

Bisphosphonates and breast cancer incidence and recurrence

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Abstract. Bisphosphonates are commonly used in patients with breast cancer to reduce skeletal-related events in metastatic disease and to mitigate bone loss associated with adjuvant therapy. Preclinical studies have shown that bisphosphonates may directly inhibit breast cancer cell proliferation and metastasis. Clinical trials evaluating the oral bisphosphonate clodronate as a component of adjuvant therapy identified a potential reduction in cancer recurrence. Subsequently, trials of zoledronic acid have demonstrated prolonged disease-free survival in postmenopausal or otherwise estrogen-depleted women with early breast cancer. In the ABCSG-12 trial, the addition of twice-yearly zoledronic acid (4 mg IV) to adjuvant endocrine therapy improved disease-free survival in premenopausal women undergoing ovarian suppression. Similar results were observed in postmenopausal women receiving aromatase inhibitors in the ZO-FAST trial, and in women who were at least 5 years past menopause in the AZURE trial. Four recent observational studies (2 cohort studies and 2 case-control analyses) generally support an association between oral bisphosphonate use and lower breast cancer incidence. Ongoing breast cancer adjuvant clinical trials are further evaluating bisphosphonates and, by their influence on contralateral cancers, may provide more evidence regarding the potential of bisphosphonates for breast cancer prevention.

Keywords: Bisphosphonates, adjuvant therapy, anticancer, early breast cancer, breast cancer chemoprevention

1. Introduction

Bisphosphonates are approved to reduce the risk of skeletal-related events in patients with bone metastases from breast cancer and for osteoporosis prevention and therapy [1]. Bone loss can occur naturally after menopause and as a consequence of aging or be induced by breast cancer therapies such as oophorectomy, breast cancer therapy-associated premature menopause or aromatase inhibitor use. Aromatase inhibitors are an effective adjuvant treatment option for postmenopausal women with early stage, hormone-receptor-positive breast cancer. Their use is generally associated with a reduction in circulating estrogen levels, a decrease in bone mineral density (BMD), and an increase in fracture risk [2]. Antiresorptive agents including bisphosphonates such as ibandronate [3,4], risedronate [5,6], and zoledronic acid [7–9], and the receptor activator

of nuclear factor kappa B ligand (RANKL) inhibitor denosumab [10] have been shown to mitigate aromatase inhibitor-associated bone loss in a series of trials.

In addition to improving skeletal health, preclinical and early clinical studies suggest that bisphosphonates may exert anticancer properties (including angiogenesis inhibition, inhibition of tumor-cell invasion, and immunomodulatory influences) and/or synergize with other cancer treatments [11,12]. Recent adjuvant trials suggest that bisphosphonates may also delay disease recurrence in some populations of estrogen-depleted women in the early breast cancer setting [13,14], supporting a potential anticancer effect.

2. Bisphosphonates and breast cancer recurrence in clinical trials

2.1. Clodronate trials

Clodronate is an oral non-nitrogen-containing bisphosphonate approved in several regions outside the United States (eg, United Kingdom, Canada, Australia,

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some parts of Asia) for the treatment of hypercalcemia of malignancy and for reducing the risk of skeletal morbidity in women with bone metastases from breast cancer. An early controlled study in patients with breast cancer with bone metastases reported fewer new metastases in clodronate-treated patients versus control [15]. Based on this finding, a study randomized 302 women with early stage breast cancer and tumor cells in bone marrow to oral clodronate (1,600 mg/day) or no additional therapy for 2 years [16]. All patients received standard systemic adjuvant therapy based on local guidelines (CMF chemotherapy [cyclophosphamide, methotrexate, and 5-fluorouracil] ± goserelin). After 36 months of follow-up, the clodronate group showed a significant reduction in the incidence of bone metastases ($P = 0.003$) and nonosseous metastases ($P = 0.003$) compared with no therapy. Additionally, clodronate use was associated with an improvement in overall survival ($P < 0.001$), which was maintained in long-term follow-up (median = 103 months; 20% mortality in the clodronate group vs. 41% in the control group, $P = 0.04$) [17].

In contrast, substantially different results were observed in a second study comparing adjuvant therapy plus clodronate (1,600 mg/day) versus no clodronate for 3 years in 299 women with node-positive, early stage breast cancer [18]. There were no differences in bone metastasis frequency or overall survival between the 2 groups. This negative result may be explained at least in part by the adjuvant therapy practice in this study as all premenopausal patients received CMF chemotherapy and all postmenopausal patients received tamoxifen, regardless of hormone receptor status. There was an excess of receptor-negative cases in the clodronate group [18]. As a result, 12% of women in the clodronate group received no effective adjuvant therapy.

