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Article

Nitrogen-based Bisphosphonate Use and Ovarian Cancer Risk in Women Aged 50 Years and Older

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Abstract

Background: There are few readily modifiable risk factors for epithelial ovarian cancer; preclinical studies suggest bisphosphonates could have chemopreventive actions. Our study aimed to assess the association between use of nitrogen-based bisphosphonate medicine and risk of epithelial ovarian cancer, overall and by histotype. **Methods:** We conducted a case-control study nested within a large, linked administrative dataset including all Australian women enrolled for Medicare, Australia's universal health insurance scheme, between July 2002 and December 2013. We included all women with epithelial ovarian cancer diagnosed at age 50 years and older between July 1, 2004, and December 31, 2013 (n = 9367) and randomly selected up to 5 controls per case, individually matched to cases by age, state of residence, area-level socioeconomic status, and remoteness of residence category (n = 46 830). We used prescription records to ascertain use of nitrogen-based bisphosphonates (ever use and duration of use), raloxifene, and other osteoporosis medicines (no nitrogen-based bisphosphonates, strontium and denosumab). We calculated adjusted odds ratios (OR) and 95% confidence intervals (CI) using conditional logistic regression. **Results:** Ever use of nitrogen-based bisphosphonates was associated with a reduced risk of epithelial ovarian cancer compared with no use (OR = 0.81, 95% CI = 0.75 to 0.88). There was a reduced risk of endometrioid (OR = 0.51, 95% CI = 0.33 to 0.79) and serous histotypes (OR = 0.84, 95% CI = 0.75 to 0.93) but no association with the mucinous or clear cell histotypes. **Conclusion:** Use of nitrogen-based bisphosphonates was associated with a reduced risk of endometrioid and serous ovarian cancer. This suggests the potential for use for prevention, although validation of our findings is required.

ARTICLE

Epithelial ovarian cancer (EOC) is the eighth most commonly diagnosed cancer in women (1), but, in contrast to other common women's cancers, the 5-year survival rate has not improved substantially over time, remaining below 50% (1). Better treatments and prevention are therefore required to reduce the burden from this disease. Unfortunately, most established risk factors for EOC are not readily modifiable (2), and thus, new avenues for prevention need to be explored.

One potential approach that has received attention is the repurposing of existing chronic diseases medicines for cancer prevention (3,4). In EOC, evidence suggests chemopreventive potential for medicines including statins (5) and aspirin (6). Nitrogen-containing bisphosphonates constitute another medicine class with anticancer potential (7), but these have been infrequently investigated in EOC. Like statins, these osteoporosis medicines act on enzymes in the mevalonate pathway, potentially inhibiting cancer cell proliferation (7). Some preclinical work suggests they inhibit growth in EOC cell lines (8,9), and in murine models, nitrogen-based bisphosphonates have been shown to suppress EOC (9). Some epidemiological studies also suggest bisphosphonate use might be inversely associated with EOC incidence (10); however, most did not separate

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nitrogen-based and no nitrogen-based bisphosphonates, or EOC histotypes, which are known to have differing etiology (11).

To investigate the potential chemopreventive effects of nitrogen-based bisphosphonates for EOC, we aimed to comprehensively assess the association between nitrogen-based bisphosphonate use and risk of EOC overall and by histotype using a large, national linked health dataset with accurate medicine dispensing information, comparing and contrasting the associations observed for other osteoporosis medicines.

Methods

Data Source and Study Population

We conducted a nested case-control study using linked administrative data to investigate the association between bisphosphonate use and EOC (see Figure 1). We assembled a cohort of Australian women aged 18 years and older enrolled for Medicare, Australia's universal health insurance scheme, between July 2002 and December 2013. All Australian citizens and permanent residents are eligible for Medicare, therefore essentially all Australian women are included on the Medicare Enrolments File. These records were linked to the Pharmaceutical Benefits Scheme (PBS), the Australian Cancer Database, and the National Death Index. The PBS included details of all subsidized dispensed medicines (including bisphosphonates) from July 2002 onward and all PBS medicines after April 2012 (the PBS includes most medicines prescribed in Australia). The Australian Cancer Database included all cancer diagnoses from 1982 to December 2013 (registration of cancer diagnoses is mandatory in Australia), and the National Death Index included all death records from 2002 to 2017. Supplementary Figure 1 (available online) describes each dataset and the period covered. We excluded women who enrolled for Medicare after July 1, 2002, as adults, because the majority would have been immigrants and we may not have had complete cancer histories for them. There were 8 672 838 women eligible for the study. The study was approved by the human research ethics committees of the University of Queensland, the QIMR Berghofer Medical Research Institute, the Australian Institute of Health and Welfare, and all other relevant governance bodies.

