Bisphosphonate use and gastrointestinal tract cancer risk: Meta-analysis of observational studies

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Abstract

AIM: To perform a meta-analysis of observational studies to further elucidate the relationship between oral bisphosphonate use and gastrointestinal cancer risk.

METHODS: Systematic literature search was conducted in MEDLINE, EMBASE, and the Cochrane Library to identify studies through January 2011. Search terms were “bisphosphonates” or trade names of the drugs, and “observational studies” or “cohort studies” or “case-control studies”. Two evaluators reviewed and selected articles on the basis of predetermined selection criteria as followed: (1) observational studies (case-control or cohort studies) on bisphosphonate use; (2) with at least 2 years of follow-up; and (3) reported data on the incidence of cancer diagnosis. The DerSimonian and Laird random effects model were used to calculate the pooled relative risk (RR) with 95% confidence interval (CI). Two-by-two contingency table was used to calculate the outcomes not suitable for meta-analysis. Subgroup meta-analyses were conducted for the type of cancer (esophageal, gastric and colorectal cancers). Sensitivity analyses were performed to examine the effect sizes when only studies with long-term follow-up (mean 5 years; subgroup 3 years) were included.

RESULTS: Of 740 screened articles, 3 cohort studies and 3 case-control studies were included in the analyses. At first, 4 cohort studies and 3 case-control studies were selected for the analyses but one cohort study was excluded because the cancer outcomes were not categorized by type of gastrointestinal cancer. More than 124 686 subjects participated in the 3 cohort studies. The mean follow-up time in all of the cohort studies combined was approximately 3.88 years. The 3 case-control studies reported 3070 esophageal cancer cases and 15 417 controls, 2018 gastric cancer cases and 10 007 controls, and 11 574 colorectal cancer cases and 53 955 controls. The percentage of study participants who used bisphosphonate was 2.8% among the cases and 2.9% among the controls. The meta-analysis of all the studies found no significant association between bisphosphonate use and gastrointestinal cancer. Also no statistically significant association was found in a meta-analysis of long-term follow-up studies. There was no negative association between bisphosphonate use and the incidence of esophageal cancer in the overall analysis (RR 0.96, 95% CI: 0.65-1.42, I^2 = 52.8%, P = 0.076) and no statistically significant association with long-term follow-up (RR 1.74, 95% CI: 0.97-3.10, I^2 = 58.8%, P = 0.119). No negative association was found in the studies reporting the risk of gastric cancer (RR 0.89, 95% CI: 0.71-1.13, I^2 = 0.0%, P = 0.472). In case of colorectal cancer, there was no association between colorectal cancer and bisphosphonate use (RR 0.62, 95% CI: 0.30-1.29, I^2 = 88.0%, P = 0.004) and
also in the analysis with long-term follow-up (RR 0.61, 95% CI: 0.28-1.35, I² = 84.6%, P = 0.011).

CONCLUSION: Oral bisphosphonate use had no significant effect on gastrointestinal cancer risk. However, this finding should be validated in randomized controlled trials with long-term follow-up.

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Key words: Bisphosphonate; Gastrointestinal tract cancer; Esophageal cancer; Gastric cancer; Colorectal cancer; Meta-analysis

Peer reviewer: Dr. Kok Sun Ho, Department of Colorectal Surgery, Singapore General Hospital, Outram Road, Singapore 169608, Singapore


INTRODUCTION

Bisphosphonates are commonly used in postmenopausal women with osteoporosis. In vitro and in vivo studies have suggested that bisphosphonate has anticancer properties\(^1\): promoting apoptosis\(^2\), inhibiting tumor cell adhesion and invasion\(^3\), inhibiting angiogenesis\(^4\), altering tumor-associated macrophage function\(^5\), and enhancing immune surveillance\(^6,7\). However, it was recently reported that the Food and Drug Administration received reports of 23 cases of esophageal cancer in the United States and another 31 cases in Europe and Japan, all occurring from 1995 through 2008 among patients using oral bisphosphonates\(^8\). Since then, there have been several cohort studies and case-control studies to elucidate the association between the use of bisphosphonate and the risk of gastrointestinal tract cancer. However, results of the observational studies are inconsistent\(^9,10\).

