALY), which is achieved by multiplying the quality-adjusted weight for each health state, ranging

on a scale from 0 (equivalent to being dead) to 1 (perfect health), by the length of time in that state and then adding up the number of QALYs.

While both CEA and CUA work with the notion that there is a defined budget and that we want to maximise the output within this budget, CBA answers whether it is economically worthwhile expanding the budget. This is done by widening the concept of the value and translating the health effects, i.e., life-years gained, medical complications avoided, or QALYs gained, into monetary values and putting them beside the costs (88).

Cost analysis (CA), cost-minimization analysis (CMA), and cost of illness (COI)

While economic evaluations consider both costs and consequences, CAs only consider costs. For example, CA may compare alternative treatments or interventions, but it does only consider costs. It simply analyses the different cost items and, in the end, presents the cost burden of a disease, treatment or intervention compared to an alternative.

A type of CA that also only focuses on costs is CMA. Traditionally it has been considered an economic evaluation since it compares interventions or treatments based on the assumption that the outcome is expected to be equal to the alternatives. With this approach, the least costly intervention will be the preferred option. CMA cannot be determined in advance as it has to be based on previous research or professional opinions, stating that the alternatives are identical regarding effectiveness (88).

COI aims to estimate the total economic burden of a specific illness or condition on society, assessing both direct costs, e.g., outpatient and inpatient care, and indirect costs, such as productivity loss (89). However, it does not consider any effects or other health benefits. The difference between CA and COI is that while both analyses involve estimating costs, CA typically focuses on measuring the costs of a specific intervention, whereas COI analysis seeks to estimate the overall economic burden of a disease.

There are different approaches when making COI analyses. It can be conducted using the top-down (paper **I** and **IV**) or the bottom-up (paper **II** and **III**) approach. The top-down approach estimates the costs of a disease, with the help of registries, and divides them into subgroups of the disease and/or the affected population. The bottom-up approach uses data for a specific study population and extrapolates them, e.g., onto a larger population using national prevalence data.

There are pros and cons to the two approaches. An advantage of the top-down approach is that extrapolation is unnecessary, and fewer assumptions must be made. A disadvantage is that it relies on registries where diagnoses may be missing or

misclassified, leading to missing costs. In addition, the lack of detailed information on diagnosis may not allow for subgroup analyses. An advantage to the bottom-up approach is the preciseness of cost data, i.e., cleared from costs of other conditions and, therefore, less exposed to misclassifications or non-reporting. Disadvantages are, for example, that it is labour-intensive and costly.

Study perspectives

All economic evaluations and cost studies can be viewed from different perspectives. It can, for example, take the view of the individual patient, the healthcare provider, the insurance company, or society. When making health economic evaluations, it is essential to address which perspective to use. The result can vary considerably depending on the perspective you choose. It can look promising from one perspective but not from another.

This was highlighted in a study by Byford *et al*. (2003) comparing two treatment strategies for recurrent deliberate self-harm. They showed that the two treatments were similar from a healthcare perspective. However, from a broader societal perspective, the costs for one of the treatments were considerably higher (90).

Several health economic studies have previously been performed in the field of HNC. Many economic evaluations use a healthcare/insurance-payers' perspective (25, 26, 28, 33). These can aid insurance companies in putting prices on a specific illness to reimburse healthcare givers, but they do not provide information on the price tag for society. Without knowing the societal cost burden, it is difficult to estimate what potential savings can be made, e.g., when including boys in the HPV vaccination program or knowing what treatment regimen is the most cost-effective for society.

Purpose and aims

Purpose

The purpose of this thesis is to provide updated information on the economic burden of HNC from a societal perspective to aid healthcare policy decisions on resource allocation and healthcare providers to make informed decisions regarding prevention, work-up, treatment, and follow-up. Ultimately to enhance the quality of care and improve the lives of individuals affected by HNC.

Aims

Paper I

To examine direct and indirect costs from a top-down perspective of precancers and cancers associated with HPV, including OPC, for Sweden.

Paper II

To assess COI from a bottom-up perspective for OPC w/wo association to HPV for the Southern Sweden Healthcare Region.

Paper III

To compare the cost and cost-effectiveness of two treatment regimens, i.e., surgery preceded or followed by RT for OCC.

Paper IV

To provide a COI analysis from a top-down perspective for HNC (for all sites) for Sweden in 2019.

Materials and methods

Paper I

This initial multidisciplinary study examined direct and indirect costs from a top-down perspective for precancers and cancers associated with HPV in Sweden. We performed a retrospective prevalence-based COI assessment by estimating all diagnosis-specific events for one year (i.e., 2006) and calculating all resources utilised or lost due to morbidity and mortality. A particular focus was on OPC associated with HPV.

The populations were identified from national registries via the International Classification of Diseases codes. We focused on diseases associated with high-risk HPV, i.e., dysplasia, cancer *in situ*, and cancer of the cervix, vulva, vagina, anus, penis, and oropharynx. National registries were used to identify the number of outpatient and inpatient healthcare events, diagnose-specific healthcare events, as well as diagnose-specific sick leave and granted early-retirement days in 2006.

We estimated direct medical costs, i.e., outpatient and inpatient healthcare associated with diagnosis, treatment, and follow-up, of precancers and cancers associated with high-risk HPV through the national CPP registry. With data from the SSIA, using the human capital approach, we estimated indirect costs, i.e., costs related to productivity loss due to morbidity and premature mortality.

A literature search was conducted to identify secondary data on prevalence rates of conditions associated with high-risk HPV (HPV16, 18, 31, 33, 45, 52, and 58) through the databases MEDLINE (PubMed), EMBASE (the Elsevier platform www.embase.com), The World Health Organization, and the Institute Català d'Oncologia Information Centre on HPV and Cancer. Prevalence rates were applied to the total cost burden to estimate HPV-attributable costs.

