18. Piccart MJ, Bertelsen K, James K, et al: Randomized intergroup trial of cisplatin-paclitaxel versus cisplatin-cyclophosphamide in women with advanced epithelial ovarian cancer: Three year results. J Natl Cancer Inst 92: 699-708, 2000

19. Stanislaus R, Carey M, Deus HF, et al: RPPAML/RIMS: A metadata format and an information management system for reverse phase protein arrays. BMC Bioinformatics 9:555, 2008

20. Zhang L, Wei Q, Mao L, et al: Serial dilution curve: A new method for analysis of reverse phase protein array data. Bioinformatics 25:650-654, 2009

21. Wong KK, Tsang YTM, Zu Z, et al: Insulin growth factor 1 pathway is a potential therapeutic target for low-grade ovarian cancers. Gynecol Oncol (in press)

22. Burger RA, Sill MW, Monk BJ, et al: Phase II trial of bevacizumab in persistent or recurrent epithelial ovarian cancer or primary peritoneal cancer: A Gynecologic Oncology Group study. J Clin Oncol 25:5165-5171, 2007

23. Cannistra SA, Matulonis UA, Penson RT, et al: Phase II study of bevacizumab in patients with platinum-resistant ovarian cancer or peritoneal serous cancer. J Clin Oncol 25:5180-5186, 2007

24. Ahmed A, Le XF, Lu Z, et al. Kinase regulated microtubule stabilization correlates with paclitaxel response in a target specific siRNA kinome screen. Proc Am Assoc Cancer Res 50, 2009 (abstr 3869)

25. Ahmed A, Jacomo RO, Lu Z, et al: The salt inducible kinase 2 (SIK2) is required for centrosome separation at the onset of mitosis. Proc Am Assoc Cancer Res 50, 2009 (abstr LB-43)

26. Ahmed AA, Le X-F, Lu Z, et al: Loss of CDK5 sensitizes cells to paclitaxel by enhancing intracellular retention. Proc Am Assoc Cancer Res 57, 2010 (abstr 1585)

27. Whitehurst AW, Bodemann BO, Cardenas J, et al: Synthetic lethal screen identification of chemosensitizer loci in cancer cells. Nature 446:815-819, 2007

28. Landen CN Jr, Chavez-Reyes A, Bucana C, et al: Therapeutic EphA2 gene targeting in vivo using neutral liposomal small interfering RNA delivery. Cancer Res 65:6910-6918, 2005

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Can Oral Bisphosphonates Really Reduce the Risk of Breast Cancer in Healthy Women?

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See accompanying articles on pages 3577 and 3582

Bisphosphonate therapy has become the pharmacologic treatment of choice for preventing bone loss and fractures in postmenopausal women with osteoporosis.[1-3] This is primarily because bisphosphonates have proven efficacy for treating bone loss, relative low cost, ease of use, and low risk of adverse effects versus hormone-replacement therapy, which has been associated with increased risk of breast cancer and cardiovascular disease.[4] In addition to the long-standing use of oral bisphosphonates in this setting, intravenous zoledronic acid (5 mg) has been approved as a yearly infusion for treating osteoporosis and as a biennial infusion for women with osteopenic disorder, and ibandronate (3 mg) has been approved as a quarterly injection for treating osteoporosis.[5-8] In addition, several recent clinical trials demonstrated the efficacy of bisphosphonates for preventing cancer treatment–induced bone loss (CTIBL) in pre- and postmenopausal women with early-stage breast cancer.[9-13] Beyond preventing osteoclast-mediated bone resorption, nitrogen-containing bisphosphonates have also demonstrated anticancer activity in a variety of preclinical and clinical studies.[14] There is also evidence for anticancer synergy between cytotoxic chemotherapy agents and zoledronic acid, a finding that was recently confirmed in women receiving neoadjuvant therapy for breast cancer.[15] Furthermore, adding adjuvant zoledronic acid in large, randomized clinical trials produced remarkable reductions in disease recurrence in women with breast cancer, and suggests that bisphosphonates have a beneficial effect on the microenvironment in which dormant tumor stem cells survive in early disease.[16] Based on these exciting findings, several recent population-based studies examined whether long-term use of oral bisphosphonates in women with postmenopausal osteoporosis may be associated with a reduced risk of breast cancer.