As yet, there have been no randomized controlled trials demonstrating a causal relationship between bisphosphonate use and gastrointestinal tract cancer. Moreover, no meta-analysis has been performed despite the inconsistent results of observational studies. Therefore, in the present study, we aimed to investigate the association between the use of oral bisphosphonate and the risk of gastrointestinal cancer via meta-analysis of cohort studies and case-control studies.

MATERIALS AND METHODS

Study selection

We conducted a systematic literature search of MEDLINE, 1977 April 2011; EMBASE, 1971 April 2011; and the Cochrane Database of Systematic Reviews in the Cochrane Library, 1973 April 2011. We identified observational studies of bisphosphonate use whose primary or secondary outcomes included gastrointestinal tract cancer. The search terms were "bisphosphonates" or trade names of the drugs, and "observational studies" or "cohort studies" or "case-control studies" (Table 1). All the searches were restricted to human studies. In addition, a manual review of references from primary and review articles was performed to locate any additional relevant studies. All the potentially relevant articles were independently reviewed by 2 investigators (Oh YH and Yoon C). Disagreements between evaluators were resolved by discussion or consultation with a third author (Park SM).

The inclusion criteria were: (1) observational studies (case-control or cohort studies) on bisphosphonate use; (2) with at least 2 years of follow-up; and (3) reported data on the incidence of cancer diagnosis.

Data synthesis

To compute a pooled relative risk (RR) with 95% confidence interval (CI), we used the RRs or odds ratios and 95% CIs that were adjusted for most confounders. Because the incidence of cancer is generally low, we did not distinguish between the various measures of RR. If the outcome measures were unsuitable for meta-analysis, we calculated a crude estimate using a two-by-two contingency table.

We also assessed the heterogeneity for each meta-analysis by using the I² value which measures the percentage of total variation across that is attributable to heterogeneity rather than chance. High value of I² index suggests increased heterogeneity. We also calculated P value of Q-test which represents heterogeneity. If P value is less than 0.10, it represents there is heterogeneity.

Because of the known clinical and methodological heterogeneity of the studies we analyzed, we calculated the pooled RR with 95% CI based on the DerSimonian and Laird random effects model. We used Stata Version 11.0 (Stata Corp., College Station, Texas) for the statistical analysis.

Statistical analysis

Subgroup meta-analyses were carried out for the study design (cohort and case-control) and type of cancer. For the cancer subgroup analyses, esophageal, gastric and colorectal cancers were analyzed independently.

We also performed sensitivity analyses to examine the effect sizes when only studies with long-term follow-up (mean 5 years; subgroup 3 years) were included.

RESULTS

Identification of relevant studies

Figure 1 is a flow diagram of how we identified the relevant studies. Of the 740 articles identified, 4 cohort studies\(^9,10,11\) and 3 case-control studies\(^8,12,13\) were selected for the analyses. Many of initial 742 articles are not in
Table 1  Search strategy

<table>
<thead>
<tr>
<th>Search strategy for MEDLINE</th>
<th>Search strategy for EMBASE</th>
<th>Search strategy for Cochrane reviews of the Cochrane Library</th>
</tr>
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<tbody>
<tr>
<td>14. 1 OR 2 OR 3 OR 4 OR 5 OR 6 OR 7 OR 8 OR 9 OR 10 OR 11 OR 12 OR 13</td>
<td>14. 1 OR 2 OR 3 OR 4 OR 5 OR 6 OR 7 OR 8 OR 9 OR 10 OR 11 OR 12 OR 13</td>
<td>14. 1 OR 2 OR 3 OR 4 OR 5 OR 6 OR 7 OR 8 OR 9 OR 10 OR 11 OR 12 OR 13</td>
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<td>15. Observational studies [ALL]</td>
<td>15. Observational studies/de</td>
<td>15. Observational studies/de</td>
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<tr>
<td>17. Case control studies [ALL] OR case-control studies [ALL]</td>
<td>17. Case control studies/de OR case-control studies/de</td>
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<td>19. 15 OR 16 OR 17 OR 18</td>
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<td>20. 14 OR 19</td>
<td>20. 14 OR 19</td>
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<tr>
<td>Date of search: April 29, 2011 (1973 April 2011); Result: 1709 articles found</td>
<td>Date of search: April 29, 2011 (1977 April 2011); Result: 2129 articles found</td>
<td>Limitation: cochrane database of systematic reviews; Date of search: April 29, 2011 (1971 April 2011); Result: 47 articles found</td>
</tr>
</tbody>
</table>

