Hormone treatment increases breast cancer risk, study shows

Susan Mayor *London*

Long term use of combined hormone replacement therapy (HRT) doubles the risk of breast cancer, according to a major epidemiological study published last week that showed for the first time the higher risk with combined oestrogen and progesterone treatment.

From 1996 to 2001 the million women study recruited 1 084 110 women in the United Kingdom aged 50-64 years. When they were invited to attend for routine mammography the women were asked to complete a questionnaire that included questions about their use of HRT. They were then followed up for mortality and incidence of cancer.

The results of the study, published in the *Lancet* (2003;362: 419-27), showed that current users of all types of HRT, including oestrogen only, combined oestrogen and progesterone, and tibolone (synthetic hormone treatment), had a higher risk of breast cancer than women who

had never used HRT (adjusted relative risk 1.66 (95% confidence interval 1.58 to 1.75; $P<0.0001$)). The risk of breast cancer increased with longer use of HRT, but the effect seemed to wear off within a few years of stopping treatment. Also, the relative risk of death was 22% higher in current users than in women who had never used HRT (relative risk 1.22 (1.00 to 1.48; $P=0.05$)).

The risk was even higher in women who used combined HRT—the type of HRT that is generally recommended for women with a uterus (relative risk 2.00 (1.88 to 2.12; $P<0.001$)). This means that for every 1000 postmenopausal women taking combined HRT for 10 years there would be 19 extra cases of breast cancer, while oestrogen only HRT would be associated with an extra five cases. The researchers estimated that use of HRT in women aged 50-64 years has resulted in 20 000 extra cases of breast cancer over the past

decade, of which 15 000 would be associated with combined HRT.

Valerie Beral, professor of epidemiology at the Cancer Research UK's Epidemiology Unit, at the Radcliffe Infirmary, Oxford, and one of the study authors, said: "Since our results show a substantially greater increase in breast cancer with combined HRT, women need to weigh the increased risk of breast cancer caused by the addition of progesterone against the

lowered risk of uterine cancer."

Richard Sullivan, head of clinical programmes at Cancer Research UK, agreed: "Each decision to start HRT should be made on an individual basis between each woman and her doctor." He pointed out that HRT speeds up—rather than causes—the onset of breast cancer, acting as "a promoter not an initiator."

"The risk of breast cancer does not start to increase until after one year of HRT," he said. □

HRT does not prevent heart disease

Janice Hopkins Tanne *New York*

Hormone replacement therapy (HRT) should not be used to prevent coronary heart disease, experts advise, after a study showed that it does not prevent the disease and almost doubles a woman's risk during the first year of use.

Furthermore, HRT does not slow progression of established coronary artery disease.

These findings come from two studies published in the *New England Journal of Medicine*.

Dr JoAnn Manson and colleagues reported final results of the arm of the Women's Health Initiative trial that compared combined oestrogen and progesterone treatment with placebo (2003;349:523-34). The trial, sponsored by the US National Institutes of Health, was stopped

in 2002 because the risks of treatment exceeded the benefits (*BMJ* 2002;325:61).

"There was no clear heart protection. No subgroup clearly showed evidence of heart disease protection," said Dr Manson, the principal investigator and chairwoman of preventive medicine at Harvard's Brigham and Women's Hospital.

The authors write, "The treatment should not be prescribed for the prevention of cardiovascular disease."

Women who took combined HRT had a 24% higher risk of myocardial infarction and death than women who were given a placebo (hazard ratio 1.24 (nominal 95% confidence interval 1.00 to 1.54, 95% confidence interval with adjustment for sequential monitoring 0.97 to 1.60)). The risk was highest in the first year of treatment (hazard ratio 1.81 (1.09 to 3.01)).

"The risk to the individual woman is low. There is still a role for oestrogen in the treatment of menopause," Dr Manson said. There were 39 cases of coronary

heart disease per 100 000 person years for women taking HRT and 33 cases per 100 000 for women taking placebo.

In the combined HRT arm of the trial 16 608 postmenopausal women aged 50 to 79 took a daily dose of Prempro or a placebo. Prempro, the most commonly prescribed HRT in the United States, contains 0.625 mg of conjugated equine oestrogens and 2.5 mg of medroxyprogesterone acetate. The mean age of the women was 63.3 years, and about a third of the women were aged 50-59 years.

Dr Manson said that only about 40% of women stopped taking the pill during the study or changed to a hormone treatment prescribed by their own doctors. Generally, about half of women taking HRT stop within a year.

More than 10 000 women who have had hysterectomies continue in the oestrogen only part of the trial. Results will be reported in 2005.

The second study (2003;349: 535-45), also a double blind,

randomised controlled study, looked at the effect of HRT on 226 postmenopausal women who already had coronary artery disease identified by coronary angiography. Their mean age was 63.5 years. They took either micronised 17- β -estradiol alone, 17- β -estradiol with sequential medroxyprogesterone acetate, or usual care. Patients with high concentrations of low density lipoproteins received statins and dietary advice.

The study compared patients' coronary angiograms of stenosis at their entry to the trial with angiograms done about three years later. No treatment produced a significant change in stenosis.

Dr Roger Lobo, an author of the study and professor of obstetrics and gynaecology at Columbia University, New York, said that oestrogen treatment has been shown to lead to a slowing in the thickening of the walls of the carotid artery, an early indicator of atherosclerosis (*Annals of Internal Medicine* 2001;135:939-53). □