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REVIEW ARTICLE

Oral bisphosphonates and incidence of cancers in patients with osteoporosis: a systematic review and meta-analysis

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Abstract

Purpose Several previous studies have shown that oral bisphosphonates (BPs) are associated with the incidence of 13 specific cancers, including lung cancer, esophageal cancer, gastric cancer, and colorectal cancer (CRC). However, the findings are heterogeneous.

Methods and results Relevant studies published in databases such as PubMed, Embase database, and Cochrane library were systematically retrieved from inception to August 25th, 2018, regardless of language, by two investigators independently. Afterwards, the maximum adjusted hazard ratios (HRs) and corresponding 95% confidence intervals (CIs) were extracted from the retrieved studies. Finally, 13 cohort studies involving 1,510,763 participants were enrolled into this meta-analysis. No significant relationship was found between oral BPs and the risk of all-cause cancer in osteoporosis (OP) patients among the entire population (HR 0.97, 95% CI 0.80–1.18; I^2 92.5%). Besides, oral BPs could remarkably reduce the incidence of breast cancer (HR 0.79, 95% CI 0.68–0.92; I^2 54%) and endometrial cancer (HR 0.79, 95% CI 0.64–0.96; I^2 0%) in postmenopausal OP females. In addition, oral BPs were also found to evidently reduce the incidence of upper gastrointestinal cancer in OP patients among the entire population (HR 0.73, 95% CI 0.54–0.98; I^2 36.1%). However, oral BPs may lead to increased risk of liver cancer in mixed genders (HR 1.69, 95% CI 1.03–2.77; I^2 30.7%).

Conclusions Taken together, oral BPs do not increase the risk of incidence of all-cause cancer; instead, they can reduce the incidence of breast, endometrial, and upper gastrointestinal cancers among the postmenopausal OP females. Our analysis stratified by gender suggests that oral BPs may increase the incidence of liver cancer in mixed genders, while no significant association was observed in females. Careful analysis of post-marketing data should be conducted to address the clinical relevance of our results on the putative association of oral BP use and liver cancer suggested by our meta-analysis.

Keywords Bisphosphonates · Osteoporosis · Cancer · Meta-analysis

Introduction

Osteoporosis (OP), a systemic osteopathy, is characterized by decreased bone density and bone mass, as well as disruption of bone microstructure, which results in increased bone fragility and fracture. At present, OP has post a long-term, large-scale, and escalating problem to the health care system. As is recommended by the North American Menopause Society (NAMS) [1], a healthy lifestyle and appropriate exercises may be sufficient for some low-risk OP patients. However, drug therapy may be necessary when these strategies are inadequate. Typically, bisphosphonates (BPs) are recommended as the first-line treatment for OP in postmenopausal females, elderly men, and glucocorticoid OP.

Recently, experimental studies have shown that BPs can inhibit tumor angiogenesis and suppress the proliferation, prevent

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the adhesion and invasion, and induce the apoptosis of tumor cells [2]. Moreover, several previous studies have suggested that oral BPs are associated with the incidence of 13 specific cancers, including lung cancer [3, 4], esophageal cancer [4, 5], gastric cancer [3, 6], and colorectal cancer (CRC) [3, 7]. However, it remains unclear whether these direct and indirect anti-tumor effects can play a role in preventing primary cancer. Therefore, this meta-analysis aimed to evaluate the relationship between oral BPs and cancer incidence in OP patients.

Methods

The protocol and report of this meta-analysis were carried out based on epidemiological guidelines for the meta-analysis of observational studies [8]. Ethical approval was not necessary since only data from published studies were used in this meta-analysis.

Briefly, relevant studies published in databases of PubMed, Embase database, and Cochrane library were systematically retrieved from inception to August 25th, 2018, regardless of language, by two investigators. Meanwhile, manual retrieval was also conducted. The Boolean operator "and" was used between the three groups of keywords, while "or" was used within one group. The detailed retrieval process is shown in *Appendix 1*. The study inclusion criteria were shown as follows: (1) cohort or randomized controlled trial (RCT), with the study population of OP patients, who had no history of cancer or precancerosis; (2) the exposure of interest was oral BP application; (3) the outcome of interest was the incidence of cancer; and (4) the hazard ratios (HRs) and corresponding 95% confidence interval (CI) were provided. Meanwhile, the study exclusion criteria were shown below: (1) studies enrolling non-OP patients or patients with a history of cancer, studies with case-control or cross-sectional design; (2) studies with non-oral BP use or non-cancer incidence; (3) studies enrolling OP patient pathological causes, such as bone tumors and drug-induced OP, like long-term and extensive use of glucocorticoids; (4) studies with no data regarding HRs and corresponding 95CIs; (5) if a data duplication was used, the study with the longest follow-up data or the largest number of population would be adopted; and (6) case reports and letters were also excluded.

