Stopping HABITS

Sir—The medical community has given almost unquestioning credence to the results of randomised clinical trials. This reliance has led to a discounting of the results of observational studies, animal trials, and basic biological data. Like all forms of investigation, the randomised trial is limited by study design (eg, selection of patients before randomisation, selection of biologically meaningful endpoints), and by differential adherence to the study protocol.

The HABITS trial (Feb 7, p 453)[1] was designed to assess the efficacy of hormone therapy given to women after treatment of breast cancer. Hormone therapy after breast cancer is becoming an increasingly relevant problem as more women survive breast cancer; there are, however, important issues to be taken into account. Because of early diagnosis, women have less advanced disease.[2] The use of hormones has different implications for women with treated limited cancers compared with those with advanced disease. Further, women are increasingly concerned about the risks and benefits of hormone therapy, specifically the risk of breast cancer. Limitations in the design and interpretation of the HABITS trial have bearing on this issue and deserve mention.

There seem to be significant differences between the two study groups (one randomised to hormone replacement therapy [HRT] and the other to no hormone therapy). There was a 24% greater incidence of positive nodes in the group receiving HRT (26% *vs* 21%); nodal status is perhaps the most accurate prognosticator of recurrence. 16% more women in the HRT group than the no hormone group had oestrogen-receptor-positive tumours (56% *vs* 48%), which is certainly an indicator of the ability to respond to hormone therapy. There was also a 9% greater incidence of breast-preserving surgery in the HRT group (62% *vs* 57%), perhaps indicating more aggressive treatment of the non-HRT group and explaining the increased number of local recurrences.

The Research letter[1] and accompanying Commentary[3] lack explanation of the basic biological principles that underlie carcinogenesis and tumour growth. It is a well established biological principle that sex steroids stimulate the breast. Also, breast cancers are indolent in nature; it is estimated that the duration from initial cancer cell to mammographically detectable lesion is at least 5 years.[4,5] A 2·1-year study can only have detected pre-existing tumours that were present but not clinically evident at the onset of the trial. Does this represent an increase in breast cancer or increased detection of existent tumour? What was the role of the oestrogen in magnifying the already present differences mentioned above?

The endpoints must be more biologically sound. The ultimate endpoint of interest is mortality, and it is not surprising that there were a greater number of breast cancer deaths in the non-HRT group (four *vs* three). Although not significant, this discrepancy illustrates the limitations of the study. We cannot conclude from the current data whether hormone therapy increases breast cancer occurrence or early detection. A 5–10-year study is required to obtain data on new cancer occurrence and to measure survival. Such a long-term prospective trial is impractical.

This randomised trial included node-positive women who most would not treat and more women with a poor prognosis in the HRT group, and did not find a difference in the appropriate endpoint: mortality. We must be careful not to accept blindly the results of randomised clinical trials as the final word. Any such results should be viewed in the context of previous scientific reports and rely on sound biological principles.

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Sir—Lars Holmberg and colleagues,[1] who did a trial of HRT in women previously treated for breast cancer, present their results in a manner that could influence treatment decisions more strongly than is merited by the data provided. HABITS is the first randomised trial with prospectively defined follow-up to study the safety of HRT for women with a previous breast-cancer. The HABITS investigators report that hormone therapy increased the risk of breast-cancer events (relative hazard 3·5, 95% CI 1·5–8·1) and serious adverse events (eight *vs* four) compared with no such therapy.

Previous retrospective and case-control studies have not found any difference in breast-cancer recurrence, disease-free survival, or global survival for women treated with HRT. In a prospective, single-arm pilot study of 211 patients, Bluming and colleagues[2] found that disease-free survival decreased with breast-cancer stage (T0N0 92%, T1N0 87%, T2N0 83%, T1N1 80%, and T23N1 73%). O'Meara and colleagues,[3] in a case-control study with 174 HRT users, saw lower risks of recurrence (relative risk 0·5, 95% CI 0·3–0·85) and mortality (0·48, 0·3–0·85) in women who used HRT after breast cancer diagnosis than in women who did not.

In the same way, in a systematic literature review of 11 studies including 669 HRT users and control groups, Col and colleagues[4] did not find a significant effect of HRT on breast-cancer recurrence (0·82, 0·58–1·15). In this series, the average disease-free interval of women who began HRT was relatively long (nearly 5 years) and inversely correlated with the rate of breast-cancer recurrence. So the risk of breast-cancer recurrence in HRT users could be restricted to women with less favourable stage and shorter disease-free interval.

In the HABITS trial, further analyses were done by subgroups defined by receptor status, tamoxifen treatment, and HRT taken before diagnosis, to elucidate whether the risk seemed isolated to any one subset or if any of these factors strongly modified the effect of HRT. First, in hormone-receptor-negative women, the relative risk was not significant (1·9, 0·4–9·6). Second, no analyses were done with respect to tumour size, nodal status, and disease-free interval before beginning HRT.

In the management of hot flashes in breast-cancer survivors, several alternative substances have been investigated. These include clonidine, soya phyto-oestrogens, vitamin E, gabapentin, newer antidepressants, and progestational agents.[5] These drugs can relieve symptoms in most cases and HRT should only be used in refractory hot flashes. So, the question is not about whether HRT is safe in breast-cancer survivors, but about which women can benefit from HRT after breast cancer.

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