Null Results in Brief

Cancer Epidemiology, Biomarkers & Prevention

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 use, but current data are 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 bisphosphonates 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 bisphosphonate exposures was positively correlated to esophageal cancer risk. The 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 bisphosphonates are not likely risk factors for esophageal cancer in Taiwan.

Impact: The study shows no evidence of an association between bisphosphonate use and esophageal cancer risk from Asian perspective. *Cancer Epidemiol Biomarkers Prev; 21(6); 993–5. ©2012 AACR.*

Introduction

Bisphosphonates 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 postmarketing surveillance over a decade, were suspected to be associated with oral bisphosphonates (2). A subsequent nested case–control analysis using the U.K. General Practice Research Database (GPRD) affirmed the risk association among those who had 10 or more bisphosphonate prescriptions or had taken them for longer than 3 years (3). Cardwell and colleagues also probed the U.K. GPRD of similar time period by comparing cancer incidences, and interestingly, found no difference in risk of esophageal cancer between bisphosphonate users and controls (4). Nguyen and colleagues further showed that oral bisphosphonates did not increase the risk of esophageal adenocarcinoma among patients with preexisting Barrett's esophagus by examining the U.S. Veterans Affairs Patient Treatment File (5). It is evident that available data about possible association between oral bisphosphonates and esophageal cancer are inconclusive. Moreover, no epidemiologic study has yet evaluated the risk association among Asian population. The study aims to investigate the association between dose intensity, that is, duration of use and exposure frequency, of bisphosphonates 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 (6). 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 4 randomly selected controls, matched by age (±1 year), sex, and date of physician visit (±1 year), from Longitudinal Heath Insurance Database 2000 (LHID 2000) and LHID 2005. Patients with previous malignancies were excluded. The index date was defined as the date of esophageal cancer diagnosis. The 5 years before the index date was set as the entire observation period.

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Bisphosphonate exposure

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

Statistical analysis

The association between oral bisphosphonates use and esophageal cancer was estimated by computing ORs at various observation periods and exposure frequencies. All analyses were conducted with SAS version 9.1 (SAS Institute) and carried out at the 5% significance level.

Results

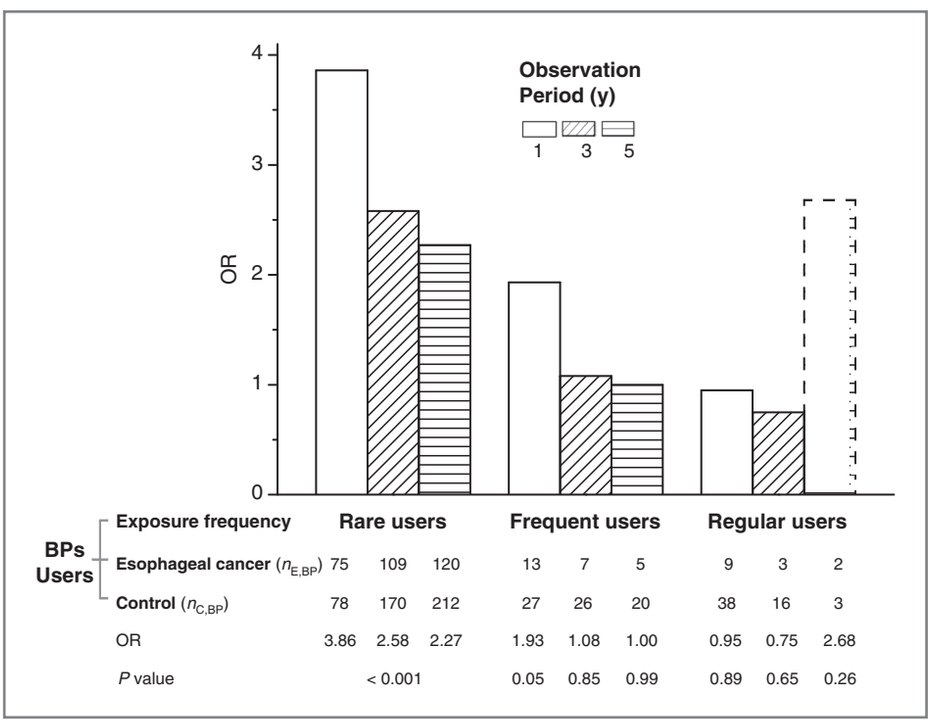
Previous oral bisphosphonate (alendronate, risedronate, clodronate, and etidronate) use was identified in 7.8% versus 3.6% of 16,204 cases versus 64,816 controls during the entire 5-year observation period. The association between oral bisphosphonates use and risk of esophageal cancer is shown in Fig. 1. Compared with 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 bisphosphonates, the lower ORs were found.

Discussion

The study points out an inverse relationship of esophageal cancer risk with bisphosphonate dose intensity, characterized by both usage duration and exposure frequency, in a nationwide population. The higher percentage of bisphosphonate users in cases and significantly increased ORs for rare users in our study might be reasoned by infamous esophagitis attributable to bisphosphonates, 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 bisphosphonates could even have a protective value. Reports of cytostatic, proapoptotic, antimetastatic effects of bisphosphonates in breast, colorectal, and various cancers are not unseen (7, 8). Certainly, the rarity of esophageal cancer necessitates further studies to



BPs Users	Exposure frequency	Rare users			Frequent users			Regular users		
	Esophageal cancer ($n_{E,BP}$)	75	109	120	13	7	5	9	3	2
	Control ($n_{C,BP}$)	78	170	212	27	26	20	38	16	3
	OR	3.86	2.58	2.27	1.93	1.08	1.00	0.95	0.75	2.68
	P value		< 0.001		0.05	0.85	0.99	0.89	0.65	0.26

Figure 1. Association between oral bisphosphonates and risk of esophageal cancer, stratified by observation period and exposure frequency. *$P < 0.001$, compared with nonusers of respective observation periods. BP, bisphosphonate; $n_{E,BP}$, number of bisphosphonate users with esophageal cancer; $n_{C,BP}$, number of controls who had used bisphosphonates. The groups of regular user of the 5-year observation period await larger samples to constitute a valid comparison.

delineate precise roles of bisphosphonates. Prospective designs of sufficient population and calendar years along with preclinical and clinical evidences are required to dissect discrepancy among current data.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Authors' Contributions

Conception and design: Y.-F. Ho, J.-T. Lin, C.-Y. Wu
Development of methodology: J.-T. Lin, C.-Y. Wu
Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): C.-Y. Wu
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): Y.-F. Ho, C.-Y. Wu
Writing, review, and/or revision of the manuscript: Y.-F. Ho, J.-T. Lin, C.-Y. Wu
Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): C.-Y. Wu
Study supervision: J.-T. Lin, C.-Y. Wu

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