Paper II

This population-based retrospective study, using the bottom-up method, assessed direct medical and indirect costs for OPC w/wo association to HPV for the Healthcare Region of Southern Sweden. We identified 121 consecutive patients

obtained from SweHNCR diagnosed with OPC, i.e., TC, BoT-cancer, and cancers of the soft palate and pharyngeal wall, treated at Skåne University Hospital, Lund, Sweden. The observation period was from 1 month before the diagnosis to 3 years after treatment was completed.

Cost data collected from the hospital's economic systems were, with the help of two specialists in ENT, Head & Neck Surgery, cleared from costs that likely occurred from unrelated comorbidities. Indirect costs were such caused by productivity loss due to morbidity (i.e., sick leave, early retirement) and premature mortality. Using the human capital approach, costs were estimated by multiplying the length of work absence by an average salary for men and women combined. Costs were stratified by HPV status and clinical stage.

Paper III

Based on the national multicenter ARTSCAN 2 RCT (19), this CEA compared the costs and CE of two treatment regimens for OCC. Briefly, 250 patients from six participating centres were randomised 1:1 to either surgery preceded by accelerated RT or surgery followed by conventionally fractionated RT, stratified by study centre, tumour site, and clinical stage.

Two-hundred-forty patients were eligible for intention-to-treat analysis, with 120 in each treatment arm. Thirty-one were excluded due to missing data, leaving 209 patients for this analysis. The CEA was conducted by taking the societal costs (direct medical and indirect costs) and OS at five years into account.

Direct costs were collected from the hospital's economic systems of outpatient and inpatient healthcare for patients treated at Skåne University Hospital (one of the participating centres). Data were cleared from comorbidity costs and imputed for the remainder of the study population using multiple imputation adjusted for age, sex, site, clinical stage, and treatment regimen.

Indirect costs for sick leave and early retirement were calculated using the number of days of work absence received from the SSIA and multiplying it by an average salary, including social fees, for the working population.

A CEA using the OS rate at five years for two treatment regimens was performed. The estimation of OS at a fixed point in time was carried out according to Klein *et al*. (91). The CE was estimated as the ICER, representing the cost per additional percentage point of OS. Non-parametric bootstrapping with 5 000 replications was used to assess the uncertainty regarding the incremental cost and effects (88). The results were presented in a CE plane.

Paper IV

A retrospective prevalence-based COI analysis was conducted to evaluate the economic burden of HNC for Sweden in 2019. Using a top-down approach, we used national health and population registry data to quantify resource utilisation and associated costs. A societal perspective was applied, including direct medical costs, i.e., outpatient and inpatient costs for work-up and treatment; informal costs, i.e., care from family and friends; and indirect costs, i.e., productivity loss due to absence from work and premature death.

The diagnose-specific cost of outpatient and inpatient care was retrieved from the CPP registry using the ICD-10 codes C00-C14, C30-C32, and C77.0. The cost of informal care was estimated using data from the literature on number of hours used for caring for terminally ill patients. The total cost was calculated by multiplying the hours of care by the value of leisure time. The cost of dental healthcare treatment (DHT), given before the start of HNC treatment, was retrieved from the three largest regions of Sweden. The cost estimates were extrapolated to the rest of the country.

ICD-10 codes were also used to extract data for sick leave spells and early retirements from the SSIA. To calculate the productivity loss, the number of sick leave and granted early-retirement days were multiplied by the average salary, including social fees, of the working population for both males and females.

Results

Paper I

Direct costs

The mean cost, in 2006-year's price level, for outpatient care events due to cervical dysplasia, cervical cancer *in situ*, and cervical cancer attributable to high-risk HPV was €350, €495, and €346 per event, respectively. For TC, the mean cost was €279 (both genders together). For BoT-cancer, it was €253 for females and €242 for males.

For inpatient care, the mean cost for cervical cancer attributable to high-risk HPV was €6 063. For females, the mean cost for TC and BoT-cancer was €7 781 and €7 420, respectively, and for males, €5 393 and €4 944. Costs for anal cancer attributable to high-risk HPV were €10 049 and €11 612, respectively, for females and males.

Altogether, cervical cancer attributable to high-risk HPV was responsible for a majority of the outpatient and inpatient events (60%), followed by vaginal (11%), vulvar (10%), anal (10%), oropharyngeal (6%), and penile cancer (3%) (**Figure 6**). Data on healthcare events stratified per gender (for all precancers and cancers) are indicated in **Figure 6**.

Indirect costs

In Sweden, in 2006, the total number of long-term sick leave days and granted early retirement days due to HPV-related cancers were 87 484 (**Table 2**). Using prevalence rates from the literature, which was 74%, 64 484 days were estimated to be associated with high-risk HPV.

Assuming the same share is associated with high-risk HPV and applying that same prevalence rate, the total of short-term sick leave days due to cancers associated with high-risk HPV was 20 199 days. For early retirement, with the same calculation, 56 464 days were attributable to high-risk HPV.