Case and Control Definition

We required a minimum 2-year PBS history, including a 6-month exclusion period before cancer diagnosis (index date for controls) to account for medicine changes related to prediagnosis cancer symptoms and 18 months or more prescription-dispensing history to ascertain medicine use. Cases included all those with EOC registered between July 1, 2004, and December 31, 2013. We used the *International Classification of Diseases for Oncology* topography codes to ascertain ovarian cancer (including fallopian tube and primary peritoneal cancer; Supplementary Table 1, available online), and morphology codes to identify epithelial ovarian cancers. We classified EOC histotype using the criteria from the 2016 CONCORD-2 study (Supplementary Table 2, available online) (12) but could not distinguish between low- and high-grade serous carcinoma. We excluded those with previous cancer diagnoses; those aged younger than 50 years at diagnosis (n = 1614, as bisphosphonate use is rare in these women); 5 women who used bisphosphonates prescribed for Paget disease or cancer (pamidronate disodium, tiludronate, ibandronate, and clodronate: Anatomical Therapeutic Chemical (ATC) codes M05BA02, M05BA03, M05BA05 and M05BA06); and those without a Socio-Economic Indexes for Areas (SEIFA) score (defined below) assigned to their postcode (n = 50), leaving 9367 cases.

We used EOC diagnosis date as the index date for cases. Using risk-set sampling, we randomly selected up to 5 controls per case from the study population alive at the index date, with no prior diagnosis of cancer or bisphosphonate use for Paget disease or cancer. Controls were matched to cases by birth year (within 1 year), state of residence, area-level socioeconomic status, and remoteness category (defined below). We identified 46 830 matched controls. Women could be selected as a control for more than 1 case, and women with EOC could be selected as controls prior to their EOC diagnosis.

We used Medicare enrollment postcodes to determine women's state of residence and to estimate area-level socioeconomic status using the SEIFA Index of Relative Socio-Economic Disadvantage (13). We classified participants into SEIFA quintiles ranging from the most disadvantaged (first quintile) to the least (fifth quintile). We assigned a remoteness-of-residence category based on postcodes using the Accessibility/Remoteness Index of Australia (14), with categories including major cities, inner regional, outer regional, remote, and very remote (combining the latter 2 groups because of their small populations). We used the earliest available SEIFA (2001) and Accessibility/Remoteness Index of Australia (2006) indices; however, if the relevant score was missing for the postcode, the 2006 or 2011 score was used. Although Medicare enrollments dated back to 1983, and residence may have changed before 2001, the socioeconomic status of the population living within each postcode is unlikely to have changed substantially during this time (15).

Exposure Variables

We categorized medicines according to the ATC classification system, PBS item codes, and dispensing dates (Supplementary Table 3, available online) and included nitrogen-based bisphosphonates, raloxifene, and other osteoporosis medicines (no nitrogen-based bisphosphonates, strontium, and denosumab). We classified participants as a medicine user when they had at least 2 dispensing records for that medicine within a 12-month period from July 2002 to 6 months prior to index date (12 months as a sensitivity analysis), except for the injectables, zoledronic acid (nitrogen-based bisphosphonate) and denosumab, for which women were classified as users after 1 dispensed prescription. We categorized women as users of nitrogen-based bisphosphonates, raloxifene, or other osteoporosis medicines only or as users of a combination of 2 or all 3 groups.