The following data were extracted using a unified data list, including first author, publication year, country, study design, sample size, follow-up, age, percentage of female, intervention, control, and maximum adjustment covariates. Moreover, the HRs of the maximum covariate adjustment were pooled. The original author would be contacted when the required information was ambiguous or missing. Any disagreements or discrepancies between the investigators were resolved through reaching a consensus. Typically, the Newcastle–Ottawa scale (NOS) [9] was used to evaluate the study quality,

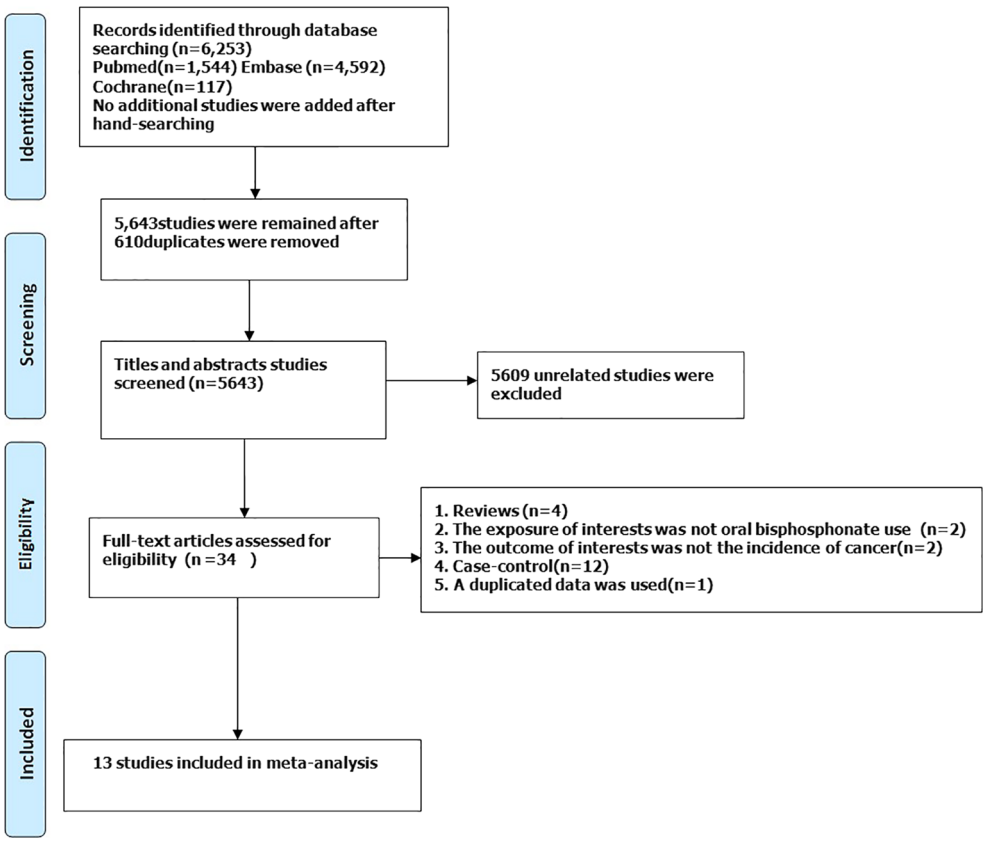

Fig. 1 Flow chart of search results

Table 1 Detailed characteristics of the 13 cohort studies included in this meta-analysis

