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Inhaled corticosteroid use and risks of lung cancer and laryngeal cancer

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Summary
Background: Chronic inflammation has been implicated in the pathogenesis of several cancers, including lung and laryngeal cancer. The objective of the study is to elucidate the association between ICS use and diagnosis of lung and laryngeal cancer.
Methods: A nested case–control study based on the Korean national claims database included new adult users of inhaled medications between January 1, 2007, and December 31, 2010. Patients diagnosed with lung cancer or laryngeal cancer after enrollment were identified as cases and up to five control individuals matched for age, sex, diagnosis of asthma or COPD, Charlson Comorbidity Index scores, number of health care visits, and initiation date were selected.
Results: From the 792,687 eligible cohort, 9177 individuals diagnosed with lung cancer were matched with 37,048 controls. Additionally, 408 laryngeal cancer patients and 1651 controls were matched. ICS use was associated with a decreased rate of lung cancer diagnosis [adjusted odds ratio (aOR), 0.79; 95% confidence interval (CI), 0.69–0.90]. The inverse association between ICS use and lung cancer risk was dose dependent ($P < 0.0001$ for the trend). However, no reduction in the risk of laryngeal cancer among ICS users was identified (aOR, 1.06; 95% CI, 0.62–1.18).
Conclusion: The use of ICS is associated with a reduced risk of lung cancer but not of laryngeal cancer.

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Introduction

Inhaled corticosteroids (ICS) uses a cornerstone treatment for chronic airway diseases, including asthma[1] and chronic obstructive pulmonary disease (COPD).[2] For patients with asthma,[3] ICS reduces asthma symptoms,[3] improves lung function and quality of life,[3] reduces the frequency and severity of exacerbations,[4] and decreases asthma mortality.[5] Among patients with COPD, ICS improves quality of life,[6] and reduces symtoms.[6,7]

The benefit of ICS in patients with asthma[8] or COPD[9,10] is based mainly on its anti-inflammatory effects. Given that chronic inflammation has been implicated in the pathogenesis of several cancers, including lung cancer and head and neck cancers,[11,12] the chemopreventive efficacy of inhaled budesonide was tested for its effect on lung carcinogenesis in mice and was reported to be effective.[13] Additionally, a report proposing that ICS may prevent development of lung cancer was published recently,[14] although the association between ICS and laryngeal cancer was not investigated.

Patients with COPD and asthma use ICS frequently and are a high risk group for lung and laryngeal cancers.[15–17] In this context, we examined the association between ICS use and diagnoses of lung and laryngeal cancers by analyzing the Health Insurance Review and Assessment Service database, which includes records for almost all South Koreans.

Material and methods

Source of data

We used the database of the Health Insurance Review and Assessment Service (HIRA, Seoul, South Korea), a government-affiliated agency responsible for examining the accuracy of claims quality for National Health Insurance (NHI, which covers approximately 96.6% of the entire 48.6 million South Korean population) and National Medical Aid (covering approximately 3.5% of the South Korean population). The NHI database includes the entire South Korean population as well as registered foreign-nationality residents as a compulsory insurance system, with exceptions for cases applicable to the National Medical Aid program or foreign military personnel.[18] The HIRA database contains information on demographics and all medical services rendered, along with the diagnostic code (ICD-10 code) and all prescription medications dispensed. Values in key fields such as drug name, quantity, date dispensed, and duration are missing or out of range in $<0.5\%$ of records. These databases have been used in previous studies.[19–23]

Study design

A nested case–control study was conducted based on the HIRA database. The source population consisted of all individuals who were dispensed at least one of the following inhaled respiratory medications between January 1, 2007, and December 31, 2010: ICS, (beclomethasone, budesonide, triamcinolone, ciclesonide, fluticasone, or flunisolide), short-acting inhaled β_2-agonists (SABA; salbutamol, fenoterol, procaterol, or terbutaline), long-acting inhaled β_2-agonists (LABA; salmeterol or formoterol), short-acting inhaled muscarinic antagonists (SAMA; ipratropium), long-acting inhaled muscarinic antagonists (LAMA; tiotropium), a combination of SABA and SAMA (ipratropium/salbutamol), or a combination of LABA and ICS (budesonide/formoterol, fluticasone/salmeterol).

The eligible cohort of new users of inhaled respiratory medication was identified from all individuals who had a prescription for an inhaled respiratory medication for 30 days or longer between January 1, 2007, and December 31, 2010. The date of the first use of the above inhaled respiratory medications was called the initiation date. Individuals who had had a prescription for inhaled respiratory medication for 30 days or longer or who had any of the ICD-10 cancer diagnoses (C00–C97, D00–D09) within the year prior to the initiation date were excluded. Additionally, individuals <20 years of age or >120 years were also excluded. The eligible individuals were monitored until the diagnosis of lung cancer or head and neck cancer or until December 31, 2010.

The protocol of this study was approved by the ethics review committee of the National Evidence-based Healthcare Collaborating Agency, Seoul, Republic of Korea.

Case definition

Within the eligible cohort, we identified case individuals based on ICD-10 diagnoses of lung cancer (C33–C34, D02.1, D02.2) or head and neck cancer other than thyroid cancer (C00–C14, C30–C32, D00.0, D02.0, D02.3) that occurred after the initiation date of the inhaled respiratory medications. The index date was defined as the date of first assignment of the above ICD-10 codes.

Control individuals

For each case individual, up to five control individuals, who were randomly matched for age (within 1 year), sex, diagnosis of asthma (J45–J46) or COPD (J41–J44), number of health care utilizations (number of hospitalizations [±1] and number of outpatient visits [±3]), and initiation date (within 15 days), were selected without replication from among individuals without an ICD-10 diagnosis of lung or head and neck cancer. The index date for the controls was defined as the index date for their matched case.

Inhaled corticosteroid exposure

ICS included orally inhaled beclomethasone, budesonide, triamcinolone, ciclesonide, fluticasone, or flunisolide, whether dispensed alone or in a combination inhaler with an inhaled β_2-agonist. The estimation of equivalencies was chosen based on relative topical potency and what experts consider to be comparable doses according to the National Asthma Education and Prevention Program Expert Panel report 3,[24] the Canadian Asthma Consensus Statement,[25] and the Global Strategy for Asthma Management and Prevention 2010 (updated).[26] Accordingly, the equivalent doses for ICS were 100 μg beclomethasone, 50 μg beclomethasone HFA,