The Effect of Menopausal Hormone Therapies on Breast Cancer: Avoiding the Risk

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KEYWORDS

• Estrogens • Progestogen • Hormone therapy • Breast cancer • Menopause

KEY POINTS

- Menopause is often accompanied by significant symptoms that affect quality of life; concerns over breast cancer risk is the principle reason women may choose to avoid treatment.
- Data from prospective randomized trials confirm an increased risk of breast cancer associated with long term use of combined estrogen and progestin (P) hormone therapy.
- In contrast with the effects of combined estrogen and P, the risk of breast cancer was decreased after use of estrogen in the WHI estrogen alone trial.
- Progestogens, not E, seem to convey the risk of breast cancer; however, estrogen cannot be used alone in a woman with a uterus, given the known risks of long-term exposure.
- The recent addition of bazedoxifene combined with conjugated estrogen provides a progestin-free regimen that can be used in a woman with a uterus.

INTRODUCTION

Menopausal hormone therapy (MHT) is an effective treatment for menopausal symptoms, and based on observational studies demonstrating numerous beneficial effects, was popularized as a first-line approach to menopause management. MHT was found to be very effective in treating vasomotor symptoms and preventing osteoporosis.[1] It was also thought to reduce the risk of coronary heart disease.[1] These findings provided support for broadening the use of MHT in an effort to help prevent age-related deficits associated with loss of sex steroid hormones. Thus, MHT was heralded for use in the prevention of disease in postmenopausal women.[2] Although

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breast cancer has always been a risk associated with MHT, the effects of treatment on other life-threatening diseases, namely cardiovascular disease, were thought to outweigh the risk of breast cancer. However, randomized controlled trials (RCTs) demonstrated that MHT did not afford the positive benefits that had previously been predicted from observational studies.[1] On the contrary, in some instances, it was found to increase the risks for breast cancer, heart disease, and pulmonary embolism.[1] The Women's Health Initiative (WHI) Trial, in its landmark study findings in 2002, reversed many of the perceptions of positive health benefits of MHT that were seen in observational studies.[1,2] Briefly, the WHI hormone trials were RCTs of postmenopausal women aged 50 to 79 (average age, 63) designed to determine whether or not MHT (estrogen only, and estrogen plus progestin combination) prevented cardiovascular disease. A global index was designed to assess the risks and benefits of MHT with respect to coronary heart disease, breast cancer, stroke, pulmonary embolism, endometrial cancer, colorectal cancer, hip fracture, and death by other causes. The WHI trials looked at combination of conjugated equine estrogen (CEE) and medroxyprogesterone acetate (MPA; together referred to as EPT) use in postmenopausal women with an intact uterus, and conjugated estrogen therapy (ET) use in those with prior hysterectomy. In the WHI EPT arm, women were randomized to receive 0.625 mg/d of CEE plus 2.5 mg MPA or placebo, whereas CEE alone was compared with placebo in the ET trial.[1]

Although the WHI trials failed to demonstrate reduction in risk or coronary heart disease with use of MHT, with regard risk to the breast cancer, these trials yielded paradoxic and intriguing data. Long-term use of EPT was associated with an increased risk of breast cancer (hazard ratio [HR], 1.25; 95% CI, 1.07–1.46; $P = .004$)[3]; the risk, however, was reversed in women who had had a hysterectomy and were randomized to estrogen alone (HR, 0.82; 95% CI, 0.65–1.04).[4]

In this review, we specifically focus on the risk of breast cancer associated with MHT. Without the potential to extend life through reduction of cardiovascular disease, a risk/benefit analysis on the use of MHT is rendered substantially less favorable. The risk of breast cancer has become the greatest concern to women considering the use of MHT to avoid hot flashes. Breast cancer is the second leading cause of cancer death in women and the most commonly diagnosed cancer. The risk of a woman in the United States developing breast cancer over her lifetime is approximately 1 in 8. Most women have experienced breast cancer in their lives, either personally or through an afflicted relative or friend. It is thus important to address this prevalent concern and put patient perceived risks in perspective.

MENOPAUSAL HORMONE THERAPY IN CLINICAL TRIALS

Although there are many factors that influence a woman's risk of breast cancer, the role of MHT deserves special consideration. Although the absolute risk of breast cancer associated with use of MHT is quite small, a lack of appreciation of the distinction between absolute and relative risks has influenced both the public and prescribers.

In observational studies, inconsistent effects of estrogen alone or estrogen combined with a progestogen (P) were seen in postmenopausal women. In the largest observational study to date—the Million Women Study—it was found that estrogen plus P treatment increased postmenopausal women's risk of breast cancer; treatment with estrogen alone, as commonly undertaken in women who have had hysterectomies, increased this risk slightly, but far less than seen with combination therapy.[5] Current users of MHT were more likely than never users to develop breast cancer (adjusted relative risk [RR], 1.66; 95% CI, 1.58–1.75; $P<.0001$) and to die from it