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ORIGINAL ARTICLE

Oral bisphosphonate use and the risk of female breast, ovarian, and cervical cancer: a nationwide population-based cohort study

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Abstract

Summary Bisphosphonate use was not associated with the risk of female breast, ovarian, or cervical cancer. The results according to bisphosphonate type or concurrent drug uses were not associated with the cancer risk. The protective effect of bisphosphonate use on female breast cancer was significant in the low comorbidity group.

Purpose Despite the antitumor mechanisms, the effect of bisphosphonates on the risk of cancer is still unclear. We investigated the association between oral bisphosphonate use and the development of female breast, ovarian, and cervical cancer.

Methods We accomplished a population-based cohort study using the National Health Insurance Services (NHIS) database. A total of 204,525 participants were included in a cohort, and we identified the incident cases of each cancer from 2007 to 2013. We assessed cumulative bisphosphonate exposure from 2003 to 2006 using the defined daily dose (DDD) system. Hazard ratios (HRs) and their 95% confidence intervals (CIs) were presented to assess the association between bisphosphonate use and cancer incidence using multivariate Cox proportional hazard regression models. Subgroup analyses were performed to assess cancer development according to risk factors and concurrent drug use.

Results There was a total of 1547, 266, and 370 incident cases of female breast, cervical, and ovarian cancer, respectively, during the study period of 1,367,294 person-years. Bisphosphonate exposure was not significantly associated with risk of female breast (adjusted HR (aHR), 0.78; 95% CI, 0.60–1.02), ovarian (aHR, 1.30; 95% CI, 0.82–2.07), nor cervical cancer (aHR, 0.70; 95% CI, 0.44–1.12). Further subgroup analyses also revealed no statistically significant effects of bisphosphonate use with various risk factors and concurrent drug use.

Conclusions Our study showed no significant associations between bisphosphonate exposure and female breast, cervical, and ovarian cancer. In the future, large prospective studies or a meta-analysis would be needed to verify the associations.

Keywords Epidemiology · Bisphosphonate · Female breast cancer · Ovarian cancer · Cervical cancer

Introduction

Osteoporosis is a prevalent disease worldwide. It became a common senile disease, especially in postmenopausal women, because of the rapid increase in the elderly population. Bisphosphonates are commonly prescribed primarily for the treatment of osteoporosis. They inhibit osteoclast-mediated bone resorption and are an established therapy in the prevention or treatment of osteoporosis [1].

Another clinical use of bisphosphonates is for the management of bone metastasis secondary to breast cancer, prostate cancer, and multiple myeloma in order to reduce fracture [2, 3]. Recently, several studies identified the anticancer mechanisms of bisphosphonates. They can induce

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cancer cell apoptosis, adhesion, and migration; while inhibiting cancer cell growth, proliferation, invasion, and metastasis in vitro [2, 4]. The simultaneous use of bisphosphonates with other anticancer treatment facilitated a significantly decreased tumor burden compared with standard treatment alone [4]. However, the association of bisphosphonate use and the risk or benefit of developing cancer is still controversial. Several previous studies have suggested that this class of drugs might be associated with reduced risk of female-associated cancers such as breast [5–12], endometrial [13, 14], and ovarian [15], but not all [6, 16–18] studies were in agreement.

Given the widespread and increasing use of bisphosphonate, any association with female-associated cancer risk would have a substantial impact on women's health. However, the association between bisphosphonate use and female-associated cancer risk has rarely been examined, especially in the Asian population. Moreover, the incidence of cervical cancer is the highest among gynecologic cancers in both developing countries and Korea, and its mortality has been increasing as well [19]. In spite of this, the association between bisphosphonate use and risk of cervical cancer has never been researched before.

This study evaluated the effect of bisphosphonate on female-associated cancers, especially breast, cervical, and ovarian cancers, among the Korean population. In addition, although most previous pharmacoepidemiologic studies utilized a nested case-control or propensity matching method, we prospectively designed a cohort observation that set the same index date for all participants to ensure equity of exposure to risk factors.

