

Role of Prophylactic Bilateral Tonsillectomy as a Cancer Preventive Strategy

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Abstract

The rate of vaccination against human papillomavirus (HPV) among adolescent girls and boys over the past few years has been stagnant in spite of the increase in incidence of HPV-positive oropharyngeal (OPX) squamous cell carcinoma (SCC). The indirect relationship between HPV cancer incidence and preventive vaccination poses a public health concern and has caused clinicians to search for other methods toward eradicating the ongoing oropharyngeal carcinoma epidemic. This alarming increase in OPX is motivating a search for therapeutic prevention strategies, including biomarker discovery, risk assessment, therapeutic vaccines, immunotherapy, and surgery. The current Danish Cancer Registry study by Fakhry and colleagues (in this issue) is the first to investigate the impact of

prior tonsillectomy on the development of HPV OPX. They report that remote tonsillectomy resulted in a decreased incidence of tonsillar SCC. While thought-provoking, this study has a small sample size. Also, tonsillectomy does not address all anatomic sites at risk; there is lack of well-defined precancerous lesions or biomarkers to identify high-risk patients, and cost and morbidity make it impractical to justify prophylactic tonsillectomy as a cancer preventive strategy at present. The provocative clinical signal reported in this study supports further research and strategies that employ surgery when the technology and epidemiology can reliably be used to identify high-risk subjects. *Cancer Prev Res*; 8(7); 580–2. ©2015 AACR.

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

The high prevalence of human papillomavirus (HPV)-related oral infection and the increase in incidence of HPV16-caused oropharyngeal (OPX) cancers calls for surveillance and/or pharmacologic or surgical preventive measures for these malignancies (1). Currently, the rate of HPV OPX squamous cell carcinoma (SCC) is about 10,000 cases per year and rising yearly (2). The goal of vaccination, immunotherapy, chemotherapy, or surgical-based prophylaxis is to decrease the number of cancers that develop in all anatomic areas at risk. It is understood, however, that in order to show a decreased incidence of cancer in a prospective manner, a large sample size of patients with an extensive follow-up period is needed. The challenges faced by prevention trials in OPX include the inability to clearly define high-risk patients through precancerous lesions or biomarkers that would reliably identify the subjects who might benefit (3–6). The current retrospective study of the Danish Cancer Registry by Fakhry and colleagues is the first report to investigate the impact of prior tonsillectomy on the development of HPV OPX (7). The authors suggest that this study may provide evidence to support the development of clinical trials that prospectively investigate the role of prophylactic tonsillectomy in high-risk patients. In the Fakhry report, a reduction in the risk of tonsillar carcinoma after a remote history of tonsillectomy was observed in patients, especially in individuals younger than 60 years old. While the rate of prophylactic tonsillectomy decreased in Denmark, as described by Fakhry and colleagues,

in the United States, tonsillectomy is still among the most common surgical procedures performed in children, now being done mainly for obstructive indications. In 1959, 1.4 million tonsillectomies were performed in the United States, and although a drop in frequency to 380,000 procedures was observed by 1996, 130,000 out of 380,000 procedures (34%) were done in patients over 15 years of age (8). The immediate impact on health and healthcare expenditure from complications of tonsillectomy is considerable and was reported by Seshamani and colleagues (9) in a cohort study of 36,210 adult patients who underwent tonsillectomy. The cost of postoperative hospitalization and emergency room (ER) visits was also included in their analysis. In their report, 10% of patients visited the ER, and 1.5% were hospitalized within 14 days of tonsillectomy, with 6% treated for hemorrhage (50% requiring return to the operating room), 2% for dehydration, and 11% for pain. The cost of uncomplicated tonsillectomy was estimated at \$3,832, for hemorrhage at \$6,388, and for dehydration and for pain at \$5,753 and \$4,708, respectively (9). Given these data, overinterpretation of the results of Fakhry and colleagues study should not be seen as a justification to perform unselected prophylactic bilateral tonsillectomies, and the authors do not advocate this approach. This study should be regarded as thought-provoking, not practice-changing. Perhaps the approach might work in high-risk cohorts.

