Re: Continuing Outcomes Relevant to Evista: Breast Cancer Incidence in Postmenopausal Osteoporotic Women in a Randomized Trial of Raloxifene

In their recent article, Martino et al. (1) concluded that raloxifene treatment reduces the incidence of estrogen receptor (ER)-positive invasive breast cancer in postmenopausal women with osteoporosis. However, venous thromboembolic events were two times higher in the raloxifene group than in the placebo group (2). We have a comment about this study.

Nonsteroidal anti-inflammatory drugs, such as cyclooxygenase-1 and -2 (COX-1 and -2) inhibitors, are frequently used to alleviate bone pain due to osteoporosis in postmenopausal women. COX-2 inhibitors have been shown to be chemopreventive agents in patients with familial polyposis coli (3). However, it has also been shown that overexpression of COX-2 is associated with increased expression of aromatase in breast cancer cells (4). The expression of COX-2 promotes the growth of microvessels within the tumor through increased expression of prostaglandin E2, which induces the expression of vascular endothelial growth factor and basic fibroblast growth factor in cancer cells and directly modulates endothelial cell proliferation (5,6). Because both an abundant vasculature and accelerated estrogen synthesis are thought to contribute to unfavorable conditions for response to endocrine therapy, it is likely that COX-2 inhibition may be a promising strategy to potentiate the effectiveness of endocrine therapy.

Martino et al. (1) did not report any information about the use of analgesics, especially COX-2 inhibitors, by the patients in their study. It is possible that patients in the placebo and raloxifene groups differed in their use of COX-2 inhibitors, which may have had a preventive effect on the development of ER-positive breast cancer. We recommend that a subgroup analysis that considers the use of nonsteroidal anti-inflammatory agents should be performed.

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DOI: 10.1093/jnci/dj090

RESPONSE

The comments from Dr. Yalcin and colleagues raise a clinically relevant question. Clinical data suggest that the use of aspirin and other nonsteroidal anti-inflammatory drugs (NSAIDs), including cyclooxygenase-2 (COX-2) inhibitors, is associated with decreased risks of several cancers, including breast cancer (1–3). That use of COX-2 inhibitors might potentiate the reduction in incidence of invasive breast cancer demonstrated with raloxifene therapy in the Continuing Outcomes Relevant to Evista (CORE) trial (4) is a reasonable hypothesis. The CORE trial protocol did not require investigators to record the subject’s use of aspirin or NSAIDs, including the COX-2 inhibitors (rofecoxib, celecoxib, and valdecoxib). However, this information could be voluntarily recorded as a concomitant medication, without specifying dosage, frequency of use, or compliance. During the Multiple Outcomes of Raloxifene Evaluation (MORE) trial, investigators were required to record all concomitant medication use but—as in the CORE trial—dosage, frequency of use, and compliance were not recorded. Because aspirin and the NSAIDs ibuprofen and naproxen are available both as prescription only and nonprescription dosages and are indicated for a variety of conditions (i.e., headache, flu symptoms, general muscle aches or pain), it is reasonable to expect that information relating to use of these agents would be unreliable and thus would confound the results and their clinical interpretation. By contrast, data relating to use of the COX-2 inhibitors may be more reliable because these agents are available only in prescription dosages with more limited indications. The COX-2 inhibitors became clinically available in the United States either while the MORE trial was concluding (rofecoxib and celecoxib) or after it was finished (valdecoxib). Therefore, it is unlikely that use of these agents would have impacted the 72% reduction in incidence of invasive breast cancer observed in the MORE trial after 4 years of raloxifene (5). Regarding the use of COX-2 inhibitors during the CORE trial, of the 4011 women who chose to enroll in the CORE trial, 137 (96 from the raloxifene group and 41 from the placebo group) reported using one of these agents sometime between the end of the MORE trial and the end of the CORE trial. There was no statistically significant difference between the raloxifene and placebo groups in reported use of COX-2 inhibitors.
(3.5% versus 3.2%, respectively; \( P = .64 \)). Only two invasive breast cancers were reported in these 137 women, one in each treatment group. In summary, our data do not allow us to answer the interesting question posed by Dr. Yalcin and colleagues.

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DOI: 10.1093/jnci/dji091