

Tonsillectomy and Risk of Oropharyngeal Cancer: Implications for Research and Prevention

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Abstract

The association of tonsillectomy, a common surgical procedure involving the removal of a majority of the palatine tonsillar tissue, with risk of tonsil cancer specifically or oropharyngeal cancers overall is not known. In this issue of *Cancer Prevention Research*, Fakhry and colleagues conduct an analysis within the Danish Cancer Registry and show that tonsillectomies were associated with significantly reduced risk of tonsil

cancer, but were unrelated to risk of base of tongue cancers. This editorial discusses the implications of the results by Fakhry and colleagues for key prevailing questions in the field related to risk, rising incidence, secondary prevention, and treatment of oropharyngeal cancers. *Cancer Prev Res*; 8(7); 577–9. ©2015 AACR.

See related article by Fakhry et al., p. 583

The incidence of cancers of the oropharynx, including the palatine tonsils, base of tongue, and the pharyngeal wall, has significantly increased over the past 30 to 40 years in several developed countries worldwide (1, 2). Molecular epidemiologic studies now show that these increases are caused by rising incidence of HPV-positive oropharyngeal cancers, believed to be a consequence of rising exposure to oral HPV infection in recent birth cohorts from changes in sexual behaviors (3–6). An often proposed alternative hypothesis is that significant declines in recent years in the conduct of tonsillectomy could have led to rising incidence of tonsil cancers (7, 8). Indeed, rates of tonsillectomy, a common surgical procedure involving the removal of a majority of the palatine tonsillar tissue (through extracapsular tonsillectomy or intracapsular tonsillotomy), have significantly declined since the 1950s in the United States and other developed countries (9, 10). With changing rates of tonsillectomies, the clinical indications for tonsillectomy have also changed over time, with a shift over time from recurrent infections to airway obstruction (9–11).

In this issue of *Cancer Prevention Research*, Fakhry and colleagues (12) address the relationship of tonsillectomy with risk of tonsil cancers, base of tongue cancers, and oropharyngeal cancers overall using data from the Denmark Cancer Registry (1977–2012). Key results from their study include a significant reduction in the incidence of tonsil cancers, but not base of tongue cancers, among individuals who previously received a tonsillectomy; a notable difference in the tonsillectomy–tonsil cancer association by age, with individuals younger than 60 years having a reduced incidence of tonsil cancer following

tonsillectomy, but individuals older than 60 years having a higher incidence of tonsil and base of tongue cancer following tonsillectomy; and higher survival of tonsil cancer cases who received a tonsillectomy less than 1 year prior to their cancer diagnosis (12).

The study by Fakhry and colleagues (12) provides the first insight into the association of tonsillectomy with risk of oropharyngeal cancers. Herein, I discuss the implications of these results for key, prevailing questions in the field related to risk, rising incidence, secondary prevention, and treatment of oropharyngeal cancers.

Do tonsillectomies reduce risk of HPV-positive cancers, HPV-negative cancers, or both?

Fakhry and colleagues (12) report that tonsillectomy was associated with a 60% reduction in risk of tonsil cancers [rate ratio (RR) for tonsillectomy vs. no tonsillectomy = 0.40], but was not statistically significantly associated with risk of base of tongue cancers (RR, 1.1). Of note, the study did not have data on tumor HPV status of cancers, which precludes definitive conclusions regarding the impact of tonsillectomies on risk of HPV-positive (or HPV-negative) oropharyngeal cancers. Nonetheless, the differential association of tonsillectomy with tonsil cancers and base of tongue cancers can provide some insight.

Both tonsil and base of tongue cancers are strongly etiologically related to HPV infection (13). Thus, the reported differential association with one HPV-associated cancer (tonsil cancer), but not the other (base of tongue cancer), suggests that the reduced risk of tonsil cancer is largely related to the removal of the relevant palatine tonsillar tissue. That is, tonsillectomy potentially reduces risk of both HPV-positive and HPV-negative tonsil cancers. Data are sparse in the literature regarding the impact of tonsillectomy on oral HPV natural history. Beachler and colleagues (14) showed that individuals with tonsillectomy had reduced incidence of oral HPV infection, determined through a rinse and gargle sample of the oral cavity. However, this remains an isolated observation and needs replication.

