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COMMENTARIES

Bisphosphonates for Breast Cancer Therapy and Prevention?

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Commentary on: Newcomb PA, Trentham-Dietz A, Hampton JM. Bisphosphonates for osteoporosis treatment are associated with reduced breast cancer risk. *Br J Cancer*. 2010 Mar 2;102(5):799-802.

Bisphosphonates are commonly used in the management and prevention of osteoporosis (1) and to reduce skeletal-related events in cancer patients with bone metastases (2). As preclinical (3) and emerging clinical observations suggested that bisphosphonates may inhibit breast cancer (4;5), Newcomb and colleagues (6) evaluated the association between oral bisphosphonate use and invasive breast cancer in a case-control study in a Wisconsin population. Controlling for some potential confounders, current bisphosphonate users were seen to have a lower incidence of breast cancer compared to non-users. This result adds to emerging literature suggesting that oral bisphosphonate use may have inhibitory effects on breast cancer.

Newcomb and colleagues (6) cite preclinical observations (3) that suggest bisphosphonates may influence breast cancer growth. Recent clinical observations provide further support for this concept. In the Austrian Breast Cancer Study Group (ABCSG)-12, Gnant and colleagues (5) reported that the bisphosphonate zoledronic acid (4 mg iv every 6 months) decreased breast cancer recurrence by 32% in early stage breast cancer patients receiving adjuvant hormonal therapy (P = .011). Patients in the zoledronic acid group also had fewer local regional and contralateral breast cancers (16 vs. 30, respectively), suggestive of direct (rather than bone-mediated) influence on breast cancer. These findings stimulated two other research groups (lead authors Rowan Chlebowski from the Los Angeles Biomedical Research Institute, and Gad Rennert from the Technion - Israel Institute of Technology) to conduct analyses investigating associations between bisphosphonates and breast cancer incidence.

Observational studies examining bisphosphonate use and breast cancer incidence face a major potential confounding issue. Bisphosphonates are given to women with bone loss (osteopenia or osteoporosis) and women with bone loss are at substantially lower breast cancer risk (7) probably because bone mineral density (BMD) reflects lower cumulative estrogen exposure. Thus, a means of adjusting for potential differences in BMD between bisphosphonate users and non-users should be available.

In the case-control study of Newcomb and colleagues (6), adjustments were made for body mass index and postmenopausal hormone use. For potential BMD differences, adjustments were made for height loss and physician-diagnosed osteoporosis. However, these are not ideal surrogates for BMD since height loss is a late finding reflecting prior vertebral fracture while physician-diagnosed osteoporosis cannot account for BMD differences in women not coming forward for medical attention. In the case-control study of Rennert and colleagues (8), information on breast cancer risk factors, calcium use and body mass index were incorporated in the analysis. However, no information to more directly adjust for potential BMD differences was presented. In contrast, the prospective cohort design in the Women's Health Initiative (WHI) report provided an

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opportunity to make an adjustment for potential BMD differences (9). Among the 154,768 postmenopausal women in the WHI cohort, as part of a sub-study, 10,418 women had total hip BMD determination. In addition, for all participants there was collection of clinical information needed to generate a hip fracture predictive score that has been published and validated (10). The hip fracture score was then related to the BMD results in the 9,748 women with both, and a strong correlation was seen ($P < 0.001$; $R = 0.43$). As a result, the hip fracture score was used to adjust for potential differences in BMD between bisphosphonate users and non-users (9).

Despite differing analytic approaches with respect to potential confounding factors, these three observational studies (6;8;9) provide remarkably similar results in their multi-variant-adjusted analyses (Table 1).

Table 1. Bisphosphonates and breast cancer incidence: observational study results.

Lead author (ref.)	Study design	Patient cases (% BP)	Control subjects (% BP)	Breast cancer association
Rennert (8)	Case-control	1822 (10.5%)	2207 (14.8%)	OR, 0.72 (0.57-0.90)
Newcomb (6)	Case-control	2336 (4.4%)	2975 (6.2%)	OR, 0.67 (0.51-0.89)
Chlebowski (9)	Cohort	154,768 women: 2816 (1.8%) BP users; 5,092 breast cancer cases		HR, 0.68 (0.52-0.88)

BP = bisphosphonate; HR = hazard ratio; OR = odds ratio

In the Wisconsin case-control analyses by Newcomb *et al*. (6), breast cancer incidence in bisphosphonate users was 4.4% vs. 6.2% for non-users (odds ratio (OR), 0.67; 95% CI, 0.51-0.89). In the Israeli case-control analyses by Rennert *et al*. (8), breast cancer incidence in bisphosphonate users was 10.5% vs. 14.8% in non-users (OR, 0.72; 95% CI, 0.57-0.90) (8). In the WHI prospective cohort analyses by Chlebowski *et al*. (9), the hazard ratio (HR) for breast cancer association with bisphosphonate use was 0.62 (95% CI, 0.52-0.88). Taken together, these independent reports support the hypothesis that bisphosphonate use may result in lower breast cancer incidence.