We calculated the total defined daily dose (DDD) for each woman using the World Health Organization Collaborating Centre for Drug Statistics Methodology (16) DDD for each ATC code, the number of DDDs for the PBS item code (Supplementary Table 3, available online), and the quantity dispensed. We calculated each woman's use period from the date first defined as a user until the date of her last prescription as well as the total daily doses dispensed at this date, excluding use in the 6 months prior to index date. We defined 1 year or more of nitrogen-based bisphosphonate use as a use period of 12 or more months and at least 80% (17) of 365.25 daily doses. Zoledronic acid is usually administered yearly (18), therefore we considered each injection as 1 year of use. We defined women as users for 3 years or more once they had a use period of 36 months or more and 80% of 3 years of daily doses (DDD $\geq$ 877) and users for 5 years or more once they had a use period of 60 months or more and 80% of

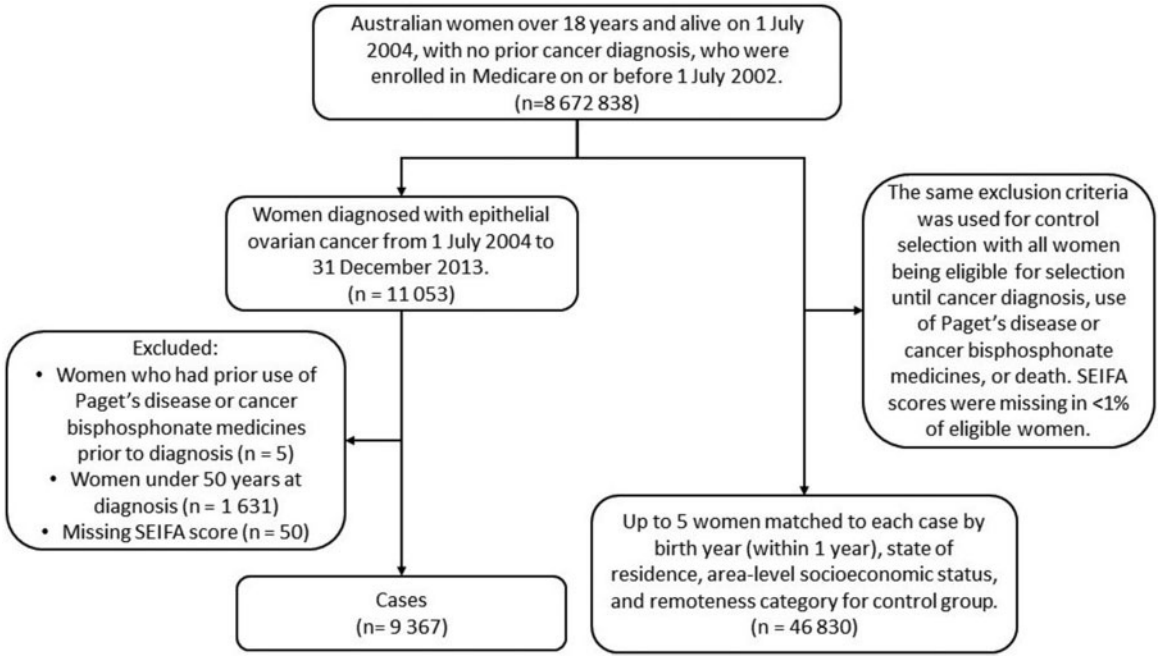

Figure 1. Flowchart of the selection of cases and controls for the study. SEIFA = Socio-Economic Indexes for Areas.

5 years of daily doses (DDD $\geq$ 1461). Each woman was assigned 1 of 5 durations of use categories (no use, <1 year, 1 to <3 years, 3 to <5 years, $\geq$5 years).

Covariates

In addition to our matching variables, we considered several other potential confounders determined using directed acyclic graphs (19).

To adjust for potential confounding by comorbidity, we used the validated weighted Rx-Risk Comorbidity Score (Rx-Risk score) (20), which has been mapped to Australian PBS item codes (21). We did not have records for all medicines included in the score (Supplementary Table 4, available online); however, most of those missing have low or zero weighting or are used for rare conditions unlikely to materially affect the likelihood of a woman being diagnosed with EOC. Medicines for respiratory disease and depression were the only weighted, common medicines not available in the dataset; however, these conditions are unlikely to confound the relationship between osteoporosis medicines and EOC. We used the Rx-Risk score for each woman calculated at 6 months prior to index date, with a maximum of 5 years of medicine history used to identify comorbidities for each woman. We excluded osteoporosis and Paget disease from the score. As a sensitivity analysis, we restricted PBS history for the Rx-Risk score to 2 years prior to the index date, to check for bias because of a shorter PBS history.

