CANCER

Bisphosphonate use and breast cancer

Bisphosphonates may protect from breast cancer, suggest two studies published in a recent issue of the *Journal of Clinical Oncology*.

In 2009, the bisphosphonate zoledronic acid was evaluated for its ability to prevent the development of bone metastases in women with breast cancer. The findings of this study indicated a decreased risk of contralateral breast cancer in women who were randomly allocated to receive bisphosphonates for the prevention of metastases. "Reduced risk of contralateral breast cancer suggests a primary prevention effect, similar to tamoxifen, which was first found to reduce the risk of contralateral breast cancer in treatment studies and later shown to be able to reduce the risk of breast cancer altogether," comments lead author of one of the studies Gad Rennert (Clalit Health Services National Cancer Control Center, Haifa, Israel).

In a case–control study, Rennert *et al.* compared the exposure to bisphosphonates before disease diagnosis (or before study recruitment in the control group) between 1,832 postmenopausal women with cancer and 2,207 healthy women, matched by a variety of demographic factors.

Rennert and co-workers found that the use of bisphosphonates (in the years before either cancer diagnosis or study recruitment) was significantly more common in healthy women than in women with breast cancer. This finding suggested that the use of bisphosphonates is 'protective', with a protection magnitude of 28% after correcting for a variety of possible confounders. Another important finding was that the effect of bisphosphonates was detectable only after 1 year of use and did not grow with increasing number of treatment years.

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Women with bone loss are already at a lower breast cancer risk than healthy women, because low BMD probably reflects lower cumulative estrogen exposure. Had the effect observed by Rennert *et al.* been the result of low estrogen exposure (leading to low BMD and thus osteoporosis), a protective effect would have been expected even in women with <1 year bisphosphonate therapy, as the effect would be associated with the indication for the drug and not its use.

Rennert's findings are corroborated by a US study led by Rowan T. Chlebowski from the David Geffen School of Medicine at the University of California in LosAngeles. Chlebowski *et al.* examined the association between oral bisphosphonate use and invasive breast cancer in postmenopausal women enrolled in the Women's Health Initiative.

To account for lower cumulative estrogen exposure in bisphosphonate users, Chlebowski and co-workers adjusted for potential differences in BMD between those using bisphosphonates and nonusers. After this adjustment, Chlebowski and colleagues discovered that women who were bisphosphonate users had 32% fewer invasive breast cancers than nonusers. A trend for fewer hormone-receptor-positive cancers was seen as well, potentially indicating an additional benefit of bisphosphonate use besides its effects on bone. If confirmed, this finding may help identify an approach to prevent hormone-receptor-negative breast cancers (given that tamoxifen, which is currently approved in the USA for breast cancer risk reduction, only influences hormone-receptor-positive cancers).

"Of course these observational studies can only demonstrate associations and not establish causality. Nonetheless, these separate analyses report nearly identical 30% lower incidence of invasive breast cancer in bisphosphonate users compared with nonusers," comments Chlebowski. Both Rennert and Chlebowski agree on the need for a prospective randomized trial to confirm their findings before bisphosphonates can be used solely to reduce breast cancer risk. "An effort to collect supporting evidence from animal studies and biomarker studies is currently under way," concludes Rennert.

Linda Koch

Original articles Chlebowski, R. T. *et al.* Oral bisphosphonate use and breast cancer incidence in postmenopausal women. *J. Clin. Oncol.* **28**, 3582–3590 (2010) | Rennert, G. *et al.* Use of bisphosphonates and risk of postmenopausal breast cancer. *J. Clin. Oncol.* **28**, 3577–3581 (2010)