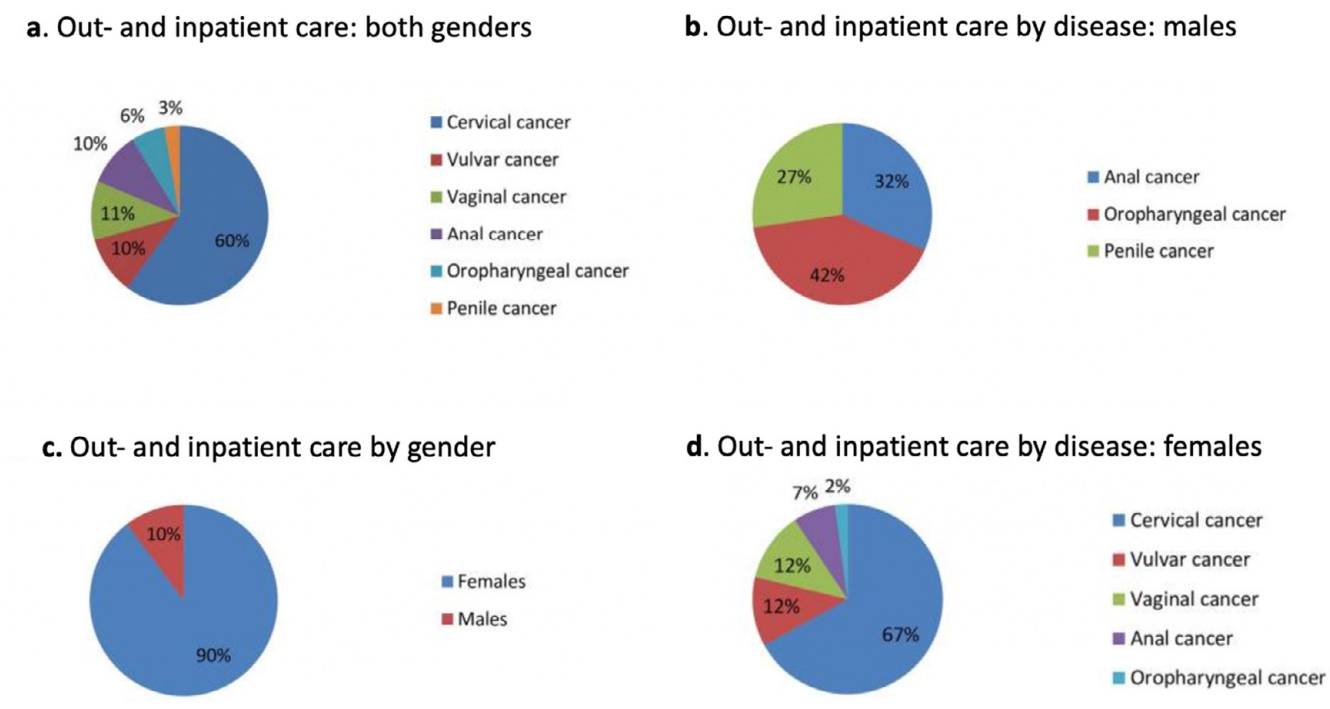

Figure 6. Distribution of outpatient and inpatient healthcare events attributable to high-risk HPV per site and gender. (**a**) Outpatient and inpatient healthcare events for males and females, (**b**) outpatient and inpatient healthcare events by disease among males, (**c**) outpatient and inpatient healthcare events by gender, and (**d**) outpatient and inpatient healthcare events by disease among females.

Females had the largest proportion of HPV-attributable sick leave and early retirement days. Cervical cancer accounted for 64% of HPV-attributable morbidity. For males, OPC represented the largest share of the HPV-attributable morbidity at 69%, followed by anal (18%) and penile cancer (13%). Total indirect cost for morbidity in 2006 was estimated at €26.6 million.

Data from the National Board of Health and Welfare's Cause of Death registry show that 376 individuals died from high-risk HPV-related cancers in 2006. Only those of working age, i.e., below the age of 65, were included in the production loss analysis (i.e., 116 individuals). When applying high-risk HPV prevalence rates, 1 071 working years were lost. The largest part, 88%, represented females, of which 93% was gynaecological cancer. Among the 127 working years lost due to cancers associated with high-risk HPV for men, OPC accounted for 65%. The indirect cost of premature death due to cancers associated with high-risk HPV was estimated at €36 million.

Total costs

When adding up direct and indirect costs, the total annual cost for cancers associated with high-risk HPV was estimated at €93.7 million. OPC accounted for €11.9 million of these costs (TC: €8.7 million and BoT: €3.2 million). The total economic burden on society for all high-risk HPV-related precancers and cancers included in this study was estimated at €124.2 million in 2006.

Table 2. Number of registered sick leave and granted early retirement days, HPV-attributable sick leave and retirement days, and HPV-attributable fraction of cost in 2006. Costs are presented in €1000.

Diagnosis	Females						Males						Both genders
	TLSL N	ALSL n	TSSL N	ASSL n	TERD N	AERD n	TLSL N	ALSL n	TSSL N	ASSL n	TERD N	AERD n	ATC €
Cervical cancer	41 195	38 311	13 551	12 001	31 770	29 546	–	–	–	–	–	–	**15 057**
Vulvar cancer	6 712	2 081	736	652	8 249	2 557	–	–	–	–	–	–	**997**
Vaginal cancer	2 043	1 083	383	339	2 966	1 572	–	–	–	–	–	–	**564**
Anal cancer	7 458	6 712	2 374	2 103	8 078	7 270	2 688	2 419	856	758	2 465	2 218	**4 050**
Penile cancer	–	–	–	–	–	–	1 285	1 038	367	325	2 890	2 355	**697**
Tonsillar cancer	4 534	2 221	786	696	5 835	2 859	16 186	7 931	2 805	2 484	11 663	5 715	**4 131**
BoT cancer	2 110	1 083	383	339	1 004	492	3 274	1 604	567	503	3 877	1 900	**1 104**
TOTAL	**64 051**	**51 491**	**18 129**	**16 129**	**57 901**	**44 296**	**23 433**	**12 993**	**4 596**	**4 070**	**20 895**	**12 168**	**26 602**

Abbreviations: N, total register-based number of days; n, prevalence-based number of days; TLSL, total long-term sick leave days; ALSL, attributable fraction of long-term sick leave days; TSSL, total short-term sick leave days; ASSL, attributable fraction of short-term sick leave days, TERD, total early retirement days; AERD, attributable fraction of early retirement days; ATC, HPV-attributable fraction of cost; BoT, base of tongue.

