

Review

# Tonsillectomy as Prevention of Tonsil and Base of Tongue Cancer: Systematic Review and Meta-analysis on the Immuno-Oncological Effect of One Among the Most Common Surgeries in the World

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**Abstract.** Otorhinolaryngology tradition is that tonsillectomy (TE) is conducted among children and adolescents for obstructive sleep apnea secondary to adenotonsillar hypertrophy and in adults for chronic disease of the tonsils and adenoids (recurrent tonsillitis). Nevertheless, over the last 50 years, we have observed a decline in TE worldwide. As a result, there is an emerging concern of a correlated possible increased risk of tonsil cancer (TC) and other subtypes of oropharyngeal squamous cell carcinoma. Since the available data on such topics are limited and controversial, our aim was to elucidate the impact of TE on the incidence mainly of TC through a systematic review of the literature and a meta-analysis of the studies. After a thorough search, 7 retrospective studies were considered eligible for review and meta-analysis (MA). At MA, patients with a history of TE seem to show a reduced risk of TC but a higher predisposition for base of tongue (BOT) cancer ( $p < 0.001$ ): however, the elevated heterogeneity of the studies hampers drawing firm and convincing conclusions (statistical inconsistency >95%). In future, randomized control trials will be welcome to elucidate the prophylactic role of TE against TC and its real impact on BOT cancer.

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**Key Words:** Tonsil cancer, base of tongue cancer, oropharyngeal cancer, tonsillectomy, prevention, review.



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Reporting on the exact number of tonsil cancers (TCs), oropharyngeal cancers (OPCs or OPSCCs) as well as tonsillectomies (TEs) occurring in the world yearly is not a simple task. Concerning the oncologic dimension, the GLOBOCAN estimates of cancer incidence and mortality produced in 2018 and 2020 by the International Agency for Research on Cancer did not analyze TC specifically and independently but together with other tumors [involving the base of tongue (BOT), soft palate, lateral and posterior pharyngeal walls] under a single, potentially nonspecific category labeled “oropharynx” (1, 2). OPCs, however, are well separated from other head and neck cancers (HNCs) which are categorized on the anatomic basis in the oral cavity-lip, larynx, nasopharynx, and hypopharynx (1, 2). The same criteria are followed by the National Comprehensive Cancer Network 2023 Guidelines for the treatment of HNCs (3). Comparing the two last versions of GLOBOCAN, OPC showed higher incidence (from 92887 in 2018 to 98412 cases in 2020) and lower mortality (51005 events in 2018 versus 48143 in 2020) (1, 2). Starting from such estimates, considering that it represents the most common form of OPC (23.1% of cancers in the oropharyngeal cavity), TC is supposed to have increased worldwide passing from 21,456 cases in 2018 to 22,733 cases in 2022 (4). Main risk factors include tobacco smoke, alcohol use and oral HPV infection (4). In comparison with TC estimates, reporting accurately on the real frequency of TE procedure throughout the world is even harder to assess: in fact, excluding few virtuous examples such as the United States, European Union, South Africa, Australia, Japan and Ontario (where, respectively, TEs are over 500,000, 400,000, 390,000, 50,000, 32,000, and 14,000 annually) (5-10), the vast majority of the world (China, Russia, India, Brazil, Mexico and so on)