In a third adjuvant clodronate trial, 1,079 patients with early stage breast cancer were randomized to standard adjuvant therapy and placebo or clodronate (1,600 mg/day) for 2 years [19]. Patients receiving clodronate demonstrated a decrease in incidence of bone metastases during the initial 2 years ($P = 0.01$) and increased survival after a median follow-up of 5.6 years (hazard ratio [HR] = 0.77, $P = 0.048$) versus placebo [20].

In view of these divergent results, the National Surgical Adjuvant Breast and Bowel Project (NSABP) is currently conducting a fourth trial in 3,323 early stage breast cancer patients receiving standard adjuvant therapy randomized to placebo or clodronate (1,600 mg/day) for 3 years [21]. Accrual was completed in 2009 and results are awaited.

2.2. Zoledronic acid trials

Several studies have evaluated the effects of zoledronic acid in early stage breast cancer. The Austrian Breast and Colorectal Cancer Study Group trial 12 (ABCSG-12) [13], randomized 1,803 premenopausal patients with early stage breast cancer to receive goserelin (3.6 mg q 28 days) plus tamoxifen (20 mg/day) or anastrozole (1 mg/day), with or without zoledronic acid (4 mg intravenously [IV] q 6 months) for 3 years. The primary endpoint of disease-free survival was not differentially influenced by anastrozole versus tamoxifen. However, at 62 months' follow-up, women receiving zoledronic acid experienced significantly longer disease-free survival (HR, 0.68; 95% confidence interval [CI], 0.51–0.91; $P = 0.008$), and there was a favorable trend for increased overall survival as well (HR, 0.66; $P = 0.09$) [13]. Additionally, there were fewer bone metastases, distant metastases and local or regional recurrences with zoledronic acid. This last observation suggests a direct bisphosphonate effect on breast cancer.

These data are generally supported by additional trials of adjuvant zoledronic acid in patients with breast cancer. For example, 3 similarly designed randomized trials (Zometa-Femara Adjuvant Synergy Trials: Z-FAST, ZO-FAST, and E-ZO-FAST) are evaluating upfront versus delayed zoledronic acid in postmenopausal patients with hormone-receptor-positive, early stage breast cancer [22]. Patients were randomized to letrozole (2.5 mg/day) and upfront or delayed zoledronic acid either given 4 mg IV q 6 months or administered for post baseline BMD decrease or fracture for 5 years. All 3 trials demonstrated that upfront zoledronic acid mitigated BMD loss associated with letrozole use [23, 24]. The ZO-FAST study also reported a significant improvement in disease-free survival (DFS) with upfront versus delayed use (HR, 0.59; $P = 0.031$ at 36 months and HR, 0.66; $P = 0.0375$ at 60 months) [24,25]. An attempt to conduct combined analyses of these similar trials found heterogeneity in treatment effects between studies, suggesting that combining study results may not be statistically appropriate [26]. In contrast, independent statistical analysis using an earlier dataset from ABCSG-12, Z-FAST, ZO-FAST, E-ZO-FAST, and a smaller randomized trial [27] found a significant reduction in breast cancer recurrence with zoledronic acid (odds ratio 0.68; 95% CI, 0.48–0.95; $P = 0.025$) [28]. We performed exploratory meta-analysis of these data with updated trial results and found no heterogeneity between the 6 studies [13,14,23,24,27,29], with an

