Letters to the Editor

Correspondence re: V. C. Jordan and V. J. Assikis, Endometrial Carcinoma and Tamoxifen: Clearing Up a Controversy. Clin. Cancer Res., *1:* 467–472, 1995.

Jordan and Assikis recently provided a valuable review of the available evidence for the relationship between tamoxifen treatment and subsequent development of endometrial carcinoma (1). In the review the authors also commented on the Danish study which randomized postmenopausal node-positive patients with early breast cancer to receive either postoperative radiation treatment alone (control group) or radiation treatment plus adjuvant tamoxifen treatment (30 mg/day for 48 weeks; experimental group). Node-negative patients did not receive any postoperative treatment. After 10 years of follow-up, the cumulative frequency of endometrial carcinoma among tamoxifen-treated node-positive patients was 1.0%, compared to 0.3% among node-positive patients who were randomized not to receive tamoxifen (log rank test, $P = 0.11$; Refs. 2 and 3). Jordan and Assikis (1) state, however, that it is not appropriate to compare the two randomized groups because the incidence of endometrial carcinoma in the control group (radiotherapy alone) was relatively low. Instead, the authors suggest that the incidence of endometrial carcinoma among tamoxifen (and radiation)-treated node-positive patients should be compared with that of the node-negative patients who were not given either tamoxifen or radiation treatment and who had a higher incidence of endometrial carcinoma (*i.e.*, 0.8%). We consider it to be generally accepted that valid conclusions require analysis of data where groups are as similar as possible except for the variable studied. A randomized trial as the one on which our study is based fulfills this requirement. We are therefore surprised that Jordan and Assikis (1) prefer to replace the control group of a properly randomized trial with another noncomparable group.

Michael Andersson[1]
Hans H. Storm
Henning T. Mouridsen
Department of Oncology
Rigshospitalet
National University Hospital
9 Blegdamsvej
DK-2100 Copenhagen Ø
Denmark

References

1. Jordan, V. C., and Assikis, V. J. Endometrial carcinoma and tamoxifen: clearing up a controversy. Clin. Cancer Res., *1:* 467–472, 1995.

2. Andersson, M., Storm, H. H., and Mouridsen, H. T. Incidence of new primary cancers after adjuvant tamoxifen therapy and radiotherapy for early breast cancer. J. Natl. Cancer Inst., *83:* 1013–1017, 1991.

3. Andersson, M., Storm, H. H., and Mouridsen, H. T. Carcinogenic effects of adjuvant tamoxifen treatment and radiotherapy for early breast cancer. Acta Oncol., *31:* 259–263, 1992.

Received 10/30/95; accepted 10/30/95.
[1] To whom requests for reprints should be addressed.

Reply

We would like to thank Drs. Andersson, Storm, and Mouridsen for their letter and for providing us with the opportunity to expand on our interpretation of their data (1–3). This was presented in our review of the controversy surrounding the association between tamoxifen and endometrial cancer (4). We absolutely agree that prospective randomized clinical trials are the most appropriate mechanism to answer therapeutic questions. However, the retrospective collection of data relating to ancillary questions may not result in an accurate answer in small populations if the effect to be assessed, as in this case, is a very rare event. We have chosen to take a common sense approach and include all provided data to assess the validity of the presented conclusion by the authors. To illustrate our point, we have reproduced the original Fig. 1 from the *Journal of the National Cancer Institute* article that showed a 5-fold increase in the incidence of endometrial carcinoma at 10 years in women treated with RT[1] + tamoxifen compared to RT alone. Most importantly, these data are stated to be not significant ($P = 0.11$), although as they are presented in the graph the cumulative incidence of endometrial cancer with and without tamoxifen appears to be very different on the expanded scale. Overall, the graph of the increased incidence of endometrial cancer and their predictable finding that 48 weeks of tamoxifen did not prevent contralateral breast cancer presents the unsophisticated reader only with concerns but no benefits when considering tamoxifen treatment as a therapeutic option. What first attracted our attention was the incidence of endometrial cancer for the no treatment group (low risk) that the authors included in Fig. 2 of their *Acta Oncologica* article they published the following year. The authors clearly show that there is virtually no difference ($P = 0.3$) between the incidence of endometrial cancer in the RT + tamoxifen group and completely untreated women with a low risk for breast cancer recurrence. It is obvious that the RT-alone group has an unusually low incidence of endometrial cancer.

If Dr. Andersson and co-authors believe that the no treatment low-risk group cannot be used to provide reasonable comparisons because they are not part of the randomization, then why are these data included at all? In both of their publications, these data are used as the control to demonstrate a significant increase ($P = 0.04$) in hematological malignancies attributed to RT. Although the authors know that their conclusion is not based on a randomized clinical study, the increased incidence of hematological malignancies is reported as their only significant finding. If women are persuaded to be concerned about a nonsignificant increase ($P = 0.3$) in endometrial cancer, it is surprising they

Received 11/10/95; accepted 11/10/95.
[1] The abbreviation used is: RT, radiotherapy.