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Is the effect of tonsillectomy on oropharyngeal cancer risk differential by age?

Fakhry and colleagues (12) report that tonsillectomy had a differential impact on tonsil and base of tongue cancer risk by age. Specifically, tonsillectomy was associated with an 80% reduced risk of tonsil cancer (RR, 0.2; 95% CI, 0.06–0.4) and unrelated to base of tongue cancer (RR, 0.5; 95% CI, 0.2–1.4) among individuals <60 years of age, whereas tonsillectomy was associated with increased risk of both tonsil cancer (RR, 1.8; 95% CI, 0.9–3.6) and base of tongue cancer (RR, 4.2; 95% CI, 1.9–9.3) among individuals ≥60 years of age. Of note, these analyses were stratified by age at cancer diagnosis rather than age at tonsillectomy. Thus, these analyses do not directly address whether having a tonsillectomy at younger versus older ages would have a differential impact on oropharyngeal cancer risk.

The authors go on to hypothesize that the differential associations of tonsillectomy by age indicate disparate impact on potentially HPV-induced versus tobacco/alcohol-induced oropharyngeal cancers. Specifically, that in individuals ages <60 years, tonsillectomy results in a reduction of the tissue susceptible to HPV-induced carcinogenesis; in contrast, in individuals ages ≥60 years, tonsillectomy results in local immunosuppression that compounds the already immunosuppressive effects of smoking and leads to enhanced smoking-induced carcinogenesis. Again, given the absence of tumor HPV status, the authors acknowledge the speculative nature of these conclusions.

The hypothesis put forth by Fakhry and colleagues (12) appears unlikely. Although the tonsils are important secondary lymphoid organs, the effects of the removal of the tonsils on humoral immunity or cell-mediated immunity appear transient and clinically insignificant (15). Additionally, the difference in the proportion of cancers caused by HPV at ages <60 years and ≥60 years is not large enough to lead to a qualitative interaction in the association of tonsillectomy with oropharyngeal cancer risk (3, 16). Indeed, a recent registry-based study in Denmark showed that approximately 61% of oropharyngeal cancers that occurred in individuals ages <60 years were tumor HPV-positive versus 53% of cancers in individuals ages ≥60 years (17). Furthermore, it is biologically unlikely that the remnant tonsillar tissue or the intact base of tongue tissue in individuals with a tonsillectomy is more susceptible to smoking-induced carcinogenesis versus HPV-induced carcinogenesis in an age-dependent fashion.

A more plausible explanation for the differential effects of tonsillectomy by age is a combination of two related biases—reverse causation (the presence or suspicion of oropharyngeal cancer leads to the conduct of a tonsillectomy) and confounding by indication (individuals at high risk of oropharyngeal cancer, such as those with unilateral tonsillar hypertrophy, are more likely to get a tonsillectomy). Reverse causation is clearly evident in the study by Fakhry and colleagues (12), as evidenced by the enormously elevated risks of tonsil, base of tongue, and oropharyngeal cancers overall (RRs of 107 to 372) within a year of tonsillectomy. Confounding by indication is relatively more difficult to assess in the absence of data on clinical indications for tonsillectomy and how these indications vary with age. It is likely that both reverse causation and confounding by indication would increase with age because the incidence of oropharyngeal cancers strongly increases with age (18).

Does a decline in tonsillectomies explain the rise in tonsil cancer incidence in recent years?

Fakhry and colleagues (12) do not explicitly quantify the contribution of declines in tonsillectomies over time to rising incidence of either tonsil cancer specifically or oropharyngeal cancers overall. Instead, they show an ecologic correlation between declining incidence of tonsillectomies in Denmark over the study period (1977–2012, most notably during 1995–2012) and rising oropharyngeal cancer incidence over time.

