

Increased risk of appendectomy due to appendicitis after tonsillectomy in women

A longitudinal follow-up study using a national sample cohort

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Abstract

The purpose of this study was to evaluate the risk of appendectomy due to appendicitis after tonsillectomy in Koreans using national cohort data. Using the national cohort study from the Korean Health Insurance Review and Assessment Service, 1:4 matched tonsillectomy participants (9015) and control participants (36,060) were selected. The Cox-proportional hazard model was used. In this analysis, a crude and adjusted model for age, sex, income, region of residence, and the past medical histories of hypertension, diabetes mellitus, and dyslipidemia were used. For the subgroup analyses, the participants were divided as follows: children (≤ 14 years old) vs adolescents and adults (≥ 15 years old) and men vs women. The adjusted hazard ratio (HR) of tonsillectomy for appendectomy was 1.06 (95% confidence interval, CI=0.89–1.27, $P = .517$). In the subgroup analysis, the HR was 1.03 (95% CI=0.82–1.30, $P = .804$) in children and 1.10 (95% CI=0.84–1.47, $P = .468$) in adolescents and adults. In another subgroup analysis, the HR was 0.89 (95% CI=0.70–1.12, $P = .314$) in men and 1.39 (95% CI=1.06–1.83, $P = .018$) in women. The risk of appendectomy was higher in the tonsillectomy group but only in women.

Abbreviations: CI = confidence interval, HIRA-NPS = Korean Health Insurance Review and Assessment Service–National Patient Sample, MALT = mucosa-associated lymphoid tissue, NHIS = Korean National Health Insurance Service, NRF = National Research Foundation, OR = odds ratio.

Keywords: abscess, appendectomy, appendicitis, appendix, gender, intraabdominal infection, sex, tonsillectomy

1. Introduction

The tonsils and appendix are part of the mucosa-associated lymphoid tissue, which is a type of secondary lymphoid tissue that provides a defensive barrier against foreign pathogens.^[1] Tonsillectomy and appendectomy (the removal of these tissues) are commonly performed procedures in children and adolescents.^[2,3] Our previous study reported that the prevalence of tonsillectomy was 2.58 per 1000 individuals under 16 years of

age in Korea.^[2] The prevalence of appendectomy was reported as 1.64 per 1000 individuals in Korea.^[3]

The alteration of immunologic function after tonsillectomy and appendectomy has been reported, although the results are controversial. For instance, 1 study found that tonsillectomy and appendectomy lead to secretory immunoglobulin A deficiency,^[1] whereas another study reported that tonsillectomy does not compromise immune function in children.^[4] Tonsillectomy and appendectomy have also been reported to be risk factors for other diseases. The removal of the tonsils and adenoids increases the risk of premature acute myocardial infarction,^[5] and tonsillectomy and appendectomy are more common in patients with Crohn's disease.^[6]

Based on these findings, it is possible that tonsillectomy is related to appendectomy, as both involve the mucosa-associated lymphoid tissue system. It means that the loss of tonsil as the gatekeeper to the digestive track might decrease the defense ability to the pathogen.^[1] Due to the loss of prior immune organ (tonsil), appendix may contact pathogen more, and be inflamed more frequently. We hypothesized that the removal of the tonsil may increase the risk of appendicitis and consequently appendectomy. To complement our hypothesis, we reviewed PubMed and Embase using the term “tonsillectomy, appendectomy, and/or appendicitis” and limited the results to articles written in English. We found only 2 studies that matched these criteria. One case–control study reported that the odds ratio (OR) of tonsillectomy for appendectomy was 2.97 (95% confidence interval, CI=1.82–4.82). This study also reported a more significant association between tonsillectomy and appendectomy in females (OR=5.20, 95% CI=2.91–9.28).^[7] However, a cohort study reported that tonsillectomy did not increase the risk of appendectomy (OR=1.4, 95% CI=0.7–2.8, $P = .58$),

Editor: Kou Yi.

