**HORMONE REPLACEMENT THERAPY: THE NEED TO COMBINE CLINICAL AND EPIDEMIOLOGICAL DATA**

Ian N Olver
Cancer Council Australia, Sydney, New South Wales.
Email: ian.olver@cancer.org.au

**Abstract**

In decision-making about the use of hormone replacement therapy, the risk/benefit analysis should encompass both clinical and epidemiological risk/benefit information. Many women benefit from the use of hormone replacement therapy to control the symptoms of menopause. However, there is evidence from observational studies and randomised trials of a temporal relationship between some hormone replacement therapy use and the risk of breast cancer. Both the Million Women Study and the Women’s Health Initiative showed an increase in the risk of breast cancer, particularly with combined oestrogen and progestagen hormone replacement therapy, which increased with duration of use and was greater if the hormone replacement therapy commenced closer to menopause. They differ in the magnitude of risk and whether there is any increased risk of breast cancer with oestrogen-only hormone replacement therapy. The Million Women Study showed increased risks of endometrial and ovarian cancer with the use of unopposed oestrogens, while the Women’s Health Initiative demonstrated an increased risk of lung cancer with combination hormone replacement therapy. Epidemiological studies show that the incidence of breast cancer falls in women over 50 years and older as hormone replacement therapy use reduces. The clinical translation of these results is that for women who require treatment for symptoms of menopause, the short-term use of unopposed oestrogens would be associated with the least risk of breast cancer (but non-hysterectomised women would have an increased risk of endometrial cancer).

HRT and breast cancer risk

There is now evidence from observational studies and randomised trials showing a temporal relationship between HRT use and breast cancer risk, which rises after initiation and declines after cessation of HRT. Risk increases with duration of use, with the effect consistent with our understanding of hormones in breast cancer biology. The effect was evident in the Million Women Study (MWS), which analysed breast cancer risk factors and outcomes in 1,084,110 women in the UK between 1996 and 2001. It showed an increased breast cancer risk, particularly with combined oestrogen and progestagen hormone replacement therapy, which increased with duration of use and was greater if the hormone replacement therapy commenced closer to menopause. They differ in the magnitude of risk and whether there is any increased risk of breast cancer with oestrogen-only hormone replacement therapy. The Million Women Study showed increased risks of endometrial and ovarian cancer with the use of unopposed oestrogens, while the Women’s Health Initiative demonstrated an increased risk of lung cancer with combination hormone replacement therapy. Epidemiological studies show that the incidence of breast cancer falls in women over 50 years and older as hormone replacement therapy use reduces. The clinical translation of these results is that for women who require treatment for symptoms of menopause, the short-term use of unopposed oestrogens would be associated with the least risk of breast cancer (but non-hysterectomised women would have an increased risk of endometrial cancer).
or a placebo. The trial was stopped early (at 5.2 years of an intended 8.5 years) because of increased breast cancer incidence in the hormone arm, which also showed increased myocardial infarction and stroke, but decreased osteoporotic fractures and colorectal cancer (although they presented with more advanced disease). The WHI also randomised 10,739 postmenopausal women to oestrogen only or placebo, with the single hormone arm experiencing reduced rates of breast cancer, myocardial infarction (although these were not statistically significant) and osteoporosis, while the increase in thrombosis and stroke remained.

Further analyses of these studies show that some uncertainty remains. A re-examination of the WHI study suggests that if corrections are made for baseline differences in the groups and for multiple comparisons, since breast cancer is a secondary endpoint of the study, there is no increase in breast cancer, and it is suggested that the apparent increase in mortality may be due to a surveillance and detection bias. It is also suggested that the 11 year follow-up results show no increase in breast cancer in women who had not previously used HRT, which would be most in that study. A more recent analysis of the MWS to explore the relationship between breast cancer risk and when the hormones were started in relationship to menopause, reaffirmed that in current users of hormonal therapy the incidence of breast cancer was greater if they started within five years of menopause, but returned to that of never users a few years after hormonal therapy ceased. However, the relative risks of breast cancer were greater in current users if the use of HRT began at, or soon after menopause, compared to later for both oestrogen only and oestrogen-progestogen combinations. With oestrogen-only HRT there was no increased risk if use began five years or more after menopause.

The WHI parallels the finding that women who use oestrogen-progestogen therapy have a greater risk of breast cancer if they start within five years of menopause, however the magnitude was less than in the MWS. In the WHI however, with oestrogen-only therapy, there was a similar timing effect, but there was no effect on breast cancer risk when oestrogen was started within five years of menopause. When started five years or more after menopause, the risk of breast cancer was reduced. There have been conflicting studies over the question of oestrogen-only HRT and the incidence of breast cancer. The European Prospective Investigation into Cancer and Nutrition and a study from Los Angeles County found that both oestrogen-only and combined menopausal hormone therapy users had an increased breast cancer risk, with continuous combined therapy being worse than sequential combined therapy. Alternatively, studies from Washington State and Sweden found only the combined HRT was associated with an increased breast cancer risk, and not unopposed oestrogens. The WHI, with a mean follow-up of just over seven years, shows no evidence of an increased risk of breast cancer in any group receiving unopposed oestrogens, although less evidence for deceased risk for those starting closer to menopause.

