

Finding the balance: the who and WHI of hormone replacement therapy

HRT—from panacea to panic

Media coverage of the Women's Health Initiative (WHI) trial led to widespread alarm about the risks of using hormone replacement therapy (HRT), with many women discontinuing its use. Appropriate hormone replacement therapy in the wake of the WHI trial hinges on *who* is being prescribed HRT and *why*.

Who will benefit from HRT?

Current recommendations are that the risks of **long-term** HRT generally exceed the benefits. A limited role for its use remains, however, depending on *why* it is being prescribed.

- For cardiovascular or cognitive protection—there is no benefit and HRT should gradually be stopped.
- For bone protection—HRT will occasionally be appropriate if fracture risk is high and other medicines intolerable. Balance benefits against the known risks.
- For menopausal symptom relief, **short-term** HRT is still an option.¹ The evidence does not show an increased risk of breast cancer with 1–2 years' therapy.

Provide women with accurate information about risks when making decisions about treatment (see *Patient insert* inside).

Does HRT cause cancer?

Breast cancer

Data collected from over one million women show that HRT increases the risk of breast cancer in postmenopausal women.^{2–5} The evidence is most convincing in women on combined HRT (see Table 1 on page 2). The risks and benefits of oestrogen replacement therapy (in women without a uterus) will be clearer when the oestrogen arm of the WHI trial ends in 2005. While safety concerns led to the early termination of the combined HRT arm of WHI, no significant safety issues have been identified after 5–6 years of oestrogen-only HRT.³

Breast cancer risk...

with combined HRT

- Increases, with around 7–8 additional invasive breast cancers per 10 000 person years than would occur in women not using combined HRT (see Table 1).^{3,4}
- Increases with the duration of therapy^{2,3,5} and is apparent after 5 years of therapy in postmenopausal women.
- Appears to be similar for the various forms of combined therapy (oral, transdermal, sequential/continuous).⁵

with oestrogen-only HRT

- May increase risk but stronger evidence is needed. From observational studies, the increase in risk is around one-third that found with combined HRT.^{2,5}

with tibolone

- May increase.⁵ Although approved to prevent postmenopausal bone mineral density loss, efficacy has not been established. Apply caution in the use of tibolone while awaiting better evidence.

Breast cancer risk appears to decrease when HRT is stopped. Women without breast cancer five years after ceasing HRT have a risk similar to women who have never been on HRT.⁵

Importantly, combined HRT apparently increases the density of breast tissue, leading to more abnormal mammograms (compared to placebo).³

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Does HRT cause cancer? (continued from p.1)

Risks of other cancers

In women with a uterus, unopposed oestrogen increases the risk of endometrial cancer while oestrogen + progestogen combinations do not. However, significantly more women on combined HRT in the WHI trial required endometrial biopsies to assess vaginal bleeding.⁶

While the risk of colorectal cancer is decreased by combined HRT (see Table 1)⁴, the absolute risk of colorectal cancer is low.

Table 1: Cancer risks of HRT users compared to non-HRT users³⁻⁵

Derived from the WHI and Million Women Study

Type of cancer	Baseline risk	Number of extra cancers compared to non-HRT users	
	In women who do not use HRT	Oestrogen replacement therapy	Combined oestrogen + progestogen HRT
Breast	30 per 10 000 person years ³	Small increases seen in observational data ^{2,5} (WHI oestrogen-only trial to be completed in 2005)	8 more cases per 10 000 person years ³
Colorectal⁴	10 per 10 000 person years		6 fewer cases per 10 000 person years
Endometrial⁵ (In women with intact uterus)	5 per 1000 women over 5 years	4 extra cases per 1000 women treated for 5 years 10 extra cases per 1000 women treated for 10 years	No change in women treated for 5–10 years

From perceived protection to increased risk

—the role of HRT in disease prevention

Trials^{3,4,6-10} designed to determine the protective effects of long-term combined HRT have found no benefit and that risks for several major outcomes might actually *increase* (see Table 2). The lack of benefit has been shown in women with⁷ and without⁹ existing cardiovascular disease.

A recent study of admissions for venous thromboembolism found an increased risk with oral, but not transdermal, oestrogen.¹¹

The Australian Drug Evaluation Committee (ADEC) advises that, in younger women with premature menopause or hypogonadism, the benefits of HRT are probably greater and the risks smaller than reported in studies.¹

Table 2: Increased risks associated with long-term combined HRT*

	No. of cases in placebo group	No. of cases in combined HRT group	Additional cases per 10 000 women per year**
Coronary heart disease ⁹	33	39	6
Stroke ¹⁰	21	29	8
Dementia ⁸	22	45	23
Mild cognitive impairment ⁸	-	-	No difference
Venous thromboembolism ⁴	16	34	18

* Estimates from the WHI trial based on significant differences

**Compared with rates observed in similar women not taking HRT (the placebo group)



Women with osteoporosis

WHI trial participants were generally healthy and had a low overall risk of fracture. Evidence from this trial may not be applicable to women with osteoporosis; benefits from using HRT could be greater for these women.

