

Evidence from randomised trials on the long-term effects of hormone replacement therapy

Valerie Beral, Emily Banks, Gillian Reeves; Cancer Research UK Epidemiology Unit, Oxford, United Kingdom

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Context Over the past few decades hormone replacement therapy (HRT) has been used increasingly by postmenopausal women in western countries. The need for objective data on long-term effects prompted the setting up of randomised trials to compare cancer and cardiovascular disease endpoints in HRT users and non-users. With the early termination of part of the Women's Health Initiative trial (*JAMA* 2002; 288: 321-33), it is timely to review the evidence from such studies.

Starting point Four randomised trials including over 20 000 women followed up for 4-9 years, on average, have now reported on the effect of HRT for major, potentially fatal, conditions. Overall, HRT users had a significantly increased incidence of breast cancer, stroke, and pulmonary embolism; a significantly reduced incidence of colorectal cancer and fractured neck of femur; but no significant change in endometrial cancer or coronary heart disease. There was no significant variation across the trials in the results for any condition. Three trials had recruited women with previous cardiovascular disease and the fourth, the Women's Health Initiative, had recruited healthy women. Combined oestrogen/progestagen HRT was used in three trials and

oestrogen alone in one. Use of HRT over a 5-year period by healthy postmenopausal women in western countries is estimated to cause an extra breast cancer, stroke, or pulmonary embolus in about 6 per 1000 users aged 50-59 and 12 per 1000 aged 60-69. Over the same period, the estimated reduction in incidence of colorectal cancer or fractured neck of femur is 1.7 per 1000 users aged 50-59 and 5.5 per 1000 aged 60-69. The increased incidence of any one of these conditions is greater than any reduction, the estimated net excess over 5 years being 1 per 230 users aged 50-59, and 1 per 150 aged 60-69.

Where next Substantial new data should soon be available from randomised trials of oestrogen-alone HRT versus placebo, whereas few additional trial data on combined HRT are expected for about a decade. Existing randomised trials are too small to describe reliably the effect of HRT on important but rarer conditions, such as ovarian cancer, or on cause-specific mortality. Nor will they provide information about other types of oestrogen or progestagen. Answers to such questions will require judicious analysis and interpretation of data from observational studies.

Use of hormone replacement therapy (HRT) has increased among postmenopausal women in western countries: an estimated 20 million women worldwide were using HRT in the late 1990s.¹ The long-term effects of HRT on cancer and cardiovascular disease have been debated since HRT was first prescribed, and various randomised trials were designed to provide reliable unbiased information on the incidence of these outcomes (panel 1).²⁻¹¹ Four of these trials,^{2,3,7,8} two of which ended prematurely,^{2,7} have published their main results (the Women's Health Initiative [WHI]²⁻¹¹ published results for part of the trial only). We review findings for seven major, potentially fatal, conditions that were primary or secondary outcomes: cancer of the breast, endometrium, and colorectum; coronary heart

disease; stroke; pulmonary embolism; and fractured neck of femur (see methods in appendix at <http://image.thelancet.com/extras/02art8214webappendix.pdf>).

The four trials with published results included over 20 000 postmenopausal women, followed for 4-9 years, on average (panel 1). The active treatment was combined oestrogen/progestagen in three trials^{2,3,7} and oestrogen-alone in one (WEST).⁸ Three trials recruited women with previous cardiovascular disease and WHI recruited healthy women. Overall, for women randomised to HRT compared with placebo, there was: a significant excess of breast cancer (relative risk 1.27, 95% CI 1.03-1.56), stroke (1.27, 1.06-1.51), and pulmonary embolism (2.16, 1.47-3.18); a significant

deficit of colorectal cancer (0.64, 0.45-0.92) and fractured neck of femur (0.72, 0.52-0.98); but no overall significant excess or deficit for endometrial cancer (0.76, 0.45-1.31) or coronary heart disease (1.11, 0.96-1.30) (figure).

There was no significant heterogeneity in any of these results across the trials, suggesting that the relative risks associated with the use of HRT do not vary substantially across women with different underlying risks of cardiovascular disease or using different hormonal preparations.

What has been learnt from the trials?

Results from randomised trials broadly agree with findings from observational studies for cancer of the breast and colorectum,^{1,12} and also for pulmonary embolism¹³ and fractured neck of femur.¹⁴ Moreover, the WHI reported an increasing risk of breast cancer over time,² corresponding to the increasing risk of breast cancer with duration of use of HRT found in observational studies.¹² Both trial and observational data showed that the risk of venous thromboembolism was greater soon after starting HRT than in later years.^{2,3,13} Since objective trial data have confirmed previous

observations for these conditions, we can conclude that the findings are true effects of HRT, and not due to bias or confounding.

