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EDITORIAL

Current status of hormone therapy and breast cancer

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This editorial comments on two similar reviews of the literature on breast cancer and post-menopausal hormone therapies (HTs), puts the results in clinical perspective and suggests where they direct future research and clinical management. Although epidemiological studies have suggested increased breast cancer risk for all menopausal HT regimens, unopposed oral estrogen regimens have not been associated with any increased risk in recent randomized placebo controlled trials (RCTs). Added progestogen after 5 years of combined HT in RCTs increases the risk of breast cancer by four cases per 10 000 per annum. As yet there is no evidence of different risk by progestogen type, dose or route. Theoretically local intrauterine progestogen may not give the same risk, but long-term trials are required. The commentary addresses the responsibility of the media in presenting levels of risk to the public, moving towards safer regimens, safer therapies, appropriate patient choice and, in particular, correct timing of HT where it is prescribed around menopause. This is in contrast to many of the trials when HT was administered after the potential climacteric window of therapeutic opportunity. The current main indication for HT remains for menopausal symptom control where it improves quality of life. HT may be required for many years. The informed woman should decide on HT based on her personal benefits and risks, which should include all aspects of her health.

There is now little doubt that combined estrogen and progestogen hormone therapy (HT) is associated with an increased risk of breast cancer. Data from the Collaborative Group on Hormone Factors in Breast Cancer (1997) analysed individual data from 51 epidemiological studies and provided strong evidence that breast cancer risk was increased in women using HT, that risk increases with increased duration of use and decreases after stopping therapy. However, confusion existed regarding the relative roles of estrogen alone or estrogen/progestogen combinations. The Women's Health Initiatives study (WHI) provided the best randomized control trial (RCT) evidence that breast cancer was indeed increased with combined HT but not with estrogen-alone therapy. The combined HT results were released first in 2002, and the media's unbridled and often histrionic interpretation of the data led to an enormous reduction in the use of HT around the world (Writing Group for the Women's Health Initiative Investigators, 2002). When the results of the oestrogen-only arm were published in 2004 showing an almost significant reduction in breast cancer rates in association with estrogen-only use, there was relatively little media reaction or interest (Women's Health Initiative Steering Committee, 2004).

Two recent articles published in this edition of *Human Reproduction Update* further dissect the role of HT in the relationship with breast cancer. The first article by Greiser *et al*. (2005) is a meta-analysis looking at invasive breast cancer in cohort studies (CS), case–control studies (CCS) and RCTs. It confirms the increased risk in breast cancer with HT and, in addition, shows a secular trend for an increased risk of breast cancer over the years, in particular in relation to combined estrogen/progestogen therapy. A second compelling article by Collins *et al*. (2005) compares results from RCTs and epidemiological data. The results of this study are summarized in Table I.

Overall, there appears to be no evidence, in level 1 RCTs, that estrogen-only regimens increase breast cancer, whereas levels 2 and 3 epidemiological studies had suggested about a 20% increase with this regimen. Whatever the effect of estrogen alone on breast cancer, it appears to be small. However, the addition of progestogen does appear to increase the risk of breast cancer when

Table I. Summary of breast cancer risk with hormone therapy (HT) (data from Collins *et al*., 2005)

Randomized controlled trial		
Unopposed estrogen	Possible 21% reduction in breast cancer (0.79, 0.61–1.02)	4:10 000 women per year
Estrogen + progestogen	Probable 24% increase in breast cancer (1.24, 1.03–1.50)	4:10 000 women per year
Epidemiological		
Current users of estrogen + progestogen	Greater risk than never users (1.35, 1.21–1.49)	
Unopposed estrogen <5 years	Risk unchanged (0.99, 0.83–1.15)	
Unopposed estrogen >5 years	Risk increased (1.34, 1.16–1.52)	
Current estrogen + progestogen <5 years	Trend to increase (1.15, 0.78–1.52)	
Current estrogen + progestogen >5+ years	Trend to increase (1.53, 0.88–2.18)	
Stopping HT	Risk decreased around 5 years	
Hormone type	No evidence for type of hormone	
Hormone dose	No evidence for dose effect	
Hormone route of delivery	No evidence for route of administration effect	
Progestogen continuous or sequential	Non-significant trend for increase is continuous	
Lobular versus ducted breast cancer	Risk increased for lobular cancer (2.19, 1.60–2.99)	
Better prognosis tumours	Trend to improvement, more likely where estrogen receptor positive	

used for 5 years or longer. Risk appears to decrease once HT is stopped, and the type of progestogen, the way that it is delivered and the dose with which it is used has no obvious role in enhancing or modifying the adverse affect of progestogen.