Paper II

The average cost per person diagnosed with HPV$^+$ OPC (from one month before diagnosis to three years after treatment completion) was €103 386. The corresponding cost for HPV$^-$ OPC was €120 244 (**Table 3**). The costs were largely stage-dependent: higher for more advanced stages, except for clinical stage IVC. When looking at the subsites of OPC, TC represented the largest group with 64% of all cases and had a mean total cost of €117 512 (**Table 4**). HPV$^+$ OPC accounted for 81% of all OPC cases and represented 79% of the total cost. Males accounted for 71% of these costs. The total cost for the study's 121 patients diagnosed with OPC was approximately €13 000 000.

Table 3. Mean direct costs, indirect costs, and total cost per HPV status (presented in € in 2017 price level).

Type of cost	HPV$^+$ OPC	HPV$^-$ OPC
Direct		
Outpatient care	26 734	19 683
Inpatient care	16 477	31 756
Palliative care	1 335	6 124
Total direct	44 546	57 563
Indirect		
Morbidity	42 926	10 026
Mortality (premature death)*	15 914	52 655
Total indirect	58 840	62 680
TOTAL	**103 386**	**120 244**

*Costs were discounted at 3% annually. Abbreviations: HPV, Human papillomavirus; OPC, oropharyngeal cancer.

Table 4. Mean direct costs, indirect costs, and total costs of oropharyngeal cancer per subsite (presented in € in 2017 price level).

Type of cost	Tonsillar C09 (n=77)	BoT C01 (n=32)	SP/PhW C10 (n=12)	All (n=121)
Direct				
Outpatient care	26 885	25 252	16 198	25 394
Inpatient care	16 169	17 569	44 827	19 381
Palliative care	2 261	558	6 644	2 245
Total direct	45 316	43 379	67 669	47 020
Indirect				
Morbidity	43 274	30 226	11 501	36 672
Mortality (premature death)*	28 922	1 568	41 119	22 898
Total indirect	72 196	31 794	52 620	59 570
TOTAL	**117 512**	**75 173**	**120 289**	**106 590**

*Costs were discounted at 3% annually. Abbreviations: OPC, Oropharyngeal cancer; BoT, Base of tongue; SP/PhW, Soft palate/pharyngeal wall.

Paper III

Cost data were obtained for 209 of the 240 patients originally included in the ARTSCAN 2 RCT, who therefore were included in the economic evaluation. The distribution was 98 patients in the pre-operative RT arm and 111 in the post-operative RT arm. Direct and indirect costs are shown in **Table 5**. Direct costs were significantly less for post-operative RT (€49 652) than pre-operative RT (€59 044). Indirect costs, i.e., productivity loss due to sick leave and early retirement, were similar between the two treatment groups.

The pre-operative RT led to a lower probability of survival specifically at the 5-year observation point (-14 percentage points). On the CE plane, most of the ICER pairs (88%) were in the northwest quadrant, indicating that the pre-operative RT was more costly and less effective and, therefore, dominated by the post-operative RT regimen. According to the sensitivity analysis, the CE result and subgroup analysis were robust to variations in costs and survival rates (**Table 6**).

Table 5. Mean (SD) direct and indirect costs per patient and treatment group for OCC. Direct costs from the population of the Southern Healthcare Region of Sweden imputed onto the remainder of the study population. All costs are presented in PPP-adjusted € in 2019 price level.

Type of cost	Pre-operative RT n=98	Post-operative RT n=111	Cost difference (95% CI)	p-value
Direct	59 044 (19 632)	49 652 (19 176)	9 392 (4 093 to 14 691)	0.001
Outpatient care	19 860 (5 322)	17 109 (5 501)	2 751 (1 270 to 4 231)	0.000
Inpatient care	39 184 (16 985)	32 543 (16 344)	6 641 (2 092 to 11 190)	0.004
Indirect	24 743 (42 675)	25 588 (47 530)	-844 (-13 229 to 11 540)	0.893
TOTAL	**83 787 (51 290)**	**75 240 (53 040)**	**8 548 (-5 725 to 22 820)**	**0.239**

Abbreviations: PPP, purchasing power parity; RT, radiotherapy; SD, standard deviation; OCC, oral cavity cancer; CI, confidence interval.

Table 6. Sensitivity and subgroup analyses of cost-effectiveness of pre-operative compared to post-operative RT. Population size for pre- versus post-operative RT in paratheses. All costs are presented in PPP-adjusted € and effects in percentage points in 2019 price level.

Scenario	Cost difference	Effect difference	ICER
Base case	8 547	-13.9	Dominated
Subgroup analyses			
Age			
23-65 (47/51)	3 542	-12.9	Dominated
66-84 (51/60)	10 792	-14.9	Dominated
Gender			
Female (32/43)	4 029	-10.1	Dominated
Male (66/68)	11 851	-14.5	Dominated
Clinical stage			
I/II (49/56)	13 392	-10.6	Dominated
III/IVA (49/55)	3 594	-17.2	Dominated
Site			
Tongue/floor of mouth (66/79)	10 404	-14.2	Dominated
Gingiva/other oral sites (32/32)	7 339	-13.9	Dominated

Abbreviations: RT, radiotherapy; PPP, purchasing power parity; ICER, incremental cost-effectiveness ratio.

Paper IV

The number of sick leave and granted early retirement days due to HNC was 134 318, where males generated 62%. OPC represented the largest group with 36% of all sick leave and granted early retirement days (48 306 out of 134 318) (**Table 7**).

