The release on July 9, 2002 of preliminary results from the study by the Women’s Health Initiative (WHI) on the risks and benefits of estrogen plus progestin in healthy postmenopausal women has left a lot of women wondering if they should continue on hormone replacement therapy (HRT).

This issue has received a lot of press and raised concern for many women. Pharmacists are frontline health professionals who are readily available to their patients to offer balanced information to allow each woman to make a decision that is right for her particular situation. The Canadian Pharmacists Association is providing this information as a service to its members to assist them in discussing this issue with their patients.

It is now evident that HRT does not provide cardio-protective effects and there is increasing evidence to suggest that combined HRT may increase the risk of a woman developing breast cancer.

The following studies are well designed and provide evidence to help women make informed decisions about HRT.

- **WHI: Women’s Health Initiative on the Randomized Controlled Trial on Risks and Benefits of Estrogen plus Progestin in Healthy Postmenopausal Women**
  - The 16,608 healthy postmenopausal women (with an intact uterus) in this study received placebo or 0.625mg conjugated equine estrogen plus 2.5mg medroxyprogesterone acetate per day. The mean age at recruitment was 63 years.
  - The trial was stopped after a mean of 5.2 years of follow-up (3.2 years early) as risks were exceeding benefits.
  - For women taking the combination HRT there were, per 10,000 women:
    - 8 more cases of invasive breast cancer
    - 7 more coronary heart disease events
    - 8 more strokes
    - 8 more pulmonary embolisms
  - Although these results show only a low risk for women developing complications it should be noted that the study was looking at healthy women on HRT for the purpose of preserving health and preventing disease.
  - Furthermore, the risks associated with developing life threatening conditions related to use of the drug add up over time.
  - On the other hand the study also found that for women taking the combination HRT there were, per 10,000 women:
    - 6 fewer colorectal cancers
    - 5 fewer hip fractures
  - The authors concluded that the risk-benefit profile did not warrant combination HRT intervention for primary prevention of chronic diseases, and that HRT should not be initiated or continued for primary prevention of coronary heart disease.

- **HERS and HERS II: Heart and Estrogen/progestin Replacement Study - Noncardiovascular and Cardiovascular Outcomes**
  - HERS was a randomized, blinded, placebo-
controlled trial of the effect of 0.625 mg of conjugated estrogens plus 2.5 mg of medroxyprogesterone daily on coronary heart disease (CHD) event risk among 2,763 postmenopausal women with documented CHD.

- Over 4.1 years of follow-up, there were no significant differences between the hormone and placebo groups in the overall reduction in risk of CHD events. There were, however, more CHD events in the hormone group during the first year of treatment, and fewer than placebo in years 3 to 5.

- HERS II is a follow up study of these women for an additional 2.7 years. After a total of 6.8 years, hormone therapy did not reduce risk of cardiovascular events in women with CHD. The authors conclude that HRT not be used to reduce risk for CHD events in women with CHD.

- HERS II also looked at noncardiovascular disease outcomes. It concluded that treatment for 6.8 years increased the rates of venous thromboembolism and biliary tract surgery. Trends in some other disease outcomes were not favourable.

- BCDDP: Breast Cancer Detection Demonstration Project Follow-up Study
  - This follow-up analysis of data from the BCDDP looked at the incidence of ovarian cancer in 44,241 postmenopausal women.
  - Indicates that women who use estrogen-only replacement therapy, particularly for 10 or more years, were at significantly increased risk of ovarian cancer.
  - The study concluded that women who used short-term estrogen/progestin-only replacement therapy (EPRT) were not at increased risk, but risk associated with short-term and longer-term EPRT warrants further investigation.

There are some instances where there is more evidence to support a recommendation of HRT. The WHI study of estrogen only use in women who had previously undergone hysterectomy is continuing with no reported increased risk of breast cancer. Moreover, hormone replacement therapy for the treatment of acute menopausal symptoms, when indicated, continues to be appropriate for short term use without an apparent increase in risk of breast cancer for up to 4 years.

It should also be noted that the WHI study was looking at oral estrogen and these findings cannot necessarily be applied to all formulations of estrogen. Furthermore, in recent years there has been a trend to use lower doses of estrogen. The WHI studied 0.625mg per day of conjugated equine estrogen plus 2.5mg per day of medroxyprogesterone acetate and did not look at regimens using lower doses of estrogen.

**So what’s the bottom line and what can I tell my patients?**

As with any medication, each woman should weigh the risks versus the benefits as they apply to her individual situation. Pharmacists should encourage women to see their physician to discuss their concerns and personal risk-benefit profile for continuing therapy, based on their years of HRT use and health history.

It is important to reassure women so that they are not unduly alarmed. The increased risks of breast cancer in the WHI study are applied to an entire population of women, not to the increased risk for an individual woman, which is very small (less than a tenth of one percent per year). The WHI has provided a fact sheet, available at [http://www.nhlbi.nih.gov/whi](http://www.nhlbi.nih.gov/whi).

Considering the information available, most healthy women are unlikely to benefit from taking combined HRT to prevent chronic disease. The WHI study, as well as the HERS and HERS II studies, cast serious doubt on whether HRT should be used long term. Other options for cardiovascular and osteoporosis prevention are available.

Current evidence supports the safety of HRT use in the short term during the menopause. Women who are taking estrogen-progestin for a short period for menopausal symptoms (e.g., for hot flashes, night sweats) do not need to discontinue their therapy.

Women without a uterus who are taking estrogen only can continue therapy. The WHI is continuing its study of estrogen only and reports that there is no evidence of an increased risk of breast cancer.

Here are a few questions that your patients should consider to help them decide whether continuing HRT is appropriate for them.

1) Why are you on HRT?
2) Have you considered or tried any of the alternatives that are available?
3) What is your personal and family history of cancer and heart disease?
4) What steps have you taken to decrease your risk of heart disease or osteoporosis, other than taking HRT? Ask about lifestyle modifications such as:
If a woman decides that the risks of HRT are not worth the potential benefits of the therapy, there are many alternatives that you could suggest.

**Menopausal symptoms:**
- avoid spicy food, alcohol and caffeine
- keep environment comfortably cool
- dress in layers
- lubricants for vaginal dryness
- Kegel exercises for bladder control
- vitamin and herbal supplements
- dietary approaches (e.g., soy products)

**Osteoporosis:**
- bisphosphonates, selective estrogen receptor modulators, and others
- calcium and vitamin D supplements
- regular weight bearing exercise
- minimize caffeine and alcohol intake
- fall prevention strategies
- smoking cessation

**Heart health:**
- smoking cessation
- weight reduction
- healthy diet consisting of low fat, high fiber
- regular exercise
- good blood pressure control
- statin medications to help lower cholesterol

If a woman decides that the risks of HRT outweigh the benefits, she should be advised to consult her physician before discontinuing therapy. Abrupt discontinuation of HRT is likely to cause return of menopausal symptoms and the patient should be reassured that continuing on HRT for a few more days, until she is able to get an appointment with her physician, will not increase her risk of developing complications. It is also advised that anyone on HRT be slowly tapered off the medication and this should be done in consultation with the woman’s physician.

Currently the Society of Obstetricians and Gynecologists (SOGC) and the American College of Obstetricians and Gynecologists (ACOG) are both putting together task forces to review the current literature and develop consensus guidelines. CPhA will be apart of the SOGC task force and will keep members up to date as new developments become available.

**REFERENCES:**