SYK and CM contributed equally to this work.

The authors have no funding and conflicts of interest to disclose.

Supplemental Digital Content is available for this article.

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Medicine (2019) 98:19(e15579)

Received: 6 January 2019 / Received in final form: 10 April 2019 / Accepted: 11 April 2019

<http://dx.doi.org/10.1097/MD.00000000000015579>

although these authors described a moderately increased risk of appendectomy in women (OR=1.9, 95% CI=0.7–5.3, $P = .21$).^[8] Both studies reported no association between adenoidectomy and appendicitis.

The purpose of this study was to evaluate the risk of appendectomy due to appendicitis after tonsillectomy in Koreans using national cohort data. We planned a subgroup analysis according to sex because previous studies have reported a more significant association between tonsillectomy and adenoidectomy in women.^[7,8] In this study, we matched the participants with tonsillectomy to participants without tonsillectomy (controls) for age, sex, income, region of residence, and the past medical histories of hypertension, diabetes mellitus, and dyslipidemia. Our study may help elucidate the unclear results of previous investigations.

2. Methods

2.1. Study population and data collection

The ethics committee of Hallym University (2017-1102) approved the use of these data. Written informed consent was exempted by the Institutional Review Board.

This national cohort study relied on data from the Korean Health Insurance Review and Assessment Service – National Patient Sample (HIRA-NPS). The detailed description of this data was described in our previous studies.^[9,10]

2.2. Participant selection

Out of 1,025,340 cases with 114,369,638 medical claim codes, we included participants who underwent tonsillectomy (claim

code: Q2300) from 2002 through 2013 ($n = 9,219$). Among these, participants who underwent tonsillectomy for malignancies were excluded ($n = 63$). Hence, only participants who underwent tonsillectomy for benign causes (e.g., chronic tonsillitis, chronic tonsillar hypertrophy, and obstructive sleep apnea) were included. The participants who had a history of appendectomy before the tonsillectomy were excluded ($n = 120$). The tonsillectomy participants were matched 1:4 with participants (control group) in this cohort who did not undergo tonsillectomy from 2002 through 2013 (11 years). The control participants were extracted from a total of 1,025,340 participants. The matches were processed for age, group, sex, income group, region of residence, and the past medical histories of hypertension, diabetes mellitus, and dyslipidemia. To prevent selection bias when selecting the matched participants, the control group participants were sorted using a random number order, and they were then selected from top to bottom. It was assumed that the matched control participants were involved at the same time (index date = tonsillectomy date) as each matched tonsillectomy participant. Therefore, in the control group, participants who had a history of any appendectomy before the index date were not included; 21 tonsillectomy participants were excluded due to lack of control group. Ultimately, the 1:4 matching resulted in the inclusion of 9,015 tonsillectomy participants and 36,060 control participants (Fig. 1).

2.3. Variables

The age groups were classified using 5-year intervals as follows: 0–4, 5–9, 10–14, . . . , and 70+ years. In total, 15 age groups