Table 1
Comparison of ABCSG-12 and AZURE

	ABCSG-12	AZURE
Design	Phase III, open-label, 2 × 2 factorial randomized trial	Phase III, open-label, controlled randomized trial
Population	1,803 adjuvant BC stage I-II, low-risk (mean age 45 yr) – 100% premenopausal – 100% ER ⁺ /PR ⁺	3,360 adjuvant BC stage II-III, high-risk, > 90% node ⁺ (mean age 55 yr) – 44% pre- and 45% postmenopausal – ER ⁺ and ER ⁻
Concomitant medication	100% endocrine Tx (Goserelin + TAM or ANA) No adjuvant chemo Tx duration 3 yr + follow-up 5 yr = 8 yr	< 5% received endocrine Tx alone ~96% received chemo ± endocrine Tx Tx duration 5 yr + follow-up 5 yr = 10 yr
Neoadjuvant	Only 5% of women received neoadjuvant chemo	<i>n</i> = 205 (~6% of total) – Tumor volume: ↓ 44% (<i>P</i> = 0.006) – pCR: ↑ ~2 fold – Mastectomy: ↓
Results	ZOL vs. no ZOL <i>48 mo</i> DFS: ↑ 36% (<i>P</i> = 0.01) RFS: 94% vs. 90.9% (<i>P</i> = 0.01) OS: ↑ 40% (<i>P</i> = 0.10) Recurrences: 54 vs. 83	ZOL vs. no-ZOL <i>Overall</i> DFS: ↑ 2% (<i>P</i> = 0.79) IDFS: ↑ 2% (<i>P</i> = 0.73) OS: ↑ 15% (<i>P</i> = 0.07)
	<i>62 mo</i> DFS: ↑ 32% (<i>P</i> = 0.008) OS: ↑ 33% (<i>P</i> = 0.14) 76 vs. 110	<i>PMW and > 60</i> DFS: ↑ 24% (<i>P</i> < 0.05) OS: ↑ 29% (<i>P</i> = 0.017)
Safety	ZOL vs. no ZOL <i>48 mo</i> ONJ: 0 cases Renal: 0 cases	<i>62 mo</i> 0 cases 0 cases 17 cases of ONJ in ZOL group Renal adverse events similar between ZOL and no ZOL

Abbreviations: BC, breast cancer; ER, estrogen receptor; PR, progesterone receptor; Tx, treatment; TAM, tamoxifen; ANA, anastrozole; pCR, partial complete response; ZOL, zoledronic acid; DFS, disease-free survival; RFS, recurrence-free survival; OS, overall survival; PMW, postmenopausal women; ONJ, osteonecrosis of the jaw.

overall odds ratio of 0.79 for DFS in favor of zoledronic acid, a finding that was not statistically significant [30].

Adjuvant treatment with zoledronic acid in breast cancer has also been evaluated in the AZURE trial (BIG 01–04) in 3,360 patients with stage II-III invasive breast cancer who had not received prior bisphosphonates within 12 months [14]. Patients were randomized to standard therapy (defined by the treating institutions) alone or plus zoledronic acid (4 mg, 6 doses q 3–4 wk, then 8 doses q 3 months, then 5 doses q 6 months, all IV, for a total duration of 5 years) [14]. An exploratory study of neoadjuvant therapy in a subset of 205 AZURE patients demonstrated that patients receiving zoledronic acid had smaller tumors at resection and increased frequency of pathologic complete response compared with patients who received chemotherapy alone [31]. However, analyses from the full AZURE trial demonstrated that zoledronic acid did not affect DFS (HR, 0.98, 95% CI, 0.85–1.13; *P* = 0.79) [14]. Nonetheless, zoledronic acid-treated patients trended toward improved overall survival (HR, 0.85, 95% CI, 0.72–1.01; *P* = 0.07). In pre-planned analyses, heterogeneity of bisphosphonate effect on DFS by menopausal status was observed. Postmenopausal women (defined as > 5 years past last menstrual period at entry [*n* = 1,041]) did benefit from zoledronic acid. In this sub-

set, there were fewer DFS events in the zoledronic acid group (HR, 0.76; *P* < 0.05) and no favorable effect was seen in the remaining participants (heterogeneity *P* = 0.02) [14]. These findings suggest that benefits of zoledronic acid may be dependent on a low estrogen environment, which is associated with reduced bone turnover and influences bone microenvironment. In this regard, an update of the ABCSG-12 trial in early breast cancer at 68 months median follow-up found benefit in DFS largely for patients > 40 years of age [32] who likely had lower estrogen levels after treatment with goserelin. The ABCSG-12 and AZURE studies are compared and contrasted in Table 1.

3. Bisphosphonates and breast cancer incidence in observational studies

As preclinical [11] and emerging clinical evidence [13,24] suggested bisphosphonates may inhibit breast cancer, interest developed in exploring this question in observational studies. However, the use of observational studies to explore relationships between bisphosphonate use and breast cancer incidence must address a major potential confounding issue. The use of bisphosphonates in women without a cancer diagno-

sis is mainly for the prevention and treatment of bone loss. However, women with bone loss are at substantially lower breast cancer risk [33], likely since BMD reflects some measure of cumulative estrogen exposure. Thus, a means for adjusting for differences in BMD between bisphosphonate users and non-users is needed to control for confounding by indication.

