Tonsillectomy and Incidence of Oropharyngeal Cancers

Abstract

Background: Rising incidence of oropharyngeal cancers in numerous countries since the 1970s has been attributed to increased oral human papillomavirus (HPV) exposure. However, the contribution of coincidental declines in the surgical removal of the tonsils (tonsillectomy) is unknown. We quantified the association of tonsillectomy with risk of tonsillar, other oropharyngeal, and other head and neck cancers and the contribution of declines in tonsillectomies to cancer incidence trends.

Methods: We conducted a nation-wide cohort study in Sweden (1970–2009). Tonsillectomies (N = 225,718) were identified through national patient registers, which were linked with the cancer register. Cancer incidence in the tonsillectomy cohort was compared with Sweden’s general population through standardized incidence ratios (SIR).

Results: Tonsillectomies were associated with reduced risk of tonsil cancers (SIR 1+ years post-tonsillectomy = 0.31; 95% confidence interval (CI), 0.08–0.79 and 5+ years post-tonsillectomy = 0.17; 95% CI, 0.02–0.62), but unrelated to other oropharyngeal or other head and neck cancers (SIRs 1+ years post-tonsillectomy = 1.61; 95% CI, 0.77–2.95 and 0.92; 95% CI, 0.64–1.27, respectively). The cumulative incidence of tonsillectomy declined significantly (40%–50%) during 1970–2009. However, tonsil cancer incidence significantly increased during 1970–2009 both without and with corrections for declines in tonsillectomies (relative risks per 5-year periods = 1.23, P < 0.001 and 1.20, P < 0.001, respectively).

Conclusions: The reduced tonsil cancer risk with tonsillectomy reflects the removal of most of the relevant tissue. The absence of associations with other head and neck cancers indicates that tonsillectomy may not impact carcinogenesis at other sites.

Impact: The significant increases in oropharyngeal cancer incidence since the 1970s in Sweden appear independent of declines in tonsillectomies, reinforcing increased oral HPV exposure as the likely cause.

Introduction

Cancers of the palate tonsils, the lingual tonsils (base of tongue), the soft palate, and the oropharyngeal wall, collectively oropharyngeal cancers, rank amongst the few cancers with rapid increases in incidence over the past 30 to 40 years in several developed countries (1–4). Notably, these increases have occurred despite declines in the prevalence of cigarette smoking, an important oropharyngeal cancer risk factor (1, 5). Changes in sexual behaviors through the sexual revolution and increased oral/oropharyngeal human papillomavirus (HPV) exposure are believed to have contributed to the rising oropharyngeal cancer incidence among cohorts born during and after the 1940s (5–8).

Coincidentally, the practice of surgical removal of the palatine tonsils (i.e., tonsillectomy) for the treatment of recurrent throat infections has significantly declined following the introduction of penicillin V (9–11). This has prompted the question whether reduced removal of the tonsils in recent birth cohorts could underlie part of the increase in tonsil/oropharyngeal cancer incidence (9, 10, 12, 13).

Tonsillectomy would be expected to decrease the risk of palatine tonsil cancers through the removal of a majority of the relevant tissue (9, 10). In addition, tonsillectomy could also influence risk of non-tonsillar oropharyngeal cancers to the extent that the palatine tonsils serve as reservoirs of HPV infection in the oropharynx and/or as key immune modulators of HPV-induced or tobacco-induced carcinogenesis. Only one study to date has addressed the association of tonsillectomy with risk of oropharyngeal cancers (9); this study found that tonsillectomy was associated with a significant reduction in risk of tonsil cancer but was unrelated to risk of base of tongue cancer. No study to date has quantified the contribution of temporal trends in tonsillectomies to the rising cancer incidence.

Characterizing the association of trends in tonsillectomies with risk of tonsillar and non-tonsillar oropharyngeal cancers has important implications for understanding the reasons for the rapid rise in incidence of these cancers in recent years, a phenomenon described as a “virus-related epidemic” (2, 4, 9). Such investigation could also have relevance for secondary prevention of oropharyngeal cancers. Here, we report on the association of tonsillectomy with risk of tonsillar, non-tonsillar oropharyngeal,
and other head and neck cancers from a nation-wide, registry-based cohort study in Sweden, where oropharyngeal cancer incidence has significantly increased since 1970 (7, 14, 15). We also specifically quantified the extent to which declines in tonsillectomies in recent years have contributed to rising oropharyngeal cancer incidence.