In this issue of *Journal of Clinical Oncology* (JCO), Chlebowski et al[17] report on an analysis of longitudinal data from the Women's Health Initiative Observational Study (WHI-OS) that included 154,768 women. In summary, their multivariate analysis revealed that women who received bisphosphonates for osteoporosis had a 32% relative reduction in the overall risk of breast cancer compared with those who did not receive bisphosphonates (hazard ratio [HR] = 0.68; 95% CI, 0.52 to 0.88). Interestingly, the risk reduction included both estrogen receptor (ER) –positive and ER-negative breast cancers. Also in this issue, Rennert et al[18] report a 28% reduced risk of breast cancer (odds ratio = 0.72; 95% CI, 0.57 to 0.90) among postmenopausal women receiving bisphosphonates for more than 1 year in a similar analysis, this time using the Breast Cancer in Northern Israel Study (BCINIS) database (N = 4,039).

These significant correlations are profound and intriguing, because they suggest that bisphosphonate-induced changes to the microenvironment surrounding potential cancer cells can be exploited in preventing breast cancer. If this application of the seed and soil axiom, first introduced by Stephen Paget,[19] becomes a reality, the potential implications would be far-reaching. However, the results presented in these two studies must be interpreted with caution. As correctly noted by the authors, several potential confounding factors may have influenced the observed outcomes, including age, ethnicity, tobacco use, alcohol use, physical activity, baseline bone mineral density (BMD), body mass index, prior hormone therapy, calcium and vitamin D supplementation, number of pregnancies, duration of breast feeding, and other unknown factors that may interact with breast cancer risk in these healthy women. Although the authors did their best to control for these confounders, the relative and interrelated risk factors for breast cancer are not yet completely understood, and thus form the major limitation of retrospective analyses. Consequently, in the absence of a prospective randomized study, the analyses should be viewed as hypothesis generating and not practice changing at this time.

Estrogen exposure has been correlated with mammary hyperplasia and ultimately with breast cancers that are stimulated by sex hormone signaling. However, estrogen is also intimately involved

in regulating the balanced and coupled processes of bone resorption and formation. Lifetime exposure to estrogen influences not only breast cancer risk but also BMD.[20] Therefore, BMD and breast cancer risk may be related. It is well established that women with high BMD are at higher risk of breast cancer compared with women with low BMD,[21-23] presumably because high estrogen levels or prolonged exposure to estrogen are more likely to stimulate the growth of ER-positive breast cancer cells. Therefore, by nature, women in whom bisphosphonate therapy would be initiated might represent a lower-risk group for breast cancer than women with normal BMD. However, the breast cancer risk reduction among bisphosphonate-treated versus non–bisphosphonate-treated women was even more pronounced for ER-negative breast cancer, which, according to our current understanding, should not be influenced by estrogen exposure. Moreover, women who developed breast cancer during bisphosphonate therapy had a higher proportion of in situ versus invasive breast cancer.[17] This suggests that bisphosphonates may have somehow inhibited breast cancer invasion or at least interfered with the continuous processes of atypia and hyperplasia at the lobuloductal end plate. It remains unclear whether the known immune-mediated anticancer effects of zoledronic acid are also present for oral bisphosphonates or whether these anticancer mechanisms even play a role in this setting. In fact, Rennert et al[18] report that women receiving bisphosphonates who developed breast cancer had tumors with better prognostic features, including a lower proportion of human epidermal growth factor receptor 2 (HER2) -positive tumors, compared with women who did not receive bisphosphonates.

Duration of bisphosphonate use also somewhat correlated with reduction in breast cancer risk, but this finding was inconsistent between the two studies. In Chlebowski et al,[17] the greatest reduction in breast cancer risk was in women who had received bisphosphonates for less than 2 years. This may suggest that oral bisphosphonates might be able to delay breast cancer, but they cannot prevent it. In contrast, Rennert et al[18] showed that the greatest risk reduction was in women who had received bisphosphonates for more than 1 year, but that the risk reduction persisted in patients with more than 5 years of exposure, reflecting a longer course of prevention. However, differences in patient demographics or criteria for bisphosphonate use between these United States–based and Israel-based studies could be responsible for the inconsistencies.

In support of these two articles, a recent population-based, case-controlled study in Wisconsin (N = 5,911) from Newcomb et al[24] found that current bisphosphonate use was associated with a comparable 33% reduction in the risk of breast cancer (odds ratio = 0.67; 95% CI, 0.51 to 0.89). Important confounders such as body mass index and hormone-replacement therapy were considered. Although it was a smaller study, this represents an additional, independent report of the correlation between bisphosphonate use and decreased breast cancer risk. It is interesting to note that the relative breast cancer risk reduction is approximately 30% across all three studies.

