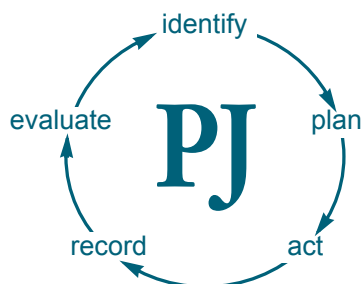


# HORMONE REPLACEMENT THERAPY:

## (2) RISKS AND BENEFITS

By Nuttan Tanna, PhD, MRPharmS

This article considers the risks and benefits of hormone replacement therapy, taking recent published data in to consideration



### identify gaps in your knowledge

1. How has the risk-benefit evaluation for menopausal women considering HRT changed in the past three years?
2. Can HRT be prescribed for the primary or secondary prevention of cardiovascular disease?
3. How long after stopping HRT does it take for the breast cancer risk to return to the level of risk in the general population?

Before reading on, think about how this article may help you to do your job better. The Royal Pharmaceutical Society's areas of competence for pharmacists are listed in "Plan and record," (available at: [www.rpsgb.org.uk/education](http://www.rpsgb.org.uk/education)). This article relates to "common disease states and their drug therapies" (see appendix 4 of "Plan and record").

Pharmacists are well placed to advise women who wish to understand how the evidence base for hormone replacement therapy (HRT) use has changed over the past few years, and how the results of recent research<sup>1-4</sup> could affect their decision to start or continue with HRT. With the current media attention on the effect of HRT on breast cancer risk, many women will discontinue treatment, often without informing their general practitioners. These women may approach pharmacists for advice on HRT and alternative ways to manage symptoms.

#### BENEFITS OF HRT

**Vasomotor symptoms** All HRT preparations are licensed for the relief of menopausal vasomotor symptoms, including hot flushes, night sweats and affected sleep. Women also complain of loss of energy or memory, and depression, which could partly be attributed to sleep deprivation. For symptom control, and where benefits outweigh risks, HRT is given for two to three years.

**Urogenital symptoms and libido** Menopausal women may also present with vaginal dryness and bladder problems, although urge and stress incontinence can result from anxiety and ageing rather than from oestrogen loss alone. In some women high androgen levels increase sexual desire, while in others desire decreases as a result of pain during intercourse caused by a dry vagina. Vaginal oestrogen preparations prescribed for local relief are particularly useful for women who do not wish to take systemic HRT.

**Osteoporosis** Higher bone loss occurs during the earlier years of the climacteric, when oestrogen levels fall as ovarian function declines. Oestrogen levels eventually stabilise, but some loss still occurs in later years. Lifestyle factors combined with medical history will determine the risk of future fracture in patients with osteoporosis. These include weight-bearing exercise, a healthy diet (high in calcium and vitamin D and low in alcohol) and smoking status.<sup>5</sup>

The Women's Health Initiative (WHI),<sup>3</sup> a randomised controlled trial (RCT), provides evidence of end-point fracture prevention with HRT use. Most HRT preparations contain oestrogen in doses shown to help maintain bone density and are therefore licensed for osteoporosis. However, other licensed treatments for osteoporosis are also available. The selective oestrogen receptor modulators (SERMs) prevent vertebral fractures and offer an alternative for asymptomatic postmenopausal patients, but the risk of thrombosis with SERMs is similar to the risk with HRT. The bisphosphonates have the strongest evidence base for bone mineral

density maintenance and end-point fracture prevention at all vulnerable sites, including wrists, hips and spine.<sup>5</sup> Because of the strict routine necessary to ensure adequate absorption of the bisphosphonates at skeletal sites, patients will benefit from appropriate counselling by pharmacists to ensure safe and efficacious medication. A new, injectable treatment for severe osteoporosis, teriparatide, was launched in the United Kingdom this week (see p637 and p641).

The evidence base both for pharmacological and non pharmacological osteoporosis treatments is currently being assessed by the National Institute for Clinical Excellence osteoporosis guideline development group, to enable them to make recommendations on treatment and prevention strategies. These national guidelines are scheduled for publication in early 2005.

**Colorectal cancer** The WHI study<sup>3</sup> confirmed data from case control and cohort studies that HRT reduces the risk of colorectal cancer by about a third, but little is known about the risk after treatment is stopped. There are three fewer cases of colorectal cancer per 1,000 women aged 60 to 69 years who have used HRT for five years, compared with non-users (eight per 1,000 women aged 60 to 69).

