There has been much debate recently on the issue of breast cancer and hormone replacement therapy (HRT). The results of the Million Women Study (MWS) reported a doubling of the risk of breast cancer in current users of combined HRT compared with never-users, along with increased mortality among those women who developed breast cancer while taking HRT. This has caused major scares among women, their doctors and the pharmaceutical industry.

Correspondence in a recent issue of the *Lancet* is worth taking a look at. A wide range of correspondents pointed out what they saw as flaws in the trials, all coming to the conclusion that the MWS’s conclusion that even short-term HRT leads to a significantly increased risk of breast cancer is difficult to interpret.

Were there differences between the health-seeking behaviour of current and never-users of HRT? One correspondent pointed out that only about one-half of the annual burden of breast cancer in this age group is picked up by screening anyway, so an increase in breast screening would lead to an increase in diagnosis of breast cancer. The Women’s Health Initiative (WHI) trial, which was discontinued early, showed a lower relative risk of breast cancer among users of combined HRT than the MWS. What was possibly more important was the fact that this study showed an unexpectedly low rate of breast cancer among the placebo group, which may mean that the higher relative risk among those taking HRT was a reflection of this.

There is also the problem of the actual time of exposure to HRT since women’s use status was recorded only at the time of entering the study, so the short [1.2 years] time of diagnosis to breast cancer may in fact have been after a longer exposure to HRT. Another correspondent pointed out problems with the interpretation of statistical significance at the levels which were accepted by the MWS. They claim that a $p$ value of 0.05 was not sufficient to show a higher mortality from breast cancer among current users of HRT, when the original hypothesis was that HRT would have no effect at all over a short time period.

Another potential problem is that of the lower sensitivity of mammograms in women who are on HRT because of increased breast density. Another correspondent thought that this may have led to women entering the trial with established breast cancer, which would have resulted in a short time to diagnosis. This could also have been the reason for the observed increased mortality since HRT may have accelerated the growth of established cancers. Trial design was also under fire, since it may have been that women who were ‘concerned’ about breast problems were overpresented as the trial, in lay persons’ terms, was ‘...about the effects of HRT on women’s breasts’.

The trial collaborators put together a well thought-out defence of their conclusions, saying that their results are, in fact, remarkably similar to those of the WHI. They plan to publish detailed results on the relation to mammography and tumour characteristics, but point out that because mammography sensitivity is altered by HRT, the most appropriate way to look at the effect of HRT on the underlying risk of breast cancer is to combine screening-detected and other breast cancers, which is what they did.

Where does it leave the practitioner and his/her patients? The past couple of years have seen a lot of confusion over a type of therapy which has been used for nearly 20 years. What the controversy brings up very well are the difficulties associated with putting clinical trial information into practice. What is important is not to be directed by anecdotal ‘evidence’. We all know of the woman who started HRT and was diagnosed with breast cancer shortly afterwards. What is important is a rational assessment of the risks versus the benefits of any treatment which may not be regarded as strictly medically necessary, although many women would hotly dispute that menopausal symptoms are something which they must ‘put up with’. The jury is still out, but my interpretation of the literature is that it is still reasonable to assess each case on its merits and prescribe accordingly — keeping a keen eye on the literature at the same time.

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Million Women Study Collaborators. *Lancet* 2003; **362**: 419 - 427
Writing Group of the Women’s Health Initiative Investigators. *JAMA* 2002; **288**: 321 - 333.

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