

Hormone replacement therapy (HRT) and breast cancer– results of the UK Million Women Study

Dear Health Professional

This message provides information to help you advise women who are using HRT and who may be concerned about their risk of breast cancer following today's publication in the Lancet of the UK Million Women Study. The Committee on Safety of Medicines (CSM) and its expert working group (EWG) on HRT have reviewed this study. The key points are:

- The previously described small increase in risk of breast cancer in association with **oestrogen-only** products has been confirmed.
- The increased risk of breast cancer in association with use of **combined (oestrogen plus progestogen** – both continuous and sequential regimens) HRT is substantially higher than with oestrogen-only therapy (see table below).
- Tibolone (Livial[®]) also significantly increases the risk of breast cancer, but to a lesser extent than combined HRT.
- An increase in the risk of breast cancer becomes apparent within 1-2 years of starting treatment, irrespective of the type of HRT used.
- The risk of breast cancer begins to decline when HRT is stopped and by 5 years reaches the same level as in women who have never taken HRT.

CSM and its EWG on HRT have advised that:

- For short-term use of HRT for the relief of menopausal symptoms, the benefits outweigh the risks for many women.
- For longer-term use of HRT, women must be made aware of the increased incidence of breast cancer and other adverse effects.
- Each decision to start HRT should be made on an *individual* basis and treatment should be regularly reappraised (at least once a year).
- For combined HRT the benefits of the lower risk of endometrial disorders, including cancer, should be weighed against the new information about the increased risk of breast cancer (see table below). The risk of endometrial cancer with tibolone is not known.
- The results of the Million Women Study do not necessitate any urgent changes to women's treatment.
- Women who wish to stop HRT, or change their current preparation, should make a routine appointment to discuss their treatment options with their doctor.
- It is important for all women to be 'breast aware' and to attend for breast screening from the age of 50 years.

Background

CSM and its EWG on HRT have kept the safety of HRT under careful review as new data have become available. Important information on the long-term risks of HRT was communicated in July 2002, following termination of one arm of the Women's Health Initiative (WHI) trial. This included new information with respect to coronary heart disease, stroke and ovarian cancer.

The findings of a large UK study, the Million Women Study, have been reported in the Lancet. This observational study examined the effects of specific types of HRT and tibolone (a steroid that has combined oestrogenic, progestogenic and androgenic activity and has the same licensed indications as conventional HRT) on the incidence of breast

cancer in nearly a million postmenopausal women in the UK. This follows the recent publication in JAMA of the final results of the WHI randomised, placebo-controlled trial.

What does the Million Women Study show?

This study confirms that HRT causes a duration-dependent increase in the risk of breast cancer that begins to decline when HRT is stopped and by 5 years reaches the same level as in women who have never taken HRT. The magnitude of the risk associated with oestrogen-only products has been confirmed. For combined HRT use, the risk is significantly higher than with oestrogen-only therapy. More specifically, the study demonstrates that:

- The increase in risk of breast cancer associated with combined HRT (relative risk - RR = 2.00 compared with no use) is significantly higher than for oestrogen-only therapy (RR = 1.30) and for tibolone (RR = 1.45).
- There is no evidence for a difference in risk of breast cancer between specific preparations or their route of administration within the classes of oestrogen-only therapy and any type of combined HRT.
- The estimated number of extra cases of breast cancer occurring after 5 and 10 years of using combined HRT were almost identical in the Million Women Study and the WHI trial.

The effect of oestrogen-only and combined HRT on the cumulative incidence of breast and endometrial cancer.

Duration of use of HRT (from age 50)	No of additional cancers per 1000 women by age 65	
	Breast*	Endometrium [§]
Oestrogen-only		
5 years	1.5	4
10 years	5	10
Oestrogen-progestogen		
5 years	6	Data not available
10 years	19	<2 [#]

*Baseline incidence of invasive breast cancer in non-HRT users is about 32 per 1000 between the ages of 50 and 65 years

[§]Baseline incidence of endometrial cancer in non-HRT users is about 5 per 1000 between the ages of 50 and 64 years

[#]There may be a difference in the risk of endometrial cancer between sequential and continuous HRT

Deciding about HRT

For all women, the balance of risks and benefits of treatment should be carefully weighed.

Women without a uterus : Oestrogen-only therapy is appropriate.

Women with an intact uterus : This will be a difficult decision for women and their doctors to make. Decisions will have to be made on an individual basis and the benefits of the lower risk of endometrial disorders, including cancer, with combined HRT will need to be weighed against the new information about the increased risk of breast cancer. Women must be made aware of the increased incidence of breast cancer and other adverse effects.

Sources Of Further Information

An information sheet for women is attached and more detailed information about the safety of HRT is available on the MHRA website (<http://www.mhra.gov.uk>).

For telephone enquirers, please call the Medicines and Healthcare products Regulatory Agency 020 7273 0000.

Professor Gordon Duff
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References:

Risks and benefits of estrogen plus progestin in healthy postmenopausal women.

JAMA 2002; 288:321-333. www.jama.com

Breast cancer and hormone replacement therapy in the Million Women Study. Lancet 2003;362:419.
www.thelancet.com