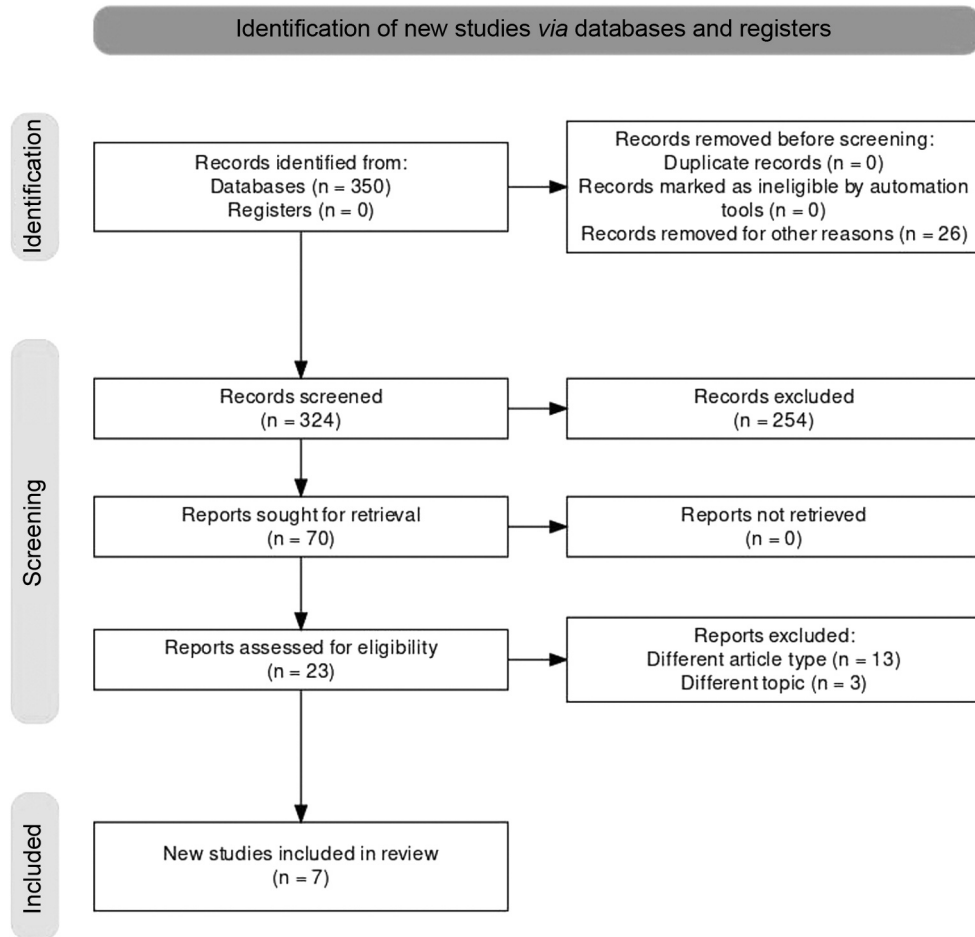


Figure 1. Work flowchart of the process and results of articles selection for our systematic review and meta-analysis using the PRISMA 2020 V2 indications.

usually does not publish the number of TEs. Despite such omitted data, in 2019 TE was the twelfth most common surgical procedure in the world (11, 12). Certainly, upper airway obstruction and recurrent infections represent the leading indications to TE in children (13). What is less known about TE, however, is its relationship with cancer (14). TE, in fact, has been described with different and conflicting connotations and summarizing the relationship between TE and cancer from the available international literature is a very laborious task (14-19). Over the course of years, in fact, TE has been advocated on the one hand as a remedy for epithelial or lymphatic (lymphoma) cancer of the tonsils and on the other hand as a causative agent of various malignancies affecting several anatomic systems including the head, neck and the oropharynx (14-19). The aim of our systematic review and meta-analysis was to assess the oncologic significance and prophylactic role of a previous TE (performed not for cancer but for other ear-nose-throat disorders) in decreasing the risk of TC.

## Materials and Methods

We burrowed into the world literature written in English and dealing with the risk of TC (squamous cell carcinoma of the tonsils) in patients with or without a former TE conducted not for oncologic reasons. All the other types of tonsillar malignancies (such as hematologic neoplasms) as well as associations between TE and other kinds of epithelial tumors (such as breast or gastrointestinal cancer) were excluded. Databases of PubMed/MEDLINE, Scopus, Cochrane Library (Cochrane Database of Systematic Reviews, Cochrane Central Register of Controlled Trials-CENTRAL), Web of Science (Science and Social Science Citation Index), ResearchGate, Publons and Google Scholar were used to identify articles of interest. We used the following keywords and key-expressions for the search: prophylactic tonsillectomy cancer, preventive tonsillectomy cancer, post tonsillectomy cancer, tonsillectomy cancer. Only original major studies (trials, prospective or retrospective works) were entertained and included in the systematic review and meta-analysis. Case reports, editorials, letters, and former reviews were excluded. To improve the reporting quality of our search, we resorted to a flow

diagram following the PRISMA 2020 Explanation and Elaboration Document (20). The meta-analysis of the included studies was conducted through MedCalc® Statistical Software version 22.006 (MedCalc Software Ltd, Ostend, Belgium, 2023).