Before implementing prophylactic tonsillectomy in high-risk patients in clinical practice, several questions should be addressed by further prospective studies, including residual cancer risk at the other anatomic sites such as base of the tongue (BOT), the role of additional biomarkers in identifying risk, patient satisfaction, quality of life, surgical complications, cost, acute and chronic pain postsurgical pain, and surgical techniques. In addition, there are accumulating data implicating tonsillectomy as the cause of increased risk of cancer in other organs; for example, breast cancer could manifest in the body as a consequence of chronic inflammation and/or reduced efficiency of immune function (10).

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As reported by Fakhry and colleagues, out of a total 5,111 patients that developed OPX SCC: 52 (1%) had remote history of tonsillectomy, 174 (3.4%) had a tonsillectomy within one year, and 4,885 (95.6%) did not have tonsillectomy. A small sample size, with total of 52 remote tonsillectomies, may lead to the overestimation of the magnitude of the true effect of tonsillectomy. Out of those 52 patients, only 10 (19%) had BOT SCC and 12 (23%) had tonsillar cancer. The improvement seen in incidence of tonsillar SCC (RR, 0.42; 95% CI, 0.24–0.74) was not accompanied by reduction of all OPX SCC in all anatomic sites at risk, especially in BOT (RR, 1.25; 95% CI, 0.67–2.33). The data do present a very provocative clinical signal that should be validated in additional studies with larger sample size, if possible. Remarkably, in the above-60-year-old age group, the incidence of SCC with history of prior tonsillectomy was increased regardless of anatomic location, seen even in the tonsillar SCC subgroup. A very small sample size, including 23 OPX SCC >60-year-old patients with 6 out of 23 (26%) that had BOT SCC and 8 out of 23 (35%) that had tonsillar SCC as well as the lack of data on a smoking history or p16/HPV involvement, may have contributed to a poor outcome of the older subpopulation reported in this study. In a separate group of patients, with a tonsillectomy done within 1 year (174 out of 5,111; 3.4%) of diagnosis, the vast majority underwent a diagnostic procedure within 7 days; thus, their improved survival can likely be explained by a surgical selection bias. In the Fakhry report, the healthier patients and the patients with smaller tumors, who were selected to receive surgery, likely have a greater probability of achieving a better outcome, regardless of intervention, simply as a result of better overall health and the smaller size of the tumor. Criteria that led to patient selection for tonsillectomy over biopsy alone are not provided in their report. Most registry-based retrospective studies lack information on surgical techniques used. Oncologic resection may range from radical tonsillectomy to composite resection or transoral robotic surgery. The goal in these procedures is generally to obtain negative margins; however, it is not yet known whether or not the same criteria should be used in prophylactic tonsillectomies as well.

The clinical implications of remote tonsillectomy are still unknown, because surgical intervention does not address the entire anatomic area at risk; patients still have a risk of cancer in the base of the tongue, as indicated in the Fakhry study. Most importantly, a reduction in the risk of tonsillar cancer development seen in those patients likely does not result in a biologic or immune effect, as reduction in cancer of the base of the tongue would have been seen. It is likely a simple removal of volume at risk. As presented by Joseph and colleagues (11), patients with tonsillar cancers that develop a second primary tumor in the contralateral tonsil harbor the same HPV variant suggestive of multifocal exposure to HPV, and carcinogenesis at distant anatomical sites may be possible, for example, in the base of the tongue. Multifocal exposure can be attributed to many possibilities. First, a constant contact to an external reservoir, e.g., the same sexual partner, may result in a second inoculation event, as described by Haddad and colleagues (12). Second, there may be a clonal expansion and migration of HPV-infected cells to other sites across extended tracts of Waldeyer's ring. Finally, there is a possibility in which multiple independent infections from several high-risk HPV types and/or variants occur in distinct areas of the oropharynx. Currently, there is no evidence in which tonsillectomy would lead to immune or biologic changes of Waldeyer's