ALL: All fields; MH: MeSH terms; NM: Supplementary concept/substance name; PT: Publication type; /de: Mapped terms; /lim: Limitation.

our scope. They are mainly about effect of bisphosphonates, effects of several types of bisphosphonate regimen, other adverse effects of bisphosphonate, such as atrial fibrillation, osteonecrosis of jaw syndrome, and anti-cancerous bisphosphonate use for breast cancer and prostate cancer. We performed review of titles and abstract of the articles, then excluded irrelevant for our study. Thirty articles were remained after overall process, but 23 of 30 articles included no available data for outcome measures. One cohort study[19] was excluded because the cancer outcomes were not categorized by type of gastrointestinal tract cancer.

We also contacted Dr. Chris Cardwell to ask the data used in our meta-analyses. The mean follow-up time in all of the cohort studies combined was approximately 3.88 years (range: 0.5-13 years). The 3 case-control studies[10,11,12] used in our meta-analyses reported the number of cases and controls: 3070 esophageal cancer cases and 15 417 controls, 2018 gastric cancer cases and 10 007 controls, and 11 574 colorectal cancer cases and 53 955 controls. The percentage of study participants who used bisphosphonate was 2.8% among the cases and 2.9% among the controls. Tables 2 and 3 summarize the general characteristics of the studies included in our analyses.

The methods of the studies we included were assessed on the basis of 5 predetermined quality assessment items (Table 4). All of the studies included in our analyses were based on the secure record linkage regarding medication use and cancer diagnosis.

**Association between bisphosphonate use and the risk of gastrointestinal tract cancer**

There was no negative association between bisphosphonate use and the incidence of esophageal cancer in the overall analysis (RR 0.96, 95% CI: 0.65 1.42, \( I^2 = 52.8\% \), \( P = 0.076 \); Figure 2A). In 2 studies with long-term follow-up, there was a tendency for bisphosphonate use to develop esophageal cancer; however, this finding was not statistically significant (RR 1.74, 95% CI: 0.97-3.10, \( I^2 = 58.8\% \), \( P = 0.119 \). No significant association was
found in the studies\(^8,14\) reporting the risk of gastric cancer (RR 0.89, 95% CI: 0.71-1.13, \(I^2 = 0\%\), \(P = 0.472\); Figure 2B).

Bisphosphonate users were less likely to receive a diagnosis of colorectal cancer; however, this finding was not statistically significant in the overall analysis (RR 0.62, 95% CI: 0.30-1.29, \(I^2 = 88.0\%\), \(P = 0.004\) or in the analysis limited to studies with long-term follow-up (RR 0.61, 95% CI: 0.28-1.35, \(I^2 = 84.6\%\), \(P = 0.01\); Figure 2C).

### DISCUSSION

#### Main findings

In the present study, we examined the association between oral bisphosphonate use and the incidence of gastrointestinal tract cancer by analyzing the results of previ-
Our meta-analyses found no significant association between the use of oral bisphosphonate and the overall gastrointestinal cancer incidence. In the study design subgroup meta-analysis, no statistically significant association was found for the cohort studies or case-control studies. The cancer type subgroup analysis identified no association between bisphosphonate use and esophageal cancer or gastric cancer. Colorectal cancer was less likely to be diagnosed in bisphosphonate users; however, this finding was not statistically significant. The results of the sensitivity analyses of the studies with more than 3 years of oral bisphosphonate use were similar to those of the overall analyses.