Author, year	Country	Follow-up, year	Age, year	Female (%)	Sample size	Intervention	Control	Outcome ascertainment	Maximum adjustment covariates
Lee W [3],2012	China	1996–2009	NA	84.4	21,918	Alendronate Use	No Alendronate Use	All-cause cancers 1–10,11,13 ICD-9	Age, sex.
Chiang C [4], 2012	China	Mean 4.8y (1998.1–2009.12)	73.4	100	27,603	Alendronate Use	No Alendronate Use	All-cause cancers 1–3,5–6,11–13 ICD-9	Age, hypertension, diabetes, chronic obstructive pulmonary disease, dyslipidemia, chronic kidney disease, coronary artery disease, colorectal polyp, benign breast disease, morbid obesity, and statin use.
Vestergaard P(b) [5],2011	Denmark	1996–2006	70.5y	84.7	414,245	Alendronate use	No Alendronate Use	2,4-5,12 National Hospital Discharge Register	Age, gender, alcoholism, use of inhaled bronchodilator or corticosteroid drug (proxy for smoking), antacid drugs, ASA or NSAID drugs, working or not, married or not, income above vs. below median, gastric surgery before
Abrahamsen B [6],2012	Denmark	Median 5.5y (1996.1–2006.12)	71.9	100	30,606	Alendronate use	No Alendronate Use	2–3,10 ICD-8 ICD-10	NC
Passarelli M [7], 2013	USA	(1993–2009)	63.1	100	156,826	Bisphosphonate Use	No Bisphosphonate Use	5 Medical Records	Age, race, education, body mass index, smoking status, alcohol consumption, physical activity, nonsteroidal anti-inflammatory drug use, aspirin use, family history of CRC, estrogen-only use, estrogen-progestin use, history of endoscopy, history of mammography, total calcium intake, total vitamin D intake, 5-year hip fracture probability
Tao MH [12], 2018	USA	Mean 13.3y (1995–2013)	>50y	100	151,432	Bisphosphonate Use	No Bisphosphonate Use	1 Medical records and pathology reports	Age, ethnicity, education, smoking status, number of cigarettes per day, duration of regular smoking in years, alcohol use status, body mass index, physical activity, total calcium intake, total vitamin D intake, statins use, hormone treatment status
Cardwell CR [13], 2010	UK	Mean 4.5y (1996.1–2006.12)	70	81	41,826	Bisphosphonate Use	No Bisphosphonate Use	2 Medical Records	BMI, alcohol, smoking, hormone therapy prescription, nonsteroidal anti-inflammatory drug prescription, Barrett esophagus diagnosis, gastroesophageal reflux disease diagnosis, H2 receptor antagonist prescription, proton pump inhibitor prescription
Cardwell CR [14], 2011	UK	Mean 4.5y (1996.1–2006.12)	70	81	46,036	Bisphosphonate Use	No Bisphosphonate Use	All-cause cancers 1,3,5–12 UK General Practice Research Database	BMI, alcohol, smoking, NSAID prescription, glucocorticoid steroid, vitamin D prescription calcium
Khalili [15],2012	USA	1998–2008	64.6	100	86,277	Bisphosphonate Use	No Bisphosphonate Use	5 Medical records	Age, race, BMI, smoking status, family history of colon cancer, history of osteoporosis, regular aspirin use, hormone replacement therapy, regular statin use, total daily calcium intake, vitamin D intake, folate intake, red meat intake, total daily alcohol intake, level of physical activity, history of polyps, history of screening
Newcomb P [16], 2015	USA	Median 12.5y	63	100	89,918	Bisphosphonate use	No Bisphosphonate Use	8 Medical and pathology records	Age, 5-year hip fracture probability, BMI, race, education, smoking status, estrogen-only use, estrogen-progestin use, oral contraceptive use, parity, mammography
Pazianas M [17], 2012	UK	Mean 3.4y 1996.1–2005.12	71.9	100	38,118	Alendronate use	No Alendronate Use	5 National Hospital Discharge Register	Age, Charlson index, known ulcerative colitis, known Crohn's disease, known coeliac disease, hormone

Table 1 (continued)

Author, year	Country	Follow-up, year	Age, year	Female (%)	Sample size	Intervention	Control	Outcome ascertainment	Maximum adjustment covariates
									replacement therapy, and amount of prednisolone, NSAID and ASA used in last 12 months.
Vestergaard P(a) [18],2011	Denmark	1977.1–2006.12	71.1y	100	348,426	Alendronate use	No Alendronate Use	6 National Hospital Discharge Register	Use of systemic hormone therapy before or after start, irradiation before or after start, chemotherapy before or after start, alcoholism before or after start
Fournier A [19], 2017	French	Mean 7.2y 2004–2011	NA	100	64,438	Bisphosphonate Use	No Bisphosphonate Use	6 drug reimbursement database	Age, BMI, time since menopause, use of hormone replacement therapy, use of calcium supplements, use of vitamin D supplements

1 lung cancer, *2* esophageal cancer, *3* gastric cancer, *4* liver cancer, *5* colorectal cancer, *6* breast cancer, *7* prostate cancer, *8* endometrial cancer, *9* ovarian cancer, *10* upper gastrointestinal cancer, *11* bladder cancer and kidney cancer, *12* pancreas cancer, *13* cervical cancer

BMI body mass index, *NC* not clear, *NSAID* nonsteroidal anti-inflammatory drug, *CRC* colorectal cancer

[a,b] Two different studies

with a total score of 9 stars. Specifically, studies with a score of ≥ 6 stars were considered to be of moderately high quality; conversely, those with a score of < 6 stars were considered as low quality.