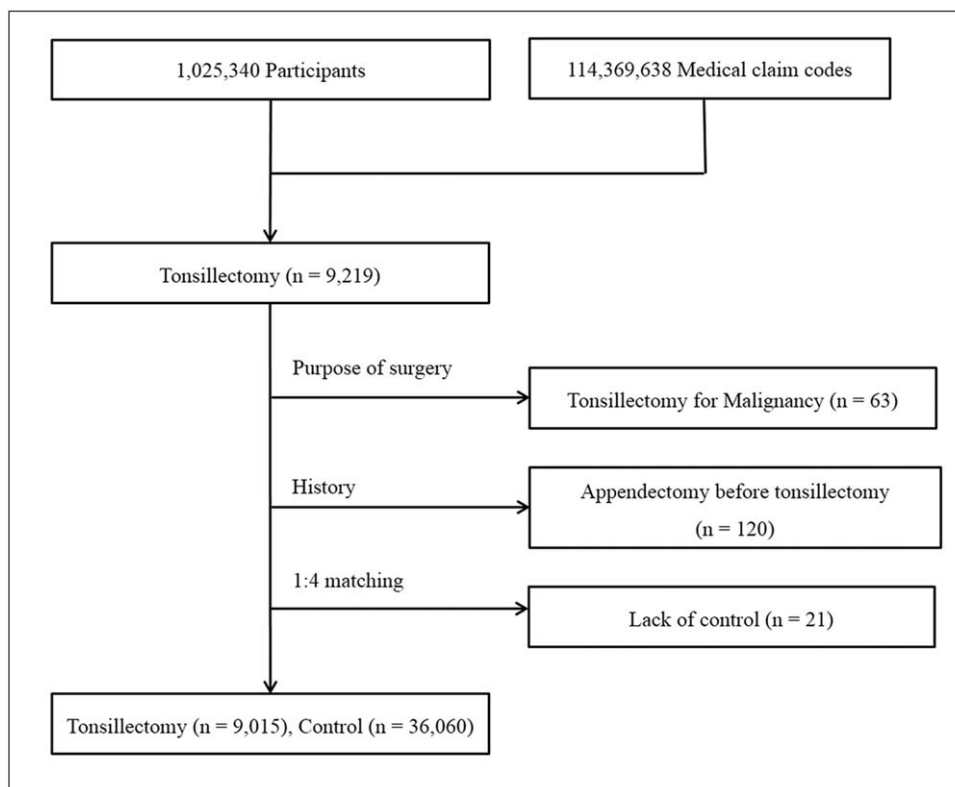


Figure 1. Schematic illustration of the participant selection process used in the present study. Of the 1,025,340 participants, 9,219 tonsillectomy participants were selected. After the removal of unconditioned participants ($n = 204$), 9,015 tonsillectomy participants and 36,060 control participants were included.

were designated. The income groups were initially divided into 41 classes (1 health aid class, 20 self-employment health insurance classes, and 20 employment health insurance classes). These groups were recategorized into 5 classes (class 1 [lowest income] to 5 [highest income]). The region of residence was divided into 16 areas according to administrative district. These regions were regrouped into urban (Seoul, Busan, Daegu, Incheon, Gwangju, Daejeon, and Ulsan) and rural (Gyeonggi, Gangwon, Chungcheongbuk, Chungcheongnam, Jeollabuk, Jeollanam, Gyeong-sangbuk, Gyeongsangnam, and Jeju) areas.

The participants' prior medical histories were evaluated using International Classification of Disease-10 codes. To ensure an accurate diagnosis, hypertension (I10 and I15), diabetes (E10–E14), and dyslipidemia (E78) were regarded as present if a participant was treated ≥ 2 times.

Appendectomies were identified using operation codes (Q2860–Q2863). Appendectomy for only appendicitis (International Classification of Disease-10: K35) was included.

2.4. Statistical analyses

Chi-square test was used to compare the general characteristics and rates of appendectomy.

To analyze the survival function of appendectomy due to tonsillectomy, the Kaplan–Meier method was used. To analyze the hazard ratio (HR) of tonsillectomy to appendectomy, the Cox-proportional hazard model was used. In this analysis, a crude and adjusted model for age, sex, income, region of residence, and the past medical histories of hypertension, diabetes mellitus, and dyslipidemia were used, and the 95% CI was calculated. In these analyses, age and income group were used as the continuous variable despite they are actually categorical variable. For the subgroup analyses, the participants were divided as follows: children (≤ 14 years old) vs adolescents and adults (≥ 15 years old) and men vs women. Two-tailed analyses were conducted, and *P* values less than 0.05 were considered to indicate significance. The results were statistically analyzed using SPSS v. 21.0 (IBM, Armonk, NY).

3. Results

Because tonsillectomy group participants were 1:4 matched for age, sex, income, and region of residence, and the past medical histories of hypertension, diabetes mellitus, and dyslipidemia, these matched variables were exactly identical between tonsillectomy and control groups (Table 1).

