

# HRT and breast cancer risk



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## Clarifying the links between hormone replacement therapy and breast cancer.

BREAST cancer is a commonly occurring malignancy with a one-in-nine risk of a woman of being diagnosed before the age of 85 years. A possible increase in the risk of breast cancer is the most emotive issue associated with any discussion of HRT for postmenopausal women.

### BACKGROUND

Before 2002, the most significant publication regarding the link was the 1997 *Lancet* paper of Beral and colleagues (350:1047-59), which was a collaborative re-analysis of available data, all of which was observational.

Breast cancer risk was reported to increase after five years of HRT use, was more evident in women of low or normal weight, and increased with duration of HRT exposure. Very helpful for practical counselling of postmenopausal women considering HRT was the information in Table 1, for 1000 women between the ages of 50 and 70 years.

This estimated an overall absolute increase in risk of 1.2% over a 20-year age range if HRT was used for more than 15 years during that time. The increase in risk returned to baseline rapidly, within five years, following cessation of HRT.

### WOMEN'S HEALTH INITIATIVE

The only major randomised controlled trials to examine the issue to date with breast cancer as a specific end point are the two Women's Health Initiative (WHI) HRT trials – combined continuous therapy for women with an intact uterus and oestrogen alone for hysterectomised women.

In the WHI combined continuous therapy trial, in women treated with conjugated equine oestrogens (0.625 mg) and



medroxyprogesterone acetate (2.5 mg), first-time users had no increase in risk over the 5.2 years of the trial, while long-term users had a significantly increased risk.

For hysterectomised women, on conjugated equine oestrogens alone, risk appeared to decrease by 23% over the 7.1 years average follow-up of the trial (not

## HRT remains the safest option for moderate to severe menopausal symptoms

quite reaching statistical significance), though there was a significant decrease in non-prior oestrogen users and in those compliant in taking therapy.

It appeared that risk with combined continuous therapy might increase after about seven years, whereas with oestrogen alone, no trend towards an increase in risk was seen in the data presented.

### DELIVERY OF HRT

Some uncertainty exists regarding the effects of different types and doses of oestrogen and progestogen. Current trends are for the use of significantly lower doses.

It has been observed, for example, that a combination of oestradiol 0.5 mg and norethisterone acetate 0.125 mg did not lead to any increase in mammographic breast density over a six-month period. Increased breast density is regarded as a significant risk factor for breast cancer.

In France, parenteral oestradiol is the most common method of administering HRT, with progesterone (rather than a synthetic progestin) given orally in women with an intact uterus. Observational data to date indicates that there is no significant increase in breast cancer risk over eight years on this combination. Thus, both dose and type of oestrogen and progestogen may influence the long-term effects of HRT on the breast.

There is no data from which to assess possible breast cancer risks associated

with the use of 'bio-identical' hormone therapy or the use of non-hormonal complementary and alternative therapies.

### UNRESOLVED DATA

Whether HRT accelerates the growth of latent breast tumours or actually causes the development of breast cancer is currently unresolved, with plausible data for both possibilities available.

On the basis of time scale of risk occurrence, the former possibility appears the more likely. It's estimated that about 30 in 1000 (3%) women starting HRT have small, undiagnosed breast cancers at the time that they begin therapy and two-thirds of the 30 (about 20) would be hormone dependent. The excess risk of breast cancer if HRT is taken for 15 years is 12 in 1000 (Table 1) and provides the basis for suggesting that HRT accelerates the growth of pre-existing breast cancers.

It is interesting in this context to note that a number of trials of statins for dyslipidaemia have reported statistically non-significant increases in breast cancer risk in the statin-treated arms, though this data does not normally attract attention.

Any possible risk of breast cancer as a result of HRT should be viewed in the context of other risk factors of similar magnitude for breast cancer, such as obesity, high fat intake, high alcohol intake (more than two standard drinks per day), early menarche, delayed menopause, and delay in initiating first pregnancy.

### CURRENT RECOMMENDATIONS

Reports from some countries, such as the USA and Australia, linking a decline in HRT prescription rates after the WHI announcement with a concomitant decline in breast cancer incidence must be viewed as observations only.

While they ask a question, they cannot be used to deduce any cause/effect relationship or to influence clinical recommendations regarding appropriate HRT prescribing. This is evidenced in the recent Australian data, where fluctuations in breast cancer incidence had been observed over a number of years, with decreases also occurring while HRT prescription rates were increasing.

The recent recommendations from the International Menopause Society (IMS) provide the most up-to-date integration of evidence with expert opinion, to provide a balanced view on HRT. The IMS concludes that HRT remains the safest and most effective management option for women with moderate to severe postmenopausal symptoms.

Prolonged use of HRT (for more than 5-7 years), particularly combined continuous treatment at doses equivalent to 0.625 mg conjugated equine oestrogens, increases breast cancer risk moderately, an observation that must be balanced against improved quality of life, protection against osteoporotic fracture, and reduction in colorectal cancer risk.

**Table 1: Breast cancer incidence per 1000 women years**

Number of breast cancers occurring between ages of 50 and 70 years	Years of HRT
45	0
47	5
51	10
57	15+