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Authors' reply

Sir—We agree that the results of a single randomised study should be interpreted cautiously, especially when the study is terminated early. We reported why we stopped recruitment in the HABITS trial and have not claimed to say "the final word". A longer follow-up, combination of our results with those of other studies, and possibly other types of studies will be needed to shed more light on the consequences of taking HRT after a previous breast cancer. How much our present results will influence practice lies above all in the eye of the beholder.

As in all randomised trials, there were some differences between the baseline characteristics of the patients. We did an analysis adjusted for these differences—including stage of disease—and several subgroup analyses, as shown in table 2. None of these analyses could convince us that bias had a major role in our findings. The amount of follow-up data was also similar in both groups, speaking against a detection bias. Further, we found no clear low-risk group for which the trial could possibly continue. Our exploratory subgroup analyses can definitely not be taken as strong evidence that women with hormone-receptor-negative tumours could be such a safe group.

We would be extremely happy if we knew "the basic biological principles that underlie carcinogenesis and tumour growth", as Hugh Taylor and Frederick Naftolin mention, but since we do not, in theory there are an infinite number of possible explanations for our findings. That the hormones stimulate deposits of micrometastases already present at randomisation is one of the theories that seem rational from biological theory and the pattern of recurrence in our study. This theory was also one part of the biological reasoning behind the study and its design, including the safety analyses. However, to make decisions about risks and benefits for patients in terms of clinical outcomes, we need not understand all the mechanisms of the actions of a medication. For many very useful medications, our understanding of the mechanisms of action is incomplete.

The HABITS study was designed to study safety. Thus, the side-effect of new breast-cancer events is a highly relevant endpoint. However, mortality will also become a very important endpoint in a longer follow-up. The difference in new breast-cancer events might carry over in a difference in mortality in the long run, and that was a major reason to halt the recruitment.

Philippe Debourdeau and colleagues argue that the observational studies of the effects of HRT in breast-cancer survivors are more likely to give a valid answer than the randomised HABITS trial. We believe on the contrary that the randomised clinical trial is necessary to challenge our often-erroneous impressions formed from studies without a randomised design. The history of medicine has many times shown—not least in conjunction with HRT—that the selection bias created by indications for treatment in non-randomised studies is strong and controllable only to a limited degree.

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Value of SERMs in postmenopausal women

Sir—The HABITS study (Feb 7, p 453),[1] along with other studies, clearly shows the potential detrimental effects of hormone replacement therapy (HRT) on women's health. The time has therefore come to move away from HRT to a treatment based on our molecular knowledge of the target for HRT—ie, oestrogen receptors α and β. Selective oestrogen-receptor modulators (SERMs) are the first generation of post-HRT therapeutic agents that offer the possibility of maintaining the health of postmenopausal women while avoiding the breast and other related problems encountered with HRT.

SERMs are non-steroidal compounds with tissue-specific agonist-antagonist activity, and currently available SERMs include tamoxifen, raloxifene, and toremifene. A failed breast cancer drug, raloxifene was seen to maintain bone density in ovariectomised rats while avoiding the oestrogenic effect on the uterus seen with tamoxifen.[2] This finding eventually led to the Multiple Outcomes of Raloxifene Evaluation (MORE) study[3] in osteoporotic postmenopausal women, which revealed that raloxifene could increase bone-mineral density and reduce the risk of spinal fracture by 30–50% compared with placebo. Additionally, there was a 76% reduction in the incidence of invasive breast cancer with no increase in the risk of endometrial carcinoma seen with tamoxifen. However, there was an increase in thromboembolic disease, similar in magnitude to that seen with tamoxifen and HRT.[4]

Currently raloxifene is being investigated in a double-blind randomised controlled trial known as Raloxifene Use for The Heart (RUTH).[5] This trial involves 10 000 postmenopausal women with coronary heart disease (CHD), peripheral arterial disease, or multiple risk factors for CHD, with the primary endpoint being the number of coronary events. This trial aims to provide information on the cardiovascular benefit of a SERM in postmenopausal women at high risk of CHD, which is particularly important in view of the cardiovascular complications seen with HRT.

The unique properties of SERMs lie in their bulky side-chain, which prevents helix 12 of the oestrogen receptor relocating over the ligand-binding pocket as it would if oestrogen were bound. This blocking effect in turn prevents key coregulator proteins (known as coactivators) from interacting with the receptor and thus prevents activation. The further differences seen between tamoxifen and raloxifene in relation to their oestrogenic and antioestrogenic properties relates to the ability of the raloxifene side-chain to interact closely with aminoacid 351, thus further influencing the function of the oestrogen receptor.[2]

Improvements in our molecular knowledge regarding the distribution, functioning, and modulation of oestrogen receptors α and β in different target organs, and the relative contribution of each receptor type to