Table 7. Number of sick leave and granted early retirement days for head and neck cancer per site and gender for Sweden in 2019.

Site	Male			Female			Both genders		
	Sick leave	Early retirement	Total	Sick leave	Early retirement	Total	Sick leave	Early retirement	**Total**
LiC	142	0	142	85	0	85	227	0	**227**
OPC	28 055	6 177	34 232	12 439	1 634	14 074	40 494	7 811	**48 306**
OCC	12 207	4 429	16 635	10 973	3 714	14 688	23 180	8 143	**31 323**
SGC	2 459	663	3 122	2 804	445	3 249	5 263	1 108	**6 371**
NPC	3 410	2 135	5 545	1 828	1 643	3 471	5 238	3 778	**9 016**
HPC	2 700	845	3 545	982	607	1 589	3 683	1 451	**5 134**
SNC	4 712	2 721	7 433	2 010	1 111	3 121	6 722	3 833	**10 554**
LaC	3 164	2 492	5 656	1 669	1 795	3 463	4 833	4 286	**9 119**
CUP	6 118	1 079	7 196	5 043	889	5 933	11 161	1 978	**13 139**
TOTAL	**62 992**	**20 048**	**83 040**	**38 808**	**13 470**	**51 278**	**100 799**	**33 519**	**134 318**

Abbreviations: LiC, lip cancer; OPC, oropharyngeal cancer; OCC, oral cavity cancer; SGC, salivary gland cancer; NPC, nasopharyngeal cancer; HPC, hypopharyngeal cancer; SNC, sinonasal cancer; LaC laryngeal cancer; CUP, cancer with unknown primary.

The total annual cost for HNC in 2019 was estimated to €92.4 million, where males accounted for 66%. Productivity loss comprised the greatest part (64%). The total cost of outpatient and inpatient care was €8 236 820 and €21 587 941, respectively (**Table 8**).

The cost per cancer site is indicated in **Table 9**. OCC was costliest (€34 280 176), followed by OPC (€21 941 265). OCC also caused the highest direct costs (€12 712 945). The least costly site was lip cancer (€842 385). The cost of DHT was €1 591 571.

Table 8. Total and mean cost per patient with head and neck cancer per gender for Sweden in 2019 (presented in PPP-adjusted € in 2019 price level).

Type of cost	Male		Female		Both genders	
	Total cost	Cost/person	Total cost	Cost/person	Total cost	Cost/person
Direct	**20 441 402**	**18 945**	**10 974 930**	**17 816**	**31 416 331**	**18 535**
Outpatient care	5 128 610	4 753	3 108 210	5 046	8 236 820	4 859
Inpatient care	14 239 029	13 197	7 348 912	11 930	21 587 941	12 736
Dental care	1 073 763	995	517 808	841	1 591 571	939
Informal care	**1 112 142**	**1 031**	**646 139**	**1 049**	**1 758 280**	**1 037**
Productivity loss	**39 449 779**	**36 561**	**19 762 410**	**32 082**	**59 212 189**	**34 933**
Sick leave	11 362 611	10 531	6 303 243	13 878	17 665 854	10 422
Early retirement	3 616 396	3 352	2 245 734	3 646	5 862 130	3 458
Premature death	24 470 772	22 679	11 213 434	18 204	35 684 205	21 053
TOTAL	**61 003 322**	**56 537**	**31 383 479**	**50 947**	**92 386 801**	**54 505**

Abbreviations: PPP, purchasing power parity

Table 9. Total annual costs for head and neck cancer per site in 2019 (presented in PPP-adjusted € in 2019 price level).

Type of cost	LiC	OPC	OCC	SGC	NPC	HPC	SNC	LaC	CUP	Total
Direct	**626 212**	**6 536 633**	**12 712 945**	**2 269 904**	**590 080**	**1 105 936**	**2 075 661**	**4 013 186**	**1 485 774**	**31 416 331**
Outpatient care	180 640	2 623 611	2 083 479	541 291	263 216	296 547	652 734	822 342	772 960	8 236 820
Inpatient care	288 763	3 460 433	10 173 122	1 613 119	288 366	748 355	1 348 748	3 019 950	647 085	21 587 941
Dental care	156 810	452 588	456 344	115 495	38 498	61 034	74 179	170 894	65 729	1 591 571
Informal care	**19 580**	**426 843**	**626 559**	**164 472**	**54 824**	**176 220**	**78 320**	**211 464**	**0**	**1 758 280**
Productivity loss	**39 783**	**14 525 201**	**20 484 328**	**5 638 170**	**4 046 473**	**4 306 637**	**5 589 073**	**2 111 642**	**2 287 200**	**59 212 189**
Sick leave	39 783	8 521 231	4 031 379	910 983	919 880	650 836	1 184 998	848 901	1 944 359	17 665 854
Early retirement	0	1 386 709	1 418 100	193 831	658 952	253 448	676 130	748 649	342 842	5 862 130
Premature death	0	6 003 970	15 034 850	4 533 355	2 467 641	3 402 353	3 727 945	514 092	0	35 684 205
TOTAL	**842 385**	**21 941 265**	**34 280 176**	**8 188 040**	**4 729 875**	**5 649 826**	**7 817 234**	**6 507 186**	**3 838 703**	**92 386 801**

Abbreviations: PPP, purchasing power parity;LiC, lip cancer; OPC, oropharyngeal cancer; OCC, oral cavity cancer; SGC, salivary gland cancer; NPC, nasopharyngeal cancer; HPC, hypopharyngeal cancer; SNC, sinonasal cancer; LaC laryngeal cancer; CUP, cancer with unknown primary.

