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Otitis and nasopharyngeal carcinoma

Association between adult otitis media and nasopharyngeal cancer: A nationwide population-based cohort study

Wen-Yen Huang [a,b], Che-Chen Lin [c], Yee-Min Jen [a], Kuen-Tze Lin [a], Muh-Hwa Yang [b,d], Chang-Ming Chen [a], Ying-Nan Chang [e], Fung-Chang Sung [c,f], Chia-Hung Kao [g,h,*]

[a] Department of Radiation Oncology, Tri-Service General Hospital, National Defense Medical Center, Taipei, Taiwan; [b] Institute of Clinical Medicine, National Yang-Ming University, Taipei, Taiwan; [c] Management Office for Health Data, China Medical University Hospital, Taichung, Taiwan; [d] Division of Hematology-Oncology, Department of Medicine, Taipei Veterans General Hospital, Taipei, Taiwan; [e] Department of Otolaryngology-Head & Neck Surgery, Tri-Service General Hospital, National Defense Medical Center, Taipei, Taiwan; [f] Departments of Public Health, China Medical University, Taichung, Taiwan; [g] Graduate Institute of Clinical Medicine Science and School of Medicine, College of Medicine, China Medical University, Taichung, Taiwan; [h] Department of Nuclear Medicine and PET Center, China Medical University Hospital, Taichung, Taiwan

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ABSTRACT

Purpose: To determine whether the diagnosis of otitis media (OM) in adults is associated with an increased risk for the subsequent development of nasopharyngeal cancer (NPC) using a nationwide population-based retrospective study.

Methods and materials: We selected 13,513 adult patients that had been previously diagnosed with OM between 2000 and 2005 from the Taiwan Longitudinal Health Insurance Database 2000 as the study cohort, and randomly extracted the data of 135,130 participants matched by sex, age, and baseline year for the comparison cohort. The follow-up period was terminated upon developing NPC, withdrawal from the national health insurance system, or the end of 2009. Cumulative incidences and hazard ratios (HRs) of NPC development were determined.

Results: The subsequent NPC incidence rates in the OM and comparison cohorts were 6.41 and 0.58 per 10 000 person-years, respectively (adjusted HR, 11.04; 95% CI, 7.68–5.87; $P < 0.0001$). The NPC risk for males was significantly higher than that for females (adjusted HR = 3.24; 95% CI, 2.16–4.85). In both female and male patients, the diagnosis of OM was associated with a significantly increased risk for NPC (adjusted HR, 11.91 vs. 10.78, respectively). Among the OM cohort, 62 participants were subsequently diagnosed with NPC, with 71% of them occurring within 1 year following the diagnosis of OM. However, even after 5-year follow-up, the OM cohort still displayed a higher risk for NPC (adjusted HR = 2.50). Stratified by the frequency of OM episodes, more than one episode per year had a significantly greater risk of developing NPC, compared with the comparison cohort (HR = 29.22; 95% CI, 20.19–42.27).

Conclusion: We found that adult OM is a warning sign for the development of NPC in Taiwan, with approximately an 11-fold higher risk for adult OM patients. We recommend that OM patients undergo follow-up examinations for at least 5 years. To extrapolate our findings, further studies are warranted in other areas in which NPC is endemic.

Otitis media (OM) is a common global health care problem, and the overall burden from OM and its sequelae is considerable. The incidence rate is estimated to be 10.85% for acute OM and 4.76% for chronic suppurative OM [1]. OM primarily occurs in childhood, and the incidence markedly declines with age, presumably a result of the maturation of the immune system and the anatomy of the middle ear, the Eustachian tube, and the nasopharynx.

Nasopharyngeal cancer (NPC) arises in the nasopharynx, in which the orifice of the Eustachian tube is located. Obliteration of the opening of the Eustachian tube by the tumor or adenoid tissue may lead to OM with effusion. Thus, much emphasis is placed on the exclusion of NPC in adult patients with OM. However, it remains unclear whether adult OM is an indicator of subsequent NPC, and whether OM patients should undergo subsequent regular medical examinations as a high-risk group.

NPC shows a distinct geographical and racial distribution. It is rare in most parts of world, but common in southern China, Hong Kong, and Taiwan. According to the 2008 cancer report released by the Taiwan Department of Health, the incidence of NPC was 9.99 per 100 000 for men and 3.47 per 100 000 for women. It is the ninth most common cause of cancer-related death for men and the 14th for women in Taiwan. The Taiwan National Health Insurance (NHI)

* Corresponding author at: Department of Nuclear Medicine and PET Center, China Medical University Hospital, No. 2, Yuh-Der Road, Taichung 404, Taiwan.
E-mail address: d10040@mail.cmuh.org.tw (C.-H. Kao).

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program was initiated in 1996, with 97% of the hospitals and clinics throughout Taiwan under contract with the system by the end of 1996 [2]. By 1998, the health care of almost 99% of the population of Taiwan was covered by the NHI. The NHI patient records provide a unique opportunity to examine our hypothesis that a diagnosis of OM in adults is associated with an increased risk for subsequent development of NPC using a nationwide population-based cohort study.

Patients and methods

Data source

The Taiwan National Health Research Institute established and managed the National Health Insurance Research Database (NHIRD) which includes the reimbursement claim data for the Taiwan NHI program. All personal identification information is encrypted before being released to the public to protect patient privacy.