Besides, the statistical heterogeneity was evaluated using the I^2 statistic. To be specific, the I^2 values of 25%, 50%, and 75% had represented low, moderate, and high heterogeneity, respectively [10]. To more conservatively estimate the pooled HRs, a random effect model, rather than a fixed effect model, was employed, since the former was more able to explain the heterogeneity between studies. In addition, subgroup analysis and sensitivity analysis were also used to explain the potential sources of heterogeneity. Meanwhile, the potential publication bias was evaluated using Begg's test [11]. All statistical analyses were performed using the Stata 12.0.

Results

As shown in Fig. 1, a total of 6253 studies were originally identified, including 1544 from PubMed, 4592 from Embase database, and 117 from Cochrane library. No additional studies were added after manual retrieval. Afterwards, the duplicated studies were eliminated, the titles or abstracts were screened, and the full-texts were read. Finally, a total of 34 studies were left. Then, a detailed review was carried out, and 21 of these 34 studies were excluded for the following reasons:(1) reviews ($n = 4$); (2) the exposure of interest was not oral BP application ($n = 2$); (3) the outcome of interest was not the incidence of cancer ($n = 2$), (4) studies with case-control design ($n = 12$); and (5) duplicated data were used ($n = 1$). Finally, 13 cohort studies [3–7, 12–19] enrolling 1,517,669 participants were included in this meta-analysis. One of these 13 cohort studies included had provided OR data [11]. Moreover, the distinctions among the various measures of relative risk were generally negligible, as the outcome of the study was rare in all the censored populations and subgroups [20]. All results were expressed as the HRs. The detailed characteristics of all studies enrolled in this meta-analysis are presented in Table 1, and all the enrolled studies were of high quality, as shown in *Supplemental Table 1*.

Meta-analysis

All-cause cancer

There were 3 articles including 95,557 patients providing data of all-cause cancer, as shown in Fig. 2. No significant relationship was found between oral BPs and the risk of incidence of all-cause cancer in OP patients among the entire population (HR 0.97, 95% CI 0.80–1.18; I^2 92.5%). Moreover, subgroup analysis stratified by the gender of the study population was

performed, as shown in Fig. 4 and Fig. 5. It could be seen from Fig. 4 that there was no significant change in the relationship between oral BPs and the incidence of all-cause cancer in the mixed genders (HR 0.94, 95% CI 0.71–1.24; I^2 91.7%).

Lung cancer

Four articles enrolling 246,989 patients had mentioned lung cancer, as shown in Fig. 2. No distinct relationship was observed between oral BPs and the risk of incidence of lung cancer in OP patients among the entire population (HR 1.02, 95% CI 0.85–1.24; I^2 71%). Besides, it could be observed from Fig. 4 that no significant change was seen in the relationship between oral BPs and the incidence of lung cancer in the mixed genders (HR 1.09, 95% CI 0.64–1.86; I^2 83.7%). Additionally, Fig. 5 revealed no significant change in the relationship between oral BPs and the incidence of lung cancer in females (HR 1.02, 95% CI 0.80–1.30; I^2 75.7%).

Esophageal caner

Five articles including 536,198 patients had discussed esophageal cancer, as displayed in Fig. 2. No markedly association was found between oral BPs and the risk of incidence of esophageal cancer in OP patients among the entire population (HR 1.15, 95% CI 0.81–1.62; I^2 40.7%). Meanwhile, Fig. 4 reveals no obvious change in the relationship between oral BPs and the incidence of esophageal cancer in the mixed genders (HR 1.28, 95% CI 0.83–1.97; I^2 26.9%). Besides, the relationship between oral BPs and the incidence of esophageal cancer was not changed in females, as presented in Fig. 5 (HR 1.0, 95% CI 0.48–2.08; I^2 68.1%).

Gastric cancer

Three articles including 80,117 patients had provided gastric cancer data, as shown in Fig. 2. There was no evident correlation of oral BPs with the risk of gastric cancer in OP patients