By contrast, the results from many observational studies, suggesting that both combined oestrogen/progestagen and oestrogen-alone HRT substantially reduce the risk of coronary heart disease, must now be regarded as severely biased. Many commentators had argued that the lower rates of coronary heart disease among HRT users compared with non-users found in observational studies did not necessarily mean that HRT protected against the disease (appendix).^{1,11,13} It was the need for unbiased data on the incidence of coronary heart disease that prompted the setting up of most of the randomised trials. Unexpectedly, results from HERS suggested an adverse effect of HRT on coronary disease in the first year after randomisation^{3,4} and findings from WHI were in a similar direction, but not significant.² Nevertheless, neither trial has shown long-term benefit for coronary disease.^{2,3,4} Given the consistent evidence from all trials of little or no benefit, previous claims that HRT substantially protects against coronary heart disease should now be discounted. The increased incidence of

Panel 1: Randomised trials of HRT versus placebo (n≥100) set up to study cancer and cardiovascular disease as endpoints

Study	Women recruited	Number*/ follow-up (yrs)	Active treatment (orally per day)	Comments
Heart and Estrogen/progestagen Replacement Study (HERS) ³⁻⁶	With previous heart disease	2763 / 4-1	0.625 mg equine oestrogen and 2.5 mg MPA	Multicentre USA; main results published. ^{3-6,19}
Estrogen in Venous Thromboembolism Trial (EVTET) ⁷	With previous VTE	140 / 1-3	2 mg estradiol and 1 mg norethisterone acetate	Norway; terminated early, after reports that HRT increased VTE risk; VTE results published. ⁷
Women's Estrogen for Stroke Trial (WEST) ⁸	With previous stroke	664 / 2-8	1 mg 17β-oestradiol	Multicentre USA; main results published. ⁸
Women's Health Initiative (WHI) ^{1,11}	(a) Healthy women with intact uterus	16 608 / 5-2	0.625 mg equine oestrogen and 2.5 mg MPA	Multicentre USA; terminated early; main results published. ¹
	(b) Healthy women without uterus	10 739 / 8 (planned)	0.625 mg equine oestrogen	Multicentre USA; due to end 2005; no results yet.
Oestrogen in the Prevention of Re-Infarction Trial (ESPRIT-UK) ⁹	With first myocardial infarction	1017 / 2 (planned)	2 mg oestradiol valerate	UK; due to end in 2002; no results yet.
Women's International Study of Long Duration Oestrogen after the Menopause (WISDOM) ¹⁰	Healthy women	~22 000 / 10 (planned)	As for WHI, except 0.625 mg equine oestrogen and 2.5 mg MPA also used in hysterectomised women	UK, Australia, New Zealand; due to end 2012; no results yet.

*Approximately equal numbers randomised to placebo and active treatment in each trial. MPA=medroxyprogesterone acetate, VTE=venous thromboembolism.

stroke among HRT users in the randomised trials is a new finding. Results from observational studies were mixed¹³ but now that there is consistent trial evidence of an increase for all strokes combined, the effect of HRT on subtypes of stroke warrants further investigation.

No trial was designed with all-cause mortality as an endpoint, as it is an insensitive marker of any specific effect of HRT. The fact that the trials found no change in all-cause mortality (relative risk 1.03, 95% CI 0.90-1.18, for all trials combined) merely means that HRT does not have an immediate, substantial, and non-specific effect on mortality. Unfortunately, the trials are too small to provide much-needed reliable evidence about the effects of long-term HRT on cause-specific mortality (see appendix).

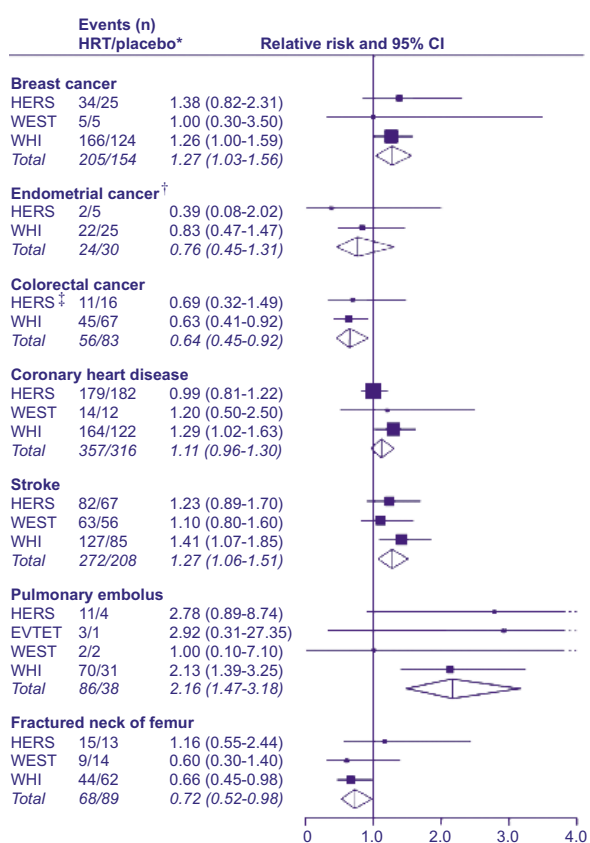
Implications of the trials for HRT users

