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Risk reduction of endometrial and ovarian cancer after bisphosphonates use: A meta-analysis

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HIGHLIGHTS

- Any use of bisphosphonates was associated with a significant risk reduction of endometrial cancer.
- The protective effects of the use of bisphosphonates against endometrial cancer are mainly found in postmenopausal women.
- The use of bisphosphonates on the risk of ovarian cancer was in favor of protective effects but no significance.

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ABSTRACT

Objective. Recent epidemiological studies have investigated the associations between the use of bisphosphonates and the development of endometrial cancer and ovarian cancer; these studies have shown controversial results. Hence, this meta-analysis was conducted to evaluate the changes in the risks of developing endometrial and ovarian cancers after using bisphosphonates based on current evidence.

Methods. A comprehensive search was performed in the MEDLINE, EMBASE, and Web of Science databases through January 2017. The summary relative risk (RR) estimates for the effects of the use of bisphosphonates on the risks of developing endometrial and ovarian cancers were calculated using a random-effects model.

Results. Seven studies were included with a total of 6471 endometrial cancer cases (7 studies with 213,920 participants) and 6783 ovarian cancer cases (4 studies with 105,507 participants). This meta-analysis suggested that any use of bisphosphonates was associated with a significant 27% reduction in the risk of endometrial cancer (RR = 0.73, 95% CI: 0.58–0.93, $P = 0.012$), but the reduction in the risk of ovarian cancer (RR = 0.81, 95% CI: 0.58–1.14, $P = 0.227$) was not significant. The protective effects of the use of bisphosphonates against endometrial cancer are mainly found in postmenopausal women (RR = 0.53, 95% CI: 0.34–0.93, $P = 0.012$) or in those who have taken bisphosphonates for longer than 1 year (RR = 0.57, 95% CI: 0.35–0.93, $P = 0.024$).

Conclusion. This meta-analysis suggests that the use of bisphosphonates is associated with a reduction in the risk of endometrial cancer but not ovarian cancer.

1. Introduction

According to GLOBOCAN 2012 [1], endometrial cancer is the 5th most common cancer in women, accounting for 319,605 new cases and 76,160 deaths. Ovarian cancer accounts for 238,719 new cases and 151,917 deaths. The incidence of endometrial cancer and ovarian cancer sharply increase during the premenopausal years and peak well after menopause [2]. Endometrial cancer and ovarian cancer share some similar risk factors, such as age and menstrual and reproductive events [3].

Bisphosphonates have been widely used to treat and prevent osteoporosis in postmenopausal women and bone metastases in patients with breast cancers [4, 5]. Since these drugs were approved by the US Food and Drug administration (FDA) in 1995, the rate of bisphosphonates use has rapidly increased [6]. Several experimental studies have proposed that bisphosphonates might have antitumor effects, including inducing apoptosis, reducing proliferation, and inhibiting tumor cell migration and invasion. Epidemiological studies also suggested that bisphosphonates might be associated with the

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reduced risk of some specific types of cancer, including colorectal cancer and breast cancer [7]. A notable risk reduction was found in breast cancers, and the previous meta-analysis by Liu et al. revealed that the use of bisphosphonates had a 15% (RR = 0.85, 95% CI: 0.74–0.98, $P = 0.03$) reduction in the risk of developing any breast cancer [8]. As endometrial cancer and ovarian cancer, like breast cancer, are closely related to hormone levels, the risk factors for breast cancer, endometrial cancer, and ovarian cancer are often similar, such as age, BMI, the use of HRT, and smoking [9]. Taken together, the mentioned evidence suggests that bisphosphonates may also have protective effects against the development of endometrial cancer and ovarian cancer. In recent years, several published studies were performed to assess the risk of endometrial cancer and ovarian cancer after the use of bisphosphonates, with inconsistent results [10–17]. Thus, we conducted this systematic review and meta-analysis to summarize current evidence from all available studies on the use of bisphosphonates in relation to the risk of endometrial cancer and ovarian cancer, and we quantified those associations with different kinds of meta-analysis methods.

2. Methods

2.1. Search strategy and inclusion criteria

We followed the Meta-Analysis of Observational Studies in Epidemiology (MOOSE; Table S1) guidelines to prepare and report this systematic review and meta-analysis [18]. Relevant articles were searched in the MEDLINE (from 1978), EMBASE (from 1998), and Web of Science (from 1997) databases up to January 2017. The following terms were searched to define exposure: *diphosphonates*, *diphosphonate*, and *bisphosphonate*. The search terms for outcomes were defined as *endometrial cancer* and *ovarian cancer*. References of identified articles were also retrieved to assess potentially eligible studies.