Discussion

Previous efforts

Previous studies on costs of HNC typically focus on healthcare consumption, resulting in a paucity of data from a societal perspective, notably for costs associated with productivity loss (20-32). Also, they often concern very specific cohorts with limited generalizability to the general Swedish settings, e.g., US Medicare patients aged over 65 (27), military service personnel (29), or individuals in hospice care (92, 93). Rezapour *et al*. reports the cost of OCC from a societal perspective in Iran for 2014. However, the analysis focuses on one site only (i.e., the oral cavity) and lacks information on informal care (94). Gyllensten *et al.* includes indirect costs in their analysis, but only in terms of sick leave and for a very specific population (i.e., patients subjected to adjuvant oncological treatment) (36). Wu *et al.,* focusing on HNC and cervical cancer, estimates indirect costs but only for premature mortality (35). Accordingly, previous studies, while very informative, do not represent HNC as a whole, lack comprehensiveness and, therefore, do not present the total societal cost. In addition, they lack HNC-characteristic depth. In contrast, this thesis provides near-total societal costs for HNC and relates them to specific disease features. It concerns costs per site of HNC (**I**-**IV**), costs in relation to HPV status (**I, II**) and clinical stage of OPC (**II**), and costs of two treatment schemes for OCC (**III**). The information generated may be important to decision-makers when considering, e.g., vaccinations for high-risk HPV and changes in the work-up/treatment of HNC. Furthermore, it may be an important reference point for future economic assessments.

COI for precancers/cancers associated with HPV

In paper **I**, using a top-down approach, COI from a societal perspective of precancers and cancers associated with high-risk HPV for Sweden in 2006 was assessed for the first time. The overall cost was €94 million, ranging from €76 million to €116 using lower and upper bounds of prevalence rates from the literature. Among cancers affecting both genders, OPC was the costliest with €11.9 million annually. The main cost driver for males was OPC, reflecting that the incidence of HPV^+ OPC has been, and still is, increasing (14-18). The analysis was

performed one year before the start of the National HPV Vaccination Program, which was initiated in 2008 and involved girls only to prevent cervical (gynaecological) cancer. Our data, published in 2017, argued for the inclusion of boys into the program, a decision later taken by authorities in 2019.

HPV vaccination is effective in preventing HPV infections and decreasing the spreading of HPV-associated diseases (95). Worldwide, about 50% of all countries have introduced such vaccination schemes, covering about one-third of the population of girls, while far from all countries have included boys in their programs (96). A gender-neutral HPV vaccination program likely slows the spread of HPV and, in turn, decreases the incidence of HPV-associated cancers. Over time, this may increase the chance of eliminating such cancers, as a cover rate above 50% is suggested to produce herd immunity (97). Of course, reducing or eliminating HPV-associated cancers will lead to lower healthcare costs, and the reduced burden on healthcare systems will free up resources that can be directed towards the prevention and treatment of other conditions.

COI studies are not economic evaluations as they do not consider outcomes. Rather, COI information is a reference point that facilitates future CEAs and CUAs. However, prevalence-based COI studies, such as study **I**, add knowledge about money spent caring for patients with diseases associated with HPV and are essential for policymakers when allocating recourses and budget planning. Furthermore, they are of relevance as they inform about the cost that may be substantially reduced if the gender-neutral vaccination program turns out to be successful. ***Limitation****:* Our study likely underestimated the societal burden of precancers and cancers associated with high-risk HPV as the cost of, e.g., primary, palliative, and informal care, was not included in the analysis due to the lack of data.

In paper **II**, the COI of OPC associated with high-risk HPV in Sweden was assessed for the first time using a bottom-up approach. Accordingly, direct and indirect costs (for sick leave, early retirement, and premature death) were estimated. The bottom-up approach allowed for analysis per clinical stage and associations to high-risk HPV, cleared (to the best of our ability) from costs of concomitant conditions. The results indicated a mean cost for OPC of €106 590 per patient regardless of HPV status. Indirect costs made up a great portion of this cost (56%), suggesting a need for efficient rehabilitation.

The cost of HPV^+ OPC was €103 386 per patient, while for HPV^- cases it was 16.3% higher. The overall cost for the 121 patients with OPC in the study was €13 million. HPV^+ accounted for 79% of these costs. The results indicated that the costs progressed with increased stage except for stage IVC, likely reflecting that patient presenting with very advanced disease were not subjected to treatment with curative intention, in turn suggesting a need for early detection.

Taken together, the detailed data on costs for OPC, as presented in papers **I** and **II** from a societal perspective, are valuable for decision-makers when planning

healthcare measures. For example, they underscore the importance of efforts towards early detection, e.g., the "standardized care plan" (**Figure 5**) and towards "standardized rehabilitation programs". In addition, the data further support the recent decision to include boys in the HPV vaccination program. For all these examples, the present data may be used in associated CEAs. ***Limitation**:* Our study likely underestimated the costs of OPC associated with HPV because costs for primary and informal care were not included due to the lack of data.

CE for two treatment schemes for advanced OCC

In paper **III**, data were retrieved from the ARTSCAN 2 RCT, which assessed the effectiveness of pre-operative RT (with accelerated fractionation) compared to post-operative RT (with conventional fractionation) administered to patients with resectable OCC. The benefit of the RCT was that patients were randomly assigned to receive either an experimental intervention (in this case, accelerated pre-operative RT) or the standard treatment. The outcomes were compared to determine whether or not the experimental intervention was more effective. The goal of RCTs is to minimize selection bias and increase the validity of the results by controlling for external variables and ensuring that the groups being compared are similar.

As the intervention/treatment was more expensive than the existing alternative while providing equal or less benefit (in terms of survival), it was dominated by the base-case alternative. Together with many-fold previous observations on survival and morbidity of advanced OCC, the present data on costs may provide decision-makers in the field with valuable information on which treatment regimen for OCC is the preferred option from a societal perspective. Furthermore, the results will reinforce the routine in hospitals where post-operative RT is the current standard. In contrast, where it is not, our results, in conjunction with other data, notably from the ARTSCAN 2 study, may be considered in terms of a change of treatment order.