We had limited information on other potential confounders for the whole national dataset, therefore we conducted several sensitivity analyses to assess the likely effect on our results. These are described in detail in the Supplementary Methods (available online). First, we restricted analyses to Western Australian women, for whom we had additional hospital morbidity information (Supplementary Table 5, available online) allowing us to exclude those with a bilateral salpingo-oophorectomy (BSO) prior to the index date (therefore essentially no longer at risk of ovarian cancer) and additionally matched controls to cases by parity. Secondly, we restricted our analyses to women defined as PBS concessional beneficiaries who had information available for the whole study period on all dispensed PBS medicines. In this group, we additionally adjusted for menopausal hormone therapy (MHT) use and specifically for use of type II diabetes mellitus medicines, which have been shown in Australian data to predict obesity well (22) (see Supplementary Methods, available online). We defined women as MHT users if they were dispensed at least 2 of either estrogen-only or combined MHT (ATC codes G03C and G03F) within a 12-month period at any point up to 6 months prior to the index date.

We also performed quantitative bias analyses (23) to assess for possible confounding by obesity or early age at menopause (younger than 45 years, as risk of osteoporosis increases and EOC risk decreases with early menopause). We used estimates of obesity prevalence among users and nonusers of bisphosphonates (24) and estimates of prevalence of early menopause among women with and without hip fracture (25). Finally, we assessed the potential for remaining residual confounding, by calculating the expect (E)–value (26,27) for our main results to determine the minimum strength of any unmeasured confounder required to explain away our effect estimates.

Statistical Analysis

We used conditional logistic regression to estimate odds ratios (ORs) and 95% confidence intervals (CIs) for the association between the osteoporosis medicines and the risk of EOC overall and by serous, endometrioid, mucinous, and clear cell histotype. Results were considered to be statistically significant if the 95% confidence intervals did not include 1.00. We estimated odds ratios as approximation for risk ratios and adjusted the models for the weighted Rx-Risk score as a continuous variable. We assessed the association for ever use of nitrogen-based bisphosphonates compared with no use and additionally

assessed the association for nitrogen-based bisphosphonate by duration of use with no nitrogen-based bisphosphonate use as the reference. We excluded cases diagnosed with EOC before July 1, 2008, for the duration of use analysis, to allow sufficient PBS history to categorize women as users for these durations. Analyses were performed in SAS 9.4 (SAS Institute Inc, NC, USA).

Results

The characteristics of the cases and controls are shown in Table 1. Table 2 shows the results of our main analyses. We found that use of nitrogen-based bisphosphonates was associated with a reduced EOC risk (OR = 0.81, 95% CI = 0.75 to 0.88) compared with no use. Reducing the period included in the Rx-Risk score calculation to 2 years before index date did not alter our results (OR = 0.81, 95% CI = 0.75 to 0.88), nor did using a 12-month exclusion period for medicine use prior to the index date (OR = 0.80, 95% CI = 0.74 to 0.87). The association was weaker for less than a year of use (OR = 0.94, 95% CI = 0.79 to 1.11) compared with longer durations; however, the odds ratio for 1 to 3 years (OR = 0.81, 95% CI = 0.67 to 0.97) did not differ materially from the estimate for 5 years or more (OR = 0.80, 95% CI = 0.68 to 0.94).

When we categorized medicine use into ever use of nitrogen-based bisphosphonate, raloxifene, or other osteoporosis medicines or users of a combination of 2 or all 3 of these groups, the association between nitrogen-based bisphosphonates and EOC risk did not change (Table 2). The odds ratios for the association between use of raloxifene or other osteoporosis medicines and EOC were less than 1, however, confidence intervals were wide because of the small number of users. For women who used medicines from more than 1 group, the results were similar to nitrogen-based bisphosphonates alone because 97.0% had also used nitrogen-based bisphosphonates.