Potential anticancer effects of bisphosphonates have also been reported in pre- and postmenopausal women with early-stage breast cancer. For example, early clinical evidence for the anticancer effects of bisphosphonates was obtained from two separate clinical trials in women with breast cancer (total N = 1,371) in which 2 years of oral clodronate delayed the appearance of bone metastases and prolonged disease-free and overall survival.[25,26] However, another trial (N = 299) found no significant clinical benefit with oral clodronate.[27,28] Similarly, a trial of oral pamidronate (N = 953) failed to show a reduction in breast cancer recurrence in bone or prolongation of survival.[29] More recently, in the ZO-FAST (Zometa-Femara Adjuvant Synergy Trial) study (N = 1,065), postmenopausal women receiving zoledronic acid plus adjuvant letrozole for endocrine-responsive breast cancer had a 41% reduced risk of disease-free survival events compared with those who received letrozole therapy alone (HR = 0.59; 95% CI, 0.36 to 0.96; $P = .0314$).[10] Similarly, premenopausal women in the Austrian Breast and Colorectal Cancer Study Group trial 12 (ABCSG-12; N = 1,803) receiving endocrine therapy (ovarian suppression plus anastrozole or tamoxifen) plus zoledronic acid experienced a 36% relative reduction in the risk of disease progression compared with endocrine therapy alone (HR = 0.64; 95% CI, 0.46 to 0.91; $P = .01$).[30] In both of these trials, adding zoledronic acid reduced disease recurrence in bone and nonbone sites (including contralateral breast cancer). The reduction in disease recurrence with adjuvant bisphosphonate therapy may result, in part, from modification of the bone marrow microenvironment, making this niche less receptive to tumor stem cells. As recently demonstrated by Aft and others,[31-34] disseminated tumor cells in the bone marrow, which are thought to seed future distant metastases, can be reduced or eliminated by indirect bisphosphonate-mediated modification of the bone marrow niche.

Bisphosphonates have also demonstrated direct and indirect anticancer effects on cancer cells—including inducing cancer cell apoptosis; inhibiting cancer cell adhesion and extravasation, anticancer synergy with endocrine therapy and cytotoxic chemotherapy; deterring angiogenesis; and activating immune cells with anticancer activity ($\gamma\delta$ T cells); among others.[14] Indeed, these anticancer effects of bisphosphonates likely account for the reduction in residual invasive tumor size and improved pathologic complete response with zoledronic acid versus no zoledronic acid reported in a recently published exploratory analysis of the subset of women who received neoadjuvant therapy in the AZURE (Adjuvant Zoledronic Acid Reduce Recurrence) trial (n = 205), a randomized study evaluating the effects of adding zoledronic acid to early breast cancer treatment regimens.[15] In this study, patients receiving neoadjuvant chemotherapy plus zoledronic acid had a 43% relative reduction in mean residual invasive tumor size compared with patients receiving chemotherapy alone (15.5 *v* 27.4 mm, respectively; $P = 0.006$). Furthermore, adding zoledronic acid improved pathologic complete response by nearly two-fold compared with chemotherapy alone (6.9% *v* 11.7%, respectively; $P = .146$) and reduced the number of mastectomies.

The bisphosphonates used varied among patients in the three published database studies. Therefore, it is possible that the reported correlations represent a class effect. However, it is unclear whether this is a class effect of bisphosphonates or of antiresorptive therapies in general. It is unknown whether a new antiresorptive agent, the antireceptor activator of nuclear factor κ B (RANKL) antibody, denosumab, will have similar anticancer activity in women with osteoporosis. Although denosumab was reported to prevent cancer treatment–induced bone loss (CTIBL) in women receiving adjuvant aromatase-inhibitor therapy[35] and was superior to zoledronic acid for reducing skeletal-related events in women with bone metastases from breast

cancer,[36] to date there has been no reported evidence of reduced breast cancer recurrence in the CTIBL trial or of breast cancer prevention in the large postmenopausal osteoporosis trial.[37]

Taken together, the results of the two studies in this issue of JCO are important additional steps toward understanding several unresolved issues, including how best to target the early precursors of malignancy and the role of the microenvironment in tumor development.[17,18] Ongoing translational and clinical research studies are scheduled to report their findings in the near future and may help to further elucidate the potential role of bisphosphonates in preventing breast and other cancers. Results from these studies and others will need to identify the precise anticancer mechanisms contributing to the different settings, but the hypothetical benefits of bisphosphonates as anticancer therapies may now extend well into the early stages of the continuum of breast cancer development and progression.