Materials and Methods
Data sources and exposure and outcome ascertainment
We conducted a retrospective cohort study using data from the Swedish National in-patient register (1970–2009) and the out-patient register (2001–2009) to identify individuals who received a tonsillectomy (16). During 1970 to 2009, Sweden’s population was between 8 and 9.3 million. The Swedish National Patient Registers have been described previously (16). Briefly, founded in 1964 as a pilot program, the in-patient register became a full program in 1970 covering six counties in the Uppsala region (~36% of the Swedish population) and achieved 100% coverage in 1987 (16). The out-patient register started collecting data on surgical day-care procedures since 1997 and all out-patient hospital visits since 2001. Although data from the out-patient register were available since 2001, tonsillectomies were not conducted as an out-patient procedure prior to the year 2006 in Sweden. These patient registers include data on patient characteristics (age, gender, county), caregivers (hospital and department), and medical care (dates of admission and discharge, diagnoses, and medical and surgical procedures; ref. 16). Prior methodologic studies show high validity (sensitivity and positive predictive value) of surgical data in the registers (16).

Tonsillectomies were identified from the patient registers using the following codes: tonsillectomy or tonsillotomy with or without adenoidectomy (Swedish Classification of Operations and Major Procedures codes: 2710 and 2720 through the year 1997 and EMB10, EMB20, and EMB99 since 1997). Data on tonsillectomies were available through December 31, 2009, for individuals born prior to 2003; tonsillectomy data were unavailable for individuals born after 2002. Only the first tonsillectomy procedure was considered for individuals who received multiple surgeries.

For outcome ascertainment, patient registers were linked with the Swedish nation-wide cancer, cause of death, migration, and general population registers. We included the following head and neck cancer sites: palatine tonsils cancers (ICD-7 codes: 145.0), base of tongue, and other oropharyngeal cancers as one group (ICD-7 codes: 145.7, 145.8, and 145.9) and other head and neck cancers as one group [ICD-7 codes: lip (140.0, 140.1, 140.8, 140.9), tongue (141.7), floor of mouth (143), other mouth (144), nasopharynx (146), and hypopharynx (147)]. All histologies were included in the analyses; however, we note that a vast majority of these cancers (90%–95%) are squamous cell carcinomas. We considered other head and neck cancers as negative controls in our analyses because they share etiologic associations with oropharyngeal cancers for some risk factors (e.g., smoking and alcohol), but not others (i.e., HPV; ref. 3). The following cancer sites were excluded owing to difficulties in assigning a primary anatomic site or distinct etiology [ICD-7 codes: multiple or unspecified parts of tongue (141.8 and 141.9), unspecified pharynx (148), and salivary gland (142)].

Statistical analyses
Of 271,148 individuals who received a tonsillectomy between January 1, 1970, and December 31, 2009, we included 227,996 tonsillectomies for analyses of temporal trends in tonsillectomies in Sweden. Tonsillectomies were excluded (n = 43,152) due to their conduct prior to full coverage of the patient registry in a region or incomplete/inconsistent data (e.g., death or migration prior to the date of tonsillectomy; Supplementary Fig. S1). In addition, because tonsillectomies could be conducted for diagnosis and/or treatment of head and neck cancers, or in rare instances other cancers (17, 18), we excluded individuals with a history of head and neck cancer or a concurrent clinical indication of cancer for tonsillectomy (2,278), resulting in 225,718 tonsillectomies for analyses of associations with risk of head and neck cancers (Supplementary Fig. S1).

Follow-up began on the date of tonsillectomy and ended at the earliest of diagnosis of head and neck cancer of interest, death, emigration out of Sweden, or end of study (December 31, 2009).

