Menopause Hormone Therapy Raises Breast Cancer Risk, Study Confirms

A large analysis finds hormone replacement therapy increases the risk about twice as much as previously thought.

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Menopausal hormone therapy (MHT) is associated with a greater increase in the risk of breast cancer than suggested by previous research, according to a recent study of more than 100,000 women. The risk rises with longer hormone therapy use and may last for more than a decade after its discontinuation.

As described in The Lancet, the analysis found that combined estrogen and progesterone MHT raises the risk of breast cancer more than estrogen-only therapy, but topical estrogen products applied in the vagina did not confer any added risk. The absolute increase was small, however. Among 100 women who used combination MHT for five years, two more women developed breast cancer than would be expected among nonusers.

“Our new findings indicate that some increased risk persists even after stopping use of menopausal hormone therapy,” study coauthor Valerie Beral, a cancer epidemiologist at the University of Oxford, said in a press statement. “Previous estimates of risks associated with use of menopausal hormone therapy are approximately doubled by the inclusion of the persistent risk after use of the hormones ceases.”

Breast cancer is classified by the type of receptors it expresses. About 75% of breast tumors are estrogen receptor positive, meaning they carry receptors for estrogen, and the presence of this hormone can spur cancer growth. Treatment for this type of breast cancer typically includes medications that inhibit the production of estrogen or block its activity.

MHT—also known as hormone replacement therapy—is used to relieve menopausal symptoms such as hot flashes and night sweats caused by falling hormone levels. It was once hoped that hormone supplements might also lower the risk of postmenopausal problems such as cardiovascular disease and bone loss (osteoporosis). A combination of estrogen plus progestagen (progesterone or synthetic equivalents) is usually prescribed for women who have not had a hysterectomy (removal of the uterus), as estrogen alone raises the risk of endometrial cancer.

Prior research has shown that MHT is associated with an increased risk for breast cancer. The large

Women's Health Initiative study was halted ahead of schedule in 2002 after it showed that combined estrogen-progesterone therapy actually increased the risk of breast cancer, heart attacks and strokes, although it decreased the risk of hip fractures and colon cancer. However, the absolute likelihood of an individual woman on MHT developing cancer remained small.

These findings led to a steep drop in the use of MHT, which is currently recommended for short-term management of menopause symptoms, not for routine long-term prevention of cardiovascular or bone problems. Nonetheless, an estimated 6 million women in North American still use MHT, and five years of use is common.

The new study, from the Collaborative Group on Hormonal Factors in Breast Cancer, analyzed data from 108,647 women who developed invasive breast cancer in 58 prospective epidemiological studies from around the world conducted between 1992 and 2018. Each woman with breast cancer was matched with up to four cancer-free women of the same age.

Just over half the women (51%) who developed breast cancer had ever used MHT. The average age at menopause was 50, and the average age at the time of cancer diagnosis was 65. Women currently using MHT had done so for 10 years on average, while those who had stopped had done so for an average of seven years.

While 6.3 out of 100 average-weight women, or 6.3%, who never used MHT would be expected to develop breast cancer between ages 50 and 70, the risk rose to 8.3 per 100 women who used estrogen plus daily progestagen (an increase of 2.0%), 7.7 per 100 women who used estrogen plus intermittent progestagen taken 10 to 14 days a month and 6.8 per 100 women who used estrogen alone for five years.

"If these associations are largely causal, then for women of average weight in developed countries, five years of MHT, starting at age 50 years, would increase breast cancer incidence at ages 50 to 69 years by about one in every 50 users of estrogen plus daily progestagen preparations; one in every 70 users of estrogen plus intermittent progestagen preparations; and one in every 200 users of estrogen-only preparations," the study authors wrote.

Looking at the increased risk over 20 years among women who used MHT for five years, the researchers found that about half the excess risk occurred during the five years of actual use and half during the following 15 years after discontinuation. Excess risk was previously thought to fall off soon after stopping hormone therapy. Further, the researchers found that the increased risk was about double for women who used MHT for 10 years rather than five.

Women who used any form of hormone therapy for less than one year—for example, to manage acute symptoms occurring around the time of menopause—had little excess breast cancer risk, according to the researchers. The excess risk became apparent between one and four years of MHT use, with progressively greater risk with longer use. The increase in risk was similar for women who used hormone pills or transdermal patches. However, those who used topical products containing estrogen, such as creams or suppositories, to relieve vaginal dryness did not see an increased risk.

The increase in cancer risk was similar for women who entered menopause and started hormone therapy at ages 40 to 44, 45 to 49, 50 to 54 or 55 to 59.

As expected, hormone therapy use was primarily associated with an increased risk of estrogen receptor-positive breast cancer. Although it is unclear why estrogen plus progestagen MHT would have a greater effect than estrogen-only therapy, “there is no good reason to distrust this statistically reliable finding,” the study authors wrote.

Of note, women who were classified overweight or obese appeared to have less added risk from using combination MHT and none from using estrogen alone. Although ovarian function ceases at menopause, adipose or fat tissue continues to produce some estrogen, the authors explained. In the absence of MHT, postmenopausal women with a higher body mass index (BMI) have a higher breast cancer risk. In fact, in this study, women with a BMI above 30 (the threshold for obesity) who did not use hormone therapy had a higher 20-year breast cancer incidence than women of average weight who used estrogen-only MHT for five years.

“Clinicians must heed the message of this study but also take a rational and comprehensive approach to the management of menopausal symptoms, with careful consideration of the risks and benefits of initiating MHT for each woman,” Joanne Kotsopoulos, MD, of Women’s College Hospital in Toronto, wrote in a commentary accompanying the study. “This might be dependent on severity of the symptoms, contraindications for MHT (i.e., breast cancer, cardiovascular disease and stroke) and BMI, and could take into account patient preference.”

Kotsopoulos added that hormone therapy should be initiated around the time of natural menopause and ideally limited to five years of use."

Experts recommend that women taking menopausal hormone therapy should receive regular mammograms to catch breast cancer at an earlier stage when it is easier to treat.

Click here to read the full study (free).

Click here to read an editorial about the study (free).

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