Analyses of the Women's Health Initiative (WHI) cohort did allow for such an adjustment. Among the 151,954 WHI cohort participants, 10,418 had total hip BMD determination as part of a substudy [34]. In addition, all cohort participants had information sufficient to calculate a 5-year hip fracture prediction score that had proven validated utility [35]. When the hip fracture score was compared to the BMD results in the 9,748 women with complete data, a statistically significant correlation was seen ($r = 0.43$, $P < 0.001$) [34]. Consequently the hip fracture score was included in analyses to adjust for potential differences in BMD between bisphosphonate users and non-users. In the subsequent multivariate-adjusted analyses, invasive breast cancer incidence was 32% lower in participants who received bisphosphonates after adjusting for hip fracture prediction score, menopausal hormone therapy use and breast cancer risk factors ($P < 0.01$). Mortality related to invasive breast cancer was also lower in bisphosphonate users (1.02 deaths/10,000 person years [PY]) than among non-users (2.13 deaths/10,000 PY). The results of time-dependent analyses, including the 9,741 women who reported bisphosphonate use either at entry or at year 1 or year 3 visits, are outlined in Fig. 1 [34]. Lower breast cancer incidence was seen for women after short-term use and was sustained over time. A provocative finding was the trend for fewer estrogen receptor-negative breast cancers in bisphosphonate users (HR, 0.66; 95% CI, 0.31–1.39, N.S.). In contrast, the incidence of carcinoma in situ was significantly greater in bisphosphonate users (HR, 1.59; 95% CI, 1.08–2.31, $P = 0.02$). This latter result suggests that oral bisphosphonate use might alter processes involved in the transition from non-invasive to invasive status rather than on an earlier phase of breast cancer development [34]. Perhaps more likely, the finding could indicate a bisphosphonate affect only on invasive, established breast cancers.

Analysis in a second cohort used a somewhat different study design. In the Danish population-based cohort, prescription drug users for agents targeting osteoporosis identified 87,104 such drug users. The breast cancer incidence in this population was compared to that in 261,322 controls of the same age randomly se-

lected from the background population [36]. There were significantly fewer breast cancers associated with alendronate versus no osteoporotic drug use (HR, 0.53; 95% CI, 0.3–0.73) and for etidronate versus no osteoporotic drug users (HR, 0.80; 95% CI, 0.73–0.89). However, because no dose-response relationship was seen, the authors were skeptical whether a causal relationship was present [35]. While large in size the Danish report has several limitations. There was a lack of information on risk factors for osteoporosis and there was no means for adjustment for BMD differences between osteoporotic drug users and non-users. Apparently in addition, the timing of the drug use could not be separated from that of the breast cancer diagnosis. As a result, breast cancer therapy, such as aromatase inhibitor use, could have prompted bisphosphonate use as a confounding factor.

While case-control studies provide somewhat less reliable evidence compared to cohort reports, two such studies have examined the bisphosphonate and breast cancer relationship. Newcomb and colleagues [37] in a study based in Wisconsin compared bisphosphonate use in women with breast cancer ($N = 2936$) and in age-matched controls ($N = 2975$) with adjustments made for adult height loss and reported physician diagnosed osteoporosis [37]. A lower breast cancer incidence in bisphosphonate users compared to non-users was described (4.4% vs. 6.2%, respectively, odds ratio [OR] = 0.67; 95% CI 0.51–0.89) [37]. The adjustments for BMD differences are reasonable but not ideal since height loss is a late finding and many with early osteoporosis would not be identified. In addition, physician-reported osteoporosis would miss women not seeking preventative medical attention.

In the Breast Cancer in Northern Israel Study, a population based, case-control study was conducted comparing bisphosphonate use in 1,832 breast cancer patients and 2,207 cancer free controls [38]. These analyses were not adjusted for BMD differences although other risk factors for breast cancer such as parity, menopausal hormone therapy use, and reproductive history were entered in the analytic models. These analyses also identified fewer breast cancer cases in women who were bisphosphonate users versus those who were not (OR, 0.72; 95% CI, 0.57–0.90) [38].