Methods

Data source and study population

This study was conducted as a population-based prospective cohort study using the Korean Health Insurance Service (NHIS)-National Health Screening database. The database consists of nationwide claims data combined with data from national health screening, which the NHIS provides biennially for all insurant over 40 years of age. Demographic profile information, average monthly insurance premium, comorbid conditions, death and disability registry, and prescription data including drug name, dosage, and duration were obtained. We confirmed that patients received the prescribed drugs by cross-checking their pharmacy visits. The health examination nearest to the index date (January 1, 2007) was selected, and we extracted the following covariates: height, weight and smoking status, alcohol consumption, and physical activity were all self-reported. The NHIS databases have been validated for epidemiologic research in the past [20].

We identified women who were 40 years of age or older and used the Korean national health screening between January 1, 2002 and December 31, 2003. Those who had already been prescribed a bisphosphonate in 2002 were excluded to minimize this prior exposure. We excluded participants who had died before the index date, been diagnosed with any kind of cancer informed by the *International Classification of Diseases code 10th Revision* (ICD-10) C codes, had a history of any cancer registered in the health screening survey data, or had female organ surgery such as mastectomy, oophorectomy, or hysterectomy before December 31, 2006. Finally, a total of 204,525 participants were included in the main analysis, and we observed the incident cases of each cancers from the index date to December 31, 2013 (Fig. 1).

This study was approved by the Institutional Review Board of Seoul National University Hospital (IRB number E-1509-004-699). The ethics committee waived the need for participant informed consents.

Assessment of bisphosphonate exposure and covariates

The exposure period was 5 years before the index date, from 2002 to 2006. We obtained the data regarding all exposures and covariates recorded during the period. The primary exposure of interest was the cumulative use of bisphosphonates. Bisphosphonates were verified through the prescription records in the NHIS database according to the Anatomical Therapeutic Chemical (ATC) classification system of drugs by World Health Organization (WHO) Collaborating Centre for Drug Statistics Methodology [21]. We considered oral bisphosphonate exposure only, not intravenous or other administrative formulations. We included all types of oral bisphosphonates that could be obtained from the NHIS claim databases during the exposure period.

We gathered data regarding bisphosphonate prescriptions such as the date of the prescription, the daily dose, the number of days supplied, and the number of pills. The prescriptions of concurrent drugs used were also obtained, such as aspirin, non-steroidal anti-inflammatory drugs (NSAIDs), and statins that might influence the risk of cancer. We also obtained the prescription information regarding calcium, vitamin D, oral corticosteroids, and use of drugs related to hormone replacement therapy (HRT).

To indicate the drug exposure, we used the DDD system, which assumes the average daily maintenance dose of an individual drug used for the drug's main indication in adults. The DDD is a unit of measurement; it does not indicate a recommended dose or a real dose. We calculated the average daily dose (in units of DDD per day) of each prescription dispensed, weighted by the intended duration of each prescription. In order to further investigate the cumulative dose

