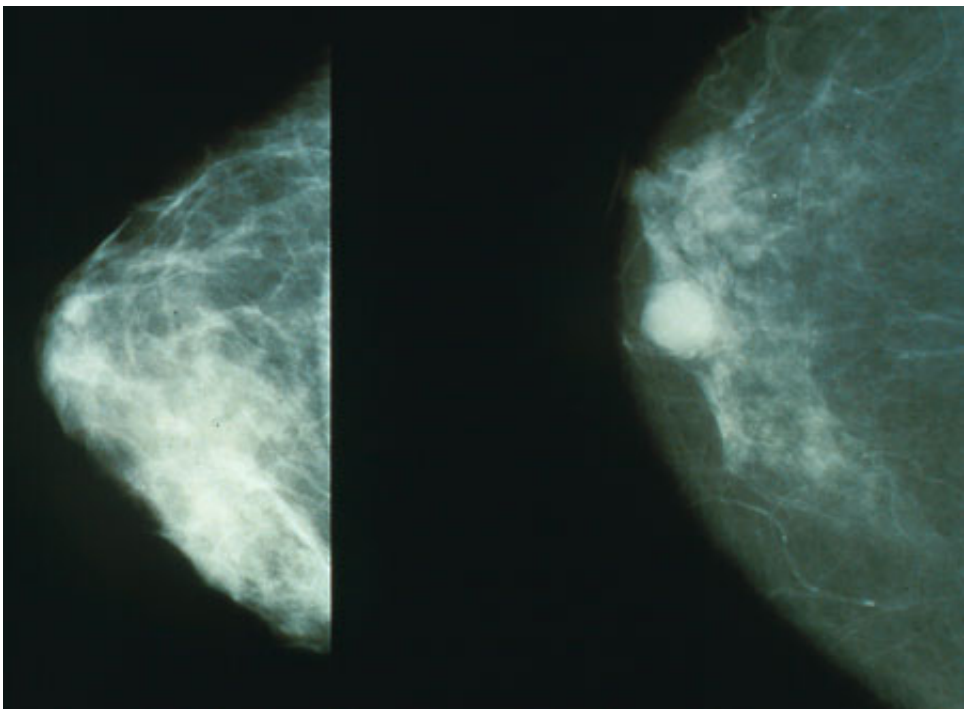
New analyses demonstrate link between different forms of menopausal hormone therapy and breast cancer incidence

August 30 2019



Mammograms showing a normal breast (left) and a breast with cancer (right). Credit: Public Domain

An international collaboration, using data from more than 100,000 women with breast cancer from 58 epidemiological studies worldwide, has found that using MHT is associated with an increased risk of breast cancer, and that some increased risk persists for more than a decade

after use stops.

The findings, published in *The Lancet*, suggest that all types of MHT, except topical vaginal oestrogens, are associated with increased risks of breast cancer, and that the risks are greater for users of oestrogen-progestagen hormone therapy than for oestrogen-only hormone therapy. For oestrogen-progestagen therapy, the risks were greater if the progestagen was included daily rather than intermittently (eg, for 10-14 days per month).

Women tend to begin MHT at around the time of the menopause, when ovarian function ceases, causing oestrogen levels to fall substantially, progesterone levels to fall to near zero, and some women to experience serious hot flushes and discomfort that can be alleviated by MHT. Although regulatory bodies in Europe and the USA recommend MHT be used for the shortest time that is needed, some clinical guidelines recommended less restrictive prescribing.

In Western countries, MHT use increased rapidly during the 1990s, halved abruptly in the early 2000s, then stabilised during the 2010s. Currently, there are about 12 million users in Western countries—about six million in North America and six million in Europe (including one million in the UK). Although some are short-term users, about five years of use is now common, whereas about 10 years of use used to be common.

A previous meta-analysis of the worldwide evidence found that current and recent users of MHT were at an increased risk of breast cancer, but insufficient information was available about the effects of different types of MHT or about long-term risks after MHT use had ceased.

Co-author Professor Valerie Beral from the University of Oxford, UK, says: "Our new findings indicate that some increased risk persists even

after stopping use of menopausal hormone therapy. 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."