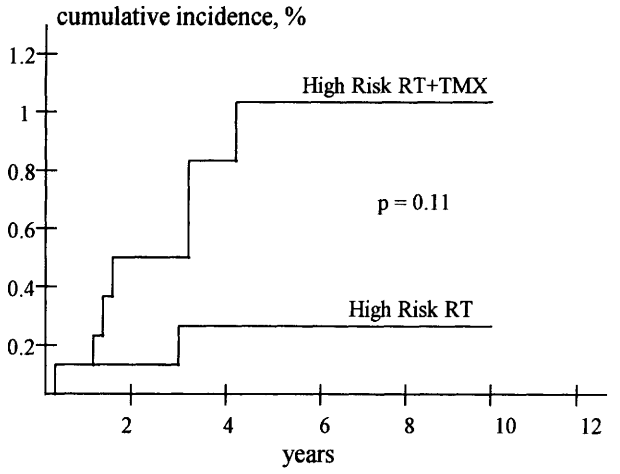

Fig. 1 Cumulative incidence of adenocarcinoma of the uterine corpus among breast cancer patients at high risk of recurrence, treated adjuvantly with postoperative RT (*High Risk RT*) or RT and tamoxifen (*High Risk RT + TMX*). Reproduced from the *Journal of the National Cancer Institute.*

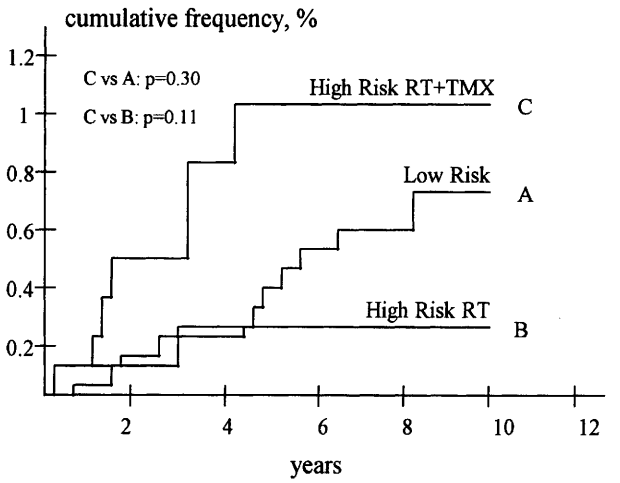

Fig. 2 Cumulative frequency of endometrial cancer subsequent to breast cancer. *A*, low-risk group; *B*, high-risk RT group; *C*, high-risk RT + tamoxifen group. Reproduced with permission of *Acta Oncologica.*

are unconcerned about a significant increase ($P = 0.04$) in radiation-induced nonlymphocytic leukemia (4). It is also unfortunate that the significance of the radiotherapy data was misprinted as $P = 0.4$ in the "Abstract" of the *Acta Oncologica* article, and the authors then chose to focus on their nonsignificant finding about tamoxifen with the ominous closing statement "Prolonged follow up of tamoxifen-treated patients . . . is recommended." In our view their findings are reassuring for patients taking 48 weeks of tamoxifen, and epidemiological data now show that short-term tamoxifen does not produce any significant increase in endometrial cancer (5). In fact, Cook *et al.* (5) found a nonsignificant decrease in endometrial cancer. However, it would be inappropriate for us to suggest that tamoxifen might protect against endometrial cancer.

Although we agree in principle that there is reason to take a cautious view about adjuvant tamoxifen, we strongly believe we should now look closely at the published randomized therapeutic trials to ensure that the association between tamoxifen and endometrial cancer incidence has not been overstated. Overstating the risks for tamoxifen cannot benefit women who are being treated for a life-threatening disease. Tamoxifen therapy is a proven lifesaving treatment for breast cancer, and the detection of endometrial cancer should be placed in perspective.

V. Craig Jordan[2]
Vasilios J. Assikis
Robert H. Lurie Cancer Center
Northwestern University Medical School
Chicago, Illinois 60611

References

1. Andersson, M., Storm, H. H., and Mouridsen, H. T. Correspondence re: V. C. Jordan and V. J. Assikis, Endometrial carcinoma and tamoxifen: Clearing up a controversy. Clin. Cancer Res., *1:* 467–472, 1995. Clin. Cancer Res., *2:* 223, 1996.

2. Andersson, M., Storm, H. H., and Mouridsen, H. T. Incidence of new primary cancers after adjuvant tamoxifen therapy and radiotherapy for early breast cancer. J. Natl. Cancer Inst., *83:* 1013–1017, 1991.

3. Andersson, M., Storm, H. H., and Mouridsen, H. T. Carcinogenic effects of adjuvant tamoxifen treatment and radiotherapy for early breast cancer. Acta Oncol., *31:* 259–263, 1992.

4. Jordan, V. C., and Assikis, V. J. Endometrial carcinoma and tamoxifen: clearing up a controversy. Clin. Cancer Res., *1:* 467–472, 1995.

5. Cook, L. S., Weiss, N. S., Schwartz, S. M., White, E., McKnight, B., Moore, D. E., and Daling, J. R. Population-based study of tamoxifen therapy and subsequent ovarian, endometrial and breast cancers. J. Natl. Cancer Inst., *87:* 1359–1364, 1995.

[2] To whom requests for reprints should be addressed, at Robert H. Lurie Cancer Center, Northwestern University Medical School, Olson Pavilion 8258, 303 East Chicago Avenue, Chicago, IL 60611-3008.

Clinical Cancer Research

Endometrial carcinoma and tamoxifen: clearing up a controversy.

M Andersson, H H Storm and H T Mouridsen

Clin Cancer Res 1996;2:223-224.