Table 3 shows the results by EOC histotype. Because of small numbers, we categorized duration of use as more or less than 1 year only. There was a strong inverse association with endometrioid EOC (OR = 0.51, 95% CI = 0.33 to 0.79), particularly for use of at least 1 year (OR = 0.44, 95% CI = 0.25 to 0.76). A statistically significant reduced risk of serous EOC was also observed (ever use: OR = 0.84, 95% CI = 0.75 to 0.93). The estimates for mucinous and clear cell cancers were close to 1 and much less precise because of the small number of women with these histotypes.

Supplementary Table 6 (available online) shows characteristics of cases and controls included in our sensitivity analyses. Our results did not materially change when we repeated our analysis restricting to Western Australian women, additionally matching cases and controls by parity and excluding women with a BSO prior to the index date (Supplementary Table 7, available online). Further adjustment for hysterectomy and unilateral salpingo-oophorectomy did not change the results.

When we included only women who were concessional beneficiaries, the odds ratio was slightly closer to 1 compared with our main analysis (OR = 0.87, 95% CI = 0.80 to 0.95; Supplementary Table 8, available online), but there was no change after adjusting for MHT or diabetes medication use (as an indicator of obesity). When we looked at the combination of nitrogen-based bisphosphonate with MHT and then without MHT use, associations with EOC were similar (Supplementary Table 8, available online). Our quantitative bias analysis accounting for obesity (Supplementary Table 9, available online) and early menopause (Supplementary Table 10, available online) suggested that estimates would not differ materially from our main analysis had we been able to adjust for obesity or early menopause. For completeness, we also calculated E-values (26,27) (Figure 2), which also suggested that result was not sensitive to confounding for this dataset, although these types of sensitivity analyses cannot be definitive.

Table 1. Characteristics of women diagnosed with epithelial ovarian cancer (cases) and matched controls

Characteristic	Cases No. (%)	Controls No. (%)
Total	9367	46 830
Age at diagnosis, y[a]		
50-59	2380 (25.4)	11 900 (25.4)
60-69	2894 (30.9)	14 470 (30.9)
70-79	2433 (26.0)	12 165 (26.0)
80-89	1450 (15.5)	7248 (15.5)
90 and older	210 (2.2)	1047 (2.2)
SEIFA[a]		
1 (most disadvantaged)	1799 (19.2)	8993 (19.2)
2	1885 (20.1)	9422 (20.1)
3	1849 (19.7)	9245 (19.7)
4	1899 (20.3)	9495 (20.3)
5 (least disadvantaged)	1935 (20.7)	9675 (20.7)
Remoteness[a]		
Major city	6448 (68.8)	32 240 (68.8)
Inner regional	1992 (21.3)	9960 (21.3)
Outer regional	814 (8.7)	4070 (8.7)
Remote/very remote	113 (1.2)	560 (1.2)
Registered state[a]		
New South Wales	3148 (33.6)	15 740 (33.6)
Australian Capital Territory	133 (1.4)	665 (1.4)
Victoria	2397 (25.6)	11 982 (25.6)
Queensland	1789 (19.1)	8945 (19.1)
South Australia and Northern Territory	813 (8.7)	4065 (8.7)
Western Australia	832 (8.9)	4160 (8.9)
Tasmania	255 (2.7)	1273 (2.7)
Weighted Rx-Risk score at index date		
Mean (minimum, maximum)	0.8 (−4, 15)	0.8 (−4, 16)

[a]Matching variable. SEIFA = Socio-Economic Indexes for Areas.

Discussion

Our large, population-based data linkage study showed that, among women aged older than 50 years, use of nitrogen-based bisphosphonates was associated with reduced EOC risk, with an almost 50% lower risk of the endometrioid histotype and a 16% lower risk of serous cancers. Risk reduction appeared stronger for use longer than 1 year compared with less but did not clearly reduce further beyond this. There was no apparent association between use of nitrogen-based bisphosphonates and clear cell or mucinous histotypes.