#### RISKS OF HRT

**Breast cancer** Since 1997, the breast cancer risk in women on HRT for five years has been accepted as greater than that in the general population. This was shown by a large meta-analysis of all available epidemiological studies.<sup>6</sup> The background population breast cancer risk for women between the ages of 50 and 69 years and not using HRT was estimated to be 45 per 1,000, with risk increasing with age. Breast cancer risk was calculated to be an additional two and six cases per 1,000 women after five and 10 years, respectively, of HRT use. After 15 years, the number of extra cases was 12 in 1,000. However, 80 per cent of the mainly North American population in the study were using unopposed oestrogen, with only about 12 per cent using combined HRT. Therefore further research was needed to assess whether or not the increased breast cancer risk was specific to particular oestrogen types, whether addition of a progestogen component (used sequentially or continuously) had any additional effect and whether results could be applied to other populations.

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TABLE 1: SUMMARY OF RISKS AND BENEFITS ASSOCIATED WITH USING HRT

Condition	Age (years)	Number of cases/1,000 non HRT users	Number of extra cases/1,000 HRT users over the same period	
			5 years' use	10 years' use
<i>Cumulative cancer risk with time</i>				
Breast cancer	50–65	32	1.5 (oestrogen only) 6 (combined HRT)	5 (oestrogen only) 19 (combined HRT)
Endometrial cancer	50–64	5	4 (oestrogen only) Data not available for combined HRT	10 (oestrogen only) <2 (combined HRT)
Ovarian cancer	50–69	9	1 (oestrogen only)	3 (oestrogen only)
<i>Cardiovascular risks over 5 years</i>				
Stroke	50–59	3	1	Data not available
	60–69	11	4	
Venous thromboembolism	50–59	3	4	Data not available
	60–69	8	9	
<i>Benefits over 5 years</i>				
Colorectal cancer	50–59	3	-1	-2
	60–69	8	-3	-5 to -6
Fracture of neck of femur	50–59	1 to 2	0 to -1	-1
	60–69	7 to 8	-2 to -3	-5

Adapted from "Hormone replacement therapy: latest update for women". Available at: [www.mhra.gov.uk](http://www.mhra.gov.uk) (accessed 28 October 2003).

The WHI study<sup>3</sup> is important because it is the first RCT to confirm the risk of breast cancer with combined HRT use. The study also noted that the risk increased more rapidly (the cumulative hazards curve is steeper) after four years' of treatment.<sup>3</sup>

More recently, *The Lancet* reported results from the Million Women study.<sup>4</sup> This large cohort study examined the effects of specific types of HRT and tibolone on the incidence of breast cancer in postmenopausal women. Women attending 66 National Health Service breast screening units between 1996 and 2001 were asked to complete questionnaires. Information on lifestyle, socio-economic and reproductive factors, past health and past and current use of HRT was collected. Of 1,084,110 completed baseline questionnaires, 828,923 were from postmenopausal women, with a mean age of 55.9 years (age range 50 to 64 years). Half of the study population had used HRT at some time, with 33 per cent reported as current users at baseline. These women were followed up for mortality and incidence of cancer. The analysis showed that HRT causes a use-dependent increase in the risk of breast cancer, but this begins to decline when HRT is stopped and, by five years, reaches the same level as in women who have never taken HRT.

The study shows that all types and doses of HRT are associated with an increased risk of breast cancer. Compared to women who have never used HRT, the relative risk in HRT users is 1.66 (95 per cent confidence interval 1.58–1.75;  $P < 0.0001$ ). The breast cancer risk associated with oestrogen-only preparations is confirmed although this is lower than the risk with combined HRT (relative risk 1.30 and 2.00, respectively). Adding progestogen to oestrogen was also found to increase mammographic density and breast tenderness. In addition, the gonadomimetic, tibolone, has a relative risk of 1.45.<sup>4</sup>

There was no evidence of a difference in breast cancer risk between specific preparations or routes of administration within the classes of oestrogen-only or combined HRT. The estimated number of extra cases of breast cancer occurring after five and 10 years of using combined HRT in the Million Women study were almost identical to the WHI trial. What is still not clear is the optimal duration of HRT use. Women will need individualised risk-benefit evaluations to help them to decide whether to take HRT or not. This decision will be influenced by the effect of menopausal symptoms on quality of life, views on breast cancer risk and information about any other medical conditions or family history that may be present.