Perhaps the most provocative finding from these observational studies is the suggestion from the WHI analyses that oral bisphosphonate use may influence both hormone receptor-positive and receptor-negative breast cancers (9). Tamoxifen and raloxifene, approved for breast cancer risk reduction in the United States, only influence estrogen receptor-positive tumors and few promising agents for receptor-negative risk reduction have been identified (11).

Other clinical trial results are supportive of a bisphosphonate-breast cancer association. In a combined analysis of the similar ZFAST (Zometa-Femara Adjuvant Synergy Trial) and ZO-FAST trials evaluating early vs. delayed zoledronic acid in early stage, postmenopausal breast cancer patients, 35% fewer recurrences were seen in bisphosphonate users (12). Finally, two of three trials evaluating the oral bisphosphonate clodronate in adjuvant settings have reported positive effects on breast cancer outcomes (4;13;14).

Several small clinical studies also report favorable effects of zoledronic acid on breast cancer. In a phase II randomized trial involving 120 stage II-III breast cancer patients, 4 mg zoledronic acid iv every 3 weeks was compared to no zoledronic acid use. Bisphosphonate users less commonly had detectable disseminated tumor cells ($P = 0.054$) with both groups receiving standard adjuvant chemotherapy (15). In a neoadjuvant trial with 205 early stage breast cancer patients, those randomized to zoledronic acid 4 mg iv with each chemotherapy dose had smaller tumors at resection (15.5 vs. 27.4 mm, respectively, $P = 0.006$) (16). These two phase II studies suggest there may be direct anti-cancer effects of bisphosphonate on breast cancer.

While some may consider the previously conducted series of randomized clinical trials targeting fracture as an endpoint, which compared bisphosphonate to placebo

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in women with established bone loss, as a potential source of definitive information on the question of bisphosphonate use and breast cancer incidence, caution is advised. Almost universally, these trials did not collect detailed information on breast cancer risk factors or frequency of mammography while on study. While such studies did control for BMD, without information on other breast cancer risk factors and ongoing mammography, the reliability of any *post hoc* analyses could be questioned.

Perhaps more reliable evidence will be forthcoming from the ongoing randomized adjuvant clinical trials in patients with early stage resected breast cancer where bisphosphonates are the sole treatment variable. The findings in these trials on incidence of contralateral breast cancer (new breast cancer) could provide the strongest evidence of a direct effect of bisphosphonates on breast cancer development. These trials include NSABP B-34 that has randomized over 3,200 stage I-II breast cancer patients receiving standard adjuvant therapy to placebo or the bisphosphonate clodronate 1000 mg po daily (17); the AZURE trial that has randomized over 3,300 stage II-III breast cancer patients receiving standard adjuvant therapy to a somewhat more intensive zoledronic acid schedule over 5 years or to placebo (16); and finally a German GAIN trial with node-positive breast cancer patients comparing two chemotherapy regimens and the bisphosphonate ibandronate 50 mg po daily vs. observation in a factoral design. While the NSABP trial closed in March of 2004, it is anticipated that the AZURE trial may be the first of these three to report clinical outcomes.

Bisphosphonates are not free of risk. Oral use is associated with gastrointestinal problems (2) and, rarely, cases of atypical femoral fractures have been reported (18). With iv bisphosphonates, using the relatively high dosage for prevention of skeletal-related events in cancer patients, osteonecrosis of the jaw (ONJ) can occur, especially after dental procedures (19).

While studies suggestive of a favorable effect on breast cancer outcomes have involved several different bisphosphonates, it may well be that differences in clinical outcome will emerge between the various bisphosphonates. In this regard, in a phase III study, patients with stage I-III multiple myeloma were randomized to one of two bisphosphonates. Those in the group given zoledronic acid 4 mg q 3-4 weeks had a significantly longer ($P < 0.01$) survival compared to those given the other, less potent bisphosphonate, daily oral clodronate (20).

In summary, while promising, current evidence does not support wide-scale use of any bisphosphonate specifically to reduce breast cancer incidence. However, emerging evidence suggestive of such findings perhaps could be considered by women in their decision to select the most appropriate intervention needed to address concerns regarding bone health. The potential influence of bisphosphonates on breast cancer recurrence risk is receiving definitive evaluation in three ongoing phase III clinical trials, two of which have completed accrual. These trials will likely provide more reliable evidence regarding the effect of bisphosphonates on breast cancer incidence when effects on contralateral new breast cancer are reported.

Conflict of Interest: Dr. Chlebowski reports that he is a consultant and receives grant support from Amgen; is a consultant and on the speaker's bureau for Novartis; and is a consultant for Pfizer.

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