Oral Bisphosphonates and Risk of Esophageal Cancer:  
a Dose-Intensity Analysis in a Nationwide Population

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Abstract

Background:

Esophageal cancer has been associated with oral bisphosphonate (BP) use, but current data is conflicting and devoid of Asian studies where esophageal squamous carcinoma prevails.

Methods:

We assessed the association between dose intensity, stratified by use duration (observation period) and exposure frequency, of oral BPs and the risk of esophageal cancer using 16,204 esophageal cancer cases and 64,816 malignancy-free controls identified from the population-based National Health Insurance Research Database of Taiwan from 1997 to 2008.

Results:

Neither duration nor frequency of BP exposures was positively correlated to esophageal risk. The odds ratios (ORs) for rare users of 1-, 3-, 5-year observation periods were 3.86, 2.58, and 2.27, respectively ($p < 0.001$). Similar trend of descending ORs was also observed for rare-, frequent-, and regular-users of 1-year observation period (ORs = 3.86, 1.93, and 0.95, respectively).

Conclusion:
Our data suggest that BPs are not likely risk factors for esophageal cancer in Taiwan.

**Impact:**

The study demonstrates no evidence of an association between BP use and esophageal cancer risk from Asian perspective.
Introduction

Bisphosphonates (BPs) are considered drug of choice for osteoporosis. An estimate of 5 million Americans fill the prescriptions annually and far more globally. (1) Recently, a total of 54 esophageal cancer cases, from post-marketing surveillance over a decade, were suspected to be associated with oral BPs. (2) A subsequent nested case-control analysis using the UK General Practice Research Database (GPRD) affirmed the risk association among those who had 10 or more BP prescriptions or had taken them for longer than three years. (3) Cardwell et al. also probed the UK GPRD of similar time period by comparing cancer incidences, and interestingly, found no difference in risk of esophageal cancer between BP users and controls. (4) Nguyen et al. further demonstrated that oral BPs did not increase the risk of esophageal adenocarcinoma among patients with pre-existing Barrett’s esophagus by examining the US Veterans Affairs Patient Treatment File. (5) It is evident that available data regarding possible association between oral BPs and esophageal cancer is inconclusive. Moreover, no epidemiologic study has yet evaluated the risk association among Asian population. The study aims to investigate the association between dose intensity, i.e. duration of use and exposure frequency, of BPs and risk of esophageal cancer in Taiwan.
Methods

Study population

Cases with a diagnosis of esophageal cancer (ICD-9 code: 150) recorded in the population-based National Health Insurance Research Database (NHIRD) of Taiwan between 1997 and 2008 were enrolled as described elsewhere. The Registry for Catastrophic Illness Patient Database, a subpart of NHIRD with specific registration procedure to confirm diagnosis, was verified to ascertain the inclusion. Each case was matched with four randomly selected controls, matched by age (± 1 year), sex, and date of physician visit (± 1 year), from Longitudinal Heath Insurance Database 2000 (LHID2000) and LHID2005. Patients with previous malignancies were excluded. The index date was defined as the date of esophageal cancer diagnosis. The five years prior to the index date was set as the entire observation period.

Bisphosphonate Exposure

Dose intensity of BPs was classified according to duration of use (observation period: 1-, 3-, 5-year, dated backwards from the index date) and exposure frequency (use of BPs: non-, rare, frequent, regular). The exposure frequency was defined by the total dates of BPs use divided by the total dates of observation. All enrollees were stratified according to
exposure frequency of BPs: regular (≥ 2/3 frequency), frequent (1/3-2/3 frequency), rare (< 1/3 frequency), and non-users.

**Statistical analysis**

The association between oral BPs use and esophageal cancer was estimated by computing odds ratios (ORs) at various observation periods and exposure frequencies. All analyses were conducted using SAS version 9.1 (SAS Institute, Cary, NC, USA), and performed at the 5% significance level.
Results

Previous oral BP (alendronate, risedronate, clodronate, and etidronate) use was identified in 7.8% vs. 3.6% of 16,204 cases vs. 64,816 controls during the entire 5-year observation period. The association between oral bisphosphonates use and risk of esophageal cancer is demonstrated in Figure 1. Compared to never users of respective observation period, rare users had significantly higher risk of esophageal cancer (all \(p < 0.001\); ORs =3.86, 2.58, 2.27 for 1-, 3-, 5-year usage duration, respectively). It is also apparent that the longer duration of use, the less the ORs. Similar trends of inverse relationship were also found within groups of frequent users (\(p \geq 0.05\); ORs = 1.93, 1.08, and 1.00 for 1-, 3-, 5-year, respectively) and regular users (\(p > 0.05\); ORs = 0.95, 0.75 for 1-, 3-year, respectively).

This inverse correlation was also noticed among groups of rare-, frequent-, and regular-users. For instance, the ORs of the respective groups for the 1-year exposure duration cohort were 3.86, 1.93, and 0.95, respectively. The ORs for frequent users and regular users were generally lower than the ORs of rare users. On the whole, the higher the use frequency of BPs, the lower ORs were found.
Discussion

The study points out an inverse relationship of esophageal cancer risk with BP dose intensity, characterized by both usage duration and exposure frequency, in a nationwide population. The higher percentage of BP users in cases and significantly increased ORs for rare users in our study might be reasoned by infamous esophagitis attributable to BPs, leading to reduced drug compliance or prompting more gastrointestinal endoscopic examinations with ensuing early diagnosis of occult cancers.

Alternatively, trend of descending ORs in relation to longer duration of use or greater exposure frequency might imply that BPs could even have a protective value. Reports of cytostatic, proapoptotic, anti-metastatic effects of BPs in breast, colorectal, and various cancers are not unseen. (7,8) Certainly, the rarity of esophageal cancer necessitates further studies to delineate precise roles of BPs. Prospective designs of sufficient population and calendar years along with pre-clinical and clinical evidences are required to dissect discrepancy among current data.
References


Figure Legend

**Figure 1** Association between oral bisphosphonates and risk of esophageal cancer, stratified by observation period and exposure frequency. *p < 0.001, compared to non-users of respective observation periods; BPs, bisphosphonates; n\textsubscript{E,BP}, number of BP users with esophageal cancer; n\textsubscript{C,BP}, number of controls who had used BPs. The groups of regular-user of the 5-year observation period await larger samples to constitute a valid comparison (.trim).
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