

MORE ON THE MILLION WOMEN STUDY

The Million Women Study hit the headlines in 2003 when it was published in the *Lancet* and changed the prescribing habits of doctors treating postmenopausal women. Many people feel that the study was flawed, unrepresentative of all women, did not provide consistent follow-up and used an inaccurate classification of hormone replacement therapy (HRT). There was also the issue of the public's understanding of what constitutes risk – highlighted by what became a generally accepted idea that using HRT increases the absolute, rather than the relative, risk of developing breast cancer. However, the fact remains that fewer people are currently willing to prescribe HRT and certainly not for long periods of time.



Now results from another arm of the study have been published, again in the *Lancet*. Study collaborators, writing in a recent issue, point out that it is known that postmenopausal women who use HRT containing unopposed oestrogen are at increased risk of endometrial cancer. To minimise this risk many HRT users who have not had a hysterectomy use combined oestrogen-progestogen preparations or tibolone. Investigators recruited 716 738 postmenopausal women in the UK who had no previous cancer or previous hysterectomy between 1996 and 2001. They provided information about their use of HRT and were followed up for an average of 3.4 years. During this time 1 320 endometrial cancers were diagnosed. The results showed that different types of HRT had sharply different effects on the overall risk of endometrial cancer. Compared with women who had never used HRT, risk was reduced with the use of continuous combined preparations, increased with last use of tibolone and oestrogen only, and not significantly altered with the use of cyclic combined preparations. The women's body mass significantly affected these associations, with the adverse effects of oestrogen-only and tibolone greatest in non-obese women, and the beneficial effects of combined HRT greatest in obese women. The increasing incidence of endometrial cancer in obese women who do not use HRT is well known and believed to be due to the proliferation of the endometrium caused by increased levels of oestradiol and other related circulating hormones that are produced by adipose tissue.

The investigators conclude that oestrogens and tibolone increase the risk of endometrial cancer and that progestogens counteract the adverse effect of oestrogen, the effect being greater the more days every month that they are added to the oestrogen and the more obese the women are. However, they refer to previous findings that combined oestrogen-progestogen HRT causes a greater increase in breast cancer than the other therapies do. They state that when endometrial

and breast cancer are added together, there is a greater increase in total cancer incidence with the use of combined HRT, both continuous and cyclical, than with use of the other therapies.

So, where are we with HRT? Various well-designed, randomised trials have failed to show that HRT reduces the risk of the various diseases that it was at one time assumed to do. Hormones effectively reduce the risk of fractures, but do not reduce the risk of most coronary, cerebrovascular and cognitive events. There is also accumulating evidence that hormones might increase the risk of ovarian cancer. HRT is definitely the most effective treatment for menopausal symptoms – which is what they were first marketed for. So, how should hormones be prescribed to allow women to benefit without risk? The consensus seems to be that women should take the lowest possible dose for the shortest possible time. But what is the shortest possible time? As yet, no-one knows. What is becoming evident is that people are looking at alternatives to hormone treatment to deal with the various physiological changes women experience as they get older. Local oestrogens can relieve urogenital symptoms. Some of the serotonin inhibitors can relieve hot flushes. We know that regular exercise, weight bearing and otherwise, can maintain cardiovascular health, bone strength and prevent, or mitigate, the effects of obesity. A balanced diet, possibly supplemented by calcium and vitamin D, can prevent osteopenia and osteoporosis. Keeping mentally active can ward off dementia. There are definitely other options. For those women whose menopausal symptoms are severe though, HRT with very careful monitoring may be the only answer.

Million Women Study Collaborators. *Lancet* 2005; 365: 1543-1551.
Brinton LA, Lacey JV, Trimble E. *Lancet* 2005; 365: 1517-1518.

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