Hormone Replacement Therapy (HRT) and risk of breast cancer

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This position statement applies only to Hormone Replacement Therapy (HRT) and breast cancer risk in women – it does not address other risks or benefits to women from HRT usage.

For more information see the Recommendations - HRT & Breast cancer risk below.

For the purposes of this position statement, Cancer Australia defines HRT as the use of exogenous hormones (e.g. oestrogens, progesterone, testosterone) to manage menopausal symptoms.

There are various forms and combinations of HRT. This position statement refers to the following types of HRT: oestrogen-alone (unopposed oestrogen), combined HRT (oestrogen and progesterone, either sequential or continuous combined), combined oestrogen and testosterone, tibolone and natural therapies.

The 2004-2005 National Health Survey (Australian Bureau of Statistics) indicates that 11% of Australian women aged 45 years and over were currently using HRT prescribed by a doctor, and that of these women the majority (65%) had been using HRT for 5 years or more.¹

The National Health and Medical Research Council (NHMRC) has undertaken an extensive review of research evidence about HRT and published several documents for women and health professionals based on this evidence (2005). For further information about the risks and benefits of HRT refer to the following NHMRC documents:

- Hormone Replacement Therapy: A Summary of the Evidence for General Practitioners and other Health Professionals²
- Hormone Replacement Therapy: Exploring the Options for Women³
- Making Decisions: Should I use hormone replacement therapy? (HRT)⁴

This position statement has two sections – a synopsis of evidence to date about the use of HRT and breast cancer risk, and recommendations based on this evidence. The information in this NBOCC* position statement is based on the NHMRC evidence review and relevant quality research evidence subsequently published.

The evidence considered in this statement relates to populations of women. Women continuing or initiating the use of HRT should discuss the benefits and risks of HRT with their doctor, in the context of their own personal history, family history and individual circumstances, so that they can make informed decisions about usage.

Further information and updates about HRT are available through the Therapeutic Goods Administration (TGA) website.
Risk of invasive breast cancer for women with no personal history

Combined (oestrogen and progestogen) HRT

There is high quality evidence from systematic reviews and clinical trials that indicates an association between the use of combined HRT and an increased risk of breast cancer that increases with duration of use. In a randomised controlled trial published in 2002 and conducted by the Women’s Health Initiative (WHI), women who had used combined HRT for 5.6 years had an increased risk of breast cancer compared with women who had not used HRT (RR: 1.24; 95%CI: 1.02, 1.50; p=0.003).

In women aged 50-79yrs, the absolute risk* of breast cancer is 38 cases per 10,000 women per year in users of combined HRT (averaged over 5yrs) compared with 30 cases per 10,000 women per year in women who have never used combined HRT (ie 8 additional cases per 10,000 women over 5 years (*where absolute risk estimate was determined from WHI population)).

It is not possible to precisely determine the duration of therapy after which risk is increased, however greater than 3 years usage appeared to be associated with increased risk (WHI, 2002). A more recent analysis of the Women’s Health Initiative trial data (2006) found that the significant increase in breast cancer risk in the trial overall after 6 years was concentrated in the women who had had prior exposure to HRT (RR: 1.96; 95%CI: 1.17, 3.27; p=0.03). While no overall increase in breast cancer risk was detected in women without prior HRT exposure (RR: 1.02; 95%CI: 0.77, 1.36), it was not possible to determine a safe interval for combined HRT usage.

Cohort studies have also indicated an increase in breast cancer risk associated with the use of combined HRT. The Women’s Health Study (2002) reported a relative risk of breast cancer of 1.37 (95%CI: 1.05, 1.78) for women who had used combined HRT for 5.6 years compared to women who had never used HRT. The Million Women Study (2006) reported a relative risk of breast cancer of 2.14 (95%CI: 2.04, 2.24) for women who had used combined HRT compared to women who had never used HRT.

It is important to note that both the randomised controlled trials and observational studies rely heavily on data from women who are older and/or who have taken HRT for a longer duration than may be current practice.

Analyses from the Women’s Health Initiative on the ‘gap time’ between onset of menopause and initiation of HRT, indicate that women who initiate combined HRT soon after menopause (with a short gap time), have a higher risk of breast cancer than those who start treatment later. Data from the French E3N cohort have also indicated that women who initiated oestrogen-progestagen HRT close to the menopause had an increased risk of breast cancer relative to nonusers, even when they had used HRT for ≤2 years.