According to our analyses, oral bisphosphonate seems to have little association with the incidence of gastrointestinal cancer. It is well known that the use of oral bisphosphonate induces gastrointestinal problems, such as erosive esophagitis[15]. The endoscopic and histological findings of mucosal injury of the esophagus in patients using oral bisphosphonates[15-20] suggest that prolonged use may increase the risk of esophageal cancer. Green et al[8] analyzed the United

<table>
<thead>
<tr>
<th>Ref.</th>
<th>Country (study type)</th>
<th>Case selection method</th>
<th>Control sampling method</th>
<th>Medication data collection method (period)</th>
<th>Sex ratio of cases (reference group)</th>
<th>Site of cancer</th>
<th>Type of drug (reference group)</th>
<th>Odd’s ratio (95% CI)</th>
<th>Adjustment</th>
<th>No. of cases/no. of controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Green et al[8]</td>
<td>United Kingdom (nested case-control)</td>
<td>Review of computerized information (within participants of GPRD between 1995-2005)</td>
<td>Matched on age (within 2 yr, sex, observation period in the database and general practice attended)</td>
<td>Review of computerized medical records (from 1995 until cancer diagnosis)</td>
<td>72 ± 11 M: 57; F: 43</td>
<td>Gastrointestinal cancer (esophageal, gastric, colorectal)</td>
<td>Any bisphosphonate use (no bisphosphonate use)</td>
<td>Esophageal cancer 1.30 (1.02-1.66); Gastric cancer 0.87 (0.64-1.39); colorectal cancer 0.87 (0.77-1.00)</td>
<td>Age, sex, observation period, general practice, BMI, cigarette smoking, alcohol intake</td>
<td>Esophageal cancer 90/345; gastric cancer 264/14 376; colorectal cancer 1949/9737; colorectal cancer 10 365/51 467</td>
</tr>
<tr>
<td>Nguyen et al[20]</td>
<td>United States (nested case-control)</td>
<td>Review of computerized information (within patients with Barrett’s esophagus in the national veterans affair database between 2000-2002)</td>
<td>Matched on age (interval of 5 yr) and Barrett’s esophagus index date</td>
<td>Review of computerized medical records (from Barrett’s esophagus diagnosis until 3 mo before cancer diagnosis)</td>
<td>65.0 ± 10.3 M: 2.6; F: 97.4</td>
<td>Esophageal cancer</td>
<td>Any bisphosphonate use, mostly alendronate (no bisphosphonate use)</td>
<td>0.81 (0.38-3.72)</td>
<td>Age, Barrett’s esophagus index date, race, non cancer disease comorbidity index, NSAID use, PPI use</td>
<td>Esophageal cancer 2/13; gastric cancer 114/683</td>
</tr>
<tr>
<td>Rennert et al[13]</td>
<td>Israel (conventional case-control)</td>
<td>Review of a computerized information (within postmenopausal women in CHS database between 2000-2006)</td>
<td>Matched on age, sex, residence, and ethnic group in CHS database</td>
<td>Review of CHS pharmacy records</td>
<td>71.1 ± NA F: 100</td>
<td>Colorectal cancer</td>
<td>Any bisphosphonate use more than 1 yr (no bisphosphonate use)</td>
<td>0.41 (0.25-0.67)</td>
<td>BMI, family history of colorectal cancer, vegetable consumption, sports participation, use of low-dose aspirin, statins, vitamin D, postmenopausal hormones</td>
<td>Colorectal cancer 53/100; 880/833</td>
</tr>
</tbody>
</table>

Table 3 Case-control studies (n = 3) included in meta-analysis regarding use of bisphosphonates and risk of cancer