Our overall results were consistent with a previous meta-analysis of observational studies (10), although the results of that analysis were not statistically significant, did not consider EOC histotype, and did not separate out effects of nitrogen-based bisphosphonates from other bisphosphonates. Some studies have focused on nitrogen-based bisphosphonates. A follow-up of a randomized controlled trial investigating the efficacy of zoledronic acid (a nitrogen-based bisphosphonate) for fracture prevention in women (aged older than 65 years) found a lower risk of gynecological cancer among those receiving zoledronic acid

Table 2. Association between nitrogen-based bisphosphonates and epithelial ovarian cancer

Medicine use category	Cases No. (%)	Controls No. (%)	OR (95% CI)[a]
Use of nitrogen-based bisphosphonates			
No user of NBB	8438 (90.1)	41 318 (88.2)	Referent
Ever user of NBB	929 (9.9)	5512 (11.8)	0.81 (0.75 to 0.88)
Use of NBB, raloxifene, or other osteoporosis medicines			
No use of NBB, raloxifene, or other osteoporosis medicines	8322 (88.8)	40 663 (86.8)	Referent
NBB	822 (8.8)	4913 (10.5)	0.80 (0.74 to 0.87)
Raloxifene	67 (0.7)	382 (0.8)	0.85 (0.65 to 1.10)
Other	48 (0.5)	252 (0.5)	0.92 (0.67 to 1.25)
Combinations[b]	108 (1.2)	620 (1.3)	0.83 (0.68 to 1.03)
Duration of nitrogen-based bisphosphonate use			
No user of NBB[c]	4948 (88.9)	24 298 (87.3)	Referent
Ever user of NBB[c]	618 (11.1)	3529 (12.7)	0.85 (0.77 to 0.94)
NBB user <1 year[c,d]	173 (3.1)	896 (3.2)	0.94 (0.79 to 1.11)
NBB user 1 to <3 years[c,d]	135 (2.4)	814 (2.9)	0.81 (0.67 to 0.97)
NBB user 3 to <5 years[c,d]	124 (2.2)	700 (2.5)	0.86 (0.71 to 1.04)
NBB user ≥5 years[c,d]	186 (3.3)	1119 (4.0)	0.80 (0.68 to 0.94)

[a]Eleven models adjusted for weighted Rx-Risk score and matched by age, Socio-Economic Indexes for Areas, remoteness, and registered state. CI = confidence interval; NBB = nitrogen-based bisphosphonates; OR = odds ratio.
[b]Combinations include use of NBB with raloxifene and/or other osteoporosis medicines or raloxifene and other osteoporosis medicines.
[c]Excludes cases diagnosed prior to July 1, 2008.
[d]Duration of use categories are mutually exclusive and are based on the following minimum use period and daily doses: <1 year: no minimum use requirements; 1 to <3 years: use period of 12 months plus 272 daily doses; 3 to <5 years: use period of 36 months plus 877 daily doses; ≥5 years: use period of 60 months plus 1461 daily doses. If a woman did not meet the minimum requirements of both the use period and daily doses, she was categorized in the previous duration of use group.

Table 3. Association between nitrogen-based bisphosphonates by epithelial ovarian cancer histotype[a]

Medicine use category	Cases No. (%)	Controls No. (%)	OR (95% CI)[b]
Serous			
No user of NBB	4800 (90.8)	23 583 (89.3)	Referent
Ever user of NBB	485 (9.2)	2840 (10.7)	0.84 (0.75 to 0.93)
NBB user <1 year	134 (2.5)	790 (3.0)	0.83 (0.69 to 1.01)
NBB user ≥1 year[c]	351 (6.6)	2050 (7.8)	0.84 (0.74 to 0.94)
Endometrioid			
No user of NBB	570 (95.8)	2741 (92.1)	Referent
Ever user of NBB	25 (4.2)	234 (7.9)	0.51 (0.33 to 0.79)
NBB user <1 year	10 (1.7)	71 (2.4)	0.67 (0.34 to 1.33)
NBB user ≥1 year[c]	15 (2.5)	163 (5.5)	0.44 (0.25 to 0.76)
Mucinous			
No user of NBB	424 (91.2)	2127 (91.5)	Referent
Ever user of NBB	41 (8.8)	198 (8.5)	1.07 (0.74 to 1.54)
NBB user <1 year	9 (1.9)	65 (2.8)	0.71 (0.35 to 1.46)
NBB user ≥1 year[c]	32 (6.9)	133 (5.7)	1.23 (0.81 to 1.86)
Clear cell			
No user of NBB	412 (92.0)	2067 (92.3)	Referent
Ever user of NBB	36 (8.0)	173 (7.7)	1.08 (0.73 to 1.60)
NBB user <1 year	16 (3.6)	40 (1.8)	2.04 (1.12 to 3.71)
NBB user ≥1 year[c]	20 (4.5)	133 (5.9)	0.78 (0.47 to 1.28)

