PRESS RELEASE

Rock My Menopause – breaking the taboo
New research into link between HRT and breast cancer.

New analyses of the worldwide epidemiological evidence demonstrate link between HRT and breast cancer incidence, and find that some risk persists for many years.

An international collaboration, using data from more than 100,000 women with breast cancer from 58 epidemiological studies worldwide, has found that using menopause hormone therapy (MHT, commonly known as hormone replacement therapy or HRT) 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 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

(i.e., 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 (i.e., 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 (i.e., 77 in every 1,000 users would develop breast cancer) – an absolute increase of 1.4 per 100 users (one in every 70 users);

- 6.8 per 100 in users of oestrogen-only (i.e., 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.

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 – 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 five 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.

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. The risks were also attenuated by adiposity (particularly for oestrogen-only MHT, which had little effect in obese women).

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.”

The Primary Care Women’s Health Forum (PCWHF), Royal College of Obstetricians and Gynaecologists (RCOG), and

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Rock My Menopause is a campaign of the Primary Care Women’s Health Forum, a group of 10,000 healthcare professionals with a special interest in women’s health. We aim to equip people with the information and support they need to become more menopause aware.
British Menopause Society (BMS) have all issued responses to the new researching linking breast cancer to HRT.

The PCWHF said:

"The latest paper in the Lancet on Breast Cancer risks and HRT is from the same group who have published repeatedly on this topic for over 20 years. It should be seen as another piece in the jigsaw rather than changing the picture.

Biological science tells us that most breast cancers are hormone responsive. Epidemiological studies such as this illustrate a population effect. The Lancet paper confirms that vaginal oestrogen does not have an influence but systemic HRT increases breast cancer diagnosis. The size of this effect is linked to duration of use and that a combination HRT including a progestogen has more impact than oestrogen alone. The addition that this paper provides is the suggestion that continuous progestogen is associated with a greater increase than cyclical use. This does not prove that the increase is caused by this factor, there may be other clinical considerations. Older women are more likely to be prescribed continuous combined HRT. It does not provide balance with the endometrial cancers avoided by a continuous regimen.

Healthcare professionals treat people as individuals not populations. Women need accurate and balanced information to understand what it means for them. These breast cancer figures need to be seen in proportion and context.

Women should understand that HRT has no greater effect than the hormones that drive their periods. Breast cancer is more likely to occur as women get older – after menopause. If a woman has an early breast cancer, then exposure to these hormones can increase its rate of growth. The size of this effect varies with the type, dose and duration of the regimen used. Other lifestyle choices will also increase breast cancer growth: two units of alcohol a day have an effect which is comparable to that of standard dose combination HRT. Obesity increases breast cancer growth as well as multiplying many other risks. HRT shows no additional effect on breast cancer in obese women – the influence is already present.

Women need to assess the impact that their symptoms are having on their quality of life. They should consider the effect on their family, their ability to work and the value that relief would represent. They need to understand that while longer duration of hormone exposure might increase breast cancer growth, attendance for screening allows early diagnosis and better treatment outcomes. They need also to factor in the avoidance of fracture, heart attacks, bladder infections and other proven benefits of HRT and make a decision that is appropriate for them and review it annually."

In a joint statement, the RCOG and BMS said:

"A study published in The Lancet shows the risk of breast cancer with hormone replacement therapy (HRT) in relation to the type and timing of hormonal intake.

The overall findings are in keeping with The National Institute for Health and Care Excellence (NICE) guidance on treatment of menopausal symptoms which notes a small increased risk of breast cancer associated with HRT.

The review covered the period January 1992 to January 2018 and included information from 58 studies of 108,647 postmenopausal women who developed breast cancer of which 55,575 (51%) had used HRT.

The report showed an increase in the risk of breast cancer with HRT intake. The risk of breast cancer was noted to be higher with combined estrogen / progesterone compounds, but was also increased, although to a lesser extent, with estrogen only systemic HRT.

The risk of breast cancer remained elevated for more than 10 years after discontinuing HRT and this appeared dependant on the duration of HRT use. Starting HRT between the age of 40 and 50 was also associated with an increased risk of breast cancer, but the number of women in this sub-group was relatively small.

Professor Janice Rymer, Consultant Gynaecologist and Vice President of the Royal College of Obstetricians and Gynaecologists, said:

"Women and doctors should be reassured that the findings of this study do not add anything new in terms of the effects of hormone replacement therapy. Research shows that, for
most women, HRT helps to manage menopausal symptoms and is safe.

"Women must be informed of the small increase in risk of breast cancer so they can weigh these up against the benefits that they may have from taking HRT. Every woman experiences the menopause differently and symptoms vary. These can be extremely debilitating and have a significant impact on a woman’s physical and psychological health, career, social life and relationships. Unfortunately, many women are still suffering in silence and are reluctant to seek advice and support due to concerns around the risks of breast cancer associated with HRT.

"The findings from this research should be helpful to both women and doctors, particularly around when considering whether to start hormone therapy, for how long and which preparation they could take – whether it includes oestrogen and progesterone combined, or oestrogen alone. These findings should not put women off taking HRT if the benefits – such as protection of bones and decrease in cardiovascular risk – outweigh the risks.

"To put the risk into context, a woman has greater risk of developing breast cancer if she is overweight or obese compared to taking HRT. Women must be aware of the effect of obesity and alcohol which increase the risk of breast cancer and modifies the additional risk of HRT."

Mr Haitham Hamoda, Chair of the British Menopause Society, said:

"We welcome this further data on the incidence of breast cancer which will help us counsel our patients and women in general better. This paper provides further data on the impact of estrogen and progesterone combined and estrogen that adds more detail to that we have already gathered from overall assessment of the literature. It also includes some new information on different types of progestogen that surprisingly were found to not vary as much as had been thought.

"Of particular interest though is the impact of estrogen, and different regimens of combined HRT on obese women, where the former is found to have little effect but the increase with the latter is greatest with continuous combined HRT.

However, in practice this must be weighed against the rapidly rising incidence of endometrial cancer which is significantly decreased by the continuous combined preparations.

"The overall findings from this study are in keeping with the NICE menopause guideline recommendations which show a small increase in risk of breast cancer with HRT. Women must be informed of the data on breast cancer risk with HRT to help them make an informed decision. This should also be considered in comparison to the risk of breast cancer with other lifestyle factors such as alcohol intake and obesity which have been shown to be associated with a higher risk compared to that with HRT. This should also be taken in the context of the overall benefits obtained from using HRT including symptom control and improving quality of life as well as considering the bone and cardiovascular benefits associated with HRT use."

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