Regarding regimens for combined HRT, there is conflicting evidence about whether risk differs between sequential or continuous-combined HRT. The inconsistent data are thought to be due to the different regimes prescribed in different countries. A significantly higher risk has been associated with continuous-combined HRT in the Scandinavian studies, however, the total doses of progestin used in these studies were much higher for continuous-combined than for sequential HRT.

Evidence suggests that the risk of breast cancer diminishes with increasing time since HRT usage has ceased, returning to a risk level comparable with ‘never-users’ within 5 years of ceasing use, or possibly as soon as 2 years after, as indicated by analysis of the WHI randomised trial and observational study.

There does not appear to be a significant difference in the risk of breast cancer for the different routes of combined HRT administration (eg oral, transdermal, or implants).

Oestrogen-only HRT
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There are inconsistent findings in relation to risk of breast cancer and oestrogen-only HRT. There is evidence that indicates the short-term use of oestrogen-only HRT in women with a prior hysterectomy has little or no effect on risk of breast cancer.\(^5\)\(^-\)\(^7\) In a randomised controlled trial conducted by the Women’s Health Initiative, women who had used oestrogen-only HRT for 7.1yrs had no increased risk of breast cancer compared with women who had not used HRT.\(^16\) A combined analysis of the Women’s Health Initiative randomised clinical trial and observational study, indicated no clear evidence for either an overall reduction or increase in breast cancer risk with conjugated equine oestrogens.\(^17\) An observational study showed no significant increase in breast cancer risk with use of oestrogen-only HRT over an average of 10 years of follow-up.\(^18\) In the Nurses’ Health Study of women with prior hysterectomy, the risk of breast cancer was increased significantly after 20 years or more of use and the relative risk was higher for ER+/PR+ cancers.\(^19\)

There is evidence however from other observational studies that also included women without prior hysterectomy, to indicate that oestrogen-only use is associated with increased breast cancer risk. The Million Women Study reported an increased risk for current users of oestrogen-only HRT (RR: 1.30, 95% CI: 1.21 - 1.40, \(p<0.0001\)), with higher relative risk for women with body mass index less than 25 compared to 25 or more, and increased risk with increasing total duration of use, even after short-tem use;\(^14\) these findings were confirmed in a later analysis.\(^9\) In the NIH-AARP Diet and Health Study, oestrogen-only HRT was associated with significantly greater risk (RR: 1.60, 95% CI:1.31-1.96) after 10 years of use in thin women with body mass index less than 25.\(^20\)

**Combined oestrogen and testosterone HRT**

One prospective cohort study - the Nurses’ Health Study - indicated that the use of oestrogen and testosterone HRT is associated with a 17% increase in risk of breast cancer per year of use.\(^21\) Data from the Women’s Health Initiative observational study showed a modest, non-significant increase in breast cancer risk associated with oestrogen and testosterone use.\(^22\)

**Tibolone**

Tibolone is a steroid with oestrogen-, progesterone- and androgen-like effects. There is evidence from the observational Million Women Study that tibolone increases the risk of breast cancer more than oestrogen-only therapy, but less than combined HRT.\(^9\) In the LIFT randomised study in older postmenopausal women with low bone mineral density, breast cancer risk was decreased in the group receiving tibolone compared to placebo (RH: 0.32, 95% CI: 0.13- 0.80, \(p=0.02\)), however the study was terminated early due to increased risk of stroke.\(^23\)

**Risk of breast cancer for women with a personal history of breast cancer**

There are inconsistent findings about the impact of HRT on breast cancer recurrence from two Scandinavian randomised clinical trials. From one trial of 434 women there is evidence that HRT use for about 2 years is associated with an increase in risk of recurrence of breast cancer.\(^24\) Another trial of 378 women, however, indicates that menopausal use of HRT for about 4 years was not associated with the increased risk of recurrence of breast cancer.\(^25\) The difference in risk levels may be due to the types of HRT used, with the increase in recurrence being associated more with combined HRT use than oestrogen alone. A pooled analysis of both trials indicated a significant increase in overall risk and both trials were terminated prior to completion.