Quantification of the contribution of declines in tonsillectomy to rising tonsil cancer incidence over calendar time needs to explicitly discount the population denominator to remove individuals who have received a tonsillectomy, presumably because those with a tonsillectomy are at reduced risk of tonsil cancer. This, in turn, involves taking into account the cumulative incidence of tonsillectomy across age/birth cohorts rather than simple age-specific or calendar-year-specific incidence rates of tonsillectomy. Analogous analyses have recently been conducted to account for trends in hysterectomies on cervical cancer incidence trends in the United States (19). These analyses are particularly problematic given the left truncation of information on tonsillectomy. For example, for an individual aged 40 years in 1977 (the beginning year of the study), no information is available regarding whether he or she received a tonsillectomy prior to age 40. Given the lack of an empirical evaluation, the question remains regarding the extent to which a decline in tonsillectomies has contributed to the rise in tonsil cancer incidence in recent years.

What are the implications for secondary prevention through prophylactic tonsillectomies?

Fakhry and colleagues (12) appropriately caution against over-interpretation of the significant reductions in tonsil cancer incidence following tonsillectomy. Their cautionary note deserves reiteration—at this time, prophylactic tonsillectomies should not be considered as a secondary prevention strategy for oropharyngeal cancers.

There are currently several knowledge gaps regarding secondary prevention of oropharyngeal cancers (20–22). First, currently available risk factors (e.g., number of sexual partners, smoking) do not allow the accurate identification of individuals at high risk, and there are no oropharyngeal cancer prediction models in the literature. Second, markers of HPV infections (e.g., oral HPV DNA or serum antibodies to HPV antigens), while associated with strongly elevated risks of oropharyngeal cancers (13, 23), do not allow localization of infection to a specific anatomic site (e.g., palatine tonsil vs. base of tongue). Third, screening modalities to identify premalignant lesions in the oropharynx do not currently exist (20–22). Fourth, the results by Fakhry and colleagues (12) indicate that tonsillectomies do not entirely remove the risk of tonsil cancer and do not affect the risk of non-tonsillar oropharyngeal cancer. Importantly, although a common surgical procedure, tonsillectomy is not without minor complications, such as postoperative bleeding, pain, and nausea, as well as major complications, such as hemorrhage and death (24, 25).

What are the implications for treatment of oropharyngeal cancers?

Fakhry and colleagues (12) report that tonsillectomy less than 1 year prior to tonsil cancer diagnosis was associated with significantly higher survival. Further, tonsillectomies more than 1 year prior to tonsil cancer were unrelated to survival, and tonsillectomies were not associated with survival of base of tongue cancers. They hypothesize that surgical removal of the primary tumor through tonsillectomy before adjuvant therapy could have led to improved survival of tonsil cancer patients. Importantly, it is unclear whether tonsillectomies conducted less than 1 year prior to tonsil cancer diagnosis were diagnostic or therapeutic. In addition, as acknowledged by the authors, these survival analyses were not adjusted for stage at cancer diagnosis. Thus, these results are potentially confounded by stage—i.e., smaller tumors, which have better survival outcomes, are more likely to be removed through a tonsillectomy. Although the observations by Fakhry and colleagues (12) are interesting, the role of surgery for treatment of tonsil cancers is best addressed in clinical trials, rather than observational, registry-based studies.

In conclusion, the report by Fakhry and colleagues (12) provides important new information regarding the potential association of tonsillectomy with oropharyngeal cancers, a hitherto unaddressed question. These results in turn raise several additional questions, and thus should be considered preliminary and

should not influence clinical practice at this time. Nevertheless, these results provide a foundation for future studies for replication in different settings and populations as well as extension of the association of tonsillectomy with risk and incidence trends for oropharyngeal cancer anatomic subsites. The incidence of oropharyngeal cancer, HPV-positive oropharyngeal cancers in particular, is rising rapidly among young individuals in several countries worldwide. Yet, there are currently no modalities for screening or secondary prevention. Primary prevention through prophylactic HPV vaccination and cessation of tobacco use remains the only tenable option at this time. The effect of prophylactic HPV vaccination on oropharyngeal cancer incidence, however, will not be observed for several decades. Therefore, studies are needed to develop secondary prevention strategies for HPV-positive oropharyngeal cancers, which constitute a vast majority of oropharyngeal cancers in the United States today. Future studies need to address the development of demographic, behavioral, and biomarker-based risk stratification tools for the identification of high-risk individuals, as well as the development of tools for screening and effective treatment of precancerous lesions.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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