E: Enrollment; F/U: Follow up; CI: Confidence interval; M: Male; F: Female; NA: Not available; BMI: Body mass index; NSAID: Nonsteroidal antiinflammatory drugs; PPI: Proton pump inhibitors; CHS: Clalit Health Service; GPRD: General Practice Research Database.
Kingdom General Practice Research Database and reported that bisphosphonate use increases esophageal cancer risk (RR 1.30, 95% CI: 1.02-1.66). The cancer-promoting effect was even greater in patients who used the drug for more than 3 years (RR 2.24, 95% CI: 1.47-3.43). We can infer from this result that bisphosphonate should be restricted among people with risk factors for esophageal cancer, such as Barrett’s esophagus. However, according to the study of Nguyen et al.[12], the use of oral bisphosphonate does not increase the risk of esophageal adenocarcinoma in patients with Barrett’s esophagus (incidence density ratio 0.92; 95% CI: 0.21-4.15). The risk of esophageal adenocarcinoma in patients with Barrett’s esophagus is 30- to 125-fold greater than the risk in the general population[21]. The carcinogenic effect of oral bisphosphonate, including damage to the esophagus due to the toxicity of the drug itself and the effect of contact between the pill and the esophageal mucosa[15], may expedite the development of esophageal cancer in patients with Barrett’s esophagus. However, a correlation between the risk of esophageal adenocarcinoma and use of oral bisphosphonate by patients with Barrett’s esophagus is inconsistent with the concept of the so-called Barrett pathway.

Several in vivo and in vitro studies suggest that bisphosphonate has anticancerous properties[1-5]. Clinical studies also implicate the anticancerous effect of bisphosphonate in breast cancer[22]. It can be inferred from these studies that bisphosphonate may have a dual role in the prevention and treatment of cancer.

**Table 4: Assessment of study quality**

<table>
<thead>
<tr>
<th>Study</th>
<th>Quality assessment items</th>
</tr>
</thead>
<tbody>
<tr>
<td>Representativeness</td>
<td>Ascertainment of exposure: Secure record or structured interview</td>
</tr>
<tr>
<td>Cohort studies</td>
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<tr>
<td>Steinbuch et al[9]</td>
<td>- (female)</td>
</tr>
<tr>
<td>Abrahamsen et al[10]</td>
<td>+</td>
</tr>
<tr>
<td>Solomon et al[11]</td>
<td>- (medicare beneficiaries)</td>
</tr>
<tr>
<td>Cardwell et al[12]</td>
<td>+</td>
</tr>
<tr>
<td>Case-control studies</td>
<td></td>
</tr>
<tr>
<td>Green et al[13]</td>
<td>+</td>
</tr>
<tr>
<td>Nguyen et al[14]</td>
<td>- (Barrett’s esophagus)</td>
</tr>
<tr>
<td>Rennert et al[15]</td>
<td>- (female)</td>
</tr>
</tbody>
</table>

BMI: Body mass index.
Figure 2  Association between bisphosphonate use and some cancer risk using the meta-analysis of the random effects model. A: Esophageal cancer risk; B: Gastric cancer risk; C: Colorectal cancer risk.
studies that there is no significant association between the use of oral bisphosphonate and the risk of esophageal cancer because bisphosphonate has anticancerous effects. As for procancerous effects, oral bisphosphonate directly irritates the esophageal mucosa and induces erosive esophagitis. On the contrary, bisphosphonate directly and indirectly interferes with cancer cell growth. Our finding about the correlation between the risk of esophageal cancer and oral bisphosphonate use suggests that the procancerous and anticancerous effects of bisphosphonate may cancel each other out.

There is also an implication about esophageal cancer within the statistical results in our study. Two observational studies that have great significance in our meta-analyses Caldwell et al[7] and Green et al[9], reported discrepant results (Figure 2A). According to the analyses of Dixon et al[23], the time-dependent RRs of esophageal cancer and oral bisphosphonate indicate no significant increased risk for esophageal cancer within 3 years of oral bisphosphonate use. However, when these investigators restricted their analyses to bisphosphonate use for more than 3 years, their results were different[23]. The Caldwell study[7] reported a RR of 1.01 (95% CI: 0.48-2.12); Green et al[9] reported a RR of 2.24 (95% CI: 1.47-3.43). The result of our meta-analysis was a RR of 1.74 (95% CI: 0.97-3.10) for the follow-up longer than 3 years. Our results show no statistical correlation between the long-term oral bisphosphonate use and the risk of esophageal cancer. However, in the study of Caldwell et al[7], the RR increased to 1.23 (95% CI: 0.66-2.3) when the analysis was restricted to a group of patients with a mean bisphosphonate use duration of 6.8 years. These results indicate that there is somewhat an association between prolonged oral bisphosphonate use and risk of esophageal cancer. Both studies used data from the United Kingdom General Practice Research Database. Inconsistency between the 2 studies may be explained by differences in study design and confounding that could not be measured.