We compared the incidence of tonsil cancers, other oropharyngeal cancers, and other head and neck cancers among individuals who received a tonsillectomy with the Swedish general population using standardized incidence ratios (SIR) and Poisson 95% confidence intervals (CI). SIRs were adjusted for attained age, gender, calendar year, and county. These SIR analyses were stratified by time since tonsillectomy (0–1 year, 1+ years, and 5+ years), age at tonsillectomy (<40 years and >40 years, cutoff chosen based on changing clinical indications for tonsillectomy), gender, or calendar year.

Temporal trends in the incidence of tonsillectomies during 1970–2009 were evaluated through log-linear joinpoint regression (19). These analyses were conducted overall as well as stratified by age at tonsillectomy and calendar period of tonsillectomy.

We quantified the impact of temporal trends in tonsillectomies on incidence trends for tonsil cancer by removing individuals who had received a tonsillectomy from the population denominator, as these individuals would theoretically no longer be at risk for tonsil cancer. We initially estimated the cumulative incidence of a tonsillectomy for the Swedish general population in each calendar period (5-year periods covering 1970–2009). We did not have information regarding tonsillectomies conducted at ages prior to study entry in 1970. For example, for individuals aged 10 years in 1970, we did not have information on tonsillectomies conducted prior to age 10, and so on. To account for this, we conducted analyses under 3 assumptions: that the unobserved age-specific incidence of tonsillectomy prior to 1970 was similar, 5 times higher, or 10 times higher than the observed age-specific incidence (in 5-year age groups) during 1970–1974. Then, within each calendar period, we utilized the cumulative incidence of tonsillectomy to remove tonsillectomized individuals from the Swedish general population. Using this new Swedish general population with “intact tonsils” as the denominator, we reestimated incidence rates and temporal trends for tonsil cancer during 1970–2009. Slopes and P values for temporal trends were calculated using Poisson regression.

Results
During 1970 to 2009, 227,996 tonsillectomies were conducted in the Swedish population covered by the in-patient and
Table 1. Description of tonsillectomies in Sweden during 1970–2009, N = 227,996a

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at tonsillectomy, years</td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>17.8 (14.0)</td>
</tr>
<tr>
<td>Median (interquartile range)</td>
<td>16.0 (6–24)</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>108,290 (47.5)</td>
</tr>
<tr>
<td>Female</td>
<td>119,706 (52.5)</td>
</tr>
<tr>
<td>Method of tonsillectomy</td>
<td></td>
</tr>
<tr>
<td>Tonsillectomy with or without adenoidectomy</td>
<td>222,862 (97.7)</td>
</tr>
<tr>
<td>Tonsillectomy with or without adenoidectomy</td>
<td>5,134 (2.3)</td>
</tr>
<tr>
<td>Source of data</td>
<td></td>
</tr>
<tr>
<td>In-patient register (1970–2009)</td>
<td>219,119 (96.1)</td>
</tr>
<tr>
<td>Out-patient register (2001–2009)a</td>
<td>8,877 (3.9)</td>
</tr>
<tr>
<td>Clinical indication for tonsillectomy</td>
<td></td>
</tr>
<tr>
<td>Chronic disease of tonsils and adenoids</td>
<td>189,156 (83.0)</td>
</tr>
<tr>
<td>Acute tonsillitis</td>
<td>4,789 (2.0)</td>
</tr>
<tr>
<td>Peritonsillar abscess</td>
<td>13,433 (5.9)</td>
</tr>
<tr>
<td>Obstructive sleep apnea</td>
<td>7,414 (3.2)</td>
</tr>
<tr>
<td>Cancer</td>
<td>2,982 (1.0)</td>
</tr>
<tr>
<td>Other</td>
<td>10,890 (4.8)</td>
</tr>
<tr>
<td>Missing</td>
<td>142 (0.1)</td>
</tr>
</tbody>
</table>

Tabulated values were identified from Sweden's in-patient and out-patient registers using codes 2710, 2720, EMB10, EMB20, and EMB99. Of 277,006 tonsillectomies, 227,996 were included for analyses of characteristics, clinical indications, and temporal trends. Reasons for exclusion are noted in the methods section.

aAlthough data from out-patient registers were available since 2001, tonsillectomies were not conducted as an out-patient procedure in Sweden until 2006.