[a]Undifferentiated cancers and less common histotypes were excluded. CI = confidence interval; NBB = nitrogen-based bisphosphonates; OR = odds ratio.
[b]All models adjusted for weighted Rx-Risk score and matched by age, Socio-Economic Indexes for Areas, remoteness, and registered state.
[c]Minimum 1 year use period and at least 80% of daily doses for 1 year or any use of zoledronic acid.

(hazard ratio = 0.50, 95% CI = 0.10 to 1.99) (28). However, this analysis included only 9 cases, and it did not specify how many had EOC. A pooled analysis found an inverse association only for risedronate use (a nitrogen-based bisphosphonate) and EOC risk but no association with bisphosphonate use overall (29), in keeping with our findings suggesting that the different mechanisms of action for nitrogen-based bisphosphonates compared with no nitrogen-based bisphosphonates may be relevant for EOC incidence. Nitrogen-based bisphosphonates have been shown to inhibit the mevalonate pathways within macrophages and monocytes thereby reducing activity of tumor-associated macrophages and activating gamma delta T cells (7). These mechanisms potentially inhibit cancer cell proliferation, including in ovarian tumor cells (8,9).

We found that raloxifene, which may be an estrogen antagonist in ovarian cancer cells (30), was associated with a nonstatistically significant reduced risk of EOC. The effects of raloxifene have been studied in several randomized controlled trials of postmenopausal women, and a meta-analysis showed a nonstatistically significant 50% lower risk of ovarian cancer in the raloxifene treatment group (31). Studies including larger numbers of women who have used raloxifene are required to confirm this association.

Our large study had several strengths. We included 9367 women with ovarian cancer, and we could therefore separately investigate the associations by EOC histotype. We used objective health records to measure medicine use rather than rely on self-report. Our use of linkage to cancer and death records meant that we had complete outcomes for the Australian population, and therefore, our results are generalizable to Australian women aged older than 50 years.

A limitation of our study was that we did not have full population data on potential confounders such as obesity, parity, MHT, and early menopause. However, our sensitivity analyses exploring the likely impact of adjusting for these variables suggested that our conclusions would not have changed. Although we did not separate types of MHT, the risk of EOC has been found to not differ materially between estrogen-only and combined preparations (32). We did not have hospital records for all women, so we could not exclude all those who had a BSO and were therefore no longer at risk of ovarian cancer. However, our