In Table 2, both crude and adjusted HR of tonsillectomy for appendicitis were 1.06 (95% CI=0.89–1.27, *P*=.517). In the subgroup analysis, the crude and adjusted HRs in children were 1.03 (95% CI=0.82–1.30, *P*=.802) and 1.03 (95% CI=0.82–1.30, *P*=.804), respectively, and in adolescents and adults were 1.11 (95% CI=0.84–1.47, *P*=.417) and 1.10 (95% CI=0.84–1.47, *P*=.468), respectively. In another subgroup analysis, both crude and adjusted HRs in men were 0.89 (95% CI=0.70–1.12, *P*=.314) and in women were 1.39 (95% CI=1.06–1.83, *P*=.018). The survival functions of appendicitis in women were higher in the tonsillectomy group than in the controls, with statistical significance (log-rank test, *P*=.017, Fig. 2).

We described the estimated coefficients and 95% CI of other variable in supplements (Table S1, <http://links.lww.com/MD/C964>). Additionally, we described the interaction model between

Table 1

General characteristics of participants.

Characteristics	No. of participants	
	Tonsillectomy group	Control group
Age (yr) (n, %)		
0–4	494 (5.5)	1976 (5.5)
5–9	2924 (32.4)	11,696 (32.4)
10–14	1331 (14.8)	5324 (14.8)
15–19	890 (9.9)	3560 (9.9)
20–24	755 (8.4)	3020 (8.4)
25–29	654 (7.3)	2616 (7.3)
30–34	560 (6.2)	2240 (6.2)
35–39	451 (5.0)	1804 (5.0)
40–44	336 (3.7)	1344 (3.7)
45–49	253 (2.8)	1012 (2.8)
50–54	180 (2.0)	720 (2.0)
55–59	97 (1.1)	388 (1.1)
60–64	52 (0.6)	208 (0.6)
65–69	30 (0.3)	120 (0.3)
70+	8 (0.1)	32 (0.1)
Sex (n, %)		
Men	5359 (59.4)	21,436 (59.4)
Women	3656 (40.6)	14,624 (40.6)
Income (n, %)		
1 (lowest)	1016 (11.3)	4064 (11.3)
2	1099 (12.2)	4396 (12.2)
3	1683 (18.7)	6732 (18.7)
4	2398 (26.6)	9592 (26.6)
5	2819 (31.3)	11,276 (31.3)
Region of residence (n, %)		
Urban	3948 (43.8)	15,792 (43.8)
Rural	5067 (56.2)	20,268 (56.2)
Hypertension		
Yes	572 (6.3)	2288 (6.3)
No	8443 (93.7)	33,772 (93.7)
Diabetes		
Yes	313 (3.5)	1252 (3.5)
No	8702 (96.5)	34,808 (96.5)
Dyslipidemia		
Yes	635 (7.0)	2540 (7.0)
No	8380 (93.0)	33,520 (93.0)

sex and tonsillectomy (Table S2, <http://links.lww.com/MD/C964>).

4. Discussion

The risk of appendectomy due to appendicitis in the tonsillectomy group was not higher in the total population but was higher when only women were included (HR = 1.39; 95% CI=1.06–1.83, *P*=.018). These results are partially consistent with the previous studies.^{17,81} Compared to the previous studies, this study included larger participants that enabled us to perform the stratified analyses. Moreover, we matched 1:4 the control group according to age, sex, income, region of residence, and past medical histories. It would decrease the possibility of selection bias.

A case–control study performed at a single hospital¹⁷ showed a clear association between tonsillectomy and appendectomy. However, the number of participants was relatively small (n of total participants=650, n of tonsillectomy patients=166). We believe that this type of small study could be easily distorted by biases involving selection or recall. In the previous cohort study, the number of participants was slightly larger (n of total participants = 1038, n of

Table 2
Crude and adjusted HRs, 95% CI of tonsillectomy for appendectomy.