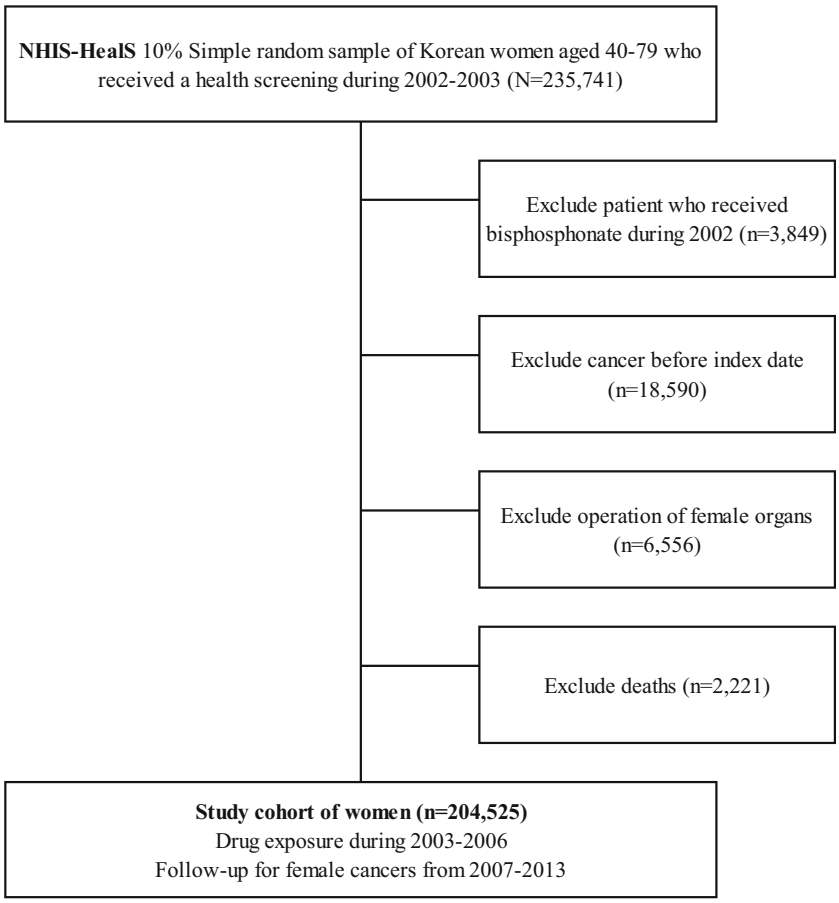

Fig. 1 Study population

responses, the total number of DDDs of oral bisphosphonates received was categorized into two groups: the first quantile (1–105 DDDs) and second quantile (106 DDDs and over).

We expressed comorbid conditions as a Charlson comorbidity index (CCI), which was derived from ICD-10 codes in the claims database, using the sum of the weighted scores of all comorbidities (e.g., cardiovascular disease, pulmonary disease, renal disease, and liver disease) [22]. We calculated body mass index (BMI) as the weight divided by the adult height squared (kg/m^2). For analysis, we classified the participants into the following categories: BMI (<23, 23–24.9, or ≥ 25 kg/m^2) [23], frequency of physical activity (none, 1–2, or ≥ 3 times/week), smoking status (never, former, or current smoker), and frequency of alcohol consumption (none, 1–2, or ≥ 3 times/week).

Outcomes

The primary outcome was a new diagnosis of female breast cancer, cervical cancer, and/or ovarian cancer. The incidence of each of these cancers was identified by the ICD-10 codes C50, C53, and C56, respectively, in the nationwide claims database. The first date of diagnosis under the code was defined as the date of the event. The NHIS databases have been used for epidemiologic research in the past, and the information about prescription use, diagnoses, and hospitalizations is of high quality [24]. Cases that met the criteria but involved a diagnosis of any other cancer prior to the date of the event were not considered for our analysis.

Statistical analysis

We used Cox proportional hazard models to estimate the hazard ratios (HRs) and 95% confidential intervals (CIs) of cancer development with or without bisphosphonate use. We calculated the accumulated person-years of risk, beginning with the index date and ending with the date of cancer diagnosis, diagnosis of any other cancer, or death to December 31, 2013. To investigate the independent effect of using bisphosphonates with each risk factor, we conducted multivariable survival analyses using the Breslow method after adjusting for all potential confounders such as demographics, health risk behaviors, concurrent medications, and medical conditions. We also conducted subgroup analyses regarding risk factors and concurrent drug use in the stratified multivariable analyses. All analyses were performed using the SAS (version 9.4, SAS Institute Inc.). All statistical test results were considered statistically significant when two-tailed p values were < 0.05.