out-patient registers (~75% overall, 100% since 1987). Tonsillectomies were performed primarily, but not exclusively, conducted among children and adolescents (mean age at tonsillectomy = 17.8 years, median = 16.0 years, interquartile range = 6–24 years) and were marginally more common among women than men (Table 1). A majority of tonsillectomies were conducted through tonsillectomy with or without adenoidectomy as in-patient procedures and were significantly more common among women than men (Table 1). The clinical indications for tonsillectomy differed significantly across calendar periods and age (Supplementary Table S1). A higher proportion of tonsillectomies in recent years was conducted due to a clinical indication of sleep apnea. Likewise, the proportion of tonsillectomies conducted due to sleep apnea or cancer significantly increased with age. Of note, tonsillectomies were not conducted as out-patient procedures prior to 2006. Clinical indications were generally similar between in-patient and out-patient tonsillectomies during 2006–2009, a period when tonsillectomies were conducted as either an in-patient (84.4%) or an out-patient procedure (15.6%) in Sweden (Supplementary Table S2).

Association of tonsillectomy with risk of head and neck cancers

Among 225,718 individuals with tonsillectomy, 144 head and neck cancers occurred over 3,168,640 person-years. The association of tonsillectomy with risk of head and neck cancer differed significantly by anatomic site (i.e., tonsil cancer, non-tonsil oropharyngeal cancer, and other head and neck cancer), as well as latency (i.e., time since tonsillectomy). Within a year after tonsillectomy, risks were substantially elevated for tonsil cancers, non-tonsil oropharyngeal cancers, and other head and neck cancers (Fig. 1A–C: SIRs = 251.7, 84.5, and 6.1, respectively) when compared with the Swedish general population. Beyond one year, however, tonsillectomy was associated with strongly reduced risk of tonsil cancers (Fig. 1A: SIR 1–5 years after tonsillectomy = 0.31; 95% CI, 0.08–0.79 and 5+ years after tonsillectomy = 0.17; 95% CI, 0.02–0.62). In contrast, no associations were observed for non-tonsil oropharyngeal cancers or other head and neck cancers (Fig. 1B and C: SIR 1–5 years after tonsillectomy = 1.61; 95% CI, 0.77–2.95 and 0.92; 95% CI, 0.64–1.27, respectively). We observed similar associations when base of tongue cancers were analyzed separately (SIR 1–5 years after tonsillectomy = 1.63; 95% CI, 0.66–3.36 and 5+ years after tonsillectomy = 1.31; 95% CI, 0.42–3.05). Likewise, associations did not differ by age at tonsillectomy, gender, or calendar period of tonsillectomy (Supplementary Table S3).

Results were similar when analyses were restricted to tonsillectomies conducted as in-patient procedures or when restricted to the years 1987–2009, when a 100% of Sweden's population was covered by the in-patient register (Supplementary Table S4).

Temporal trends in tonsillectomies and impact on tonsil cancer incidence

The incidence of tonsillectomies followed a variable pattern during 1970–2009 (Fig. 2A). Tonsillectomies declined significantly from 1970–1978 (joinpoint annual percent change (APC) = −9.3%; P < 0.001), increased during 1978–1994 (APC = 7.4%; P < 0.001), declined again through 2001 (APC = −8.1%; P < 0.001), and remained stable thereafter (APC = 0.3; P = 0.72). This variable pattern was generally observed across all ages (Fig. 2B). Across all calendar periods, the incidence of tonsillectomies was highest at ages <20 years and significantly declined thereafter (Fig. 2C).

We estimated the cumulative incidence of tonsillectomy by a particular age under three assumptions: that the age-specific incidence of tonsillectomy prior to 1970 was similar, 5 times higher, or 10 times higher than that observed during 1970–1974. Under all three assumptions, across birth cohorts, the age-specific cumulative incidence of tonsillectomy declined for each successive birth cohort through 1970 and increased for each successive birth cohort after 1970 (Supplementary Fig. S2A–S2C).

Across the calendar periods under observation (1970–2009), cumulative incidence of tonsillectomy declined significantly when 5 times higher or 10 times higher tonsillectomy rates were assumed prior to 1970 (Fig. 3A). For example, under the latter assumption, the cumulative incidence of tonsillectomy declined from 30.1% in 1970–1974 to 15.5% during 2005–2009.