**Explaining divergent results**

Although the design of the large MWS and the WHI are sufficiently different to make direct comparisons problematic, weight is added to the observations where the studies agree, but the explanation of divergent results is open for speculation. The authors of the MWS suggest that the difference in the risk of breast cancer with HRT between the studies stems from different risk factors. In the WHI, this means particularly obesity and the time of commencing HRT relative to the menopause. Chlebowski et al, who wrote an editorial to accompany the update of the MWS, suggested that it was more likely that post menopausal breast cancer HRT recipients had more frequent mammographic screening than non-users and therefore had more breast cancers identified. It has been previously reported that postmenopausal hormone therapy users have mammograms at more regular intervals than non-users and these identify more slow growing receptor-positive tumours that are diagnosed at an earlier stage. Chlebowski also cites prior mammography as a risk factor for subsequent breast cancer. In the WHI, the prior and subsequent mammographic screening in both arms was more tightly controlled than in the MWS.

The MWS also reported that unopposed oestrogen use for more than five years increased ovarian and endometrial cancer risk, while more recent studies attribute long-term HRT use to increased risk of cutaneous melanoma. The WHI showed that women using combined oestrogen and progestogen had higher lung cancer mortality. Also, an analysis of a group of 36,588 peri and postmenopausal women from the Vitamins and Lifestyle Study, found an increased risk of lung cancer associated with increasing duration of oestrogen plus progestin use. The duration of use also correlated with advanced stage at diagnosis, with an approximate 50% increase with HRT use of 10 years or longer. The association with lung cancer was not seen with oestrogen-only HRT.

**Breast cancer incidence**

Population studies show associations but cannot demonstrate causal connections. There is however, further evidence from population studies that HRT usage does have an impact on breast cancer incidence. The link between HRT use and breast cancer has been reinforced by epidemiological data from Australia and elsewhere, showing that the reduced HRT use following the initial publication of the results from the MWS and WHI was paralleled by a fall in breast cancer incidence among women aged 50 years and older. This decline has been to a different degree in different countries. In countries such as the US, Canada, Australia, Belgium and France – with a high peak prevalence of HRT usage – the decline is more marked than in low prevalence countries such as Italy, Spain, China or Japan. Any change in mammography screening could confound the results and must be taken into account.

**Weighing the risks for patients**

Clinicians who treat the distressing symptoms of menopause with HRT have questioned the generalisation of these findings to individual women in an Australian...
clinical setting. Wren in the Medical Journal of Australia in 2009 suggested the WHI study overestimated risk, because the women had other breast cancer risk factors – they were older than women typically commencing HRT and 69% were obese or overweight. HRT given earlier in menopause, he argued, improved the risk/benefit ratio, while the observation that decreased breast cancer incidence paralleled reduced HRT use was more consistent with HRT promoting, not initiating, cancer. And the increase in breast cancer years after starting HRT might be due to the growth of carcinoma in situ or micro-invasive disease, however this is speculation and is not evidence based.

These considerations do not negate the evidence of risk. And some claims are inconsistent with the additional reports, such as the further WHI review that showed hazard ratios for breast cancer and total cancer were still significantly higher in women commencing combined oestrogen and progestogen use in early menopause. Moreover, doubt can also go two ways – while there is no conclusive evidence of breast cancer risk increasing after HRT use for less than two years, the link cannot yet be dismissed. Post hoc sub-study analyses may never definitively resolve these doubts, irrespective of the result of a specific analysis. So applying large studies to decisions about individual patients will also depend on the clinical indication for HRT and the patients’ specific needs and biological profile.

Two things are clear. The relationship between HRT use and cancer risk is important, and clinicians need more than claims and counter-claims in the literature to inform their practices.

Improved regulation of HRT use through listing, scheduling and reimbursement has a role to play in reducing harm. The Australian Drug Evaluation Committee guideline acknowledged the effectiveness of HRT for symptoms of menopause, subject to six monthly re-evaluation. When clinicians feel constrained by or tempted to prescribe HRT outside the guideline, they and their patients should have recourse to clinical guidelines weighing up the evidence for alternative uses. Over time new information may help select individuals who may be at less risk from HRT. For example, there is a protective effect against breast cancer risk in women using HRT for 10 years or more when they have the CYP2C19*17 allele, because it increases the risk in women using HRT for 10 years or more when they have the CYP2C19*17 allele, because it increases the risk of adverse effects such as breast cancer balanced against a great improvement in quality of life. The data on the timing in relation to menopause may be less helpful in clinical decision-making, since the timing of symptoms would dictate when the HRT was commenced. However, the information about the increased risk of breast cancer when initiating HRT close to the menopause should still be provided to patients.

A population health goal where the vast majority of HRT use is short-term unopposed oestrogens is highly desirable, and this would accommodate population data into individual patient care, rather than selectively arguing against the application of such data.

**Conclusion**

In conclusion, to use the population data in clinical decision-making, unopposed oestrogens have a better risk profile than combined oestrogen/progestogen combinations. Even in women who have not had a hysterectomy and are at risk of endometrial cancer, their overall cancer risk has been shown as lower with unopposed oestrogens. Secondly, the duration of use is important. There are no data, for example, which would preclude prescribing short-term unopposed oestrogen HRT for a woman with severe symptoms of menopause, considering the low risk of adverse effects such as breast cancer balanced against a great improvement in quality of life. The data on the timing in relation to menopause may be less helpful in clinical decision-making, since the timing of symptoms would dictate when the HRT was commenced. However, the information about the increased risk of breast cancer when initiating HRT close to the menopause should still be provided to patients.

**References**