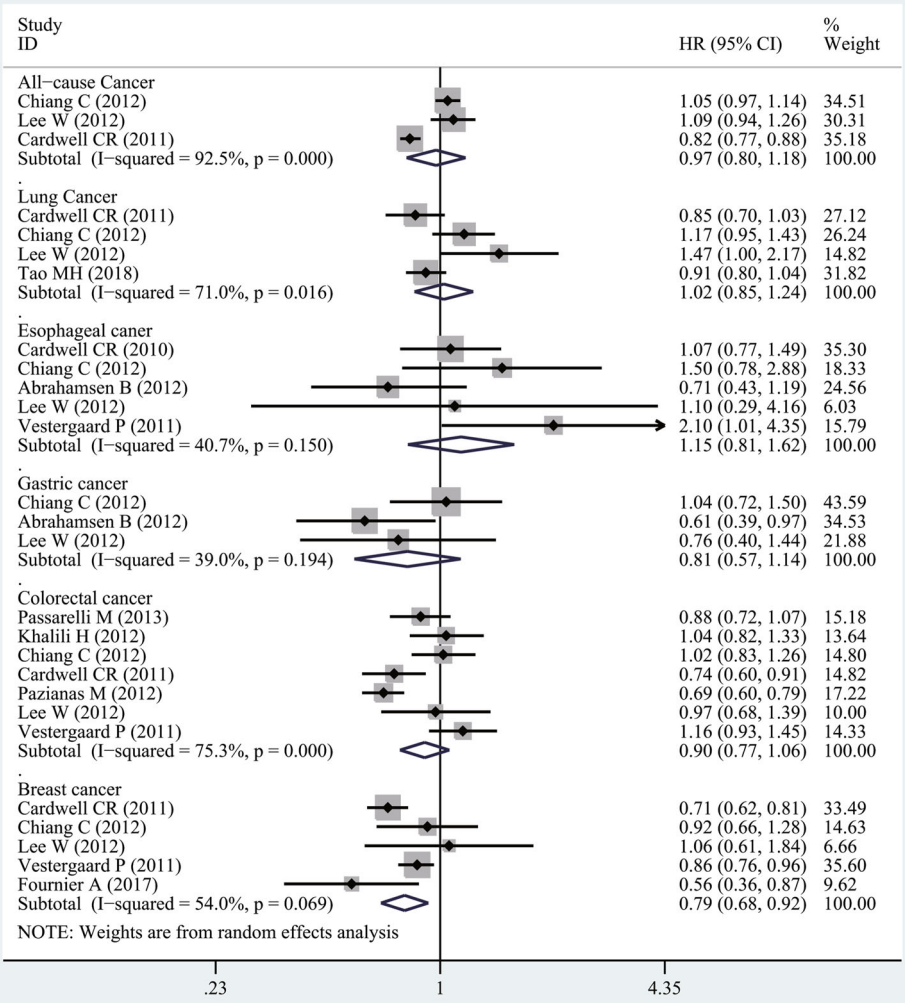

Fig. 2 The HRs of oral bisphosphonates for the incidence of cancers in the entire population