Many questions remain to be answered in the use of HT and breast cancer. For instance, we do not know the affect of drugs such as the synthetic steroid tibolone in association with breast cancer. The Million Women Study (2003), a study with potential selection and detection biases (Shapiro, 2004), implied that tibolone was associated with an increased risk. Many longer-term RCTs with tibolone are currently in progress and, to date, their safety committees have encouraged the trials to continue. The use of continuous or sequential therapy is also unresolved with respect to progestogen, and the favourable or unfavourable prognostic factors in any breast cancer associated with HT is also unclear. However, a recent analysis of two Swedish RCTs of combined HT after breast cancer showed no trend to increased recurrence of breast cancer in the trial using cyclical progestogens 10 days every 3 months (Hazard Ratio (HR) = 0.82, 0.35–1.9), whereas the trial using a continuous combined therapy was stopped when a significant increase in breast cancer was seen (HR = 3.3, 1.5–7.4) (von Schultz *et al*., 2005).

There are several issues that we in the scientific community need to address.

(1) When the WHI was published, the scientific community were kept in the dark for a couple of days, whereas the media ran riot in explaining (often very badly) the adverse consequences of HT to the general public. Those with vested interests in other products, such as complementary medicines misrepresented the role of HT and promoted their products without adequate data of the long-term risks and efficacy of their alternative products. Absolute risk and the details of the limitations of the WHI were not presented, and over the past few years as this has been dissected out in the scientific literature, the risks have become much clearer and less concerning for the profile of women where HT is usually indicated. This particularly applies to those using estrogen-only regimens and women initiating HT around menopause. The impact of media headlines was that more than half of the HT users stopped HT without medical consultation, and for many, return of severe menopausal symptoms and a subsequent loss of quality of life occurred (MacLennan *et al*., 2004).

For some women on long-term HT, it was time for review and an appropriate time to cease HT but many women who were taking HT for osteoporosis prevention or therapy did not seek review and did not move to any other form of treatment. An informed medical practitioner should review all women on HT yearly, and the need for HT reconsidered. To know whether HT is still required for menopausal, symptom control and quality of life it is necessary to try off therapy every few years.

(2) There has been relatively little publicity about the affects of unopposed estrogen on breast cancer. It is clear that there is no significant increase over 7 years of estrogen therapy in the WHI, and overall level 1 RCTs suggest a 20% reduction in breast cancer risk. This is in marked contrast to the level 3 Million Women Study that reported a relative risk of 1.30 (1.22–1.38). It is unfortunate that some of the publications relating to WHI and the associated reassuring data about both estrogen-only therapy and therapy from early menopause have not made their findings more public and have not been picked up by the media. The opportunities for delivering progestogens by non-systemic routes need exploration given the interesting studies related to estrogen-therapy alone. Current literature gives little justification for the use of added progestogens except for endometrial cancer protection and the control of uterine bleeding.

(3) The relative roles of RCTs, CCS and CS need to be explained better to the general public and to the prescribers. Although RCTs are the gold standard, they are expensive, difficult to conduct and the results may only reflect the population and regimen studied. The WHI was a rigorously conducted large long-term RCT but treated an atypical population who were mostly without symptoms and well beyond menopause. Many had established cardiovascular risk factors, and it can be argued that the WHI was a mixed primary and secondary prevention trial for many of the outcomes measured. CCS and CS are cheaper to run and are able to obtain much bigger numbers but suffer from retrospective reporting and selection and detection biases. Such errors can be magnified in large epidemiological studies, such as the Million Women Study.

(4) A decision about the use of HT cannot be based on the risk of breast cancer alone. Other increased risks, such as thromboembolism, heart disease and stroke, must be considered and

individualized because the absolute risk of these adverse events are uncommon in healthy newly menopausal women but increase with age and the presence of thrombophilia or established atherosclerosis. However, many women with moderate to severe menopausal symptoms greatly value the increased quality of life they experience when their symptoms are effectively ameliorated. This is the main indication for the use of HT, and symptoms can remain for many years after menopause. No phyto-estrogen or complementary therapy has been shown to be as effective as HT. Also now there is level 1 evidence for the prevention of fractures with HT. HT is one of several therapeutic options for the management of osteoporosis particularly in symptomatic women near menopause where there is the option of changing to other effective therapies in later years as need and risk profiles change.

(5) The possibility that there is a therapeutic window of opportunity for neuro- and cardio-protection by HT initiated around menopause is one of the most exciting hypotheses that has arisen from this research. Reanalyses of the WHI data show a significant reduction in cardiovascular events in the younger women when both arms of the trial are combined. An increase in such events was seen when HT was initiated many years after menopause. This fits with most epidemiological data, which derives from use around menopause, laboratory studies that suggest blood vessels lose their receptivity to estrogen after about 5 years and finally monkey studies. These confirm an early primary protective effect from atherosclerotic plaque when HT is commenced at surgical menopause but is without effect when initiated in late menopause once there is established plaque (Rossouw, 2005). There is a great need for a new long-term trial of potentially better HT regimens in a population around menopause where the benefits may be greater and the risks smaller. One such study with surrogate cardiovascular endpoints is underway (Harman *et al*., 2005).

