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Managing menopause Part 2: Hormone therapy and breast cancer, cardiovascular disease, and premature ovarian insufficiency

This second article in a two-part series reviews the Society of Obstetricians and Gynaecologists of Canada's 2021 clinical practice guideline on managing special circumstances associated with menopause.

ABSTRACT: Updated guidelines for the use of hormone therapy during menopause and its role in patients with breast cancer, cardiovascular disease, and premature ovarian insufficiency were released by the Society of Obstetricians and Gynaecologists of Canada in 2021. The relationship between hormone therapy and breast cancer remains complex and controversial. Although risks are low in healthy postmenopausal women, systemic use remains contraindicated in breast cancer survivors due to higher relapse rates. Hormone therapy is also not recommended for the prevention of cardiovascular disease, the leading cause of mortality in Canada. Furthermore, estrogen is associated with increased risks of venous thromboembolism across all age groups. For women with premature ovarian insufficiency, hormone therapy is advised until the average age of menopause to mitigate chronic disease risks such as osteoporosis, cardiovascular complications, and impaired cognition.

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The first part of this review focused on guideline A of the Society of Obstetricians and Gynaecologists of Canada's 2021 *Managing Menopause* guideline: managing vasomotor symptoms via hormone therapy and nonpharmacologic measures. This second part focuses on guidelines E and F: the role of hormone therapy in patients with breast cancer, cardiovascular disease, and premature ovarian insufficiency.[1,2]

Hormone therapy and breast cancer

After nonmelanoma skin cancer, breast cancer is the most prevalent malignancy in Canadian women, representing 26% of new cancer cases and 13% of all cancer deaths. It is estimated that 1 in 8 women will develop breast cancer during their lifetime, and 1 in 31 will die from it.[3]

Similar to the 2014 guideline on managing menopause,[4] the 2021 guideline reiterates that there is a complex and controversial association between hormone therapy and breast cancer development. The North American Menopause Society states that breast cancer risk may be influenced by the type of menopausal hormone therapy, duration of use, regimen, route of administration, prior exposure, and an individual's characteristics.[5]

To better understand breast cancer risks, much of the 2021 guideline focuses on long-term follow-up data from clinical trials mentioned in the 2014 guideline. Of note, the 2002 Women's Health Initiative study consisted of two randomized clinical trials involving more than 20 000 participants. In the first trial, women received either estrogen–progesterone therapy or placebo. Results showed a 27% increase in relative breast cancer risk from hormone therapy based on 38/10 000 and 30/10 000 cases in the treatment and control groups, respectively.[6] However, to put this into perspective, eight additional breast cancer cases per 10 000 women per year translates to an absolute risk of merely 0.0008. Overall, the initial study showed a small increase in breast cancer risk after 5 years of hormone therapy. The 2021 guideline highlights the agreement between the postintervention and recently released long-term Women's Health Initiative data. After being followed for 9 to 14 years, women who received estrogen–progesterone hormone therapy had a higher

risk of breast cancer (hazard ratio [HR] 1.28; 95% CI, 1.13-1.45; $P < .001$) but no significant difference in breast cancer death (HR 1.35; 95% CI, 0.94-1.95; $P = .11$).[7]

In a second Women's Health Initiative trial, women with prior hysterectomy received either conjugated estrogen alone or placebo. Those who received conjugated estrogen had a significant decrease in breast cancer risk (relative risk [RR] 0.77; 95% CI, 0.62-0.95).[8-10] This aligned with the recently released Women's Health Initiative follow-up data (HR 0.78; 95% CI, 0.65-0.93; $P = .005$), thus confirming that estrogen–progestogen therapy carries greater risk for breast cancer than estrogen alone.[7] For this reason, the 2021 guideline highlights estrogen only as the preferred treatment for vasomotor symptoms in patients without a uterus (because they do not require a progestogen to prevent endometrial hyperplasia).

Both the 2014 and 2021 guidelines emphasize the importance of putting breast cancer risk into perspective. The 2014 guideline includes a table that compares cases and deaths from breast cancer to deaths from all causes in order to highlight that women on hormone therapy are much more likely to die from cardiovascular disease and other chronic conditions. The 2021 guideline also includes a table of risk factors for breast cancer and their attributed relative risks. This highlights how factors overscrutinized by the media (such as estrogen–progestogen hormone therapy, alcohol consumption, and obesity) actually carry only modest relative breast cancer risks of 1.2 to 1.3. Unmodifiable factors such as genetic predisposition (the BRCA1 mutation) have more significant implications, with a relative risk of 200.[11]

To mitigate breast cancer concerns, the 2021 guideline emphasizes the importance of providing the hormone therapy regimen with the lowest possible risk for healthy postmenopausal women with vasomotor symptoms. This can be achieved by careful consideration of both the timing and type of hormone therapy. For instance, new studies have shown that oral micronized progesterone (Prometrium, PMS-Progesterone, Reddy-Progesterone, Teva-Progesterone) is associated with a lower risk of breast cancer than are synthetic progestins.[12,13] In addition, long-cycle combined hormone therapy, with continuous estrogen and the addition of progestogen every 3 months, may be protective against breast cancer due to progestin withdrawal prompting apoptosis of breast epithelial cells. However, this potential benefit must be balanced against the increased risk of endometrial hyperplasia.[14]