**Results**

The process and results of article selection for our systematic review and meta-analysis are presented with a work flowchart according to the PRISMA 2020 V2 indications (Figure 1). After an initial review of 234 studies, 23 articles were finally considered. Of these, 16 were excluded for non-scientific nature of the studies (editorials) or because the focus was on cancers different from TC. As of 2023, no meta-analysis of studies on TC risk after TE exists. Therefore, seven studies were eventually included in the systematic review: they were all population-based retrospective cohort studies (21-27). The results of our literature review are presented in Table I. Of note, two studies witnessed the progressive reduction in performing TE [33.8% less in Denmark in 35 years (21); 40-50% less in Sweden in 39 years (23)] and the constant increase of TC rate both in TE and in not previously tonsillectomized subjects ( $p<0.001$ ) (23). Of interest, only one research found a statistically significant association between cancers (TC and/or BOT) and HPV/P16 presence ( $p<0.0001$ ) (25), whereas two other studies did not find any correlation (24, 26). All the seven reviewed studies were then considered for meta-analysis and the results are presented in Table II, Table III, Table IV, Table V, Figure 2, Figure 3, and Figure 4. More precisely, Table II, Figure 2, and Table III and Figure 3 show the odds ratio (OR) of developing TC in TE patients [considering, respectively, all the tonsillectomized (TE) patients -OPC and control groups- or just the subgroups of TC patients with or without history of TE]. Five and four studies, respectively, showed that TE patients are at lower risk ( $OR<1$ ) of developing TC ( $p<0.001$ ); however, the elevated heterogeneity (inconsistency) (99.54% and 96.12%) of the analysis affects the reliability of the results. Table III-Figure 4 and Table IV-Figure 5 illustrate the risk (OR) of BOT in TE subjects (considering, respectively, all the TE patients -OPC and control groups- or just the subgroups of BOT with or without history of TE). In this meta-analysis, three (Figure 4) and four studies (Figure 5) showed that TE patients are at higher risk ( $OR>1$ ) of developing BOT cancer ( $p<0.001$ ). Also in these cases, however, the elevated heterogeneity of the studies (99.47% and 97.68%, respectively) affects the validity of the results.

**Discussion**

Starting from the observation of a male adult patient (recovered at our service from an acute appendicitis) tonsillectomized thirty years and complaining now with a three-month history of a painless laterocervical swelling,

Table I. Systematic review of the literature dealing with the risk of tonsil and base of tongue cancer in tonsillectomized patients.

Ref	Year	Country	Study type	Time	Year from TE	TE	TC	TC/TE	TC/TE TE	BOT	BOT/TE	BOT/TE TE	Age	M Sex %	Alcohol %	Tobacco %	HPV-P16 status	TC/BOT RISK
21	2015	Denmark	R	1977-2012	0	90,755	2788	135	2608	753	26	727	59	n.a.	n.a.	n.a.	n.s.	Reduced $p<0.01$ / Higher $p<0.05$ Higher $p=0.06$ / n.s.
22	2015	Taiwan	R	2000-2005	1	997	12	4	8	12	4	8	39	56	n.a.	n.a.	n.s.	Reduced $p<0.05$ / NSS
23	2016	Sweden	R	1970-2009	0	225,718	80	80	n.s.	31	31	0	18	47	n.a.	n.a.	n.s.	Reduced $p<0.001$ / Higher $p=0.003$ Reduced $p<0.0001$ / NSS
24	2016	US	R	2002-2006	1	544	198	22	173	108	56	49	60	83	NSS	100	NSS	Reduced $p<0.001$ / Higher $p=0.003$ Reduced $p<0.0001$ / NSS
25	2020	US	R	1996-2013	5	230	62	4	58	47	28	25	555	88	n.a.	NSS	104+ vs. 11- $p<0.0001$	Reduced $p<0.01$ / Higher $p=0.001$ Reduced $p<0.0001$ / Reduced $p<0.0001$ / Reduced $p<0.0001$ / Reduced $p<0.0001$
26	2021	France	R	2013-2018	15	331	85	16	66	76	35	36	59	71	70.6 (NSS)	NSS	NSS	Reduced $p<0.01$ / Higher $p=0.001$ Reduced $p<0.0001$ / Reduced $p<0.0001$
27	2023	US	R	2010-2021	1	3,620	995	58	937	964	26	938	60	81	n.a.	n.a.	n.a.	Reduced $p<0.0001$ / Reduced $p<0.0001$

Ref: Reference; TE: number of tonsillectomies; Year from TE: number of years after TE; TC: number of tonsil cancers; TC/TE: number of TC in TE patients; TC/no TE: number of TC in patients without history of TE (control group); TC BOT: base of tongue cancer; Age: median age in years; M Sex %: percentage of male sex; Alcohol: percentage of alcohol users; HPV-P16 status: status of human papilloma virus or P16 in association with TC/BOT cancers; R: population-based retrospective cohort study; n.a.: not assessed; n.s.: not studied; NSS: not statistically significant ( $p>0.05$ );  $p$ -values  $\leq 0.05$ : statistically significant.