Characteristics	Crude HR (95% CI)	P-value	Appendectomy	
			Adjusted HR (95% CI) [†]	P-value
Total (n=45,075)				
Tonsillectomy	1.06 (0.89–1.27)	.517	1.06 (0.89–1.27)	.517
Control	1.00		1.00	
Children (n=23,745)				
Tonsillectomy	1.03 (0.82–1.30)	.802	1.03 (0.82–1.30)	.804
Control	1.00		1.00	
Adolescents and adults (n=21,330)				
Tonsillectomy	1.11 (0.84–1.47)	.417	1.10 (0.84–1.47)	.468
Control	1.00		1.00	
Men (n=26,795)				
Tonsillectomy	0.89 (0.70–1.12)	.314	0.89 (0.70–1.12)	.314
Control	1.00		1.00	
Women (n=18,280)				
Tonsillectomy	1.39 (1.06–1.83)	.018*	1.39 (1.06–1.83)	.018*
Control	1.00		1.00	

* Cox-proportional hazard regression model. Significance at $P < .05$.

[†] Adjusted model for age, sex, income, region of residence, hypertension, diabetes, and dyslipidemia. CI=confidence interval, HR=hazard ratio.

tonsillectomy patients = 55) than that in the case-control study. However, the cohort study did not show a clear association between tonsillectomy and appendectomy.^[8] We believe that this study did not have sufficient power to prove the nonassociation between tonsillectomy and appendectomy. If the effect of tonsillectomy on appendectomy is too weak to be proven with small numbers of cases, then the number of participants must be large. In the study with fewer participants, it was not possible to conclude the absence of an association. In the present study, we included 9015 tonsillectomy participants and 36,060 well-matched, control participants. Despite this large number of participants, we did not find an association between tonsillectomy and appendectomy in the total population.

In accordance with the previous investigations,^[7,8] our study revealed that tonsillectomy increases the risk of appendectomy in

women. The previous case-control study reported a more significant association between tonsillectomy and appendectomy in women,^[7] and the cohort study reported an increased risk of appendectomy in the tonsillectomy group, albeit with a modest OR.^[8] We are unable to provide an appropriate explanation regarding the different effects of tonsillectomy on appendectomy according to sex; however, hormonal and X chromosome-related factors are known to affect various diseases differently.^[11] One previous study reported a slight increase in the lymphocyte subpopulation in boys with tonsillectomy but no increase of the lymphocyte subpopulation in girls with tonsillectomy compared with a control group.^[12] This increase in immunologic function might compensate for tonsil loss in men; hence, the risk of appendicitis might be increased only in women. In a recent twin study, appendicitis was affected differently according to sex and genetic and environmental factors.^[13] The researchers reported that no genetic effect was found in men, whereas a 20% heritability effect was found in women.^[13] Another twin study also reported similar results.^[14] These findings suggest that the risk of appendicitis is affected by various factors differently according to sex. The higher incidence of appendicitis in women could be explained because it is known that women have more intense immune reactions than men, so they suffer more immune diseases.^[15] The different effects of tonsillectomy on appendectomy might be explained by the different incidences of appendectomy between the sexes. However, in this study, the incidence of appendectomy barely differ according to sex ($P = .044$, Table S3, <http://links.lww.com/MD/C964>).