In the new study, the authors brought together and re-analysed centrally all the eligible prospective studies from 1992-2018 that had recorded MHT use and then monitored breast cancer incidence, with 108,647 women subsequently developing breast cancer at an average age of 65 years. They looked at the type of MHT last used, duration of use, and time since last use in these women.

Among women who developed breast cancer in the prospective studies, half had used MHT, the average age at menopause was 50 years and the average age at starting MHT was also 50 years. The average duration of use of MHT use was 10 years in current users and seven years in past users.

For women of average weight in Western countries who have never used MHT, the average risk of developing breast cancer over the 20 years from ages 50 to 69 inclusive is about 6.3 per 100 women (ie, about 63 in every 1,000 women who never use MHT develop breast cancer during the 20 years from ages 50 to 69).

The authors estimate that for women with five years use of the three main types of MHT, starting at age 50, the 20-year breast cancer risks from ages 50 to 69 inclusive would increase from 6.3 per 100 in never-users to:

- 8.3 per 100 in users of oestrogen plus daily progestagen (ie, 83 in every 1,000 users would develop breast cancer) - an absolute increase of 2 per 100 users (one in every 50 users);
- 7.7 per 100 in users of oestrogen plus intermittent progestagen

(ie, 77 in every 1,000) - an absolute increase of 1.4 per 100 users (one in every 70 users);
- 6.8 per 100 in users of oestrogen-only (ie, 68 in every 1,000 users) - an absolute increase of 0.5 per 100 users (one in every 200 users).

Increases in breast cancer risk would be about twice as great for women who use MHT for 10 years rather than 5 years (see Figure 7).

The increases in the 20-year risk include the increased risks both during the five years when MHT is being used and during the 15 years after use had stopped. The excess risks during and after MHT use depended on how long MHT had been used for (see Figures 2 and 7—for MHT taken for five years, about half of the excess risk would be during the five years of current use, and the other half would be during the following 15 years after a woman stopped taking MHT). There was little excess risk after using any form of MHT for less than a year.

Co-author Professor Gillian Reeves from the University of Oxford, UK, says: "Use of menopausal hormone therapy for 10 years results in about twice the excess breast cancer risk associated with 5 years of use. But, there appears to be little risk from use of menopausal hormone therapy for less than one year, or from topical use of vaginal oestrogens that are applied locally as creams or pessaries and are not intended to reach the bloodstream."

Overall, MHT use was much more strongly associated with oestrogen-receptor-positive (ER+) breast cancer than with other types of breast cancer (as hormonal factors mainly affect ER+ breast cancer). The increased risk of developing ER+ breast cancer accounted for most of the excess breast cancer risk associated with MHT (see Figure 5).

As menopause usually occurs in women's 40s and 50s, almost all the

evidence was for women who had had their menopause and started MHT in this age range. The proportional increases in risk were similar for women starting MHT at ages 40-44, 45-49, 50-54 and 55-59. The risks appeared, however, to be somewhat attenuated among the few who had started using MHT after age 60 years (see Figure 3). The risks were also attenuated by adiposity (particularly for oestrogen-only MHT, which had little effect in obese women: figures 6-7).

The findings were robust to variations in the analytical methodology used. Nor did they differ by family history of breast cancer, or by any characteristics of the women (other than obesity).

The authors note that a limitation of the currently available epidemiological evidence is that there is still not enough information on women who had used MHT for long periods and had stopped more than 15 years ago. In addition, they did not collect information on breast cancer mortality, although evidence is cited that the results for breast cancer mortality would parallel the results for incidence.

Writing in a linked Comment, Dr. Joanne Kotsopoulos, Women's College Hospital, Canada, notes that it is important to estimate accurately the increased risks of breast cancer from MHT. She says: "Clinicians must heed the message of this study but also to 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. This might be dependent on severity of the symptoms, contraindications for MHT [...], and BMI, and could take into account patient preference."

More information: Type and timing of menopausal hormone therapy and breast cancer risk: individual participant meta-analysis of the worldwide epidemiological evidence, *The Lancet* (2019). DOI: 10.1016/S0140-6736(19)31709-X

Provided by Lancet