Combined HRT, containing conjugated equine oestrogen and medroxyprogesterone acetate, was selected for study in the largest trials^{2,3,10} because these were the most commonly used constituents of HRT in the USA when the trials were set up. At that time, the available evidence suggested that the effects of particular types or combinations of oestrogen or progestagen did not differ materially, with the exception of the greater risk of endometrial cancer with oestrogen-alone than oestrogen/progestagen combinations.¹¹ There is no trial evidence to contradict this view, although the power to detect such differences is limited.

The cause-specific relative risks in the trials did not differ significantly for women with varying background risks of disease or personal characteristics, including different ages, ethnic groups, smoking patterns, and previous illnesses and users of various medications.²⁻⁶ Thus the results are generally applicable to postmenopausal women.² We have, therefore, estimated the change in age-specific incidence of conditions significantly associated with HRT, for healthy postmenopausal women in western countries who use HRT for 5 years (panel 2 and appendix). The estimated excess incidence of breast cancer, stroke, and pulmonary embolism is greater than the estimated deficit of colorectal cancer and hip fracture, and the net excess is greater at age 60-69 (1 extra event per 150 HRT users) than 50-59 (1 per 230). At age 50-59, when use of HRT is most

prevalent,¹ breast cancer makes the greatest contribution to the excess, whereas cardiovascular disease becomes increasingly important at older ages.

The estimates of excess risk provide, at best, a rough guide to the likely change in incidence for these conditions over a 5-year period for typical HRT users in western countries. Equal weight was given to each condition, whereas individuals have varying background risks for each disease, and may well assign different weights to their importance, as well as to the relief of menopausal symptoms. No attempt was made to estimate mortality or lifetime risk, since little is known about case-fatality or the persistence of the effects of HRT. Yet such information is vital, because for example, the incidence of certain conditions, such as vertebral fracture and other severe complications of osteoporosis, increases sharply with age. As for some other outcomes, the largest double-blind randomised trials to date suggest that



Summary of results for seven major conditions in trials of HRT

Tests for heterogeneity: breast cancer ($\chi^2=0.24$, $p=0.9$), endometrial cancer ($\chi^2=0.75$, $p=0.4$), colorectal cancer ($\chi^2=0.04$, $p=0.8$) coronary heart disease ($\chi^2=2.81$, $p=0.2$), stroke ($\chi^2=1.26$, $p=0.5$), pulmonary embolus ($\chi^2=0.74$, $p=0.8$), fractured neck of femur ($\chi^2=1.98$, $p=0.4$). *Equal numbers randomised to HRT and placebo in each trial; †results for WEST (2/0) not included, as oestrogen alone has different effect from oestrogen/progestagen on endometrial cancer; ‡colon cancer only.

Panel 2: Estimated change in incidence of major, potentially fatal, conditions in 1000 healthy postmenopausal women from western countries using HRT over 5-year period, based on results from randomised trials (see appendix for methods)

	Women aged ~50-59 years	Women aged ~60-69 years
Excess incidence per 1000 HRT users, over 5-year period, for:		
Breast cancer	3.2	4.0
Stroke	1.2	4.0
Pulmonary embolism	1.6	4.0
Total excess*	~6 per 1000, ~1 in 170 users	~12 per 1000, ~1 in 80 users
Reduction in incidence per 1000 HRT users, over 5-year period, for:		
Colorectal cancer	1.2	3.0
Fracture of neck of femur	0.5	2.5
Total deficit*	~1.7 per 1000, ~1 in 600 users	~5.5 per 1000, ~1 in 180 users
Overall balance*	Net excess: ~4.3 per 1000, ~1 in 230 users	Net excess: ~6.5 per 1000, ~1 in 150 users

*Giving equal weight to each type of event.