Studies were included that met the following criteria: (1) Observational epidemiologic study (cohort, nested case-control, or case-control study) that assessed the risk of endometrial cancer or ovarian cancer after the use of bisphosphonates in women; (2) studies that reported the relative risk (RR), odds ratio (OR), or hazard ratio (HR) and the corresponding 95% confidence interval (CI) or sufficient information to calculate these; (3) the study with most relevant information was included in the case of duplicate studies.

2.2. Data extraction and quality assessment

Data extraction and quality assessment for each included study were conducted independently by two authors, and disagreements were resolved by consensus. Information was extracted from each included study regarding the first author's last name, year of publication, study design, name of design, study location, study period, age of participants, numbers of endometrial cancer cases and ovarian cancer cases, number of participants, measurement of the use of bisphosphonates, risk estimates with 95% CIs, and adjustment factors in multivariate analysis. The 9-star Newcastle-Ottawa Scale (NOS, Table S2) was used to assess the quality of each included study [19].

2.3. Statistical analyses

All statistical analyses were performed using Stata statistical software version 12 (StataCorp, College Station, Texas, USA). A two-sided *P*-value of <0.05 was considered statistically significant. The pooled RRs and 95% CIs for endometrial cancer and ovarian cancer were combined using a random-effects model considering within-study and between-study variation [20]. Because the incidences of endometrial cancer and ovarian cancer were low, the ORs and HRs were considered approximations of the RRs [21]. The statistical heterogeneity across the included studies was assessed using Q and I^2 statistics [22]. The low, moderate, and high degrees of heterogeneity were indicated by I^2 values of <25%, 25–75%, and >75%, respectively. The maximally adjusted study-specific risk estimates with 95% CIs for the risk of endometrial cancer and the risk of ovarian cancer, which compared women who had ever used bisphosphonates with those who had never used them, were pooled as the main outcomes. To assess changes in the risks of endometrial cancer and ovarian cancer due to increased duration of the use of bisphosphonates, the use of bisphosphonates was stratified by duration with two categories, <1 year and >1 year, based on the information in most of the studies reported. Meta-regression analyses by publication year and number of cases were conducted to explore the sources of heterogeneity based on the random-effect method. A cumulative meta-analysis was performed with the publication years and number of cases to evaluate the additional contribution of an individual study to the summary effects [23]. Then, the trends over time in the cumulative meta-analysis were assessed based on the method of comparing the results with a "first vs. subsequent" approach and the Generalized Least Squares (GLS) approach [24–26]. We also conducted subgroup analyses by study design (cohort study, case-control study), study location (America, Europe), measurement of the use of bisphosphonates (self-report, medical record), and number of endometrial cancer cases (<100 cases, ≥100 cases) to determine the association between the use of bisphosphonates and the risk of endometrial cancer. The sensitivity analyses were performed by repeating all analyses using a fixed-effects model. Sensitivity analyses were conducted by removing a single study and calculating the results to evaluate whether the pooled results were markedly influenced by a single study. Begg's rank correlation [27] and Egger's linear regression tests [28] were performed to quantify the potential publication bias. Finally, Trial sequential analysis (TSA) was performed for endometrial cancer by anticipating a 27% relative risk reduction, an overall 5% risk of type I error, and a statistical test power of 90% [29].

3. Results

3.1. Literature search

The detailed results of the literature search are shown in Fig. S1. A total of 609 articles were identified from our initial search among the EMBASE, PUBMED, and Web of Science databases. After reviewing the full texts and excluding 2 duplicate articles [11, 13], 6 eligible articles were identified. Of these, all 6 articles focused on endometrial cancer, and 3 also focused on ovarian cancer. The article by Vinogradova et al. used two primary care databases (QResearch and CPRD) [14]; the results of the two databases were included separately in our meta-analysis. Finally, 7 studies (3 cohort studies, 3 case-control studies and 1 nested case-control study) were included in this meta-analysis, all of which all assessed the association between the use of bisphosphonates and the risk of endometrial cancer [10–17] and 4 of which assessed the association between the use of bisphosphonate and the risk of ovarian cancer [12, 14, 15].

3.2. Study characteristics and quality assessment

The characteristics of the 7 included studies (7 studies on endometrial cancer and 4 studies on ovarian cancer) are shown in Table 1. The publication years of the 7 included studies ranged from 2009 to 2015. This meta-analysis included 6471 women with endometrial cancer from 213,920 participants and 6783 women with ovarian cancer from 105,507 participants (Table 1). Three studies were conducted in America and 4 in Europe (Table 1). Three studies enrolled only postmenopausal women, and 4 studies enrolled both premenopausal and postmenopausal women (Table 1). For the measurement of the use of bisphosphonates, 2 studies were based on participants' self-reports, while 5 studies were based on medical records (Table 1). The study quality scores of the 7 included studies ranged from 6 to 8 according to the NOS guideline (Table 1).

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