During 1970 to 2009 in Sweden, tonsil cancer incidence increased significantly from 0.37 per 100,000 during 1970–1974 to 1.57 per 100,000 during 2005–2009 (RR for 5-year periods = 1.23; 95% CI, 1.21–1.25; Fig. 3B). Accounting for the cumulative incidence of tonsillectomies did not materially impact the rising incidence of tonsil cancer across calendar periods (Fig. 3B). For example, even under the extreme assumption that the incidence of tonsillectomies was 10 times higher prior to 1970 than in 1970–1974, tonsil cancer incidence increased significantly during 1970–2009 (RR across 5-year periods = 1.20; 95% CI, 1.18–1.22). The incidence of other oropharyngeal cancers also increased significantly during 1970–2009 in Sweden; however, we did not correct their incidence for declines in tonsillectomies given the lack of association with this procedure.
Discussion

In a nation-wide, population-based investigation of the association of tonsillectomy with risk of head and neck cancers in Sweden, our key observation was that tonsillectomy was associated with a substantial reduction in the risk of tonsil cancers. In contrast, tonsillectomy was unrelated to risk of either non-tonsil oropharyngeal cancers or other head and neck cancers, underscoring that removal of the tonsils may not impact risk of cancer at other head and neck sites. Importantly, we provide the first empirical evidence that the increase in oropharyngeal cancer incidence in recent years and birth cohorts persists even after accounting for temporal trends in tonsillectomies; this observation reinforces increased oral HPV exposure from changing sexual behaviors as the likely cause of rising oropharyngeal cancer incidence.

Figure 1.
Shown are the SIRs (squares) and 95% CIs (error bars) for the association of tonsillectomy with risk of tonsil cancers (A), other oropharyngeal cancers (B), and other head and neck cancers (C). SIRs are shown stratified by time since tonsillectomy (0–1, 1+, and 5+ years). The observed number of cancers and person-years are also shown below the x-axis for each cancer and latency category.

Figure 2.
Shown are temporal trends in the incidence of tonsillectomy during 1970–2009 in Sweden overall (A), age-specific rates across calendar periods (B), and period-specific rates across age (C).
Tonsillectomies were associated with very high risk of all head and neck cancers within the first year following the procedure (SIRs ranging from 6 to 250). We interpreted this elevated risk as a consequence of reverse causation (i.e., the presence or suspicion of head and neck cancer led to a tonsillectomy). Indeed, tonsillectomy is often a diagnostic procedure for anatomic localization of unknown primary cancers in the head and neck (17, 18). Although rare, individuals with other cancers could also receive a tonsillectomy, which could lead to confounding by indication. In that, a small proportion of individuals who receive a tonsillectomy have risk factors that predispose them to head and neck cancers. To guard against these biases, our primary analyses considered cancers that occurred beyond 1 year or beyond 5 years following tonsillectomy and excluded individuals who received a tonsillectomy due to a clinical indication of cancer.

We expected tonsillectomies to be associated with substantially reduced risk of palatine tonsil cancers because this procedure involves the removal of a vast majority of the relevant tissue (9, 10). Consistent with this expectation, tonsillectomy was associated with a >70% reduction in tonsil cancer risk. This reduction is perhaps applicable to both HPV-induced and tobacco/alcohol–induced cancers.

The shared etiology of tonsil cancers with other oropharyngeal cancers (HPV, smoking, and alcohol) and other head and neck cancers (smoking and alcohol) can also provide important clues (3). The absence of associations between tonsillectomy and risk of other non-tonsillar oropharyngeal cancers or other, non-oropharyngeal head and neck cancers is consistent with the hypothesis that the palatine tonsils do not act as reservoirs of HPV infection in the oropharynx and that their removal may not impact HPV-induced or tobacco-induced carcinogenesis in non-tonsillar head and neck sites.

Our results of reduced tonsil cancer risk with tonsillectomy are similar to a recent study conducted in Denmark by Fakhry and colleagues (9). That study, however, found that tonsillectomy was associated with reduced risk of diagnosis of tonsil cancer before age 60 and that tonsillectomy increased the risk of diagnosis of tonsil and base of tongue cancers after age 60 (9).