(6) Finally, it is likely that future studies will be able to identify *safer women* for HT, e.g. those without thrombophilia, *safer estrogens* and progestogens, e.g. estrogen with endometrial opposing selective estrogen receptor modulators (SERMs) or local uterine progestogen, *safer routes* for HT, e.g. the possible advantages of transdermal therapy need to be confirmed, *safer doses*, e.g. it is logical that effective low dose therapy should have less side effects, effective and *safer long-term alternative treatments* to HT, e.g. tibolone, SERMs and lastly *safer timing* of initiation of HT, e.g., second menopause (MacLennan *et al*., 2005).

In the early days of HT, the use of unopposed estrogen in women with a uterus led to an increased rate of endometrial cancer and a reduced use of HT. The introduction of progestogens either as sequential or combined regimens led to the second burst of enthusiasm for HT with a wide uptake across the world and in women over the age of 50. This phase has now ended, particularly with the publishing of the WHI. We now need to decide where to go with the next phase of HT. Most clinicians looking after women in menopause recognize that there has to be some form of HT for up to half of women during their life time for symptom control or as an initial option for long-term management of osteoporosis. The exact form of strategy has to be individualized, but the two articles in this edition of *Human Reproduction Update* help us to decide which avenues are going to be valuable to pursue in respect to breast cancer risk. The fact that estrogen alone may not cause problems with respect to breast cancer must lead us to look at ways in which we can deliver estrogen without any significant endometrial or pharmacological side effects. The identification of progestogens as a potential problem should indicate further research into the different types of progestogens that may have less oncological potential or else to deliver progestogens in ways that do not impact directly on the breast. For instance, the use of intrauterine progestogen systems has great potential to provide endometrial protection without systemic side effects. The challenge for reproductive endocrinologists, gynaecologists and epidemiologists is to use our knowledge of the last 50 years to develop forms of HT that are going to be acceptable and safe for women where HT is clearly indicated. Pharmaceutical companies' enthusiasm for promoting HT a decade ago has waned. Patients needs, however, have not disappeared, and as practising clinicians we need to offer evidence-based choice and allow each woman to make an informed decision about all the benefits and risks of hormonal, non-hormonal and life-style strategies that apply specifically to her and be able to advise on a tailored regimen that will be optimal for her. The absolute risks for an individual are low (Coombs *et al*., 2005). All women will want to minimize their risk of future breast cancer, but they also want to maintain the health of the rest of their body and optimise their quality of life. Our challenge is to minimize risk and maximize benefits from tested therapies and not to abandon women to the often-false promises of the complementary therapy industry.

References

Collaborative Group on Hormonal Factors in Breast Cancer (1997) Breast cancer and hormone replacement therapy: collaborative reanalysis of data from 51 epidemiological studies of 52.705 women with breast cancer and 108.411 women without breast cancer. Lancet 350,1047–1059.

Collins JA, Blake JM and Crosignani PG (2005) Breast cancer risk with postmenopausal hormonal treatment. Hum Reprod Update (Epub ahead of print 8th September 2005).

Coombs NJ, Taylor R, Wilcken N and Boyages J (2005) Hormone replacement therapy and breast cancer: estimate of risk. BMJ 331,347–349.

Greiser CM, Greiser EM and Doren M (2005) Menopausal hormone therapy and risk of breast cancer. A meta-analysis of epidemiological studies and randomized controlled trials. Hum Reprod Update (Epub ahead of print 8th September 2005).

Harman SM, Brinton E, Cedars M, Lobo R, Manson JA, Merriam G, Miller V, Naftolin F and Santoro N (2005) Keeps: the Kronos early oestrogen prevention study. Climacteric 8,3–12.

MacLennan AH and Sturdee DW (2005) Towards safer women and safer doses safer routes and safer timing of administration of safer menopausal therapies. Climacteric 8,1–2.

MacLennan AH, Taylor AW and Wilson DH (2004) Hormone therapy use after the Women's Health Initiative. Climacteric 7,138–142.

Million Women Study Collaborators (2003) Breast cancer and hormone-replacement therapy in the Million Women Study. Lancet 362,419–427.

Rossouw JE (2005) Coronary heart disease in menopausal women: implications of primary and secondary prevention trials of hormones. Maturitas 51,51–63.

von Schultz E, Rutqvist LE and the Stockholm Breast Cancer Study Group (2005) Menopausal hormone therapy after breast cancer: the Stockholm randomized trial. J Natl Cancer Inst 97,533–535.

Shapiro S (2004) The Million Women Study: potential biases do not allow uncritical acceptance of the data. Climacteric 7,3–7.

Women's Health Initiative Steering Committee (2004) Effects of conjugated equine oestrogen in postmenopausal women with hysterectomy – The Women's Health Initiative randomized controlled trial. JAMA 291,1701–1712.

Writing Group for the Women's Health Initiative Investigators (2002) Risks and benefits of oestrogen plus progestin in healthy postmenopausal women, principal results from the Women's Health Initiative randomized controlled trial. JAMA 288,321–333.