Results

Demographics of the cohort

Among 204,525 participants, 7.26% used bisphosphonates. Table 1 shows the demographics, medical conditions, and medication use of the study cohort. The mean age of bisphosphonate users and non-users was 65.9 and 56.5 years, respectively. Compared with the bisphosphonate non-users, users of the drug were less likely to drink alcohol or exercise. Bisphosphonate users had higher socioeconomic status (SES) and CCI scores and more prescribed aspirin, NSAIDs, statins, calcium, vitamin D, oral steroids, and drugs related to hormone replacement therapy. We found that 79.54% of users had been prescribed alendronate, and 8.65% of users had received both alendronate and risedronate during exposure period.

Bisphosphonate use and risk of cancer

There were total 1547, 266, and 370 cases of female breast, cervical, and ovarian cancer, respectively, in the total cohort during the observation period of 1,367,294 person-years. Table 2 presents the risk of each of the cancers associated with bisphosphonate use and the covariates. A fully adjusted Cox proportional hazard model revealed no statistically significant associations in female breast cancer (HR, 0.78; 95% CI, 0.60–1.02), ovarian cancer (HR, 1.30; 95% CI, 0.82–2.07), and cervical cancer (HR, 0.70; 95% CI, 0.44–1.12).

To explore the dose-response relationship, we categorized the bisphosphonate users into two groups of 105 DDDs, which was the median cumulative dose. The adjusted HRs (95% CI) for the use of bisphosphonate among those ≤ 105 DDDs and > 105 DDDs were 0.75 (0.51–1.09) and 0.82 (0.57–1.17) in female breast cancer, 0.96 (0.47–1.97) and 1.63 (0.93–2.87) in ovarian cancer, and 0.49 (0.23–1.05) and 0.92 (0.52–1.62) in cervical cancer, respectively. This showed no statistically significant association as well (Table 2).

We conducted subgroup analyses stratified by risk factors and concurrent drug use. To evaluate the effect of menopause, we performed a stratified analysis by dividing women into two groups: those who were under the age of 60 and those who were older. Further analyses regarding the effects of BMI, SES, and CCI were demonstrated. In the low CCI group (score 0 to 2), a significantly reduced risk of female breast cancer was shown (HR, 0.63; 95% CI, 0.44–0.90). However, there were no significant associations when stratified by age, BMI, or SES. We explored additional analyses concerning concurrent drugs used such as statins, aspirin, non-steroidal anti-inflammatory drugs (NSAIDs), oral corticosteroids, and hormone replacement therapy (HRT), as these can affect cancer development. The results showed no statistically significant association, which were correlated with the main analysis (Table 3).

Table 1 Baseline characteristics of the study population

	All	Bisphosphonates	
		Non-user	User
Number	204,525	189,678	14,847
Bisphosphonate type (%)*			
Alendronate user			79.5
Risedronate user			26.1
Age (years) (%)			
40–49	31.5	33.7	3.2
50–59	33.3	34.3	21.3
60–69	23.7	22.0	46.1
70 or greater	11.5	10.1	29.5
Body mass index (kg/m^2) (%)			
< 23.0	39.8	39.9	39.2
23.0–24.9	26.8	26.8	26.5
≥ 25.0	33.3	33.2	34.2
Smoking status (%)			
Never	93.0	93.0	93.1
Former	0.8	0.8	0.6
Current	2.4	2.4	2.6
Alcohol consumption, number per week (%)			
None	90.9	90.7	93.8
1–2	5.0	5.2	2.3
≥ 3	1.7	1.7	1.1
Exercise number per week (%)			
None	59.4	59.0	63.9
1–2	18.3	18.7	14.4
≥ 3	19.2	19.3	18.1
SES, lowest quartile (%)			
0	26.2	26.2	25.9
1	25.0	25.2	22.0
2	19.6	19.5	20.4
3	29.3	29.1	31.7
CCI score (%)			
0	22.2	23.2	9.2
1–2	56.9	57.4	50.8
≥ 3	20.9	19.4	40.0
Aspirin user (%)	13.5	12.8	22.4
NSAIDs user (%)	34.0	31.6	64.8
Statin user (%)	9.9	9.4	16.5
Calcium ± vitamin D user (%)	65.3	63.9	84.1
Oral steroid user (%)	73.0	72.3	81.3
HRT user (%)	18.7	18.5	20.0