Table II. Meta-analysis of studies on the occurrence of tonsil cancer in formerly tonsillectomized patients (considering all the oropharyngeal cancers).

Study	Intervention	Controls	OR	95%CI	z	p-Value	Fixed	Random
Fakhrt <i>et al.</i> 2015	135/90,755	2,608/4,825	0.00127	0.0010-0.00151			57.73	16.92
Sun <i>et al.</i> 2015	4/997	8/3,996	2.008	0.603-6.682			1.27	16.23
Zevallos <i>et al.</i> 2016	22/544	173/1,000	0.201	0.128-0.318			8.76	16.83
Altenhofen <i>et al.</i> 2020	4/230	58/83	0.00763	0.00255-0.0228			1.53	16.35
Combes <i>et al.</i> 2021	16/331	66/628	0.433	0.246-0.760			5.77	16.77
Alharbi <i>et al.</i> 2023	58/3,620	937/2,895	0.0340	0.0260-0.0446			24.94	16.90
Total (fixed effects)	239/96,477	3,850/13,427	0.0146	0.0125-0.0170	-54.04	<b>&lt;0.001</b>	100.00	100.00
Total (random effects)	239/96,477	3,850/13,427	0.0612	0.00564-0.663	-2.298	<b>0.022</b>	100.00	100.00

Test for heterogeneity

Q	DF	Significance level	I <sup>2</sup> (inconsistency)	95% CI for I <sup>2</sup>
1,092.2	5	<b>p&lt;0.0001</b>	99.54%	99.42-99.64

OR: Odds ratio; CI: confidence interval; z: Z-score; Fixed/Random: percentage of weight; Q: the weighted sum of squares on a standardized scale; DF: degree of freedom; statistically significant p-values (≤0.05) are shown in bold.

Table III. Meta-analysis of studies on the occurrence of tonsil cancer in formerly tonsillectomized patients (considering tonsil cancer only).

Study	Intervention	Controls	OR	95%CI	z	p-Value	Fixed	Random
Fakhrt <i>et al.</i> 2015	135/226	2,608/4,825	1.261	0.961-1.655			37.87	18.14
Sun <i>et al.</i> 2015	4/998	8/3,996	2.006	0.603-6.675			1.94	14.24
Zevallos <i>et al.</i> 2016	22/573	173/1,000	0.191	0.121-0.301			13.42	17.66
Altenhofen <i>et al.</i> 2020	4/32	58/83	0.0616	0.0195-0.194			2.12	14.54
Combes <i>et al.</i> 2021	16/331	66/628	0.433	0.246-0.760			8.82	17.30
Alharbi <i>et al.</i> 2023	58/725	937/2,895	0.182	0.137-0.240			35.84	18.12
Total (fixed effects)	239/2,885	3,850/1,342	0.364	0.313-0.424	-13.014	<b>&lt;0.001</b>	100.00	100.00
Total (random effects)	239/2,885	3,850/1,342	0.364	0.140-0.945	-2.076	<b>0.038</b>	100.00	100.00

Test for heterogeneity

Q	DF	Significance level	I <sup>2</sup> (inconsistency)	95%CI for I <sup>2</sup>
129.0277	5	<b>p&lt;0.0001</b>	96.12%	93.69-97.62

OR: Odds ratio; CI: confidence interval; z: Z-score; Fixed/Random: percentage of weight; Q: the weighted sum of squares on a standardized scale; DF: degree of freedom; statistically significant p-values (≤0.05) are shown in bold.