ring that decrease the incidence of OPX cancer in other oropharyngeal anatomic sites. Therefore, unless tonsillectomy is paired with an easily accessible biomarker tested in a prospective study, prophylactic tonsillectomy should still remain investigational, even in high-risk patients. Current epidemiological studies define a high-risk patient based on an increased number of oral sex partners instead of on the basis of an objective biomarker, and the current model does not take into account that 80% of OPX occurs in people who are not promiscuous or the constant reexposure and exchange in monogamous couples (13). As reported by D'Souza and colleagues (13), the prevalence of HPV16 infection detected in saliva samples of 5,579 men and women ages 14 to 69 years was 1.0% (95% CI, 0.7%–1.3%). This prevalence corresponds to an estimated 2.13 million infected subjects in United States (14). Importantly as reported by others, HPV16 seropositivity is present years before diagnosis in OPX cancer patients; therefore, even high-risk patients without OPX cancer should be evaluated carefully and presented with alternatives such as surveillance before undergoing an irreversible surgical intervention (14, 15).

Per current guidelines for breast cancer, most experts consider prophylactic bilateral mastectomy too drastic for the moderate level of risk associated with lobular carcinoma *in situ* in the absence of other contributory risk factors; thus, prophylactic bilateral rather than unilateral mastectomy is recommended only for high-risk patients, which represents resection of all the anatomic sites at risk. However, there are no randomized trials addressing the comparative efficacy of surveillance versus prophylactic mastectomy in a population of high-risk women. A randomized clinical trial addressing biomarkers for HPV identifying high-risk patients undergoing either active surveillance or bilateral tonsillectomy could potentially provide more concrete data on the role of bilateral tonsillectomy as a surgical preventive strategy. Some of the currently reported strategies using biomarkers obtained from body fluid, such as serum and saliva, show promise and can be considered in future trials in healthy populations (5, 6, 16–18). In the Denmark Registry Study by Fakhry and colleagues, the majority of tonsillectomies were done in persons under the age of 20, and in the United States a large number of tonsillectomies were done in children over 15 years of age (8). Gardasil, a vaccine for use in the prevention of certain strains of HPV, was approved in the United States on June 8, 2006, by the FDA for girls and in October 2009 for males ages 9 to 26 (19). The question remains, however: "What is the role of prophylactic tonsillectomy in patients that received a HPV vaccine?" It is a well-known fact that vaccination rates among boys and young men are much lower than those for girls (14% in 2013) but have been increasing since the recommendation was issued in 2011. In the United States, the vaccination rate for males ages 13 to 17 was 1.3% in 2011 and 7% in 2012 (20). In Europe, vaccination rates are approximately 17%, although some countries, such as Great Britain and Portugal, have vaccination rates as high as 80% (21). As the number of HPV vaccination increases, prophylactic tonsillectomy may become unnecessary (22).

In conclusion, the decision-making process about risk-reducing bilateral tonsillectomy, which may be influenced by many conflicting parameters, such as the patient's fears and desire to achieve a survival advantage and the medical community's orientation toward action should be done with caution. Due to the potential for overinterpretation of current data on this subject, it is mandatory for otolaryngologists to take a conservative approach and

not recommend tonsillectomy as a prophylactic measure until further investigation provides better evidence based guidance. In light of the lack of the data and knowledge on the topic but also overall public awareness, in order to ensure patient safety, bilateral prophylactic tonsillectomy should only be offered in the context of prospective clinical trials that are based more on biomarker endpoints rather than patients' fears, especially in

current media-dominated world with reports on public figures such as Angelina Jolie that underwent cancer-preventive surgery.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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