SES socioeconomic status, *CCI* Charlson comorbidity index, *NSAIDs* non-steroidal anti-inflammatory drugs, *HRT* hormonal replacement therapy

*Alendronate users, participants who had ever prescribed alendronate. Risedronate users, participants who had ever prescribed risedronate

Table 2 Risk of cancers associated with bisphosphonate use and covariates

		Exposure to bisphosphonates					
	Non-user	Any user		≤ 105 DDDs		> 105 DDDs	
Person-year	1,270,261	97,033					
Breast							
Cases	1487	60		28		32	
aHR[a] (95% CI)	1 (Ref.)	0.78	0.60–1.02	0.75	0.51–1.09	0.82	0.57–1.17
Ovarian							
Cases	244	22		8		14	
aHR[a] (95% CI)	1 (Ref.)	1.30	0.82–2.07	0.96	0.47–1.97	1.63	0.93–2.87
Cervical							
Cases	350	20		7		13	
aHR[a] (95% CI)	1 (Ref.)	0.70	0.44–1.12	0.49	0.23–1.05	0.92	0.52–1.62

DDD cumulative daily defined dose, *aHR* adjusted hazard ratio, *CI* confidential interval, *ref.* referent

[a] Using a multivariate Cox proportional hazard model adjusted for age, body mass index, smoking, alcohol consumption, exercise frequency, blood pressure, total cholesterol, diabetes, quartiles of socioeconomic status, Charlson comorbidity index, hormonal replacement therapy, oral steroid, aspirin, NSAIDs, statin, calcium, and vitamin D use

Discussion

Based on this population-based prospective cohort study, bisphosphonate exposure did not show any significant effects on female breast, cervical, or ovarian cancer. There was also no significant association in the analysis according to the bisphosphonate type, cumulative bisphosphonate dose, or covariates.

Several preclinical studies have shown that bisphosphonates have potent antitumor activity that reduces proliferation of tumor cell lines and induces apoptosis [25]. In addition, previous researchers demonstrated a protective effect to reduce the risk of breast [5–12], endometrial [13, 14], and ovarian cancer [15] in individuals using bisphosphonate. However, several clinical studies have demonstrated conflicting results regarding the effect of bisphosphonates on the development of malignancies. Chlebowski et al. [7] showed that the use of oral bisphosphonate significantly reduced the incidence of invasive breast cancer in 2816 postmenopausal women, although in their study, the use of bisphosphonate significantly increased the incidence of in situ breast cancer. Rennert et al. [15] conducted a case-control study and identified a protective effect of bisphosphonate use on ovarian cancer risk but showed no significant association after adjustment for hormone replacement therapy and ethnicity. In this study, we adjusted all confounders including demographics, comorbidities, lifestyle variables, and drug use that might affect cancer development. However, the results were still not statistically significant.

One of the most interesting aspects of the current study is the possibility that it will contribute to race or ethnicity-specific relationships between oral bisphosphonate use and female breast, ovarian, and cervical cancer especially in Asians. The protective association with breast, endometrial, or ovarian cancer tended to be significant in Western population [5–15]. Chlebowski et al. [7] and Newcomb et al. [13] conducted the association between bisphosphonate use and breast cancer and endometrial cancer, respectively, using data from Women Health Initiative, and the white was dominant up to 90%. Likewise, Vinogradova et al. [11] used UK practice-based QResearch and Clinical Practice Research Datalink (CPRD), but they had no access to detailed ethnic information regarding more than 75% of study population, so they assumed the non-recorded ethnicity as white for analyses. Alford et al. [14] demonstrated the protective effects of bisphosphonate and endometrial cancer, but did not evaluate the Asian population. Two studies were conducted in Israel with database from Northern Israel Study [12] and the Haifa Cancer in The Ovary and Uterus Study (CITOUS) [15], which were dominant in Jewish and Arabs. However, only few studies were conducted in Asians, and the protective effect was not clear. Our results were similar to a previous study researched in the Asian population [18], where the authors also showed no statistically significant association. Since the prevalence of female breast and gynecologic cancers is higher in western and white populations than among Asians, it might be beneficial to evaluate the precise risk factors that lead to cancer among the Asian population [19].