which eventually resulted to a TC, our research team commenced to investigate the relationship between TE and TC through the pertinent world literature. Data from Western countries shows that the rate of TE has progressively decreased up to 50% in the last decades (21, 23, 27). The main reason for this decline resides in the fact that over the years most pediatric TE conducted for recurrent tonsillitis began to be widely considered unnecessary by the medical community because of ambiguous supportive evidence (28, 29) and, as an invasive surgical procedure, potentially risk-carrier (25). In 2015, Fakhry and colleagues pioneered the investigation on the association between TE and OPC and in particular the risk of TC and BOT cancer in TE patients: they demonstrated that TE, formerly conducted for non-oncological reasons, was a

preventive factor of TC and OPC at age <60 years (p<0.01) but, at the same time, a condition of higher risk of BOT cancer for TE subjects aged more than 60 years (p<0.05) (21). Their findings had an immediate worldwide repercussion in the scientific community being followed by other retrospective studies, literature reviews, case reports and commentaries coming from several parts of the world (19, 22-27, 30, 31). As demonstrated by our literature systematic reviews and meta-analysis, data on the correlation between TE and TC/BOT available as of 2023 are in keeping with the results first discussed by Fakhry: a former “ordinary” TE (conducted one or more years before for chronic benign disorders of tonsils and adenoids) seem to reduce the risk of developing future TC but, at the same time, it could increase the odds of BOT

Table IV. Meta-analysis of studies on the occurrence of base of tongue cancer in formerly tonsillectomized patients (considering all the oropharyngeal cancers).

Study	Intervention	Controls	OR	95%CI	z	p-Value	Fixed	Random
Fakhr <i>et al.</i> 2015	26/90,755	727/4,825	0.00162	0.00109-0.00239			24.20	16.76
Sun <i>et al.</i> 2015	4/997	8/3,996	2.008	0.603-6.682			2.58	16.29
Zevallos <i>et al.</i> 2016	56/544	49/1,000	2.227	1.495-3.318			23.45	16.76
Altenhofen <i>et al.</i> 2020	28/230	25/83	0.322	0.174-0.594			9.91	16.68
Combes <i>et al.</i> 2021	35/331	36/628	1.944	1.196-3.160			15.80	16.73
Alharbi <i>et al.</i> 2023	26/3,620	938/2,895	0.0151	0.0102-0.0224			24.06	16.76
Total (fixed effects)	175/96,477	1,783/1,342	0.0586	0.0506-0.0679	-37.786	<b>&lt;0.001</b>	100.00	100.00
Total (random effects)	175/96,477	1,783/1,342	0.200	0.0130-3.071	-1.155	0.248	100.00	100.00

Test for heterogeneity

Q	DF	Significance level	I <sup>2</sup> (inconsistency)	95%CI for I <sup>2</sup>
949.6464	5	<b>p&lt;0.0001</b>	99.47%	99.32-99.59

OR: Odds ratio; CI: confidence interval; z: Z-score; Fixed/Random: percentage of weight; Q: the weighted sum of squares on a standardized scale; DF: degree of freedom; statistically significant ( $\leq 0.05$ ) p-values are shown in bold.

Table V. Meta-analysis of studies on the occurrence of base of tongue cancer in formerly tonsillectomized patients (considering base of tongue cancer only).

Study	Intervention	Controls	OR	95% CI	z	p-Value	Fixed	Random
Fakhr <i>et al.</i> 2015	26/226	727/4,825	0.733	0.483-1.111			24.01	17.22
Sun <i>et al.</i> 2015	4/998	8/3,996	2.006	0.603-6.675			2.88	15.51
Zevallos <i>et al.</i> 2016	56/573	49/1,000	2.102	1.412-3.130			26.24	17.24
Altenhofen <i>et al.</i> 2020	28/32	25/83	16.240	5.153-51.178			3.16	15.66
Combes <i>et al.</i> 2021	35/331	36/628	1.944	1.196-3.160			17.62	17.13
Alharbi <i>et al.</i> 2023	26/725	938/2,895	0.0776	0.0521-0.116			26.10	17.24
Total (fixed effects)	175/2,885	1,783/1,342	0.450	0.380-0.533	-9.253	<b>&lt;0.001</b>	100.00	100.00
Total (random effects)	175/2,885	1,783/1,342	1.340	0.328-5.474	0.407	0.684	100.00	100.00

Test for heterogeneity

Q	DF	Significance level	I <sup>2</sup> (inconsistency)	95% CI for I <sup>2</sup>
949.6464	5	<b>p&lt;0.0001</b>	99.47%	99.32-99.59

