



Acid reflux and head and neck cancer risk: A nationwide registry over 13 years



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ABSTRACT

Objective: Gastro-esophageal reflux disease (GERD) is a highly prevalent disorder; however, important questions remain regarding the link between GERD and extra-esophageal cancers. This nationwide cohort study investigated the risk of developing head and neck cancers (HNCs) among patients with GERD.

Methods: Newly diagnosed GERD patients aged ≥ 20 years without antecedent cancer were included. Case data were obtained from the National Health Insurance Research Database covering period from 1998 to 2010. We compared the standardized incidence ratios (SIRs) of cancer among GERD patients with those of the general population.

Results: A total of 98 cancers were identified among the 39,845 GERD patients in the study, representing 128,361 person-years. The SIR for all cases of cancer was 1.59 (95% CI 1.29–1.93). GERD patients exhibited significantly higher SIRs for oropharyngeal (SIR 3.58, 95% CI 1.85–6.25) and hypopharyngeal (SIR 3.96, 95% CI 2.35–6.26) cancers. Male patients had a significantly higher risk of HNCs (SIR 1.70, 95% CI 1.36–2.10), particularly oropharyngeal (SIR 4.01, 95% CI 2.00–7.17) and hypopharyngeal (SIR 3.91, 95% CI 2.28–6.26) cancers. Following adjustment for age and co-morbidities, the hazard ratio was 9.06 (95% CI 4.70–17.44) for males compared to females.

Conclusion: There may be a potential association between GERD and risk of HNCs, which however merits further studies to confirm the causal relationship. Our observations indicate a need for careful extra-esophageal examination of patients with acid reflux. Our findings also underline the importance of raising awareness among clinicians regarding the possibility of concurrent HNCs in GERD patients with refractory laryngo-pharyngeal symptoms.

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1. Introduction

Gastro-esophageal reflux disease (GERD) is very common in Taiwan as well as in western countries, affecting 20–50% of the

population [1–3]. Increasing prevalence and the impact of this disorder on quality of life impose a considerable burden on society in terms of hospitalization and related medical costs [4]. More importantly, GERD-related malignancies are an additional burden on affected individuals and their families.

All doubts surrounding a possible relationship between GERD and esophageal adenocarcinoma have been eliminated [5]. However, critical questions remain with regard to the link between GERD and head and neck cancers (HNCs). HNCs are among the ten most common forms of cancer worldwide, with an incidence of 9% in Taiwan and 2–4% in western countries [6]. In the last two

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decades, the overall 5-year survival rate associated with HNC has been among the lowest, of all common cancers [6]. Despite a lack of available data on the subject, an increasing number of investigators believe that a relationship exists between GERD and HNCs, particularly with regard to laryngo-pharyngeal malignancies [7]. Nonetheless, most previous studies used only a small number of subjects and focused primarily on the link between GERD and laryngeal cancer [8–11]. To date, no research has been conducted to elucidate the differential carcinogenic effects of GERD on specific sub-sites of the head and neck. Thus, existing evidence is too limited to definitively establish an increased risk of extra-esophageal cancer in GERD patients.

The low relative incidence of HNCs has created a need for additional epidemiologic research capable of ensuring sufficient statistical power and effect size to define the actual risk of HNC among patients with GERD [10]. This study employed data from the national health registry in Taiwan to conduct a large population-based cohort study to clarify the relationship between acid reflux and HNCs.

2. Methods

2.1. Ethics statements

The Institutional Review Board of the Taipei Veterans General Hospital exempted this study from review because it used existing de-identified and public-use data.

2.2. Data sources

The National Health Insurance Program (NHIP) of Taiwan was launched in 1995. This mandatory system provides complete medical coverage to all residents of Taiwan (99.5%) [12]. The National Health Insurance dataset consists of de-identified secondary data for research purposes. In 1999, the National Health Insurance Research Database project began releasing registry and claims data from the NHIP [13]. This study defined diseases according to the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes.