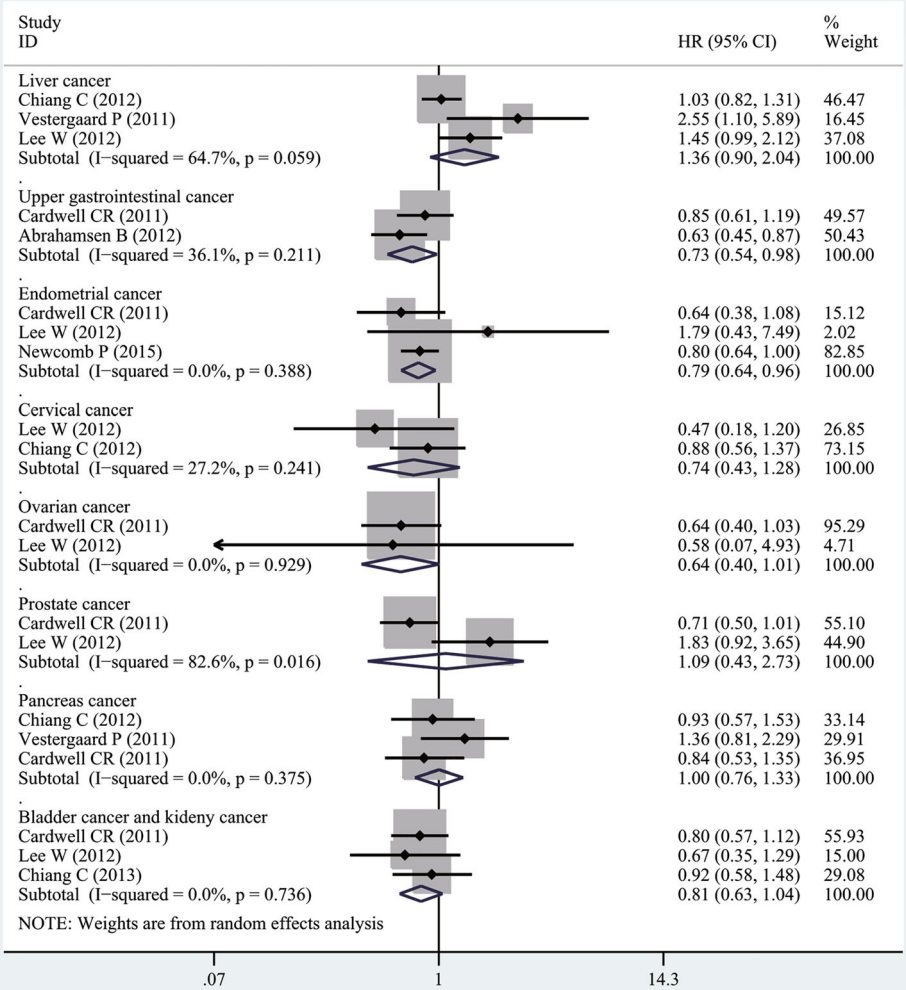

Fig. 3 The HRs of oral bisphosphonates for the incidence of cancers in the entire population

among the entire population (HR 0.81, 95% CI 0.57–1.14; I^2 37%). As illustrated in Fig. 5, no significant change was observed in the relationship between oral BPs and the incidence of gastric cancer in females (HR 0.81, 95% CI 0.48–1.37; I^2 68.7%).

Colorectal cancer

There were seven articles including 791,023 patients mentioning CRC, as shown in Fig. 2. The relationship between oral BPs and the risk of CRC in OP patients among the entire population was not significant (HR 0.90, 95% CI 0.77–1.06; I^2 75.3%). Moreover, Fig. 4 indicates no marked change in the relationship of oral BPs with the incidence of CRC in the mixed genders (HR 0.94, 95% CI 0.69–1.27; I^2 76.4%). Figure 5 suggests that change in the relationship between oral BPs and the incidence of CRC in females was not significant (HR 0.88, 95% CI 0.72–1.09; I^2 79.1%).

Breast cancer

Five articles involving 508,421 patients had discussed breast cancer, as shown in Fig. 2. Oral BPs could remarkably reduce the incidence of breast cancer in female OP patients (HR 0.79, 95% CI 0.68–0.92; I^2 54%).

Liver cancer

Three articles enrolling 463,766 patients had mentioned liver cancer, as presented in Fig. 3. The relationship between oral BPs and the risk of liver cancer in OP patients among the entire population was not significant (HR 1.36, 95% CI 0.90–2.04; I^2 64.7%). Additionally, Fig. 4 had suggested that oral BPs would increase the risk of liver cancer in the mixed genders (HR 1.69, 95% CI 1.03–2.77; I^2 30.7%).

Upper gastrointestinal cancer

Two articles comprising 76,642 patients had described upper gastrointestinal cancer, as demonstrated in Fig. 3. It could be seen that oral BPs could evidently reduce the incidence of upper gastrointestinal cancer in OP patients among the entire population (HR 0.73, 95% CI 0.54–0.98; I^2 36.1%).

Endometrial cancer

Three articles consisting 157,872 patients had mentioned endometrial cancer, as shown in Fig. 3. Oral BPs could notably lower the incidence of endometrial cancer in female OP patients (HR 0.79, 95% CI 0.64–0.96; I^2 0%).

Cervical Cancer

Two articles involving 49,521 patients had studied cervical cancer, as shown in Fig. 3. Oral BPs displayed no significant association with the risk of cervical cancer in female OP patients (HR 0.74, 95% CI 0.43–1.28; I^2 27.2%).

Ovarian cancer

Two articles enrolling 67,954 patients had investigated ovarian cancer, as shown in Fig. 3. Oral BPs were not markedly correlated with and the risk of ovarian cancer in female OP patients (HR 0.64, 95% CI 0.40–1.01; I^2 0%).

Prostate cancer

Two articles consisting 67,954 patients had examined prostate cancer, as shown in Fig. 3. The relationship between oral BPs and the risk of prostate cancer was not significant in male OP patients (HR 1.09, 95% CI 0.43–2.73; $I^2$82.6%).

Pancreatic cancer

Three articles including 489,105 patients had discussed pancreatic cancer, as shown in Fig. 3. There was no significant relationship between oral BPs and the risk of pancreatic cancer in OP patients among the entire population (HR 1, 95% CI 0.76–1.33; I^2 0%).