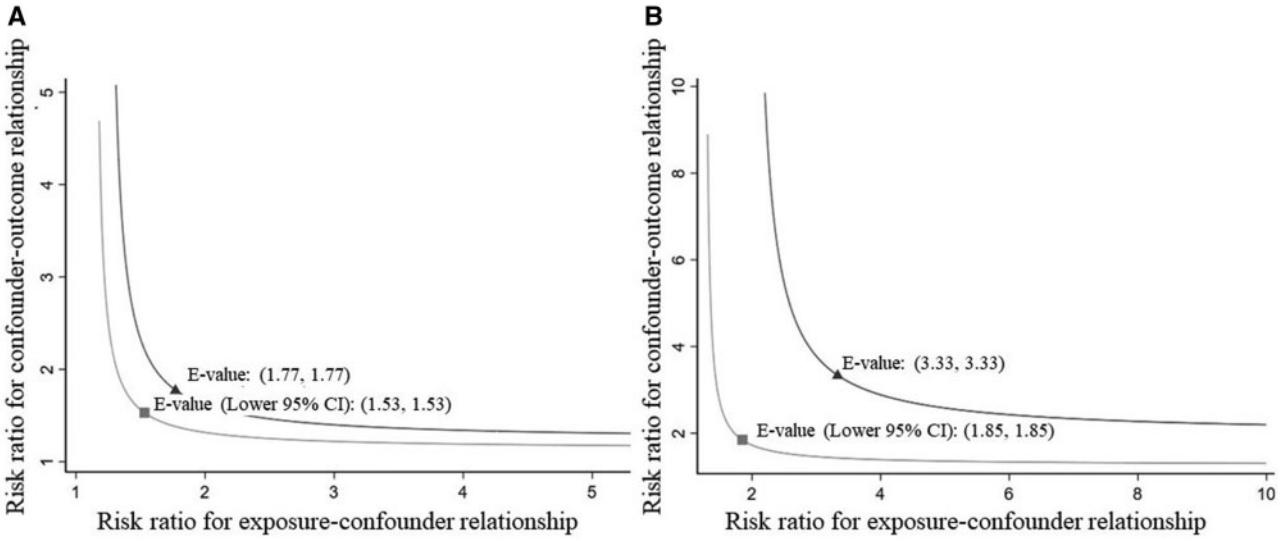

Figure 2. E-values for the associations between **(A)** nitrogen-based bisphosphonate use and risk of epithelial ovarian cancer and **(B)** nitrogen-based bisphosphonate use and risk of endometrioid epithelial ovarian cancer histotype. The E-value indicates the strength of association required between the exposure and the unmeasured confounder and the confounder and the outcome to remove the observed association. Thus, here, the relative risk for the relationship between the confounder and nitrogen-based bisphosphonates, and the confounder and epithelial ovarian cancer would need to be at least 1.77 (lower 95% CI = 1.53) (or values per the curve). The equivalent value for the endometrioid histotype is 3.33 (lower 95% CI = 1.85). If 1 of the 2 parameters is smaller than the E-value, the other must be larger, as defined by the plotted curve (26, 27). CI = confidence interval.

analyses restricted to Western Australian women (approximately 10% of the Australian population), for whom we had this information, excluding those with a BSO did not materially change the results. It is possible there is residual confounding by other unmeasured factors. However, most other established ovarian cancer risk or protective factors (family history, oral contraceptive pill use, tubal ligation) do not have strong links to bisphosphonate use (33), therefore they are unlikely to be strong enough confounders to explain the association. We were unable to separate low-grade and high-grade serous carcinoma. Given that these have been shown to have different etiologies, this may have affected the magnitude of our estimate and our dose-response calculations.

Another possible explanation for our results is confounding by indication. Bisphosphonates are used mainly for osteoporosis, which is associated with relatively lower estrogen levels (34). Estrogen receptors are present in the majority of serous and endometrioid carcinomas but only a small percentage of mucinous and clear cell carcinomas (35), and MHT use has been linked to an increased risk of serous and endometrioid EOC (36) suggesting that estrogen plays a role in the development of these cancers. However, arguing against confounding by indication, a large, prospective cohort study of 36 115 women with an average follow-up of 8.3 years did not find an association between incidence of osteoporotic fractures and risk of EOC (37). We also found some evidence of a dose response for nitrogen-based bisphosphonate of more than 1 year overall and for the endometrioid histotype, as well as a stronger association for nitrogen-based bisphosphonate use compared with other osteoporosis medications. This suggests the association found between nitrogen-based bisphosphonates and EOC is unlikely to be purely because of an inverse association between osteoporosis and EOC.

Although our findings require replication in other datasets with accurate medicine data, our results have the potential to help inform medicine choice for women with osteoporosis and suggest additional avenues for exploration of mechanisms of ovarian carcinogenesis. The possible benefit of using an existing chronic disease medication, potentially just a yearly injection, to reduce the risk of ovarian cancer warrants further investigation.

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Data Availability

Because of the nature of this population-based research, participants of this study did not agree for their data to be shared publicly, so supporting data is not available.

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