Re: Should Observational Studies Be a Thing of the Past?

In her editorial, Kathleen Pritchard (1) stated that the results of several randomized trials “clearly provide a definite answer” regarding the influence of hormone replacement therapy (HRT) administered after a diagnosis of breast cancer on the prognosis of women with this disease. The trials to which she referred are the multinational Hormonal Replacement Therapy After Breast Cancer—Is it Safe? (HABITS) study (2,3) and the Stockholm Randomized Trial (4). The “definite answer” appeared to have been provided by the observation in the HABITS trial of a substantial increase in the incidence of local recurrence and contralateral cancer in the women assigned to HRT—there were 29 such events in the HRT arm, compared with only 9 among women in the equal-sized control arm. However, no such association was seen in the Stockholm study—the corresponding numbers were 8 and 8. Chance conceivably could account for difference in results between the studies, but a formal test of statistical heterogeneity suggests otherwise—the P value was .02. Another possible explanation relates to the difference in the type of progestogen typically given to women in the two studies—northeastosterone acetate in the HABITS trial vs medroxyprogesterone acetate in the Stockholm trial—but in the HABITS trial, use of estrogen alone was associated with a recurrence risk similar to that of use of combined hormone therapy (3). Finally, even though in both studies an effort was made to standardize the frequency of follow-up of study participants, the lack of blinding possibly could have led to differentially complete ascertainment of the more subtle forms of recurrence between women in the two arms of the trials.

The lack of blinding in the trials argues that relatively more weight should be given to the results for the relatively more serious outcomes of breast cancer mortality and the development of metastatic disease. Examination of these outcomes does not suggest an adverse influence of HRT. There was no increase in breast cancer mortality in either trial. In the HABITS trial, during an average of 4 years of follow-up there were six deaths from breast cancer among 221 women assigned to receive HRT, vs five deaths among an equal number assigned to not receive HRT (3). In the Stockholm trial (4), there were two deaths from breast cancer among the 188 women assigned to receive HRT during an average of 4.1 years of follow-up, vs four such deaths among 190 women in the control arm. In the HABITS trial (3), distant metastases developed in 10 women assigned to HRT and in eight not so assigned; the corresponding numbers in the Stockholm study were three and five. Thus, neither trial observed an appreciable increase in risk of metastatic disease associated with administration of HRT.

I wholeheartedly agree with Dr. Pritchard that “interventional studies with robust controlled designs” should be implemented when feasible. However, in the case of HRT administration following a diagnosis of breast cancer, I believe that in spite of several randomized trials that sought to address the question there is not yet convincing evidence that the earlier results of nonrandomized studies, which observed no altered risk of recurrence or mortality associated with hormone use, were invalid.

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References


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Response

I am pleased to consider Dr. Weiss’ comments about my editorial. I was indeed aiming to be somewhat provocative and am pleased that I succeeded.

Certainly my comment that these randomized trials “clearly provide a definite answer” is debatable. One must consider, however, that the Stockholm trial, which ran concurrently with the HABITS trial and which showed no negative effect of hormonal replacement therapy (HRT), was closed to further accrual based on the statistically significant detrimental effects seen in the HABITS trial at interim analysis. It is my view that the negative results seen in HABITS, together with the underlying biology/physiology, which would strongly suggest that HRT could be harmful, have, together, probably closed the door to the possibility of further randomized trials in this area.

Dr. Weiss makes an important point in suggesting that the difference between progestin-containing HRT and estrogen alone could be an important one. This is also supported by randomized data from the Women’s Health Initiative study. Whether another group of investigators, their research ethics boards, and patients would be willing to mount and carry out an additional randomized study in this area, however, seems dubious.

Although I agree that the outcomes of breast cancer mortality are most definitive, I disagree with Dr. Weiss’ suggestion that breast cancer recurrence is not a valid endpoint. It is hard to be biased in ascertaining breast cancer recurrence, which is generally quite clear. Furthermore, breast cancer recurrence is clearly a harbinger of ultimate breast cancer mortality but of course occurs sooner and more frequently in the early years of follow-up. In a trial this small and with only an additional 2 years of follow-up, the

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fact that no additional deaths have occurred following recurrences is not surprising because many women live much longer than 2 years after recurrence of breast cancer.

I am pleased that Dr Weiss agrees with me that interventional studies with robust control design should be implemented when feasible. However, as mentioned above, I think that another randomized trial of HRT in this setting might prove difficult.

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