OR: Odds ratio; CI: confidence interval; z: Z-score; Fixed/Random: percentage of weight; Q: the weighted sum of squares on a standardized scale; DF: degree of freedom; statistically significant p-values ( $\leq 0.05$ ) are shown in bold.

cancer (21-27) (Table I, Table II, Table III, Table IV, Figure 2, Figure 3, and Figure 4). While for some authors this phenomenon remains unclear (24), others speculate on oropharyngeal anatomopathobiology. Patients with palatine TE would show a reduction in the tissue susceptible to oral HPV exposure, infection and, at last, malignant transformation of squamous cell carcinoma. At the same time, however, the absence of immunological tonsil-specific tissue in the context of smoking (which is independently immunosuppressive), alcohol and, again, HPV, could aggravate the loss of the local immune response and, therefore, the oropharyngeal immunosuppressive status increasing the risk of lingual

tonsillar hypertrophy and, eventually, BOT cancer (21, 23, 25, 27, 32). In contrast Alharbi *et al.*, demonstrated in 2023 a statistically significant reduction both of TC and BOT cancer in 3,620 individuals subjected to TE (27). According to them, in fact, being the largest lymphoid tissues within the Waldeyer's ring, the palatine tonsils represent major reservoirs for microorganisms (including HPV) in the oropharyngeal region: removal of such structures can eradicate these microbes, infections and cancer risks. Furthermore, Alharbi and colleagues interestingly did not find any increased incidence of lingual cancer, as well as any altered rate of lingual hypertrophy (27). The risk of TC in individuals

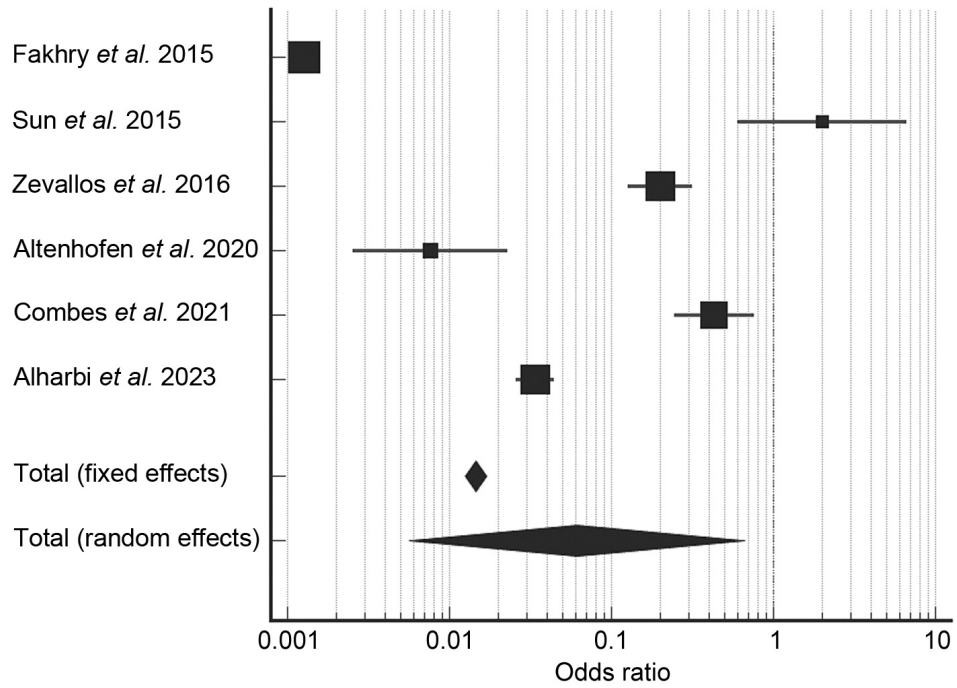


Figure 2. Meta-analysis (Forest plot) of the examined studies showing the odds ratios of tonsillectomized patients to develop tonsil cancer (considering all the oropharyngeal cancers).