Apart from this study, no information is available comparing the cost of (accelerated) pre-operative RT and (conventional) post-operative RT for resectable OCC when combinations of surgery and radiotherapy are considered. ***Limitation**:* Our study likely underestimate the costs of OCC since costs for primary, palliative, and informal care are not included due to the lack of data.

COI for HNC in Sweden in 2019: all sites

In paper **IV**, we conducted a retrospective prevalence-based COI analysis to evaluate the economic burden of HNC (for all sites) for Sweden in 2019. Our study

is the first to estimate the near-total economic burden of HNC in Sweden, which was €92.4 million. Direct costs were €31.4 million (34%), informal costs €1.8 million (2%), and indirect costs €59 million (64%). OCC followed by OPC were the two costliest sites with €34.3 million and €21.9 million, respectively.

This COI does not offer any information on the gain of these costs. However, as discussed previously, cases where a specific disease may be preventable and therefore available for eradication, it is a valid method and provides the sum that potentially can be saved. In this study, this again can be applied to OPC, which, to a large extent, is caused by high-risk HPV and, therefore, potentially available for preventive vaccinations. However, there are costs in a COI that cannot be avoided even if we eradicate the disease tomorrow: i.e., the effects of prior exposure.

Regardless of the above reasoning, the results from this COI are also of key value for further economic evaluations, leading to new information and, hopefully, to informed decisions on the allocation of resources and development of programs and policies. ***Limitation**:* Our study likely underestimates the costs of OCC since the cost of primary care is not included due to the lack of data. For other specific limitations, see paper **IV**.

Savings of early detection and speedy rehabilitation

This thesis shows that direct costs, as well as costs associated with productivity loss, are dependent on the clinical stage at diagnosis: briefly, the higher the stage, the greater the cost (**II**). For example, low-stage HNC may only require surgery, while advanced-stage tumours often require surgery and RT, the latter more costly combination contributing to extended sick leaves and increased frequency of early retirements. The exception seems to be very advanced-stage cancers, potentially not available for curative treatment. Given the relationship between HNC and the societal cost it incurs, actions for early detection and rehabilitation of HNC seems well warranted. Arguably, these may be underpinned by corresponding CE assessments for their evaluation.

It is apparent from the present studies (**I-IV**), and the literature in general for cancer (98-100), that a large part of the COI reflects productivity loss. Arguably, these may depend on, and be affected by, whether or not successful rehabilitation is enforced. Such may include "individualized rehabilitation plans" and close collaboration between healthcare professionals. As a basis for such introductions, CEAs are warranted, and the data presented in papers **I**, **II**, and **IV** may the basis for such analyses.

Top-down and bottom-up retrieval of costs

Two principal approaches may be used to retrieve healthcare costs, i.e., top-down and bottom-up (88, 101). In this thesis, as for many other studies (23, 29, 30), prevalence-based top-down approaches were used, which allowed for a quick and broad-brush assessment of resource utilization and costs (**I**, **IV**). The benefit of this method is that it requires less data and that resources are easily accessible. In addition, it facilitates comparisons between healthcare systems, interventions, and population groups. However, the top-down approach only provides aggregate information. It does not allow for a deeper understanding of complex mechanisms involved in the cost and benefits of, e.g., a particular intervention.

In contrast, the bottom-up approach, which was used in papers **II** and **III**, provides detailed assessments of the costs of an intervention as it considers its specific characteristics and complexities. It provides a profound understanding of the mechanisms involved in the cost of an intervention, making it possible to identify potential sources of cost savings. Furthermore, it allows for a tailored analysis that accounts for local factors, e.g., resource utilization and costs. It can be adapted to various circumstances, making it a flexible method for evaluating the costs of a healthcare intervention. The accuracy of the results depends on the availability and quality of data. In this thesis, from a cohort of 121 consecutive patients with OPC (**II**) and from the ARTSCAN 2 RCT (**III**), bottom-up approaches allowed for non-biased, detailed data collection cleared from unrelated comorbidities.

The human capital approach (HCA) and the friction-cost approach (FCA)

When estimating productivity loss, there are two principal methods available: the HCA and the FCA (102-104). In this thesis, productivity loss was estimated using the HCA (**I-IV**). It is well-established and often used for evaluating costs and benefits of healthcare interventions, making the results comparable to other studies. The HCA relies on assumptions about future earnings, which may not always be accurate. In contrast, the FCA considers the costs of lost earnings only for the period it takes to replace the worker and of searching for new employment and retraining. Accordingly, it may provide a more realistic assessment of productivity loss since it acknowledges unemployment. However, it is resource-intensive and requires data collection and analysis at a very detailed level. Furthermore, comparisons between scenarios are less possible simply because this method is not as frequently used. Generally, the HCA yields higher values for productivity loss than the FCA (102).

General limitations

We did not include costs for primary care since, in the present series of studies, such information was not available through national registries in Sweden. Similarly, national registries lack reliable data on the costs for palliative or other social care taking place outside the hospital setting: such costs were, therefore, not considered. Non-market productivity loss was not assessed, again due to the lack of data. Apart from paper **III**, CEAs were not performed. On the other hand, the present studies, notably **I** and **IV**, provide a basis for such assessments. In future studies, quality-of-life aspects would add valuable input to the assessments.

Conclusions

Overall

This thesis provides updated information from a societal perspective on the economic burden of HNC in Sweden, with special reference to OPC associated with high-risk HPV and two treatment schemes for OCC, respectively. The information may be used by healthcare providers to make informed decisions on resource allocations and optimize work-up, treatment, and follow-up. It may also serve as a reference point for future economic assessments.