While there are clear differences in the analytic approaches taken and the degree to which the important potentially confounding variable of BMD differences between bisphosphonate users and non-users could be controlled for, nonetheless, these four observational studies provide a fairly consistent picture regarding bis-

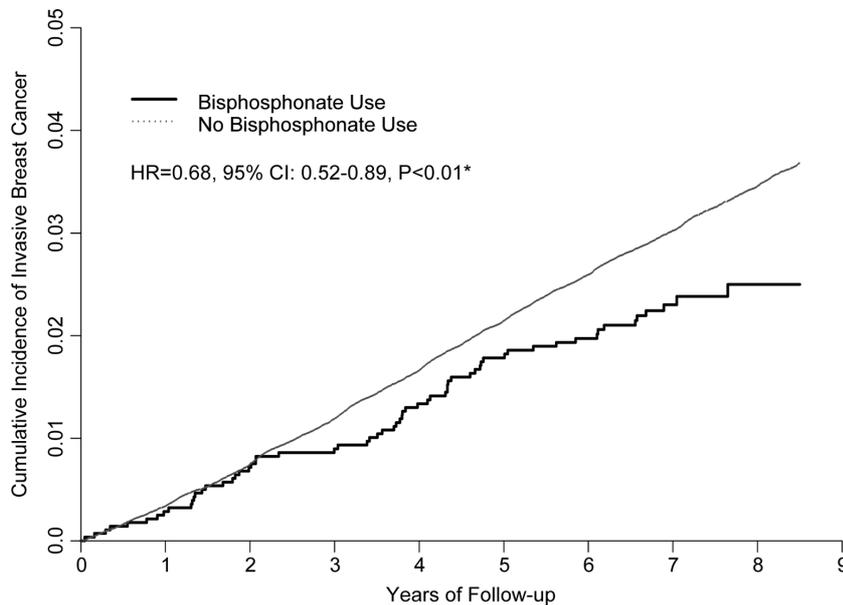


Fig. 1. Cumulative breast cancer incidence by bisphosphonate use in the Women's Health Initiative Cohort. The cumulative incidence of invasive breast cancer in the Women's Health Initiative cohort ($n = 151,954$) by bisphosphonate use (yes = 9,741, no = 142,213). HR = hazard ratio and 95% confidence interval from a multivariate-adjusted Cox proportional hazards analysis. (Adapted from R.T. Chlebowski, Z. Chen, J.A. Cauley et al., *J Clin Oncol* **28** (22) (2010), 3582–3590.)

phosphonate use being associated with lower breast cancer incidence. The major study design components of the four observational studies are compared and contrasted in Table 2. Future reports of this question must include the most rigorous possible means of adjusting for BMD differences. The model used in the report by Chlebowski and colleagues [34] namely to use commonly collected clinical risk factors to generate a fracture prediction score which can then be correlated with BMD difference provides a means of moving forward in this area.

4. Bisphosphonates and side effects

As analyses of clinical data continue to suggest that bisphosphonates may potentially provide benefit in terms of chronic disease and cancer risk reduction in populations largely free of disease, careful consideration of potential side effects of therapy are warranted.

Bisphosphonates are not free of risk, with the potential for renal toxicity, osteonecrosis of the jaw [39], and, rarely, atypical femoral fractures [40]. Oral bisphosphonates are also commonly associated with gastrointestinal problems [41], which might contribute to generally poor long-term compliance and persistence with therapy [42,43]. The concerns regarding osteonecrosis

of the jaw and the rare complication of atypical femoral fractures are recognized, are under continuing evaluation [41,44] and their potential influence should be considered in any future risk-benefit considerations of more general bisphosphonate use.

There is one emerging area of concern. Esophagitis is a known complication of bisphosphonate use [45]. In 2009, the U.S. Food and Drug Administration reported that a small number of oral bisphosphonate users were diagnosed with esophageal cancer [46]. As a result, more formal evaluations of a potential relationship between oral bisphosphonate use and increased esophageal cancer risk were undertaken. However, two reports using the same general dataset (The United Kingdom General Practice Research Database [GPRD]) had discordant results. One reported no association between bisphosphonate use and esophageal cancer (HR, 1.07, 95% CI, 0.77–1.49) [47] while a second reported that bisphosphonate users had a significantly higher esophageal cancer incidence (OR, 1.30; 95% CI, 1.20–1.66) [48]. While these studies are far from definitive, this issue deserves ongoing attention.