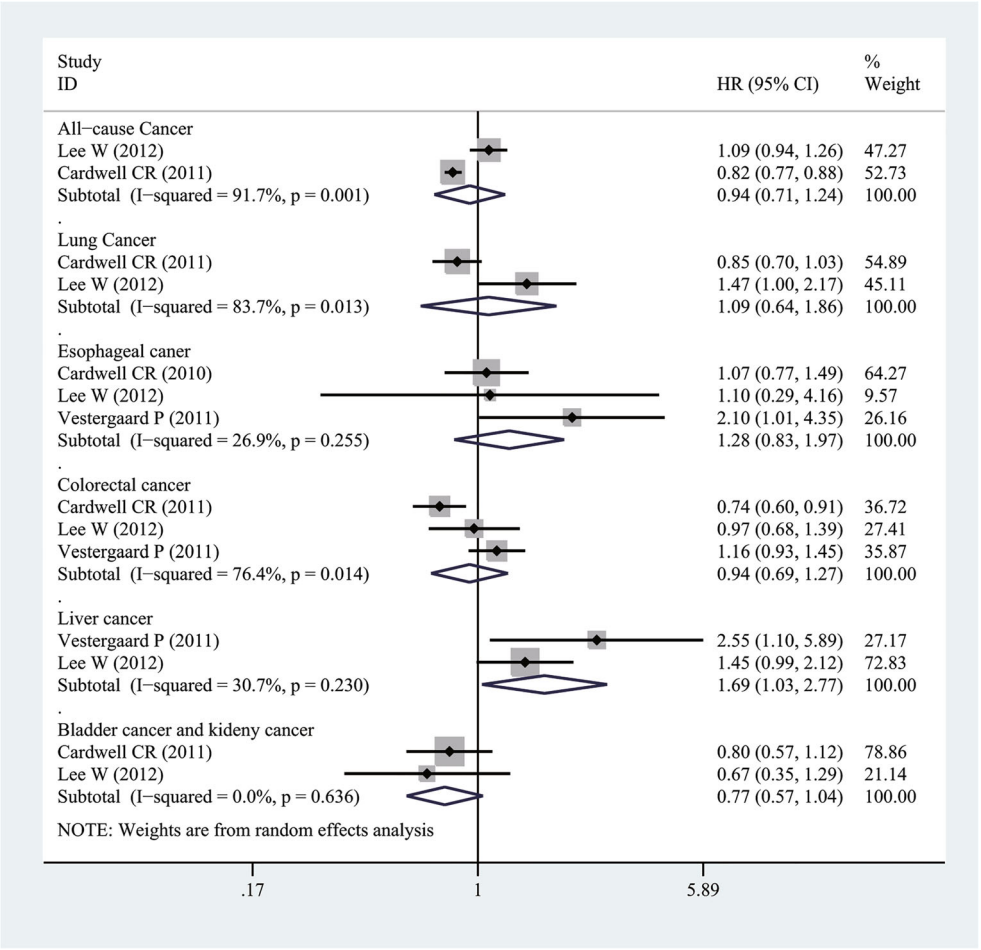

Fig. 4 The HRs of oral bisphosphonates for the incidence of cancers in mixed genders

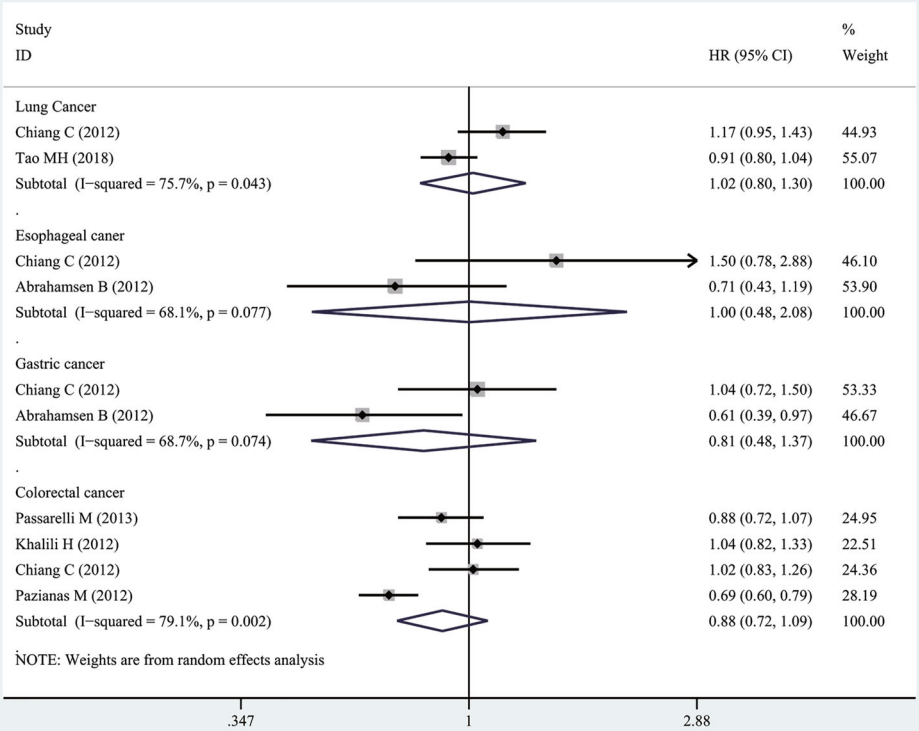

Fig. 5 The HRs of oral bisphosphonates for the incidence of cancers in the females

