CORRESPONDENCE

Re: Endometrial Cancer in Tamoxifen-Treated Breast Cancer Patients: Findings From the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-14

Three issues in the report of the National Surgical Adjuvant Breast and Bowel Project regarding endometrial cancer and tamoxifen (/) are worthy of further consideration.

First, if a primary hypothesis is "Tamoxifen is associated with an excess of second primary cancers," what are the results when the data from Hôpital Saint-Luc are removed?

A second issue concerns consideration of other factors besides treatment with tamoxifen that are known to be associated with the occurrence of endometrial cancer. In a large study like this, one might expect each of these factors to be equivalently distributed among the two groups, e.g., obesity, previous exogenous estrogen exposure, and diabetes (each associated with increased risk) and cigarette smoking and hysterectomy (each associated with decreased risk).

(2). Compliance with tamoxifen therapy may vary with each of these factors. A standard epidemiologic approach is to assess these factors and to adjust for possible differences in the analysis. Presumably, aside from hysterectomy, these data are not available for these patients. It is interesting to note that in the tamoxifen group versus the placebo group, there is an apparent excess of lung cancers (nine versus three events) and urinary bladder cancers (three versus no events), two cancers that are associated with smoking. These data suggest that there is a possibility that the tamoxifen group had more smokers. If so, then the relative risk of endometrial cancer expected should be less than one in the tamoxifen group with no tamoxifen effect, and the estimated excess risk for endometrial cancer has been underestimated in the analysis presented. At a minimum, the authors should acknowledge the existence of such possible confounding.

Third, the discussion of the Breast Cancer Prevention Trial (BCPT) risk-benefit reanalysis concludes without presenting data that "the BCPT continues to favor a benefit." The continuation of public and published statements of this kind in the absence of presented quantitative analyses should be unacceptable to the scientific community, to the Journal editorial staff, and, most importantly, to the BCPT participants. It is of interest that the lead author of the accompanying editorial is quoted to this effect in the lay press (in commenting on treatment data) (3). Critics of the BCPT have presented their analyses in rigorous publications (4-5). An operational consensus can be reached only with numerical exploration of the epidemiologic and statistical case for the continuation of this trial.

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References


Response

We are pleased to have the opportunity to respond to Dr. Love's three points of contention.

First, we did not present the results of analysis for second primary cancers with data from the Hôpital Saint-Luc removed because it was inappropriate to do so. Of the 186 patients randomly assigned by the Hôpital Saint-Luc to Protocol B-14, all had invasive breast cancer and were appropriately followed. The audit by the Office of Research Integrity (Division of Policy and Education, Public Health Service, U.S. Department of Health and Human Services) verified that this was the case. When assessing the toxicity of a therapy, we believe it is improper and unethical to delete any patients who were appropriately followed and who may have had toxic effects that could be associated with treatment. Doing so could result in an underestimation of toxic side effects that might exist. Furthermore, the exclusion from analyses of patients from the Hôpital Saint-Luc does not result in any modification of conclusions reached from the full analysis. This fact has been verified externally by an independent analysis commissioned by the National Cancer Institute (NCI). A report of this independent analysis has been distributed by the EMMES Corporation (/) and has been made available to the public by the NCI.

In response to Dr. Love's second issue regarding other factors that may be associated with the occurrence of endometrial cancer, it is highly unlikely that there is any difference between treatment groups in the distribution of such factors in this study. The speculation of noncomparable treatment groups made by Dr. Love is based on a comparison of differences between treatment arms of the absolute numbers of cases for only selected subsets of second cancers. The differences are not significant and the number of cases are relatively few. Protocol B-14 is a double-blinded, randomized study involving more than 2800 patients. The purpose of randomization was to ensure the comparability of the treatment groups. With a sample size as large as that of Protocol B-14, there is a high probability that this was accomplished. In fact, comparability between the treatment groups is evident for all factors that we have assessed. Although we do not have information on every factor that may be