HRT does not slow the progress of Alzheimer's disease or improve cognitive function,¹⁵ and that it has little effect, if any, on quality-of-life other than reducing menopausal symptoms.¹⁶

The future

New results on about 12 000 women randomised to oestrogen-alone versus placebo are expected soon, from ESPRIT-UK⁹ and part of WHI² (panel 1). The data for combined HRT reviewed here are, however, unlikely to be superseded in the immediate future. Results from WISDOM,¹⁰ which is randomising about 22 000 healthy women to similar oestrogen/progestagen combinations as WHI, are not expected for a decade. These trials are also studying the effect of HRT on quality-of-life and cognitive function.

Existing trials are too small to provide reliable information on other important, but rarer conditions, such as ovarian cancer,¹⁷ or on cause-specific mortality. Nor are they examining the effects of other specific types of oestrogen and progestagen used in HRT formulations. Observational studies will thus be needed to answer many outstanding questions about the effects of HRT. Judicious data analysis and interpretation of results will be essential.

Correspondence to Prof V Beral, Epidemiology Unit, Gibson Building, Radcliffe Infirmary, Oxford OX2 6HE, United Kingdom.

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References

- Beral V, Banks E, Reeves G, Appleby, A. Use of HRT and the subsequent risk of cancer. *J Epidemiol Biostat* 1999; 4: 191-215.
- Writing Group for the Women's Health Initiative Investigators. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results from the Women's Health Initiative randomized controlled trial. *JAMA* 2002; 288: 321-33.
- Hulley S, Grady D, Bush T, et al. Randomized trial of estrogen plus progestin for secondary prevention of coronary heart disease in postmenopausal women. *JAMA* 1998; 280: 605-13.
- Grady D, Herrington D, Bittner V, and Heart and Estrogen/progestin Replacement Study Follow-up (HERS II). Cardiovascular disease outcomes during 6.8 years of hormone therapy. *JAMA* 2002; 288: 49-57.
- Hulley S, Furberg C, Barrett-Connor E, and Heart and Estrogen/progestin Replacement Study Follow-up (HERS II): Noncardiovascular disease outcomes during 6.8 years or hormone therapy. *JAMA* 2002; 288: 58-66.
- Simon JA, Hsia J, Cauley JA, for the HERS Research Group. Postmenopausal hormone therapy and risk of stroke: the Heart and Estrogen-progestin Replacement Study (HERS). *Circulation* 2001; 103: 638-42.
- Hoibraaten E, Qvigstad E, Arnesen H, Larsen S, Wickstrom E, Sandset PM. Increased risk of recurrent venous thromboembolism during hormone replacement therapy: results of the randomized, double-blind, placebo-controlled estrogen in venous thromboembolism trial (EVTET). *Thromb Haemost* 2000; 84: 961-67.
- Viscoli CM, Brass LM, Kernan WN, Sarrel PM, Suissa S, Horwitz RI. A clinical trial of estrogen-replacement therapy after ischemic stroke. *N Engl J Med* 2001; 345: 1243-49.
- Kahn MA, Heagerty AM, Kitchener H, McNamee R, Cherry NM, Hannaford P. Oestrogen and women's heart disease. *Q J Med* 2000; 93: 699-702.
- Vickers MR, Collins N. Progress on the WISDOM trial--Women's International Study of long duration oestrogen after the menopause. *Climacteric* 2002; 5: (suppl 1) 133-34.
- The Women's Health Initiative Study Group. Design of the Women's Health Initiative Clinical Trial and Observational Study. *Control Clin Trials* 1998; 19: 61-109.
- Collaborative Group on Hormonal Factors in Breast Cancer. Breast cancer and hormone replacement therapy: collaborative reanalysis of data from 51 epidemiological studies of 52 705 women with breast cancer and 108 411 women without breast cancer. *Lancet* 1997; 350: 1047-59.
- Meade TW, Vickers MR. HRT and cardiovascular disease. *J Epidemiol Biostat* 1999; 4: 165-90.
- Weiss NS, Ure CL, Ballard JH, Williams AR, Daling JR. Decreased risk of fractures of the hip and lower forearm with postmenopausal use of oestrogen. *N Engl J Med* 1980; 303: 1195-98.
- Mulnard RA, Cotman CW, Kawas C, for the Alzheimer's Disease Collaborative Study. Estrogen replacement therapy for treatment of mild to moderate Alzheimer disease: a randomized controlled study. *JAMA* 2000; 283: 1007-15.
- Hlatky MA, Boothroyd D, Vittinghoff E, for the HERS Research Group. Quality-of-life and depressive symptoms in postmenopausal women after receiving hormone therapy: results from the Heart and Estrogen/Progestin Replacement Study (HERS) Trial. *JAMA* 2002; 287: 591-97.
- Lacey JV, Mink PJ, Lubin JH, et al. Menopausal hormone replacement therapy and risk of ovarian cancer. *JAMA* 2002; 288: 334-41.