For breast cancer, we demonstrated a marginally significant protective association in the low Charlson comorbidity index group. It is well known that cancer development is related with individual comorbidities such as chronic inflammatory diseases, infection, and cardiovascular and pulmonary diseases [26]. Additionally, analysis

Table 3 Risk of cancers according to risk factors and concurrent drug use (references: bisphosphonate non-users)

	Female breast cancer			Ovarian cancer			Cervical cancer		
	Cases	aHR[a]	95% CI	Cases	aHR[a]	95% CI	Cases	aHR[a]	95% CI
Risk factors									
Age (years)									
< 60	18	0.70	0.44–1.12	6	1.65	0.72–3.79	4	0.74	0.27–2.01
≥ 60	42	0.86	0.62–1.20	16	1.12	0.64–1.96	16	0.68	0.40–1.15
BMI (kg/m^2)									
< 23	19	0.77	0.48–1.24	8	1.51	0.70–3.27	5	0.46	0.19–1.16
≥ 23	41	0.79	0.57–1.10	14	1.21	0.67–2.15	15	0.85	0.49–1.45
SES									
0~1	29	0.85	0.58–1.24	8	0.98	0.46–2.06	13	0.93	0.52–1.67
2~3	31	0.73	0.51–1.06	14	1.63	0.90–2.97	7	0.48	0.22–1.04
CCI									
0~2	32	0.63	0.44–0.90	9	0.89	0.45–1.78	15	0.90	0.53–1.55
≥ 3	28	1.12	0.74–1.70	13	1.92	0.98–3.77	5	0.41	0.16–1.05
Concurrent drug uses									
HRT									
Non-user	44	0.77	0.56–1.05	19	1.36	0.81–2.29	11	0.72	0.43–1.22
User	16	0.79	0.47–1.33	4	0.99	0.34–2.88	4	0.69	0.24–1.95
Statin use (DDDs)									
< 30	45	0.75	0.55–1.02	15	1.13	0.65–1.97	13	0.56	0.32–0.99
≥ 30	15	0.88	0.51–1.53	7	1.95	0.79–4.78	7	1.42	0.60–3.37
Aspirin (DDDs)									
< 30	47	0.81	0.60–1.09	15	1.21	0.70–2.09	15	0.68	0.40–1.16
≥ 30	17	0.67	0.38–1.21	7	1.53	0.64–3.68	5	0.88	0.34–2.30
NSAIDs (DDDs)									
< 30	21	0.65	0.42–1.00	7	1.39	0.64–3.02	4	0.38	0.14–1.03
≥ 30	39	0.91	0.64–1.28	15	1.17	0.65–2.08	16	0.93	0.54–1.61

BMI body mass index, *SES* quartiles of socioeconomic status, *CCI* Charlson comorbidity index, *HRT* hormonal replacement therapy, *NSAID* non-steroidal anti-inflammatory drugs, *aHR* adjusted hazard ratio, *CI* confidential interval, *p p* value

[a] Using a multivariate Cox proportional hazard model adjusted for age, body mass index, smoking, alcohol consumption, exercise frequency, blood pressure, total cholesterol, diabetes, quartiles of socioeconomic status, Charlson comorbidity index, hormonal replacement therapy, oral steroid, aspirin, NSAIDs, statin, calcium, and vitamin D use

according to menopause status, BMI, SES, or concurrent drug use showed no significant relationship. Moreover, the median cumulative dose was 105 DDDs in our study, so the relative short-term use and exposure time may have attenuated the effect of the drug. A recent meta-analysis [9] found that bisphosphonate use was associated with a protective effect in breast cancer (pool RR 0.84, 95% CI 0.77–0.90), but short-term use (< 1 year) of bisphosphonate use led to no significant reduction in the risk of breast cancer.