Two datasets from the National Health Insurance Research Database were investigated by this study. One was the Longitudinal Health Insurance Database, which includes the data of 1,000,000 patients randomly sampled from the registry of all National Health Insurance enrollees in the year 2000. No significant differences were observed between the sample group and all enrollees in terms of age, sex, or health care costs [13]. The other dataset was the Catastrophic Illness Registry, which provides comprehensive information related to all patients with severe diseases, including malignancies. Measures taken to protect the confidentiality of data conform to the regulations of the Bureau of National Health Insurance and the National Health Research Institutes.

2.3. Study cohort

This retrospective cohort study was based on data covering the period from January 1, 1998 to December 31, 2010. Patients with GERD were identified from the 1,000,000-person sampled cohort dataset (ICD-9-CM codes 530.11 or 530.81), and had been diagnosed based on results from endoscopy or a 24-h pH-meter inspection before proton pump inhibitor was prescribed, as required by the Bureau of National Health Insurance. The diagnosis of GERD was valid, and this criterion has been used in similar previous studies [14–16]. Patients aged <20 years or those diagnosed with GERD or antecedent malignancies prior to enrollment were excluded. Information regarding co-morbidities was also collected for analysis.

2.4. Outcomes

The main dependent variable was the occurrence of HNC (ICD-9-CM codes 140.0–160.9). Identifying cancer using insurance claims is a valid method that has been used in previous research [17–19], and this study used the Catastrophic Illness Registry to identify patients diagnosed with HNCs, which requires histopathologic confirmation. Cancer sites were coded according to the International Classification of Diseases for Oncology issued by the Department of Health. Patients with GERD were followed until the development of cancer, death, dropout from the NHIP, or the end of year 2010.

2.5. Statistical analysis

The risk of cancer in the GERD cohort was determined using the standardized incidence ratio (SIR), defined as the observed number of cancer cases in GERD patients divided by the expected number derived from the incidence rate among the general population in Taiwan. The expected number of cancer cases was calculated by multiplying the national incidence rate of cancers according to age (in 5-year intervals), sex, and calendar year by the corresponding stratum-specific person-time accrued in the cohort [17]. The incidence rates of cancer among the general population were acquired from the Taiwan Cancer Registry, which was initiated in 1979. The entire follow-up period was covered by the registry. The 95% confidence intervals (CIs) of SIRs were estimated under the assumption that the observed number of cancers followed a Poisson distribution [17,18]. SIRs were also determined for age and sex subgroups. To minimize the possibility of detection bias, we also performed subgroup analysis stratified according to duration of enrollment [17,20]. To determine whether GERD was associated with specific types of HNC, SIRs were also calculated according to cancer site. The Cox regression model was used to adjust potential confounders, including age, sex, and co-morbidities. Perl programming language (version 5.12.2; Perl Foundation, Walnut, CA) was used for data extraction and computation. Microsoft SQL Server 2012 (Microsoft Corp., Redmond, WA, USA) was used for data linkage, processing, and sampling. All statistical analyses were conducted using STATA statistical software (version 12.0; StataCorp., TX, USA). Statistical significance was set at $p < 0.05$.

3. Results

3.1. Characteristics of the study population (Table 1)

A total of 39,845 patients with GERD were identified, and the cohort was observed for 128,361 person-years from 1998 to 2010. No gender bias was observed in the sampling (49% male vs. 51% female). The median age was 51.6 ± 16.6 years, and the median follow-up period was 3.2 ± 1.7 years.

3.2. External analysis: SIRs of all head and neck cancers (Table 2)

During the study period, 98 cases of HNC developed. Compared to the general population, GERD patients had an elevated overall risk of HNC (SIR 1.59; 95% CI 1.29–1.93). Additionally, the risk of all cancers increased in males with GERD (SIR 1.70, 95% CI 1.36–2.10), but not in females (SIR 1.03, 95% CI 0.51–1.84). Sub-group analysis by age at the time of diagnosis revealed a higher risk of cancer in patients aged <60 years, particularly in males aged 40–59 years (SIR 1.72, 95% CI 1.26–2.28). Finally, an investigation based on duration of GERD showed that within the first 5 years following diagnosis, the risk of cancer increased, especially in male patients (SIR 1.81, 95% CI 1.27–2.49).

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