At this point, it would be premature to recommend the use of oral bisphosphonates to prevent breast cancer in all postmenopausal women. However, it is not unreasonable to consider the potential anticancer benefits of bisphosphonate therapy, in addition to its bone-protecting effects, when evaluating treatment options in women with postmenopausal osteoporosis, especially considering that bisphosphonates are generally well tolerated in this population.

In summary, there are strong signals that bisphosphonate therapy for postmenopausal osteoporosis might significantly reduce the risk of breast cancer. This supports the idea that the seed and soil theory is equally relevant in preventing breast cancer in healthy postmenopausal women as it is in preventing breast cancer recurrence in women with early-stage breast cancer. The growing body of evidence suggests that targeting the microenvironment in addition to the cancer cells themselves may be an important aspect of future anticancer strategies. The two reports presented in this issue of JCO now add further support to this exciting possibility.[17,18]

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REFERENCES

1. National Osteoporosis Foundation: Clinician's Guide to Prevention and Treatment of Osteoporosis. Washington, DC, National Osteoporosis Foundation, 2010, pp 1-36
2. World Health Organization: Prevention and management of osteoporosis—WHO Technical Report Series 921. Geneva, Switzerland, World Health Organization, 2003, pp 1-192
3. Rosen CJ: Clinical practice: Postmenopausal osteoporosis. N Engl J Med 353:595-603, 2005
4. Stevenson JC: Hormone replacement therapy and cardiovascular disease revisited. Menopause Int 15:55-57, 2009
5. Aclasta: Summary of Product Characteristics. http://www.ema.europa.eu/humandocs/PDFs/EPAR/aclasta/emea-combined-h595en.pdf
6. Bonviva: Summary of Product Characteristics. http://www.ema.europa.eu/humandocs/PDFs/EPAR/Bonviva/emea-combined-h501en.pdf
7. Boniva: Prescribing Information. http://www.accessdata.fda.gov/drugsatfda_docs/label/2006/021858s001lbl.pdf
8. Reclast: Prescribing Information. http://www.accessdata.fda.gov/drugsatfda_docs/label/2009/021817s004lbl.pdf
9. Brufsky AM, Bosserman LD, Caradonna RR, et al: Zoledronic acid effectively prevents aromatase inhibitor-associated bone loss in postmenopausal women with early breast cancer receiving adjuvant letrozole: Z-FAST study 36-month follow-up results. Clin Breast Cancer 9:77-85, 2009
10. Eidtmann H, Bundred NJ, DeBoer R, et al: The effect of zoledronic acid on aromatase inhibitor associated bone loss in postmenopausal women with early breast cancer receiving adjuvant letrozole: 36 months follow-up of ZO-FAST. Presented at the 31st Annual San Antonio Breast Cancer Symposium, San Antonio, TX, December 10-14, 2008
11. Gnant M, Mlineritsch B, Luschin-Ebengreuth G, et al: Adjuvant endocrine therapy plus zoledronic acid in premenopausal women with early-stage breast cancer: 5-year follow-up of the ABCSG-12 bone-mineral density substudy. Lancet Oncol 9:840-849, 2008
12. Lester JE, Dodwell D, Purohit OP, et al: Prevention of anastrozole-induced bone loss with monthly oral ibandronate during adjuvant aromatase inhibitor therapy for breast cancer. Clin Cancer Res 14:6336-6342, 2008
13. Van Poznak C, Hannon RA, Mackey JR, et al: Prevention of aromatase inhibitor-induced bone loss using risedronate: The SABRE trial. J Clin Oncol 28:967-975, 2010
14. Winter MC, Holen I, Coleman RE: Exploring the anti-tumour activity of bisphosphonates in early breast cancer. Cancer Treat Rev 34:453-475, 2008
15. Coleman RE, Winter MC, Cameron D, et al: The effects of adding zoledronic acid to neoadjuvant chemotherapy on tumour response: Exploratory evidence for direct anti-tumour activity in breast cancer. Br J Cancer 102:1099-1105, 2010
16. Gnant M: Bisphosphonates in the prevention of disease recurrence: Current results and ongoing trials. Curr Cancer Drug Targets 9:824-833, 2009
17. Chlebowski RT, Chen Z, Cauley JA, et al: Oral bisphosphonate use and breast cancer incidence in postmenopausal women. J Clin Oncol 28:3582-3590, 2010
18. Rennert G, Pinchev M, Rennert HS: Use of bisphosphonates and risk of postmenopausal breast cancer. J Clin Oncol 28:3577-3581, 2010
19. Paget S: The distribution of secondary growths in cancer of the breast. Lancet 133:571-573, 1889
20. Chen WY: Exogenous and endogenous hormones and breast cancer. Best Pract Res Clin Endocrinol Metab 22:573-585, 2008
21. Cauley JA, Lucas FL, Kuller LH, et al: Bone mineral density and risk of breast cancer in older women: The study of osteoporotic fractures—Study of Osteoporotic Fractures Research Group. JAMA 276:1404-1408, 1996
22. Chen Z, Arendell L, Aickin M, et al: Hip bone density predicts breast cancer risk independently of Gail score: Results from the Women's Health Initiative. Cancer 113:907-915, 2008
23. Zmuda JM, Cauley JA, Ljung BM, et al: Bone mass and breast cancer risk in older women: Differences by stage at diagnosis. J Natl Cancer Inst 93:930-936, 2001
24. Newcomb PA, Trentham-Dietz A, Hampton JM: Bisphosphonates for osteoporosis treatment are associated with reduced breast cancer risk. Br J Cancer 102:799-802, 2010
25. Diel IJ, Jaschke A, Solomayer EF, et al: Adjuvant oral clodronate improves the overall survival of primary breast cancer patients with micrometastases to the bone marrow: A long-term follow-up. Ann Oncol 19:2007-2011, 2008
26. Powles T, Paterson A, McCloskey E, et al: Reduction in bone relapse and improved survival with oral clodronate for adjuvant treatment of operable breast cancer [ISRCTN83688026]. Breast Cancer Res 8:R13, 2006
27. Saarto T, Blomqvist C, Virkkunen P, et al: Adjuvant clodronate treatment does not reduce the frequency of skeletal metastases in node-positive breast cancer patients: 5-year results of a randomized controlled trial. J Clin Oncol 19:10-17, 2001
28. Saarto T, Vehmanen L, Virkkunen P, et al: Ten-year follow-up of a randomized controlled trial of adjuvant clodronate treatment in node-positive breast cancer patients. Acta Oncol 43:650-656, 2004
29. Kristensen B, Ejlertsen B, Mouridsen HT, et al: Bisphosphonate treatment in primary breast cancer: Results from a randomised comparison of oral pamidronate versus no pamidronate in patients with primary breast cancer. Acta Oncol 47:740-746, 2008
30. Gnant M, Mlineritsch B, Schippinger W, et al: Endocrine therapy plus zoledronic acid in premenopausal breast cancer. N Engl J Med 360:679-691, 2009
31. Aft R, Naughton M, Trinkaus K, et al: Effect of zoledronic acid on disseminated tumour cells in women with locally advanced breast cancer: An