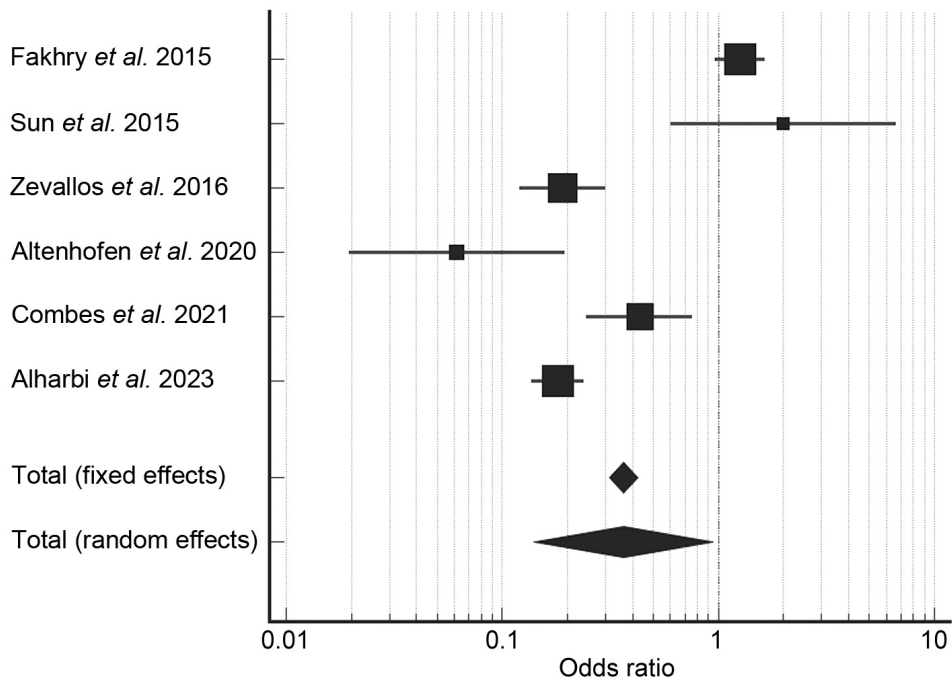


Figure 3. Meta-analysis (Forest plot) of the examined studies showing the odds ratios of tonsillectomized patients to develop tonsil cancer (considering tonsil cancer only).

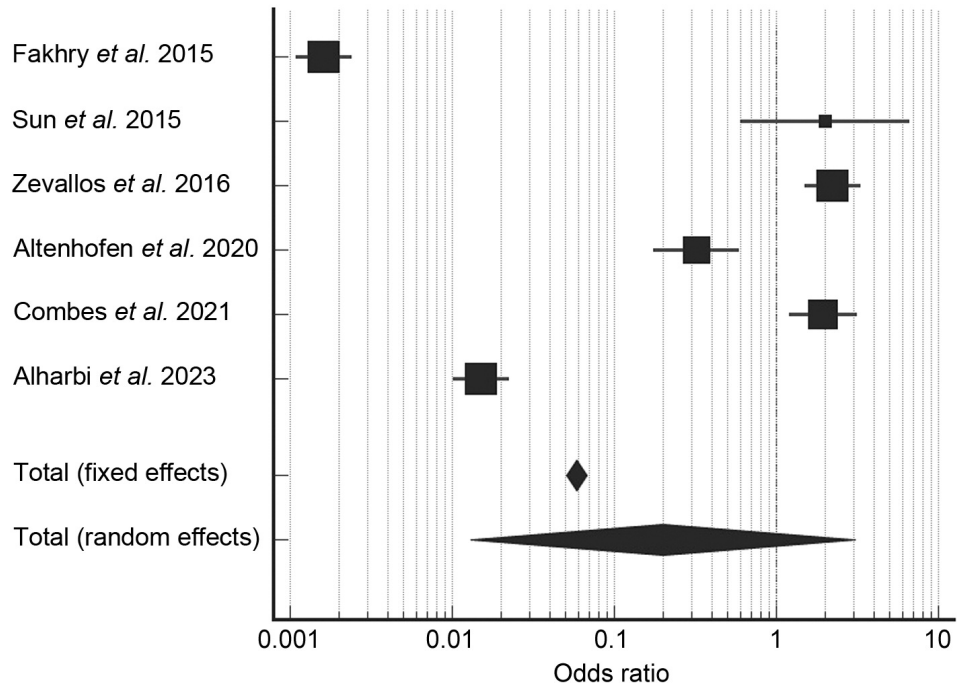


Figure 4. Meta-analysis (Forest plot) of the examined studies showing the odds ratios of tonsillectomized patients to develop base of tongue cancer (considering all the oropharyngeal cancers).