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Systemic hormone therapy continues to be contraindicated in breast cancer survivors with vasomotor symptoms. This contraindication was initially informed by preliminary results from the HABITS (hormonal replacement therapy after breast cancer—is it safe?) and Stockholm studies discussed in the 2014 guideline and reinforced by 10-year follow-up data mentioned in the 2021 guideline, as both showed increased rates of breast cancer relapse in these women.[15-17] Nonhormonal alternatives can be used to treat vasomotor symptoms in patients with a personal breast cancer history. In particular, venlafaxine is considered the first-line alternative therapy for breast cancer survivors.[18] Second-line options for refractory vasomotor symptoms include oxybutynin and clonidine. A long-acting form of paroxetine has recently been approved for breast cancer survivors in the United States but has not been approved in Canada.[19]

Hormone therapy and cardiovascular disease

Cardiovascular disease continues to be the leading cause of death in women and a significant contributor to chronic illness, costing Canadians $22 billion annually.[20] However, most cases of cardiovascular disease are preventable. More specifically, the INTERHEART study showed that 94% of cardiovascular disease risk could be attributable to modifiable factors such as diabetes mellitus (odds ratio [OR] = 2.37), hypertension (OR = 1.91), abdominal obesity (OR = 1.62), current smoking (OR = 2.87), and psychosocial stress (OR = 2.67).[21] Consequently, early identification of risk factors and intervention is key. The Canadian Cardiovascular Society's 2016 *Dyslipidemia Guidelines* recommend that women older than 40 years or those who are postmenopausal undergo a cardiovascular risk assessment every 5 years using the modified Framingham Risk Score, an estimate of an individual's 10-year risk for cardiovascular events. The 2014 *Managing Menopause* guideline had an extensive, checkbox-style appendix, "Menopause Lifestyle and Risk Assessment Tool," which included the Framingham Risk Assessment. This was not included in the 2021 guideline.[4]

In line with the 2014 guideline, the 2021 guideline cautions that hormone therapy is not indicated for primary or secondary prevention of cardiovascular disease. Primary prevention, in particular, has long been an area of controversy because age has been found to be a confounding variable for coronary artery disease outcomes in patients receiving hormone therapy. This led to the development of the "critical window" hypothesis outlined in the 2014 guideline. It suggests that in younger postmenopausal women with healthy coronary arteries, hormone therapy may be cardioprotective via anti-atherosclerotic effects. In contrast, in older postmenopausal women who are more likely to have undetectable atherosclerosis, hormone therapy can promote plaque rupture and thrombosis.[22-24]

The 2021 guideline emphasizes a Cochrane review that further supported the critical window hypothesis. It showed that hormone therapy within the first 10 years of menopause was associated with lower rates of both coronary heart disease (RR = 0.52; 95% CI, 0.29-0.96) and all-cause mortality (RR = 0.70; 95% CI, 0.52-0.95).[25] In contrast, when hormone therapy was initiated more than 10 years after menopause, it had no effect on coronary heart disease (RR = 1.07; 95% CI, 0.96-1.20) or all-cause

mortality (RR = 1.06; 95% CI, 0.95-1.18).[25] This is one of the reasons the 2021 guideline emphatically defines the time frame in which postmenopausal women can safely begin hormone therapy: less than 60 years of age or less than 10 years postmenopause.

The 2021 guideline reaffirms that hormone therapy is also associated with increased risk of venous thromboembolism in all age groups. However, based on the Cochrane data, the degree of risk varies with age. Women less than 10 years postmenopause or more than 10 years postmenopause had relative risks for venous thromboembolism of 1.74 (95% CI, 1.11-2.73) and 1.96 (95% CI, 1.37-2.80), respectively.[25] As a result, the 2021 guideline claims that for women with vasomotor symptoms who are less than 10 years postmenopause, there is insufficient evidence to advocate any route of administration over another for venous thromboembolism safety. However, for older users or women with additional risk factors, lower dose transdermal estrogen may have safety advantages. More details are provided in Part 1 of this review. The prescription of hormone therapy, with consideration of special circumstances, is outlined in the **Figure**.[26,27]

Premature ovarian insufficiency and menopause

Premature ovarian insufficiency, referred to as "premature ovarian failure" in the 2014 guideline, is defined as the onset of menopause at less than 40 years of age, with serum follicle-stimulating hormone levels greater than 40 international units per litre. It can be attributed to genetic, autoimmune, and iatrogenic causes.[28]

The 2014 guideline had a chapter dedicated to addressing special considerations, including management of women with premature menopause. In the 2021 guideline, recommendations for women with premature ovarian insufficiency are addressed throughout the different sections. However, new data continue to support treatment recommendations made in 2014. Because women with loss of ovarian function have an increased risk of osteoporosis, cardiovascular disease, cognitive impairment, and early mortality, those who are less than 45 years of age should consider undergoing replacement hormone therapy until the average age of menopause.[29-32]