A randomised clinical trial (LIBERATE) investigating the impact of tibolone on breast cancer recurrence in women with a personal history of breast cancer, was stopped in May 2007 prior to completion. The risk of breast cancer recurrence was higher for women on tibolone compared to placebo (HR: 1.40, 95% CI: 1.14-1.70, \(p=0.01\)).\(^26\)

**Women with a family history of breast cancer**

There is limited evidence about HRT and risk of breast cancer for women with a family history of breast cancer. Available evidence suggests that family history has no additive impact on risk of breast cancer with HRT usage.\(^27\)\(^-\)\(^28\) Short-term, oestrogen-only HRT usage in women with a family history of breast cancer increases the risk of breast cancer.\(^29\)\(^-\)\(^31\) This is supported by the Million Women Study, which reported that current users of oestrogen-only HRT had a significant 30% increased risk of breast cancer (HR: 1.30, 95% CI: 1.21-1.40) compared to never users.\(^32\) The association was stronger for women with body mass index less than 25 compared to 25 or more, and more so for those aged 70 years or more.\(^33\)

There is evidence however from other observational studies that also included women without prior hysterectomy, to indicate that oestrogen-only use is associated with increased breast cancer risk. The Million Women Study reported an increased risk for current users of oestrogen-only HRT (RR: 1.30, 95% CI: 1.21 - 1.40, \(p<0.0001\)), with higher relative risk for women with body mass index less than 25 compared to 25 or more, and increased risk with increasing total duration of use, even after short-tem use;\(^14\) these findings were confirmed in a later analysis.\(^9\) In the NIH-AARP Diet and Health Study, oestrogen-only HRT was associated with significantly greater risk (RR: 1.60, 95% CI:1.31-1.96) after 10 years of use in thin women with body mass index less than 25.\(^20\)
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History with a prior hysterectomy may be preferable to combined HRT as it does not appear to be associated with increased breast cancer risk. There are no data to support using lower dosages for any particular type of HRT as being more ‘breast safe’.27

‘Natural’ therapies

Hormone preparations referred to as ‘natural’ or ‘bio-identical’ HRT are typically prepared by compounding chemists and sold in pharmacies as troches (lozenges) or creams. These preparations are neither tested nor approved by the Therapeutic Goods Administration. There are no large, good quality studies on these ‘natural’ hormone preparations to show whether they are effective in treating menopausal symptoms, and whether they carry health risks.5

Recommendations - HRT & Breast cancer risk:

These recommendations are from Cancer Australia’s position statement Hormone Replacement Therapy and Risk of Breast Cancer (see above).

Women continuing or initiating the use of HRT should discuss the benefits and risks of HRT with their doctor, in the context of their own personal history, family history and individual circumstances, so that they can make informed decisions about usage.

Women with no personal or family history of breast cancer

- Women who are considering using combined HRT should be advised that the use of combined HRT (oestrogen and progestogen) is associated with an increased risk of breast cancer which increases with duration of use. Although this risk appears to be associated with more than 3 years usage, it is not possible to determine a safe interval for use of combined HRT. For this reason, combined HRT should only be considered as a short-term option for the control of severe menopausal symptoms.
- Women who are already using combined HRT should be aware that there are both benefits and risks associated with the use of HRT. Women should review their needs every six to 12 months in consultation with their general practitioner, as their menopausal symptoms and underlying risk of breast cancer will have changed over time.
- Women using combined HRT should be advised that the risk of breast cancer decreases with increasing time since ceasing HRT usage, returning to the level of ‘never-users’ within 5 years, and possibly within 2 years after ceasing use.
- Women with a prior hysterectomy should be advised that the use of oestrogen-alone HRT for up to 7 years appears to have little or no effect on risk of breast cancer. For all women, the risk may be increased with increased duration of use, and postmenopausal women with low BMI (<25), have a higher relative risk associated with oestrogen-only HRT, than women with higher BMI.
- Women should be advised that there is limited evidence indicating that combined oestrogen and testosterone HRT is associated with an increased risk of breast cancer.
- Women should be advised that there is inconsistent evidence indicating that tibolone may be associated with an increased risk of breast cancer.

Women with a personal or family history of breast cancer

- Women with a personal history of breast cancer should be advised that there is evidence that the use of tibolone, and limited evidence that the use of other HRT, is associated with an increased risk of breast cancer recurrence.
- Women with a family history of breast cancer should be advised that family history does not appear to have an additive impact on risk of breast cancer with HRT usage.
- Women with a family history of breast cancer with a prior hysterectomy should be advised that short-term, oestrogen-only HRT would appear preferable to combined HRT.
'Natural' therapies

- Women should be advised that the risks of ‘natural’ HRT in relation to breast cancer are unknown.

References:


Resource status:
- Greater than 5 years

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