Re: Tamoxifen and Contralateral Breast Cancer: the Other Side

In her editorial (1) regarding our report (2) on the relationship between tamoxifen therapy for primary breast cancer and risk of contralateral breast cancer by estrogen receptor (ER) status, Dr. Swain comments that we “did not find a statistically significant reduction in contralateral breast cancer in women treated with adjuvant tamoxifen, with a hazard ratio [HR] of 0.9 (95% confidence interval [CI] = 0.7 to 1.2). This negative finding seriously calls into question the generalizability of the results of the subset analyses presented by Li et al. . . . The results presented by Li et al. . . . are inconsistent with other data in the literature.” Dr. Swain then compares our findings to those from a meta-analysis of 55 randomized trials by the Early Breast Cancer Trialists’ Collaborative Group (3), which reported a 30% reduction in contralateral breast cancer in women with ER-positive tumors that increases with duration of treatment. However, Dr. Swain’s comparison of our results with those of the meta-analysis is not a fair one. As we reported (2), when we restricted our analysis to women whose first tumor was ER positive, tamoxifen users experienced a 20% overall reduction (HR = 0.8; 95% CI = 0.6 to 1.2) in the risk of developing a contralateral tumor compared with non-users of tamoxifen. Furthermore, we also noted that the mean follow-up time for women in our study was 3.9 years. As Dr. Swain noted, the meta-analysis reported that tamoxifen’s benefit in reducing the risk of contralateral cancers increased as duration of tamoxifen use increased. Thus, given that many women in our study were unlikely to have received the recommended full 5 years of tamoxifen treatment, we would, in fact, expect to have observed a less than 30% reduction in risk.

As Dr. Swain points out and as we describe in our report, there are certain limitations to our study. Specifically, given the exposure data available to us, we did limit our study to women 50 years of age and older who had localized or regional-stage disease and who did not receive chemotherapy. These exclusions are consistent with those in other studies evaluating tamoxifen use with the National Cancer Institute’s Surveillance, Epidemiology, and End Results (SEER) Program1 data (4). Furthermore, although we were able to identify which subjects’ tumors were assessed for ER status using an immunohistochemical assay, not all of the tumors were assessed in the same laboratory.

With respect to our classification of tamoxifen exposure though, we do take issue with Dr. Swain’s claim that “a 6% treatment misclassification error may be substantial, considering that the conclusions are based on a very small number of contralateral breast cancer cases with ER-negative tumors.” Even if we assume that 6% of the data on treatment was misclassified, there would be no reason to think that this misclassification in treatment status would be differential, that is, that it would be dependent on the ER status of contralateral tumors. Thus, any misclassification present would be nondifferential and would bias our reported results toward the null, suggesting that, if anything, we underestimated the true risk of contralateral breast cancer in tamoxifen users.

Dr. Swain also made the following argument: “If, as Li et al. suggest, more ER-negative contralateral breast cancers occur in women treated with tamoxifen, one would have expected a decrease in survival in women treated with tamoxifen. This is not the case. In fact, the opposite has been found.” Certainly, we agree that tamoxifen has been shown to reduce mortality by up to 26% in women who use it for 5 years (3). However, our results are not inconsistent with this known reduced risk of mortality associated with tamoxifen, since the primary means by which tamoxifen reduces mortality is by reducing a woman’s risk of breast cancer recurrence. The reduction in mortality associated with this reduction in risk of recurrences would overshadow any added mortality associated with an increased risk of developing an ER-negative contralateral tumor.

We believe that our findings should not change current clinical practices because tamoxifen has clearly been shown to reduce the risk of recurrence and to improve survival. Our findings do suggest, however, that, in terms of the incidence of contralateral breast cancer, one type, ER-negative tumors, may actually occur more commonly than expected in women who have used tamoxifen.

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REFERENCES


NOTES

1Editor’s note: SEER is a set of geographically defined, population-based, central cancer registries in the United States, operated by local non-profit organizations under contract to the National Cancer Institute (NCI). Registry data are submitted electronically without personal identifiers to the NCI on a biannual basis, and the NCI makes the data available to the public for scientific research.

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RESPONSE

The study by Li et al. (1) is prone to systematic bias. I agree with the authors’ statement that their findings should not change current clinical practice. I disagree that their findings suggest that estrogen receptor-negative tumors may be more common. Instead, I would suggest that this is a hypothesis that needs to be tested.

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