Bladder cancer and kidney cancer

Three articles including 95,557 patients had discussed bladder cancer and kidney cancer, as shown in Fig. 3. The relationship between oral BPs and the risk of bladder and kidney cancers was not significant in OP patients among the entire population (HR 0.81, 95% CI 0.63–1.04; I^2 0%). Additionally, Fig. 4 suggests that the relationship of oral BPs with the incidence of bladder and kidney cancers was not significant in the mixed genders (HR 0.77, 95% CI 0.57–1.04; I^2 0%) (Fig. 5).

Furthermore, the pooled HRs were adjusted by the maximum covariate, and the random model was employed to make the results more stable. However, subgroup analysis and sensitivity analysis could not be well performed due to the limited number of studies.

Discussion

Findings of this meta-analysis indicated that oral BPs would not increase the risk of incidence of all-cause cancer. Instead, oral BPs were found to reduce the incidence of breast and endometrial cancers in elderly or postmenopausal females and upper gastrointestinal cancer in the elderly. However, no significant relationship was discovered between oral BPs and the incidence of other cancers.

Studies by Abrahamsen B et al. [6] showed that frequent endoscopy after oral BPs may be beneficial for patients to capture this risk.

The study conducted by Vestergaard et al. [5] has shown that liver cancer occurred more frequently throughout the observation of oral BPs. Meanwhile, the study of Lee et al. [3] has shown that the risk of liver cancer increased when the oral ALN dose was 1.0 g/year. However, from the limited data available, we could not find sufficient explanations to link the relationship between oral BPs and liver cancer risk.

The study by Newcomb P et al. [16] indicated that oral BPs could decrease the risk of endometrial cancer based on the complicated underlying mechanism, which might be related to hormone mediation. Moreover, the study of Monsees et al. [21] demonstrated that oral BPs may lower the incidence of breast cancer in patients with positive estrogen receptor, which was consistent with our conclusion.

It was worth mentioning that our meta-analysis was associated with the following strengths. Firstly, to the best of our knowledge, this was the first meta-analysis to systematically summarize the relationship between oral BPs and cancer incidence in OP patients, including the all-cause cancer and the 13 specific cancers. Secondly, to ensure a high level of evidence for the study, only cohort or randomized controlled studies were enrolled in this meta-analysis. Thirdly, the included studies have a large sample size with sufficient follow-up period.

Fourthly, the random-effect model was employed to summarize the HRs, so as to ensure the stability of the results.

Meanwhile, this meta-analysis was also inevitably associated with some limitations, as shown below. Firstly, there was a high heterogeneity between studies; however, Begger test and subgroup analysis could not be conducted due to the limited number of studies enrolled. Secondly, the types of oral BPs could not be obtained in some of the included studies. Thirdly, in the mixed gender studies related to liver cancer, the proportion of males was relatively low. Besides, the effect of the proportion of males on the study results remained unknown as a result of the limited number of available studies. The end point of this study was the incidence of cancer, but several included studies did not follow the unified protocols to carry out appropriate detection of such cancers, which were thereby lack of the background information of patients regarding family history, hormone levels, hormone-related disease treatment, history of alcohol consumption, and cancer stage. Although it was discovered in this study that oral BPs might increase the incidence of liver cancer in the mixed genders, it was not sufficiently explained after referring to a large number of relevant literature. The deficiency of this paper might provide a direction for future studies, and such conclusion should be further verified and supplemented in more high-quality studies in the future. Fourthly, the included studies were mainly from Europe, the United States, and Asia, while relevant studies in other regions were lacking. Fifthly, data of prostate cancer in the enrolled studies were only derived from males, whereas those of breast cancer were only from females. Sixthly, the doses of oral BPs might differ between studies, but dose-response analysis could not be performed due to the lack of data. Seventhly, the extracted HRs were adjusted for multiple variables, and some potential confounding factors could not be excluded.

Conclusions

Taken together, oral BPs do not increase the risk of incidence of all-cause cancer; instead, they can reduce the incidence of breast, endometrial, and upper gastrointestinal cancers among the postmenopausal OP females. Our analysis stratified by gender suggests that oral BPs may increase the incidence of liver cancer in mixed genders, while no significant association was observed in females. Careful analysis of post-marketing data should be conducted to address the clinical relevance of our results on the putative association of oral BP-use and liver cancer suggested by our meta-analysis.

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Compliance with ethical standards

Conflict of interest None.

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