Our research used the Longitudinal Health Insurance Database (LHID), a subset of the NHIRD. LHID is composed of historical claim data for one million claimants randomly sampled from the total insured population between 1996 and 2000. Anonymous identification numbers are used to link each claimants demographic information, including sex, birth date, occupation, residential area, and registry of medical services. The disease diagnosis that was used in our study was defined by the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) from outpatient data, inpatient data, and the registry of catastrophic illness. Our study was approved by the Ethics Review Board of the China Medical University (CMU-REC-101-012).

Study population

Our study used a population-based retrospective approach. The OM cohort included participants that were initially diagnosed with OM (ICD-9-CM 381.0-381.4 and ICD-9-CM 382) between 2000 and 2005, and the baseline was set as the date of the initial OM diagnosis. Ten comparison cohort participants were randomly selected for each OM cohort participant. Comparison cohort participants were matched by sex, age, and baseline year. The event of the study was defined as subsequent NPC based on the diagnosis code, ICD-9-CM 147, from the registry of catastrophic illness. We excluded patients with a history of cancer before the baseline year, and those who were aged 20 years or under during the baseline year. The follow-up period was terminated upon developing NPC, withdrawal from the insurance system, or the end of 2009.

The demographic data included sex, age, occupation, and residence area. Occupation was classified into three groups: White collar, blue collar, and others. The urbanization of Taiwan cities grouped into seven levels that were based on the following indices: (1) Population density (people/km^2); (2) the population ratio of different educational levels; (3) the population ratio of elderly persons; (4) the population ratio of agriculture workers and the number of physicians per 100000 people [3]. The subjects in levels 5, 6 and 7 were small so that these levels were combined into level 4. Level 1 was considered to represent the highest degree of urbanization and level 4 represented the lowest.

Statistical analysis

We used the chi-square test for category variables and the *t*-test for continuous variables to assess the difference in baseline demographic characteristics between the OM cohort and the comparison cohort participants. The total NPC incidence and the demographic-specific NPC incidence was calculated per 10000 person-years. The cumulative NPC incidence curves for the study cohorts were also evaluated by the Kaplan–Meier method, and the differences between the incidence curves were evaluated by the log-rank test. The Cox's proportional hazards regression model, adjusted for potential confounding factors, was used to estimate the hazard ratio (HR) and confidence interval (CI) for the OM cohort and the comparison cohort. The average OM frequency was calculated as the total number of OM diagnoses during the follow-up period divided by the follow-up duration in years. The average OM frequency was separated into 3 groups by percentile (33rd percentile and 66th percentile). To measure the association between the average OM frequency and the risk of NPC, we estimated the risk in every level of average OM frequency, and the OM frequency was considered a continuous variable to evaluate the trends using the Cox's proportional hazards regression model.

Data management and analysis were performed using SAS version 9.1 software (SAS Institute, Cary, NC, USA), and the cumulative incidence curve was plotted using R software (R Foundation for Statistical Computing, Vienna, Austria). *P* values for the two-tailed tests that were less than .05 were considered to represent significant differences among the data sets.

Results

Our study evaluated 13,513 OM participants and 135,130 comparison cohort participants between 2000 and 2005 (Table 1). The average age (47.5 y) and sex ratio were identical between the two cohorts. In both cohorts, approximately 30% of the participants lived in the highest urbanization level, and approximately 50% were classified as white-collar.

The NPC incidence rate in the OM cohort was 6.41 per 10000 person-years, and was approximately 11-fold higher than the NPC incidence rate in the comparison cohort (0.58 per 10000 person-years; Table 2). The NPC cumulative incidence curve showed that the OM cohort had a significantly higher risk for NPC than the comparison cohort (*P* value for log-rank test <0.0001; Fig. 1). After adjusting for potential confounders, the HR of subsequent NPC in the OM cohort was 11.04 (95% CI, 7.68–15.87), compared with the comparison cohort. We also applied sensitivity analysis to measure the NPC risk in the study population throughout the follow-up duration. While 71% of the NPC events occurred in the OM cohort within 1 year of OM diagnosis, approximately 10% of the NPC events in the comparison cohort occurred within the same period. These results suggest that the OM cohort displayed a significantly increased risk of NPC, compared with the comparison cohort.

Table 1
Baseline demographic status and comorbidity compared between Comparison and otitis media cohorts.

Variable	Comparison group	Otitis media group	*p*-Value
	N = 135130 (%)	*N* = 13513 (%)	
Age, years (SD)*	47.5 (15.7)	47.5 (15.7)	0.99
⩽40	50790 (37.6)	5079 (37.6)	1.0000
41–50	30450 (22.5)	3045 (22.5)	
>50	53890 (39.9)	5389 (39.9)	
Sex			1.0000
Female	74120 (54.9)	7412 (54.9)	
Male	61010 (45.1)	6101 (45.1)	
Urbanization level			0.0012
1	41119 (30.4)	3950 (29.2)	
2	39396 (29.2)	3872 (28.7)	
3	24003 (17.8)	2522 (18.7)	
4	30610 (22.7)	3169 (23.5)	
Occupation			0.0005
White collar	70160 (51.9)	6918 (51.2)	
Blue collar	46206 (34.2)	4827 (35.7)	
Others	18764 (13.9)	1768 (13.1)	

* *t*-Test.