Differences in study methodologies perhaps contribute to these contrasting results.

Despite the strongly reduced risk of tonsil cancer, we do not believe tonsillectomies should be considered as a secondary prevention strategy for tonsil cancers or other oropharyngeal cancers at this time (9, 10, 20). Tonsillectomies did not alter risk of non-tonsillar oropharyngeal cancers, which constitute approximately 30% to 40% of all oropharyngeal cancers (5). Several knowledge gaps also warrant caution. At the population-level, mortality due to tonsillectomy (deaths within 30 days of the procedure) of ~3–30 per 100,000 outnumber the incidence of oropharynx cancers (~1–18 per 100,000; refs. 1, 21). Furthermore, the current state-of-the-science does not allow adequate risk stratification for the identification of high-risk individuals, the identification and location of premalignant lesions in the tonsils or other oropharyngeal regions, or efficacious, low-morbidity, cost-effective treatments for premalignant lesions (10, 22).

The incidence of tonsillectomy was variable during 1970–2009 in Sweden, with a decline from 1970–1978, an increase from 1978–1994, another decline from 1995–2001, and being stable thereafter. This pattern is similar to prior reports in Scandinavian countries, other European countries, and the United States over a comparable era and is consistent with changing indications of tonsillectomy, from throat infections to obstructive airway diseases (23–27).

Several of our observations provide the first empirical evidence that declines in tonsillectomies in recent years do not explain the concomitant rise in tonsil or other oropharyngeal cancer incidence in Sweden. First, although associated with a 6% to 83% reduction in tonsil cancer risk, tonsillectomies were relatively rare during our study period (annual rates of 40–150 per 100,000). Second, even an assumption that tonsillectomies were 10 times more common prior to 1970 did not materially impact the rising incidence of tonsil cancers in Sweden. Third, tonsillectomies were not associated with risk of other oropharyngeal cancers, which have also significantly increased in recent years in Sweden (28). Collectively, these results support the prevailing belief that changes in sexual behaviors led to increased oral HPV exposure.
and thereby HPV-positive oropharyngeal cancers in recent birth cohorts [1, 2, 4, 5].

We note the strengths and limitations of our study. We conducted a nation-wide analysis of Sweden’s population of approximately 9 million people over 40 years. However, our sample sizes for cancer outcomes were low, particularly for subgroup analyses. Our analyses were also limited by incomplete population coverage of the age of the patient register prior to 1987. Nevertheless, we observed similar results when analyses were restricted to 1987–2009. Also, we did not have information on key risk factors for head and neck cancers, such as tobacco or alcohol use. Likewise, we did not have information on the HPV status of head and neck cancers. These limitations notwithstanding, we exploited the etiologic similarities and differences across head and neck cancer sites to arrive at scientifically valid interpretations.

Our results have public health and research implications. We showed that rising incidence of oropharyngeal cancers in Sweden persists even after accounting for declines in tonsillectomies and represents a true increase. Similar increases have occurred in most economically developed countries worldwide, and a vast majority (>70%) of oropharyngeal cancers today are caused by HPV infection (6–8). Importantly, oropharyngeal cancers (particularly HPV-positive oropharyngeal cancers) are projected to become the most common head and neck cancer in the coming 15 to 20 years (6–8), underscoring the need for prevention strategies. At this time, prophylactic HPV vaccination holds the greatest promise to curb this rise (29). We also show that tonsillectomy was associated with substantial reductions in tonsillar cancer risk. However, screening and secondary prevention for tonsillar or other oropharyngeal cancers is currently infeasible. This underscores the need for studies to develop methods for risk stratification of high-risk individuals.

and the identification and treatment of premalignant lesions in the oropharynx (10).

Disclosure of Potential Conflicts of Interest
No potential conflicts of interest were disclosed.

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Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): E. Munck-Wikland, W. Ye
Writing, review, and/or revision of the manuscript: A.K. Chaturvedi, H. Song, P.S. Rosenberg, T. Ramqvist, W.F. Anderson, E. Munck-Wikland, W. Ye, T. Dalianis
Study supervision: A.K. Chaturvedi, T. Dalianis

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References