Combined HRT significantly improved hip bone mineral density and reduced total fractures, although risk reductions for hip and clinical vertebral fractures were smaller than for wrist and lower arm fractures (see Table 3). However, when all other risks associated with combined HRT were taken into account, there was no net benefit despite fewer bone fractures.¹²

Table 3: Benefit of HRT in fracture prevention

Fracture type	Reduction in cases per 10 000 women per year*
Hip	5
Clinical vertebral	6
Lower arm/wrist	18
Total	47
Prevention of bone loss (for subgroup of 1024 women with bone mineral density measurements available)	4–5% increase in bone mineral density at lumbar spine and total hip after 3 years

*Compared with rates observed in similar women not taking HRT (the placebo group)

Women with menopausal symptoms unresponsive to other treatments who wish to use HRT

The evidence does not suggest an increased risk of breast cancer with short-term HRT.

If HRT appears a reasonable treatment option:

- provide detailed information on the actual risks of therapy. In some women the risk may be lower than perceived.
- use the lowest effective dose. Doses of combined HRT less than oestrogen 0.625 mg and medroxyprogesterone 2.5 mg have shown similar efficacy to usual doses in preventing hot flushes.¹³
- review women using HRT for symptom relief 6–12 monthly and assess the need for ongoing therapy.

When stopping HRT

When stopping HRT, it is important to reduce doses incrementally over a few months to prevent rebound symptoms. If symptoms re-emerge, do not reduce doses further until symptoms subside again. Some specialists suggest stopping HRT in the cooler months to ease the transition.

As the effects on bone are not sustained when HRT is stopped, assess fracture risk and the need for other treatment if HRT is stopped. Note that some of these therapies are not available on the PBS for women without existing fractures (e.g. bisphosphonates).

Risk factors for fracture include bone mineral density, alcohol use, smoking, lack of exercise, and low vitamin D and calcium levels. The recommended daily requirement of vitamin D is 400–800 units. Recommended daily calcium intakes differ by age; see the Osteoporosis Australia website for details (www.osteoporosis.org.au/html/preventmain.php) or *Australian Prescriber* December 2003. (See also *NPS News 26* for a review of osteoporosis fracture prevention).

Communicating risk

The confusion among many women that arose in response to the reporting of results from WHI highlights the perils of communicating risk. Some women perceived the 25% increased risk to mean that they had a 1 in 4 chance of developing breast cancer. In fact their baseline risk of developing breast cancer (30 in 10 000 women per year) was increased by 25% to 38 in 10 000—an increase in risk of 8 in 10 000.

When talking about risk^{14,15}

- Avoid use of percentages or probability estimates—use whole people equivalents or ‘natural frequencies’ (e.g. 1 in 1000, 38 of every 10 000 women treated in a year).
- Provide a reference point for context—the risk is increased (or decreased) compared to whom? Is this a big or a small change in risk?
- Consider the population that the estimate was derived from, and whether your patient differs in an important way from this population.





Complementary Update

Alternatives to HRT—the devil or the deep blue sea?

Middle-aged women are the highest users of alternative therapies¹⁶ and many menopausal women will have turned to non-prescription alternatives in the wake of WHI.

Almost all prescribed or non-prescribed hormonal or non-hormonal alternatives are likely to have much less information about either long-term risks or benefits than HRT, making choices difficult. The important point for consumers and prescribers is that there are not enough data on the long-term safety of many complementary medicines to make their use necessarily any safer than HRT.

Many products claim to be supported by evidence, however a recent review¹⁷ found the evidence to be of varying quality, almost always based on small samples with trials of 3–4 months' duration at most. Perhaps the most striking aspect of the trials conducted with alternative treatments for hot flushes is the huge placebo effect—sometimes as high as 50%.¹⁷

Black cohosh has the best evidence of commonly used alternatives.¹⁷ Because of a lack of uniformity, different brands of complementary medicines may contain very different quantities of the standardised extracts, and the evidence of benefit for black cohosh applies only to the product used in the trials (Remifemin).¹⁸

Phytoestrogens from dietary sources are apparently safe, but have little effect on bone, and their effect on menopausal symptoms seems to be no greater than placebo.¹⁹

Red clover (Promensil) was shown in one small trial to reduce the severity and frequency of hot flushes²⁰, however a larger randomised controlled trial recently found an effect no greater than placebo.²¹

Non-drug alternatives include: staying in a cool, well-ventilated environment; avoiding spicy foods, hot drinks and other stimulants; relaxation and meditation; paced respiration; and cognitive behavioural therapy, although most of these have not been rigorously assessed.

If women are using complementary therapies, remind them of the importance of adequate vitamin D, calcium and exercise in staying healthy through the menopause, and review the effects regularly.

What's what

Type of HRT	Brand name of medicine
Oestrogen-only products	Aerodiol, Climara, Dermestril, Estraderm, Estrofem, Femtran, Genoral, Menorest, Ogen, Ovestin, Premarin, Progynova, Sandrena Primogyn, Zumenon
Combined oestrogen + progestogen products	Climen, Estalis, Estracombi, Femoston, Kliogest, Kliovance, Premia, Provelle 28, Triphasil, Trisequens
Tibolone	Livial

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The information contained in this material is derived from a critical analysis of a wide range of authoritative evidence.

Any treatment decisions based on this information should be made in the context of the individual clinical circumstances of each patient.



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