Paper I

The economic burden of high-risk HPV-related precancers and cancers is a growing healthcare concern. The rapid increase in the incidence of HPV^+ OPC may be addressed by including boys in National HPV Immunization Programmes, which now (since 2020) is the case for Sweden. The results of our study may serve as a point of reference for future economic evaluations of the benefits of such vaccinations. They may also be valuable for policymakers in other counties when deciding whether or not to include males in HPV immunization programs.

Paper II

The societal cost of OPC is substantial. This study specifically examines the cost of HPV^+ OPC, which can be prevented through HPV vaccination. The findings indicate that HPV^+ OPC accounts for 81% of all OPC cases and 79% of their societal cost. The results underscore that the decision to implement a gender-neutral HPV program in Sweden, potentially preventing a further increase in OPC, is correct.

Paper III

This study suggests that from a societal perspective, post-operative RT for OCC is a more cost-effective alternative when compared to pre-operative RT. If hospitals adhere to the standard practice of administering post-operative RT, this study's results will strengthen the existing protocol. Conversely, if the opposite is true, the findings, alongside other ARTSCAN 2 data, suggest that reordering the treatment approach may be considered.

Paper IV

The societal burden of HNC is markedly high. The findings in this study underscore a need for continued efforts in prevention, early detection, and treatment of HNC to reduce its burden on individuals and the society. They give an understanding of the make-up of the societal costs for HNC in Sweden and may serve as a basis/reference for further economic evaluations of HNC and other conditions.

Future perspectives and closing remarks

Societies strive to optimize the use of taxes that fund healthcare systems, and with limited resources, decisions must be taken and trade-offs experienced. To support such decisions, health economic evaluations are necessary, and these ideally rely on reliable data.

This thesis provides updated and detailed estimates of the societal costs of HNC, including associations to key aspects of the disease, which can be used *per se*, but also in future CE-evaluations. Such, in turn, can be used when allocating healthcare resources for maximum societal benefit.

Considering the relationship between HNC and the societal cost it incurs, as well as current healthcare trends, actions for early detection and rehabilitation of HNC are well warranted. In these areas, the present data can be used for CE-evaluations.

Areas for utilization of CEAs may be programs for early detection of HNC (or even screening programs for cancers associated with high-risk HPV). Similarly, such analyses may be used to evaluate programs for the rehabilitation of HNC.

In order to assess costs of HNC from a societal perspective even more accurately than in the present studies, new registries may need to be developed. One such may be a national register for primary care focusing on post-cancer-treatment activities.

Populärvetenskaplig sammanfattning på svenska

Huvud- och halscancer är en heterogen grupp av cancrar lokaliserade till ett område som sträcker sig från näsan och bihålorna via munnen, tungan, och spottkörtlarna till svalget och struphuvudet. Varje år diagnostiseras över 1 600 fall i Sverige, och de vanligaste lokalisationerna är munhålan och svalget.

Behandlingen består oftast av kirurgi (”operation”) och radioterapi (”strålbehandling” (med eller utan tillägg av cellgifter), och vid avancerad sjukdom är en kombination av dessa nödvändig. Behandlingen, och sjukdomen i sig, leder ofta till bestående biverkningar som påverkar patienternas livskvalité.

Tidigare har rökning och alkohol varit de främsta riskfaktorerna för att utveckla huvud- och halscancer, men succesivt har infektioner orsakade av s.k. humant papillomvirus (HPV) blivit den dominerande orsaken till cancer i tonsiller (halsmandlarna) och tungbas.

I två studier har vi beskrivit kostnaderna för HPV-orsakad tonsill- och tungbascancer (**I**, **II**). Kostnaden är ca. 1,1 miljoner SEK per patient, eller totalt ca. 200 miljoner SEK per år, vilket avspeglar direkta (för utredning och behandling) och indirekta kostnader (för sjukskrivning, sjukpensionering och förtida död).

Informationen enligt ovan är relevant då summan motsvarar den samhällskostnad som kan sparas om sjukdomen ”utrotas”, vilket skulle kunna ske genom att vaccinationsprogrammet för HPV utvidgades år 2019 till att även omfatta pojkar.

Våra studier av tonsill- och tungbascancer har omfattat analyser av kostnader i relation till hur avancerad en cancer är vid diagnos. Generellt visar våra data att samhällets kostnad för sjukdomen ökar ju mer avancerad cancern är när den upptäcks. Detta understryker vikten av tidig diagnostik.

Munhålecancer, en typ av huvud- och halscancer, behandlas ofta med en kombination av kirurgi och radioterapi. Vi har studerat kostnaden i relation till överlevnad för två alternativ i en s.k. randomiserad klinisk prövning (ARTSCAN 2-studien): pre-operativ och post-operativ strålbehandling (**III**). Vi visar att det senare alternativet var kostnadseffektivt då det uppnådde en i stort sett likvärdig behandlingseffekt, men till en lägre kostnad.

I den avslutande studien (**IV**), har vi tagit ett helhetsgrepp på all huvud- och halscancer och skattat samhällskostnaden för Sverige under 2019. Detta inkluderar till exempel kostnader för öppen- och slutenvård, speciell tandvårdsbehandling som är nödvändig i anslutning till strålbehandling, informell vård, sjukskrivning, sjukpensionering och förtida död.

Sammanfattningsvis visar avhandlingens studier att huvud- och halscancer orsakar stora samhällskostnader. De visar även att vissa av dessa kan ”sparas in” av det nu aktuella vaccinationsprogrammet mot HPV. Vidare visar de att tidig diagnostik, till exempel genom screeningprogram, kan vara kostnadssparande.

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