

HRT: The history

HRT timeline

1965: HRT becomes available to women in the UK.

1993: A clinical trial starts in the USA – the Women's Health Initiative – looking at the health effects on women taking either estrogen-only HRT or combined HRT, compared to women taking an identical placebo.

1996: A study starts in the UK, called the Million Women Study, collecting questionnaires on HRT use and its effects on certain issues of women's health.

2002: WHI study stopped the combined (estrogen and progestogen) HRT arm of the study prematurely in light of findings of safety issues with combined HRT – a small increased risk of breast cancer, heart disease, stroke and blood clots.

2003: Million Women Study publishes findings.

2003: Both doctors and HRT users are confused regarding safety issues. Many doctors advise their patients to come off HRT. Some women stop taking HRT immediately. Such actions were, and continue to be, unduly influenced by a high level of media interest which has tended to attract some health scare headlines.

2004: WHI finishes the estrogen-only arm of the HRT study, finding trends for beneficial effects on breast cancer and heart disease risk but a small increased risk of stroke.

2003-07: Amongst continuing health safety fears, HRT users fall from 2 million to less than 1 million in the UK.

2004-07: The investigators of WHI publish a further analysis of the trial which is an about turn on some of the findings published in 2002 and indicates that risks for certain safety aspects were over-estimated. These new findings also show the additional benefits of HRT use for those initiating HRT in the 50-59 age group, or for those less than 10 years past the menopause – trends to a lower risk from heart disease; a lower risk of death from any cause; no clear increased risk from stroke. They also show a general increased risk for those starting HRT after the age of 60, which is later than normal UK clinical practice.

2012: Publication of Danish study of combined HRT use for 10 years in healthy women started shortly after menopause showing reduced heart disease and mortality.

2012: Further report from MWS showing no increased risk of thrombosis (blood clots) with use of transdermal (skin patch or gel) estrogen HRT.

The two studies

The Women's Health Initiative (WHI) estrogen plus progestogen trial

- From 1993 to 2002
- Studied over 16,600 women in the United States
- Participating women were aged 50-79, around 50% of whom were randomly chosen to take HRT and 50% to take a placebo (dummy)
- Looked at the effects that HRT had on heart disease and other aspects of women's health.

Publication of the preliminary findings 2002

Of those taking HRT there were:

- An increase in coronary events, stroke, breast cancer and vein blood clots, and a decrease in osteoporotic fractures and colon cancer
- The study was stopped three years early by the safety monitoring committee as a previously specified limit for breast cancer cases was exceeded and overall risks were thought to exceed benefits
- Subsequent publication of the full findings from the same WHI Study showed different effects. When the results were adjusted for other influencing factors, the apparent increased risk of breast cancer was only in those who had taken HRT before entering the study
- When the results were split down by age:
 - Those starting on HRT under age 60 may actually be protected by HRT in some health aspects
 - Those starting on HRT over 70 don't accrue the same benefits and could be at certain increased risks.

The Women's Health Initiative (WHI) estrogen alone trial

- From 1993 to 2004
- Studied over 10,700 hysterectomised women in the United States
- Participating women were aged 50-79, around 50% of whom were randomised to take estrogen and 50% to take a placebo
- Looked at the effects that HRT had on heart disease and other aspects of women's health.

Publication of the preliminary findings 2004

Of those taking HRT there were:

- Increases in stroke and venous thrombosis (blood clots)
- No increase in coronary events
- No decrease in colon cancer and a decrease in breast cancer and osteoporotic fractures
- The study was stopped just under two years early by the trial sponsor but not by the safety monitoring committee
- Publication of the full findings from the same WHI Study in 2007 again showed different effects when the results were split down by age
- Those starting on HRT under age 60 may actually be protected by HRT in some health aspects
- Those starting on HRT over 70 don't accrue the same benefits and could be at certain increased risks
- In 2011 further evidence of reduced risk of breast cancer.

The Million Women Study (MWS)

- From 1996 to 2001
- One million women in the UK who were attending breast screening clinics as part of the NHS Breast Screening Programme were surveyed by questionnaire
- Participating women were over 50 years old
- Looked at the risks of breast cancer and other health issues in HRT users compared with non-users in a total of 828,923 women.

Published findings:

- Estrogen-only HRT causes a small increase in the risk of breast cancer
- Estrogen-only HRT causes a small increase in the risk of womb cancer
- Estrogen-only HRT causes a small increase in the risk of ovarian cancer
- Combined HRT increases the risk of breast cancer more than estrogen-only HRT
- Combined HRT reduces the risk of womb cancer
- The longer HRT is used, the higher the risk of breast cancer
- The risk of breast cancer disappears as soon as HRT is stopped
- No increased risk of venous thrombosis (blood clots) with transdermal estrogen.

2019: The Collaborative Group on Hormonal Factors in Breast Cancer: The prospective follow up identified 108,647 postmenopausal women of which 55,575 (51%) had used HRT. The study reported a duration-dependent increased risk of breast cancer diagnosis with both estrogen only and combined HRT, the latter being greater. Continuous combined preparations demonstrated greater risk than sequential preparations. The study did not report on breast cancer related mortality.

There are some limitations noted with the trial such as the inclusion of the MWS data, exclusion of the placebo controlled WHI study data and very little data was included on women who used micronized progesterone, a preparation which has been demonstrated to be 'breast neutral' in the large observational French E3N cohort study.

This study also noted that obese women using estrogen only HRT added little additional breast cancer risk to their already elevated risk but lean or obese women had the same additional risk when using progestogen containing HRT.