To the best our knowledge, this is the first study to evaluate the impact of bisphosphonate use on cervical cancer in Asians, although we found no statistically significant reduced risk of cervical cancer. In a mouse study, daily doses of zoledronic acid inhibited angiogenesis in both premalignant lesions and cervical tumors, and reduced new cervical malignancy incidence to 30% [27]. However, there are few clinical studies of cervical cancer in humans, and further studies are needed to fully evaluate the effect of bisphosphonate on cervical cancer.

We explored a subgroup analysis relating concurrent drug use with bisphosphonate type, but there was no significant association with cancer development as well. The most commonly used type of bisphosphonate was alendronate, followed by risedronate, but the result was not significant when the subgroup analysis compared bisphosphonate type. Among the bisphosphonates, risedronate has been shown to have the greatest impact on bone resorption, a nearly four times more potent effect

than the next highest alendronate; clodronate and etidronate demonstrate even lower effects [28, 29]. In addition, it is also suggested that high potency bisphosphonates have greater direct antineoplastic, antiinvasive, antiproliferation, and antimigration properties; indirectly inhibit angiogenesis; and possess immune modulatory antitumor effects [28]. Although there are a limited number of cases in the risedronate-only and combined alendronate and risedronate groups, the results from our study are still meaningful because they suggested that the risk of cancer did not significantly change depending on the particular type of bisphosphonate.

Previous epidemiologic studies have shown the controversial relationship between bisphosphonate use and cancer risk and have revealed the pitfalls of past pharmacoepidemiologic study designs. The nested case-control design or standardization incidence ratio analysis did not allow subgroup analyses according to common risk factors affecting both exposure and outcomes. We conducted this prospective cohort study with same calendar date for both user and non-user groups to avoid survivor bias or immortal time bias [30]. Moreover, bisphosphonate use was obtained by the national health insurance claims system, so we were able to achieve reliable prescription data. For the same reason, the prevalence of cancers reported here is in accordance with the cancer registry. Our study also utilized national health examination databases as well as pharmacy databases, thus decreasing the risk of misclassification for all exposure covariates.

Our study has several limitations. First, the number of cases was small and follow-up duration of 6 years was short, which might have attenuated the effect of the bisphosphonates to reduce cancer risk. Moreover, the number of bisphosphonate users was smaller than that of non-users, and the number of cancers in user groups was small as well, which could have led to type II error and the weakening of statistical power. Second, we could not obtain information on histological type, TNM (tumor, lymph nodes, and metastasis) staging, tumor grade, receptor status, and bone mineral density, all of which are major risk factors for female-associated cancers. They were not available from the NHIS database and might influence the results. Finally, our results cannot be generalized to other ethnicities, because all participants were Korean, although the risk contributors for cancers are similar across the population. An imbalance in the unobserved covariates between bisphosphonate users and non-users could attenuate the results, although we fully adjusted the results statistically for all the observed covariates.

In conclusion, our study showed no significant effects between bisphosphonate exposure and female breast, cervical, and ovarian cancers. Larger prospective studies or a meta-analysis of randomized control trials are suggested to further verify our findings.

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Authors' contributions SM Park had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: YS Bae, J Chang, and SM Park.
Acquisition of data: YS Bae and J Chang.
Analysis and interpretation of data: YS Bae, J Chang, and SM Park.
Drafting of the manuscript: YS Bae and SM Park.
Critical revision of the manuscript: YS Bae, J Chang, and SM Park.
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Administrative, technical, or material support: YS Bae.

Compliance with ethical standards

Conflict of interest None.

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