As stated previously, oral bisphosphonates induce esophagitis[15] and esophageal cancer that can be developed from reflux esophagitis through the Barrett pathway[19,20], and this is not a one-time process; it takes time. For this reason, recurrent injuries and healing processes induced by prolonged oral bisphosphonate use could be clinically meaningful factors. The long-term effect of oral bisphosphonate could be confirmed by an observational study that focuses on much longer periods of oral bisphosphonate use.

Regarding gastric cancer, our results show no significant association with oral bisphosphonate use. There is only 1 study that estimates RR dependent on duration of oral bisphosphonate use. Although there is no statistical significance, Green et al[9] found that RR is less for those using oral bisphosphonate longer than 3 years (RR 0.54, 95% CI: 0.24-1.18) than for those using oral bisphosphonate shorter than 3 years (RR 1.03, 95% CI: 0.67-1.59 for less than 1 year; RR 0.89, 95% CI: 0.52-1.53 for 1-3 years). This implies that there is no cumulative effect of oral bisphosphonate on the risk of gastric cancer. If bisphosphonate has competing procancerous and anticancerous properties, it may not affect the risk of cancer.

We performed a random-effects model analysis of the data on colorectal cancer because of high heterogeneity (I² = 88.0%, P = 0.004). According to our meta-analysis, oral bisphosphonate use demonstrates no effect on the risk of colorectal cancer (RR 0.62, 95% CI: 0.30-1.29). The analysis of the long-term use (more than 3 years) revealed that there is no statistically significant association between oral bisphosphonate use and colorectal cancer (RR 0.61, 95% CI: 0.28-1.35). However, the subgroup analysis shows a significant negative association between oral bisphosphonate use and the incidence of colorectal cancer (RR 0.87, 95% CI: 0.77-1.00; RR 0.41, 95% CI: 0.25-0.67). Therefore, it may be hasty to conclude on the basis of overall meta-analysis that oral bisphosphonate use does not affect colorectal cancer. In the study by Rennert et al[13], cases and controls were matched for age, ethnicity, family history of colorectal cancer, sports activity, vegetable consumption, body mass index (BMI), low-dose aspirin use, statin use, postmenopausal hormone use, calcium supplement use, and vitamin use, all of which can affect the risk of colorectal cancer. However, in Green et al[9], RRs were only adjusted for smoking status, alcohol intake and BMI. Thus, there were important differences in the study design and quality of methods.

The study by Rennert et al[13] implies that oral bisphosphonate has a protective effect against colorectal and breast cancers. The anticancerous effects of bisphosphonate, such as promoting apoptosis[8], inhibiting tumor cell adhesion and invasion[13], inhibiting angiogenesis[14], altering tumor-associated macrophage function[16], and enhancing immune surveillance, as previously mentioned, may have a key role in such a protective effect. One study reported that ibandronate reduces the incidence of colorectal dysplasia in mice with induced ulcerative colitis[24]. In colorectal cancer, different from esophageal cancer, oral bisphosphonate does not directly injure the intestinal mucosa or induce chronic mucosal inflammation and healing processes.

Considering this background, the results of our meta-analyses should be interpreted as inconclusive. A well-designed randomized controlled study or prospective cohort study is needed to confirm the preventive effect of oral bisphosphonate against colorectal cancer.