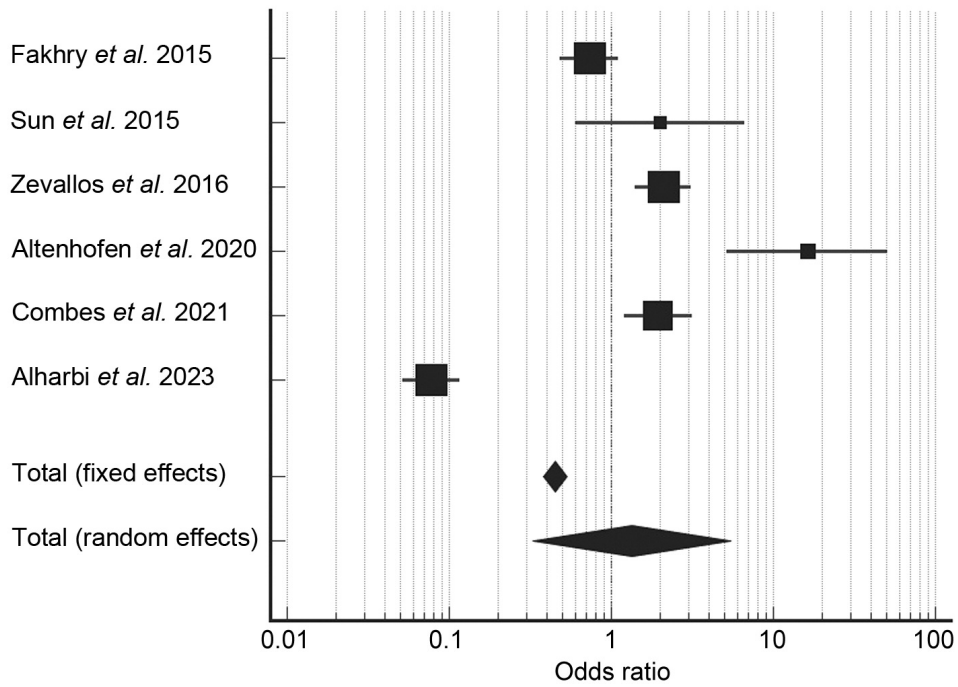


Figure 5. Meta-analysis (Forest plot) of the examined studies showing the odds ratios of tonsillectomized patients to develop base of tongue cancer (considering base of tongue cancer only).

subjected to TE with or without oral HPV infection is another topic deserving clarification: data on HPV-p16 status was available only in 3 of 4 studies (25-27) and the association was not statistically significant in two (25, 27). Incomplete removal of the tonsils at the time of original TE and resorting to a modern surgical approach (robotic tonsillectomy) can further impact the risk of OPC (including TC and BOT cancer) in tonsillectomized individuals (25, 33). Undoubtedly, the main limit of our systematic review and meta-analysis is represented by the retrospective nature of the studies dealing with this subject. The reliability of our findings depends on the quality and quantity of features, items, aims and survivals established and analyzed (or not analyzed) in every single study. The elevated heterogeneity (>95%) among the examined studies encountered with our tests heavily affects the results and does not allow us to reach any firm conclusion. In the future, we hope that randomized control trials (RCTs) will be conducted on the immune-oncologic role of TE to better assess the anti-cancer potential of this surgery and the validity of our meta-analysis.

## Conclusion

Prophylactic HPV vaccination may contribute to curbing the current worldwide increasing trend of TC, which is determined by oral HPV infection, tabagism, alcohol consumption and, at last, general reduction in surgery of TE. RCTs investigating such a topic could corroborate the results found through our meta-analysis clarifying the relationship between TE and the risk of TC and BOT cancer.

## Conflicts of Interest

The Authors declare no conflicts of interest in relation to this study.

## Authors' Contributions

All the Authors agreed with the content of the article. Dr. Virgilio conceived the presented research and wrote the manuscript. Dr. Virgilio, Dr. Bonfili, Dr. Bettoni, Dr. Vona, Dr. Mercuri and Dr. D'Agostino reviewed the literature and selected the articles to be included in the present work. Dr. Salvemini supervised the review phase. Dr. Virgilio, Dr. Baldinu and Dr. Montali performed the statistical analysis. Dr. Virgilio and Prof. Costi supervised the entire project.

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*Received June 11, 2023*

*Revised July 12, 2023*

*Accepted July 14, 2023*