5. The future of bisphosphonates for prevention and treatment of breast cancer

Bisphosphonates have shown increased potential in breast cancer prevention and treatment over the last few

Table 2
Bisphosphonate use and breast cancer incidence in observational studies

Study population	Adjustment for BMD	Breast cancer association	Comment	Lead author	
Women's Health Initiative, cohort	151,954 participants, 2,816 oral bisphosphonate users at entry; 9,741 cumulative users 5,092 breast cancer cases	Used published hip fracture prediction model, significantly associated with BMD ($P < 0.001$), to make adjustment	For bisphosphonates; HR = 0.68, 95% CI, 0.52–0.88	For ER+, HR = 0.70, 95% CI 0.52–0.94 For ER-, HR = 0.66, 95% CI 0.31–1.39 For DCIS, HR = 1.58, 95% CI 1.08–2.31	Chlebowski 2010
Danish population-based cohort of prescription drug use against osteoporosis	87,104 drug users 261,322 controls of the same age randomly selected from background population	None: Lack of information on risk factors for osteoporosis; no adjustment for BMD	For alendronate; HR = 0.53, 95% CI, 0.38–0.73 For etidronate; HR = 0.80, 95% CI, 0.57–0.89	No dose response relationships seen	Vestergaard 2009
Breast cancer in Northern Israel Study, population based case-control	1,832 breast cancer cases 2,207 cancer-free controls	None	For bisphosphonates; OR = 0.72; 95% CI 0.57–0.90	Breast cancers in bisphosphonate users were more often ER positive	Rennert 2010
Wisconsin case-control study	2,936 breast cancer cases 2,975 cancer-free controls	Adjustment for menopausal hormone therapy use, height loss and physician-diagnosed osteoporosis	For bisphosphonates; OR = 0.67; 95% CI, 0.51–0.89	Lower risk only in non-obese women. A duration effect with longer use associated with lower risk (P trend 0.01)	Newcomb 2010

Abbreviations: HR – hazard ratio; OR – odds ratio; CI – confidence interval.

years. Nonetheless, bisphosphonate use for these purposes needs careful consideration. While the negative AZURE trial results have led to a hypothesis that a low estrogen environment is a prerequisite for a favorable bisphosphonate effect on breast cancer [14], this hypothesis requires prospective evaluation. In addition, to date, only one head-to-head comparison of different bisphosphonates has been conducted in the adjuvant therapy setting for breast cancer (SWOG 0307, comparing zoledronic acid, clodronate, and ibandronate), and results are still awaited. Therefore, the effectiveness of one bisphosphonate versus another has yet to be determined. Additionally, it is noteworthy that selective estrogen receptor modulators (SERMS; eg, tamoxifen) are already in use for adjuvant therapy of breast cancer as well as breast cancer prevention in high-risk populations [49]; SERMs are not only associated with reduced bone turnover, thus affecting the same process as bisphosphonates [50,51], but also with reduced breast cancer risk through direct effects on breast epithelium. Ongoing clinical trials will assess the effects of bisphosphonates in combination with SERMs on breast cancer outcomes. In ABCSG-12, early results suggest that zoledronic acid may add to tamoxifen's favorable influence on reducing breast cancer recurrence in the adjuvant setting [13].

The recent report that the aromatase inhibitor, exemestane, in a full-scale, randomized, placebo-controlled clinical prevention trial reduced breast inci-

dence by 65% [52] provides another potential opportunity for bisphosphonates. There was no difference in fractures in the trial comparing the steroidal exemestane to placebo [52]. However, non-steroidal aromatase inhibitors are associated with bone loss and fracture risk [2,49] and it is not clearly established that exemestane will not cause some bone loss. Therefore, a combination regimen using aromatase inhibitor plus bisphosphonate has the intriguing potential to reduce breast cancer risk, especially if, as suggested by the finding from Chlebowski and colleagues [34], bisphosphonate influences the progression of estrogen receptor-negative breast cancer.

Despite the promising results cited above, it will likely be difficult to conduct a full-scale bisphosphonate primary prevention study given the current broad use of bisphosphonates. However, the ongoing randomized clinical studies using bisphosphonates in the breast cancer adjuvant therapy setting provide an opportunity to evaluate bisphosphonate influence on contralateral breast cancer as a surrogate for primary breast cancer risk reduction. There are currently seven ongoing randomized trials evaluating antiresorptives in a variety of schedules for patients with early breast cancer (AZURE, D-CARE, GAIN, NATAN, NSABP B-34, SUCCESS, and SWOG 0307) [53]. These adjuvant trials will enroll more than 24,000 breast cancer patients and provide ample opportunity to assess the influence of antiresorptives on contralateral breast cancer devel-

opment. These ongoing adjuvant trials will provide important information regarding the risk-to-benefit ratio of moderate-term bisphosphonate use to influence breast cancer outcome.

6. Conflict of interest

Rowan Chlebowski is a consultant for AstraZeneca, Novartis and Pfizer. He also is a consultant for Amgen and has grant funding support from that company.

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