Our study has a few limitations. First, the number of studies we analyzed is small. There have been few studies about the correlation between oral bisphosphonate use and the risk for gastrointestinal cancer. For this reason, each study that reported on colorectal cancer reported a negative association, but the overall meta-analysis showed no statistical significance. Thus, oral bisphosphonate use is seemingly irrelevant to colorectal cancer. Second, the quality of our study depends on data from
original publications. Our study inevitably inherits some problems from the observational studies, such as selection bias, surveillance bias, and confounding. For example, more esophageal and gastric abnormalities might be observed in bisphosphonate users simply because they receive more endoscopic exams for abdominal discomfort caused by oral bisphosphonate.

We discussed the small number of studies regarding bisphosphonate use and development of gastrointestinal cancer in our article as a limitation. However, the actual number of overall subjects in our meta-analysis is not too small. In cohort studies, 124,686 subjects with mean follow up of 3.88 years were included in the final analysis. In case of case-control studies, there were 3070 esophageal cancer cases, 2018 gastric cancer cases and 11,574 colorectal cancer cases were included as well. Moreover, the results of two large observational studies were inconsistent. Caldwell et al showed no significant association between bisphosphonate use and esophageal cancer. On the other hand, Green et al had revealed the significant association. The inconsistent results of observational studies suggest the need of further studies as well as a meta-analysis.

Despite the negative results, our study is meaningful since it provides not an ultimate but a reasonable interim conclusion regarding the safety of bisphosphonate use before definite accumulation of long-term observational studies.

In summary, our meta-analyses indicate that there is no significant association between oral bisphosphonate use and the risk of gastrointestinal cancer. Oral bisphosphonate use has no significant association with the risk of esophageal cancer. There is an increased, though not statistically significant, risk of esophageal cancer in long-term users of oral bisphosphonate. An observational study focused on long-term use of bisphosphonate is needed to confirm this finding. The risk of gastric cancer is not associated with oral bisphosphonate use. Each study reporting on colorectal cancer indicates a negative association between the risk of colorectal cancer and oral bisphosphonate use, but our meta-analysis showed no statistically significant association. The confidence intervals were large (95% CI: 0.30-1.29). Thus, a randomized controlled trial or prospective cohort study should be performed to confirm the preventive effect of oral bisphosphonate.

**REFERENCES**


**Peer review**

This is a good descriptive study in which authors perform a meta-analysis of observational studies to further elucidate the relationship between oral bisphosphonate use and gastrointestinal cancer risk. The results are interesting and suggest that oral bisphosphonate use had no significant effect on gastrointestinal cancer risk.

**Innovations and breakthroughs**

This meta-analysis systemically assessed the relation between bisphosphonate use and gastrointestinal cancer risk, and also showed site specific, long-term follow up results.

**Applications**

The results of meta-analysis in this study show that use of bisphosphonate has no significant association with gastrointestinal cancers. According to the results, bisphosphonate can be used without charge of carcinogen for now. But there should be a far more long-term observational studies to guarantee the long-term safety.

**Terminology**

Meta-analysis is method focused on contrasting and combining results from different studies to show the overall conclusion. It is essential component of a systematic review procedure.

**COMMENTS**

**Background**

There rises concerns about bisphosphonate use after the reports of 23 cases of esophageal cancer in the United States and another 31 cases in Europe and Japan, all occurring from 1985 through 2008 among patients using oral bisphosphonates. Bisphosphonate induced esophagitis, Barrett’s esophagus and gastric ulcer can be the precancerous condition. There were observational studies to evaluate the risk between esophageal cancer and bisphosphonate use. But the results were inconsistent. So the overall evaluation of the association between gastrointestinal cancer and bisphosphonate is required.

**Research frontiers**

Meta-analysis was used to evaluate the risk of bisphosphonate for gastrointestinal cancer (esophageal, stomach, and colorectal cancer) in this study.

**Applications**

The results of meta-analysis in this study show that use of bisphosphonate has no significant association with gastrointestinal cancers. According to the results, bisphosphonate can be used without charge of carcinogen for now. But there should be a far more long-term observational studies to guarantee the long-term safety.
Oh YH et al. Bisphosphonate and gastrointestinal tract cancer

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