The International Menopause Society comment on:

"Type and timing of menopausal hormone therapy and breast cancer risk: individual participant meta-analysis of the worldwide epidemiological evidence."
Collaborative Group on Hormonal Factors in Breast Cancer.
The Lancet 29th August 2019

Is there new information that menopausal hormone therapy (MHT) substantially increases breast cancer risk as suggested by a paper published in the Lancet this month (1) and should women be worried?

- Much of the information regarding breast cancer risk and MHT reported in this paper is not new, although findings in relation to estrogen-only therapy do differ from those reported in the Women's Health Initiative randomised trial. It is important to note that, because of when the data included in this report was collected, most of the MHT regimens were different from those currently recommended.
- This paper provides an important public health message about obesity and breast cancer risk.
- The reported effects of MHT for women who go through early menopause (before the age of 45 years) must be seen in the context of what is "normal" for women of this age.
- Potential breast cancer risk is one component of the benefit : risk analysis of MHT use for an individual woman which needs to include symptom severity and the potential beneficial effects of MHT on bone and cardiovascular health.

The Women's Health Initiative randomised clinical trials contributed substantially to our understanding of the benefits and risks of MHT. This new paper primarily reports the findings from large observational studies to which women were recruited and followed for several years. In these studies the use of MHT, including dose and formulation, was a personal choice, as opposed to randomised controlled trials where women have been randomly allocated to MHT or placebo. Women who developed breast cancer (cases) were identified in the large prospective cohort studies and then matched with multiple controls per case. The authors have tried to minimise bias in their analyses, but it is important to recognise that observational studies include unquantifiable confounding effects, for which corrections cannot be made, and so as in all studies, there are limitations.

The paper reports slightly larger risks for estrogen+progestogen therapy compared with the findings of the randomised clinical trials they have listed in their paper (1). A smaller, but statistically significant, risk of breast cancer is also reported for estrogen-only use, whereas the randomised trials did not report an increase in breast cancer risk with estrogen-only therapy.

It is extremely important to note that this paper does not inform us of the impact of current recommended MHT prescribing practices on breast cancer risk.

The median year of diagnosis of breast cancer cases from North America (25% of the included data) was 1999, and for the European studies, 2007, with one as early as 1981. With an average use of 10 years of MHT in current users at diagnosis, and 7 years in past users, much of the exposure to MHT preceded the first publication of the Women's Health Initiative study, after which prescribing practices changed substantially. Consequently, virtually all of the included information pertains to MHT formulations and doses known to have adverse breast effects that are no longer recommended. Specifically, the use of the progestogens medroxyprogesterone acetate and norethisterone (norethindrone) is now discouraged because of their known adverse effects, but these account for nearly all of the data for combined estrogen-progestogen therapy included in the paper. The one analysis of data from prospective studies of the effects of different progestogens provides inadequate data to draw conclusions about the effects of the preferred progestogens, progesterone (50 included cases) and dydrogesterone (253 included cases). Additionally, the majority of cases were women who took oral estrogen, which results in high blood levels of the hormone estrone, whereas transdermal therapy does not (2). Estrone is not only the main estrogen produced by postmenopausal women, but levels are higher in overweight/obese women, such that estrone may be a key factor linking obesity with breast cancer.

A take home message of this paper should be that obesity is an important risk factor for breast cancer

The authors estimated that from the age of 50 years, the increase in breast cancer risk with obesity did not differ substantially from the estimated impact of estrogen-only MHT on breast cancer risk [20 year risk of breast cancer 7.4% for estrogen-only, 6.3% for overweight women not using MHT and 7.2% for obese women not using MHT]. The increase in breast cancer risk with estrogen-progestogen therapy was 9-10%.

If obesity was a drug, we would be recommending people did not use it.

Considering the high proportion of women over 50 who are overweight or obese, and the progressive increase in we are seeing in the prevalence of obesity, this is an important public health message.

Research findings in context for women experiencing early /premature menopause

A particular concern about the possible interpretation of the findings of this paper pertains the analysis to women who commenced MHT before the age of 45 years.

10% of women experience menopause before 45 years. However the "norm" for women younger than 45 is to be premenopausal. In this study MHT users younger than 45 years were compared with postmenopausal women younger than 45 years not using MHT, whereas in terms of breast cancer risk, the clinically meaningful comparator would be age-matched premenopausal women.

As the authors of this paper have previously reported, women who become postmenopausal before the age of 45 years have a 30% lower risk of breast cancer compared with women who remain premenopausal until the age of 45 years (3). In the current paper the authors report that young postmenopausal women who use MHT have an increase in breast cancer risk compared with young postmenopausal women who are not using MHT. But what they fail to highlight is that for young women, MHT restores their breast cancer risk to approximately what it would have been if they had not gone through an early menopause. This is extremely important as menopause before the age of 45 years is associated with a greater risk of premature death from all causes, including premature death from cardiovascular disease (4), as well as substantially greater risk of osteoporosis and fragility fracture in later life. Therefore early/premature menopause is a relative hormone deficiency state, and in these young women, MHT is a hormone restorative therapy.

The average age of menopause is 51.5 years, with most women experiencing menopause between the ages of 45 and 55 years. Women aged 45-54 years who are premenopausal are at greater risk of breast cancer than age-matched counterparts who have become postmenopausal (RR at age 45–54 years 1·43, 1·33–1·52, $p<0·001$). However, for women in this age group who have become postmenopausal, MHT also restores (reduces) the risks of conditions such as bone loss, diabetes and cardiovascular disease to those of women of the same age who are still premenopausal. If one then takes into account relief of vasomotor symptoms, there is much to be considered in weighing up the benefit-to-risk ratio for an individual woman.

Recommendations from the IMS

Women enter menopause across a range of ages, with diverse symptoms and health risk profiles.
The International Menopause Society advocates the comprehensive assessment of women, including attention to modifying risk factors for chronic disease such as being overweight or obese, the importance of which have been highlighted in this Lancet paper. The benefits and risks of MHT differ according to the timing of menopause such that individualisation of therapy is essential. As prescribing practices have changed significantly over the last decade, further research is needed to determine the impact of currently recommended regimens.

References

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