**Endometrial cancer** Unopposed oestrogen causes endometrial hyperplasia and increases endometrial cancer risk (four extra cases per 1,000 women after five years' use). The recommendation since the early 1980s, therefore, has been to prescribe progestogen when women with an intact uterus are put on oestrogen replacement therapy. However, this excess endometrial risk is not completely eliminated with the continued use of monthly sequential progestogen for more than five years.<sup>7</sup> This is also the case with tricyclic HRT. No increased risk of endometrial cancer has been found with continuous combined regimens.

The Million Women study<sup>4</sup> authors have proposed that the lower risk of endometrial disorders with unopposed oestrogen, including cancer, should be weighed against the findings of increased risk of breast cancer with long-term combined HRT use (four and six extra cases per 1,000 at five-years' use, respectively). The risk of endometrial cancer with tibolone is not known. Further research is needed, with data from RCTs to help inform decision making with respect to HRT use.

**Venous thromboembolism** Postmenopausal HRT increases the risk of venous thromboembolism (VTE) two-fold. Risk is highest in the first year of use.<sup>8</sup> The baseline risk in menopausal women is low, at three to eight cases per 1,000 women between the ages of 50 and 69, who are not using HRT. After five years of HRT, there are four extra cases of VTE per 1,000 women aged 50 to 59 years. Advancing age and obesity significantly increase risk.

**Stroke** The WHI<sup>3</sup> study reported an increased risk for ischaemic stroke but not haemorrhagic stroke, with combined HRT use in postmenopausal women. There is one extra case of stroke per 1,000 women aged 50 to 59 who use HRT for five years. Risk increases with age in both HRT and non HRT users.

**Ovarian cancer** Risk of ovarian cancer significantly increases with long-term unopposed oestrogen use (between 10 and 19 year's use in study populations). Further research studies are needed to understand the risk for ovarian cancer with combined HRT use.

#### CARDIOVASCULAR DISEASE — BENEFIT OR RISK?

Until recently, it was thought, based on large epidemiological and cohort studies, that HRT reduced the incidence of cardiovascular disease. Various mechanisms have been proposed to understand how oestrogen may offer cardiovascular benefits. This includes changes in lipid subfractions, for example, oral oestrogens lower cholesterol. Other mechanisms include effects on clotting factors and blood vessel walls, positive changes in insulin metabolism and redistribution of body fat. However, the HERS study,<sup>1</sup> one of the first randomised, placebo controlled trials, showed no cardiovascular benefit. Over 4.1 years, 2,763 older postmenopausal women (mean age 67 years) with established ischaemic heart disease were studied. In the first year the HRT group suffered significantly more thrombotic events than the control group, but in years three and four there were significantly fewer events.

HERS II,<sup>2</sup> the follow-on, open-label study, was designed to extend the evaluation period to see if the trend for fewer events matched the observation of cardiovascular benefit with time. This study did not demonstrate the same trend, further confirming that HRT should not be prescribed for secondary prevention of cardiovascular disease.

## action: practice points

Reading is only one way to do CPD and the Society will expect to see various approaches to CPD in a pharmacist's portfolio.

1. Use patient medication records or audits within local GP surgeries to provide patients taking HRT with current evidence-based information on using HRT or to carry out medication reviews for these patients.
2. Write a summary of the risks and benefits of different types of HRT. Work with local GP practices and primary care trust medicines management committees to update menopausal patient management guidelines.
3. The UK National Breast Screening Programme offers women over 50 years, three-yearly mammograms until the age of 70, but all women should regularly self-examine their breasts. Visit [www.cancerscreening.nhs.uk/breastscreen/breast-awareness.html](http://www.cancerscreening.nhs.uk/breastscreen/breast-awareness.html) and obtain information leaflets advising on breast awareness and the correct examination technique.

## evaluate

For your work to be presented as CPD, you need to evaluate your reading and any other activities. Answer the following three questions: What have you learnt? How has it added value to your practice? For example, have you applied this learning or had any feedback? What will you do now and how will this be achieved?

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