2020: The WHI long term randomised clinical trials was published and reported breast cancer incidence and mortality on 27,000 women followed up until 2017. It reported that women using estrogen only HRT had a reduced risk of breast cancer incidence and mortality but those on combined HRT had a slight increased risk of breast cancer incidence. Importantly, this did not translate into an increased risk of mortality.

They also reported on an increased risk of invasive breast cancer and breast cancer mortality in obese women.

Regarding cardiovascular disease, they reported that women commencing HRT within 10 years on the onset of menopause or under 60 years old having a lower risk of cardiovascular disease, cardiovascular related death and all cause mortality.

Shortcomings of the WHI and MWS studies and their findings

The publication of these results triggered an immediate response from experts through the British Menopause Society, the International Menopause Society and others, who considered that both the WHI and the MWS studies had shortcomings and so were flawed.

Issues with the studies:

- WHI looked at only one dose and type of combined HRT or estrogen only HRT
- The dose used, whilst appropriate for younger menopausal women starting HRT, was considered by many experts as too high for older women
- The profile of the American women in the WHI study is very different from the women in the MWS. The American women tended to be much older (average age 63.2) than the women on HRT in the UK study, with two-thirds over the age of 60 and therefore would have a higher absolute risk of stroke, heart disease and breast cancer (which increases with age)
- The majority of the women in the study were overweight (average BMI of 28.5) and this is a recognised risk factor for heart disease and certain cancers, including breast cancer
- There were a substantial number of drop-outs from the study
- MWS's methodology has been criticised. It was not a randomised controlled trial, where two groups of women are recruited and half given HRT and half a placebo. The women were self-selecting and self-reporting HRT users
- The MWS women were already having a mammogram so that may make them at higher risk for cancer (they may already suspect a lump, for instance) or more aware of potential cancer risks because they were taking HRT
- Follow-up was done by reports from national cancer registries, not by subsequent questionnaires, so changes in HRT use after initial registration were not recorded.

Women's Health Concern also expressed its concern at that time, wanting to ensure that decisions on HRT usage were based on fact. Today it is important that the medical profession and the media do not create the impression that these flawed studies should significantly influence a women's decision making about HRT – which they should not.

Latest analyses of trial and NICE Guidance including the WHI follow up analysis 2020

Heart disease risk/benefit:

Starting on HRT at age range 50-59 or within 10 years of menopause onset:

- HRT does not increase cardiovascular disease risk when started in women aged under 60 years
- HRT does not affect the risk of dying from cardiovascular disease
- HRT with estrogen alone is associated with no, or reduced, risk of coronary heart disease
- Cardiovascular risk factors are not a contraindication to HRT use providing they are appropriately managed.

Starting on HRT at age >60 or more than 10 years post menopause onset:

- HRT does not appear to increase the risk of cardiovascular events, cardiovascular mortality or all cause mortality.

Breast cancer risk:

Increase in risk with combined HRT in WHI was much less than initially reported and now equates to 4 extra cases per 1000 women after five years [It should be noted that this risk is less than that caused by smoking 10 cigarettes/day, alcohol and obesity]. The risk was significantly reduced in women taking estrogen alone who had never previously taken HRT. Breast cancer risks from MWS appear to be grossly overestimated in comparison to WHI. Breast cancer risk appears to be duration dependant and may vary with the type of progestogen used. Micronised progesterone and dydrogesterone are likely to be associated with a lower risk of invasive disease compared to other progestogens.

Ovarian cancer risk:

A 2015 meta-analysis of 52 epidemiological studies has shown an increased risk of ovarian cancer with estrogen only and combined HRT.

- However, with 5 years of HRT use, there could be 1 additional ovarian cancer per 1,000 users and 1 additional death per 1,700 users among women of all ages
- After 5 years of HRT there is only a 0.1% increase in ovarian cancer and less than 0.6% additional deaths.

Endometrial (lining of womb) cancer risk:

- Slightly increased risk with estrogen-only HRT in MWS, but this risk has been known for over 30 years, which is why this HRT should only be used by women who have had a hysterectomy. The addition of a progestogen every day reduces the risk of this cancer compared to non-users.

Risk of stroke:

- Oral (but not transdermal under 50mcg/24h) estrogen is associated with a small increase in the risk of stroke. However, the baseline risk of stroke in women aged <60yrs is very low so the increased risk is non-significant
- The risk is increased in women who smoke and are overweight.

Risk of weight gain:

- It is thought that for the number of people that gain weight on HRT there is approximately an equal number who will lose weight taking HRT. It depends on the individual. Women tend to gain weight with age and also after the menopause there is a redistribution of fat towards the abdomen.

.....
This fact sheet has been prepared by Women's Health Concern and reviewed by the medical advisory council of the British Menopause Society. It is for your information and advice and should be used in consultation with your own medical practitioner.

Use for osteoporosis:

- HRT is not at present recommended by regulatory authorities as the first treatment of choice to prevent brittle bones, although it is currently the only validated treatment for younger postmenopausal women. The randomised controlled trial data suggest there are 23 fewer fragility fractures per 1000 in postmenopausal HRT users. The benefit might continue in women taking HRT for longer and the protection stops when HRT stops.

HRT is not *generally* recommended for **women with a history of:**

- Stroke or deep-vein thrombosis (transdermal may be acceptable)
 - Breast cancer or endometrial cancer
 - Severe liver disease.
-

Author: Miss Lynne Robinson in collaboration with the medical advisory council of the British Menopause Society

UPDATED: NOVEMBER 2020
REVIEW DATE: NOVEMBER 2023



Women's Health Concern is the patient arm of the BMS.
We provide an independent service to advise, reassure and educate women of all ages about their health, wellbeing and lifestyle concerns.

Go to www.womens-health-concern.org