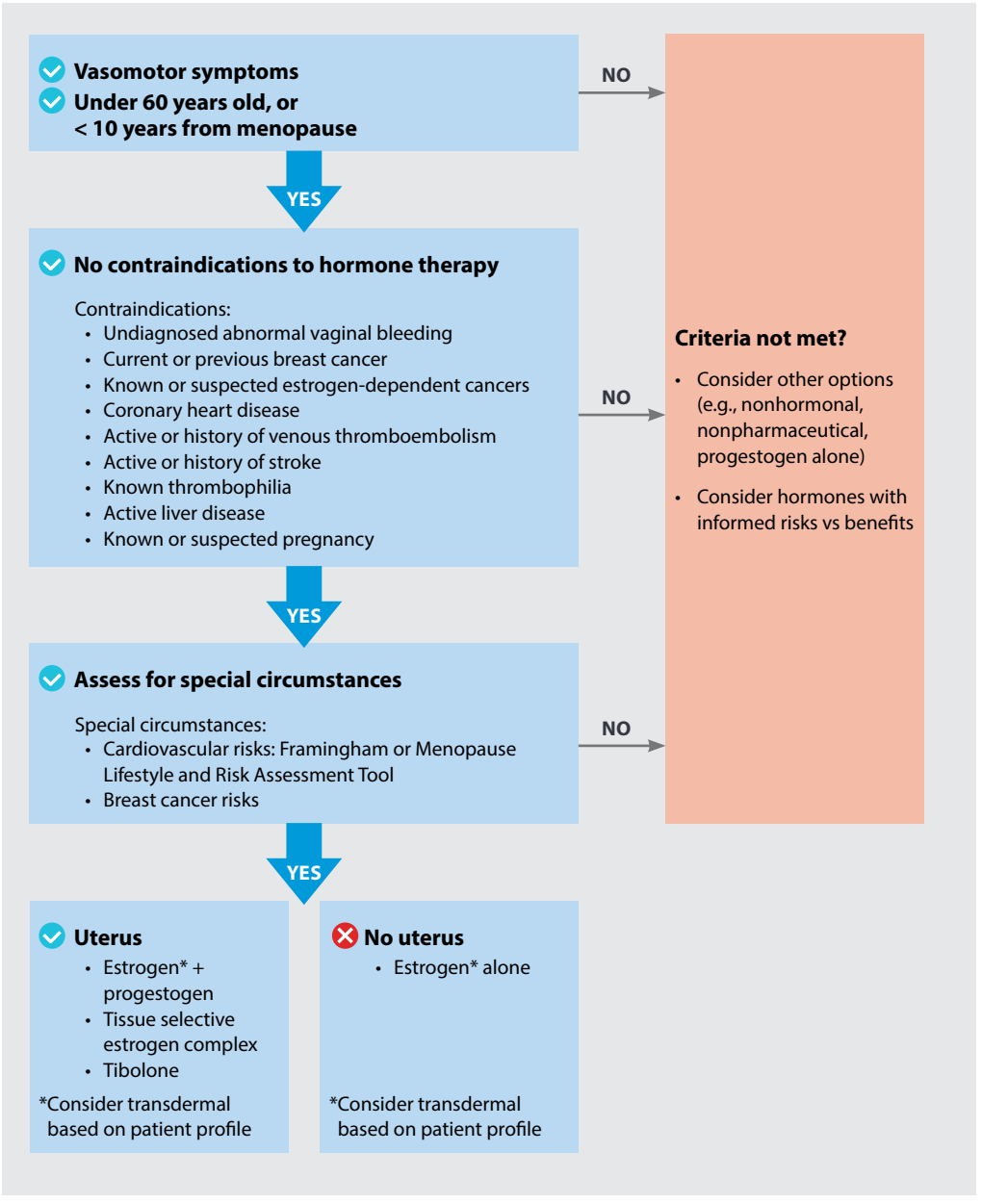

FIGURE. Prescribing menopausal hormone therapy.[26,27]

Summary

Although breast cancer is a common concern for women with vasomotor symptoms, the relative risks of hormone therapy are very low in comparison to women with unmodifiable risk factors such as genetic susceptibility. Estrogen therapy alone is preferred for women who have had a hysterectomy. For those with a personal history of breast cancer, systemic hormone therapy is contraindicated, and nonhormonal alternatives for vasomotor symptoms are available. Cardiovascular disease remains the leading cause of mortality in Canada, and screening and prevention are key. Although hormone therapy is not indicated for primary or secondary prevention of cardiovascular disease in postmenopausal women, it is recommended prophylactically for those with premature ovarian insufficiency to reduce chronic disease risks. ■

Competing interests

Dr Rowe was involved in writing the Society of Obstetricians and Gynaecologists of Canada recommendations and is a past member of the *BCMJ* Editorial Board. He is also a current member of the advisory boards for BioSyent, Lupin Pharma Canada, Pfizer Canada, and Astellas. Dr Dunne was a member of the *BCMJ* Editorial Board when this article was written, and is now the journal's editor, but did not participate in making the publication decision regarding this article.

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