Bisphosphonates for osteoporosis not associated with reduced breast cancer risk

August 11 2014

An analysis of data from two randomized clinical trials finds that three to four years of treatment with bisphosphonates to improve bone density is not linked to reduced risk of invasive postmenopausal breast cancer.

The authors are Trisha F. Hue, Ph.D., M.P.H., of the University of California, San Francisco, and colleagues.

Some studies have suggested that bisphosphonates, which are commonly used to treat osteoporosis, may have antitumor and antimetastatic properties. Some observational studies have suggested bisphosphonates may protect women from breast cancer.

The authors analyzed the relationship of postmenopausal breast cancer and bisphosphonate use by examining data from two randomized, double-blind, placebo-controlled trials. The Fracture Intervention Trial (FIT) randomly assigned 6,459 women (ages 55 to 81 years) to alendronate or placebo with an average follow-up of 3.8 years. The Health Outcomes and Reduced Incidence with Zoledronic Acid Once Yearly-Pivotal Fracture Trial (HORIZON-PFT) randomly assigned 7,765 women (ages 65 to 89 years) to annual intravenous zoledronic acid or placebo with an average follow-up of 2.8 years. The authors compared rates of breast cancer in the bisphosphonate treatment groups to the placebo groups.

There was no significant difference in breast cancer rates between the bisphosphonate and placebo groups. In FIT, the breast cancer rate was 1.5 percent in the placebo group and 1.8 percent in the alendronate

group. In HORIZON-PFT the rate was 0.8 percent in the placebo group and 0.9 percent in the zoledronic acid group. There also was no significant difference when data from the two trials were combined.

"These data provide evidence that three to four years of treatment with bisphosphonate, alendronate or zoledronic acid, therapy does not reduce the risk of incident breast cancer in postmenopausal women. The discrepancy between our results and the reports of associations in observational studies may be an example of indication bias and illustrates the limitation and hazard of drawing conclusions about treatment effects from observational studies (even those that are very well done) and emphasizes the value of confirming such associations in randomized trials. The effect of bisphosphonate treatment on breast cancer risk in nonosteoporotic populations should be investigated in other randomized trials."

In a related editor's note, Joseph S. Ross, M.D., M.H.S., a *JAMA Internal Medicine* associate editor, writes: "Whereas these findings highlight why it is so important for new therapies to be evaluated using RCTs (randomized clinical trials), they also reinforce the importance of assessing the methodological rigor of observational studies before interpreting real-world effects."

"Just as we closely scrutinize RCT design, so must we understand the quality and statistical power of the data used for observational studies, how participants were identified, the duration of follow-up, the end points examined, and the analytical strategy used. Observational studies are particularly valuable for clinical situations unlikely to be tested using RCTs, and many provide valid and reliable real-world evidence," Ross continues.

"Thus, whereas we all can remember examples of when RCTs and observational studies differed, less memorable are the even more

numerous examples in which results were consistent. In the end, we should be open to all types of evidence and rely on rigorous clinical science to guide practice," Ross concludes.

More information: *JAMA Intern Med*. Published online August 11, 2014. DOI: 10.1001/jamainternmed.2014.3634