open label, randomised, phase 2 trial. Lancet Oncol 11:421-428, 2010

32. Lin AY, Park JW, Scott J, et al: Zoledronic acid as adjuvant therapy for women with early-stage breast cancer and disseminated tumor cells in bone marrow. Presented at the 44th Annual Meeting of the American Society of Clinical Oncology, Chicago, IL, May 30-June 3, 2008

33. Rack BK, Jueckstock J, Genss E-M, et al: Effect of zoledronate on persisting isolated tumor cells in the bone marrow of patients without recurrence of early breast cancer. Presented at the 30th Annual San Antonio Breast Cancer Symposium, San Antonio, TX, December 13-16, 2007

34. Solomayer EF, Gebauer G, Hirnle P, et al: Influence of zoledronic acid on disseminated tumor cells (DTC) in primary breast cancer patients. Presented at the 31st Annual San Antonio Breast Cancer Symposium, San Antonio, TX, December 10-14, 2008

35. Ellis GK, Bone HG, Chlebowski R, et al: Randomized trial of denosumab in patients receiving adjuvant aromatase inhibitors for nonmetastatic breast cancer. J Clin Oncol 26:4875-4882, 2008

36. Stopeck A, Body JJ, Fujiwara Y, et al: Denosumab versus zoledronic acid for the treatment of breast cancer patients with bone metastases: Results of a randomized phase 3 study. Presented at the Joint ECCO 15-34th ESMO Multidisciplinary Congress, Berlin, Germany, September 20-24, 2009

37. Bone HG, Bolognese MA, Yuen CK, et al: Effects of denosumab on bone mineral density and bone turnover in postmenopausal women. J Clin Endocrinol Metab 93:2149-2157, 2008

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