The huge number of participants is the advantage of this study ($n=45,075$). Therefore, we could overcome the low power of previous studies and could confirm the increased risk of appendectomy due to appendicitis in women receiving tonsillectomy, albeit with a relatively low HR (1.39). In addition, we used medical claim codes to confirm all medical treatments. Therefore, there was no possibility of recall bias in the surveyed study. All citizens of our country were included in this national health insurance data without exception. Therefore, there were no missing participants during the follow-up period. We also matched the controls according to age, sex, income, region of

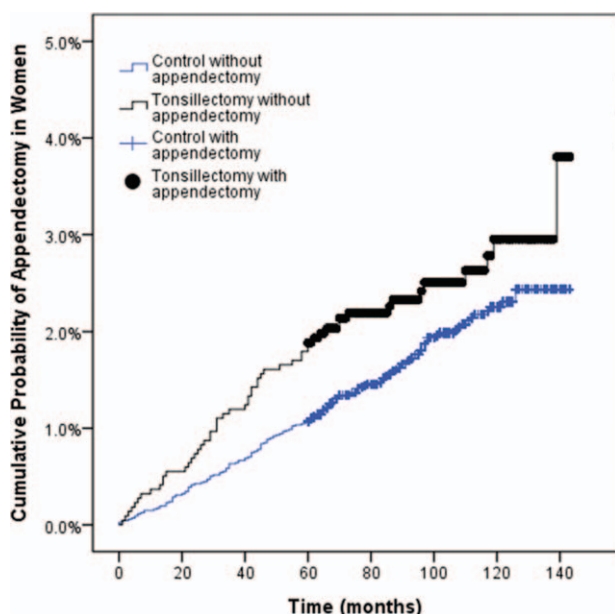


Figure 2. Survival functions of appendicitis in women.

residence, and the past medical histories of hypertension, diabetes mellitus, and dyslipidemia. Because of this matching, we did not have to calculate crude ratios. We matched the income and region of residence. It was important because they are decision factors of medical procedures. In this Korean NHIS system, the premium was determined by the income level. Because the patient's premium was decided by the income, it would be very accurate. The statistician designed the data to represent the mother population (the entire population data of Korea). Therefore, the results of our study could represent the entire Korean population. Additionally, we adjusted the past medical histories of hypertension, diabetes mellitus, and dyslipidemia to compensate heterogeneity of the tonsillectomy and control group.

Nevertheless, our study has some limitations. We could not evaluate the purpose of tonsillectomy. Therefore, the participants might undergo tonsillectomy for chronic tonsillitis, chronic tonsillar hypertrophy, or obstructive sleep apnea. We could also not find sufficient explanations to support our results. Because we followed up the participants from 2002 through 2013, participants who underwent tonsillectomies before 2002 might have had the chance of being included in the control group, and participants who underwent appendectomies before 2002 might have had the chance of being included with participants who had no history of appendectomy. However, considering the annual incidence and timing of surgery in Korea, this possibility is very low. We also did not analyze the risk of adenoidectomy, which is commonly performed with tonsillectomy, although no study has reported a clear association between adenoidectomy and appendectomy. We analyzed the risk of appendectomy rather than appendicitis because the medical diagnosis of appendicitis can be complicated, with the possibility of misdiagnosis. Therefore, we used the operation code for appendectomy because these codes are very reliable with respect to claim data. Despite the matching of variables, there is the possibility of difference general health status might results in the difference of results. In our previous publications using the same database of this study,^[16,17] we found that tonsillectomy dose not reduce upper respiratory infection, whereas tonsillectomy increases the risk of retropharyngeal abscess. Actually, the risk of upper respiratory infection was slightly higher in tonsillectomy group compared to control group for 2 years. It means that increased risk of infection in other sites after tonsillectomy could affect the risk of appendectomy rather than tonsillectomy affect the risk of appendectomy directly. In this study, we did not adjust these variables (other sites of infection) that might confound the association between tonsillectomy and appendectomy.

5. Conclusion

The adjusted HR of appendectomy due to appendicitis in the tonsillectomy group did not show statistical significance in the total population. However, this value was barely significant when only women were included in the analysis.

Acknowledgments

This work was supported in part by a research grant (NRF-2018-R1D1A1A02085328) from the National Research Foundation (NRF) of Korea.

The manuscript was edited for proper English language, grammar, punctuation, spelling, and overall style by the highly

qualified native English-speaking editors at American Journal Experts (F1B4-0787-CFDD-9783-CF0P).

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