Menopausal hormone therapy and ovarian cancer

Key Words

A recent meta-analysis of epidemiological studies of the relationship between menopausal hormone therapy (MHT) and the risk of ovarian cancer published in Lancet Oncology has reported an increased risk of epithelial ovarian cancer among the users of MHT compared with controls.[1]

Individual data sets from 52 epidemiological studies were identified and analyzed centrally. Prospective and retrospective studies were examined separately. The principal analysis involved only prospective studies with MHT use extrapolated forward for up to 4 years.

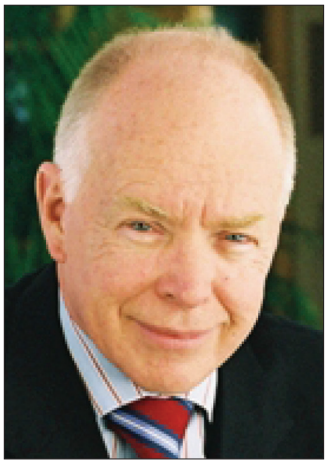
Retrospective studies were included in the sensitivity analyses. Adjusted Poisson regressions produced relative risks (RRs) compared to never users.

During prospective follow-up, 12,110 postmenopausal women, 55% (6601) of whom had used MHT, developed ovarian cancer. Among women who were last recorded as current users, risk of ovarian cancer was increased, irrespective of the duration of use (RR: 1.43, 95% confidence interval [CI]: 1.31-1.56). When current or recent users of MHT were considered (any duration of use but stopped <5 years before the diagnosis), the risk remained elevated (RR: 1.37, 95%CI: 1.29-1.46). Overall, this increased risk was similar for European and North American prospective studies and for both estrogen only and estrogen plus progestogen preparations but differed across the subtypes of epithelial ovarian cancers, being increased only in serous and endometrioid subtypes and decreased in mucinous and clear cell subtypes.

While the risk of ovarian cancer was increased in the prospective studies, it was not increased in the retrospective studies. Increased risk persisted after stopping the treatment for some years among women who had used MHT for more than 5 years.

There was neither effect of dose or duration of MHT use nor was the risk different for estrogen only therapy when compared to estrogen plus progestogen therapy. The authors estimated the absolute increased risk of ovarian cancer for the users of MHT to be 1 extra case per 1000 women after 5 years of use.

The method used to calculate absolute risk was complicated and included the assumptions of events in later life. The estimated absolute risk of ovarian cancer associated with 5 years of MHT use starting at age 50 was calculated as 1/1000 women after 5 years of MHT use.



Rodney John Baber

However, ovarian cancer risk increases with age and in women most likely to use MHT (50-54), the change from the baseline risk of 1.2/1000 per 5 years (1.2 × 1.37) gives rise to an incidence of 1.64/1000 women per 5 years. This is an absolute excess of only 0.44/1000 women per 5 years. Similar calculations for women aged 55-59 results in an excess of only 0.78/1000 women per 5 years. The absolute risk, therefore, appears to lie closer to 1/2000 women over 5 years.

Epithelial ovarian cancer constitutes a heterogeneous collection of subtypes, the most common being serous, endometrioid, mucinous, and clear cell carcinomas. Ovarian cancer is the 7th most common female cancer worldwide and the 8th most common cause of cancer death. It is thought that over 90% of ovarian cancer has its origin in the epithelial cells of the fallopian tubes.

Risk factors for ovarian cancer include age, family history, obesity, cigarette smoking, endometriosis, nulliparity, a greater number of lifetime ovulations, Lynch syndrome, and mutations of the BRCA genes. Whereas the lifetime risk of ovarian cancer is around 1.5% overall, for women with Lynch syndrome this risk is approximately 12%, and up to 40% for women with specific BRCA gene mutations. There are also regional and ethnic differences with ovarian cancer, most common among nonhispanic white women followed by Hispanic, African and Asian women in that order.[2]

Factors associated with a reduced risk of ovarian cancer include increasing parity, breastfeeding, fewer lifetime ovulations, the combined oral contraceptive pill, tubal ligation, and hysterectomy. The incidence has not changed over the past 30 years.

An effect of MHT on ovarian cancer risk has not been clearly established with previous studies providing inconsistent results and varying effects on the different subtypes of ovarian cancer.

The first observational study to investigate a possible link between MHT and ovarian cancer was conducted on a cohort of 4544 British women.[3] Mean duration of use was 5.6 years and no increased risk was detected. In 1998, the first meta-analysis of nine studies[4] found no increase in risk overall, although with use over 10 years, an increased risk just failed to achieve statistical significance (RR: 1.27, 95%CI: 1.00-1.61). In 2002, a Swedish case-control study[5] of 1205 cases and 3899 controls reported an increased risk of ovarian cancer for the users of estrogen only (RR: 1.43, 95%CI: 1.02-2.00) and sequential combined MHT (RR: 1.54, 95% CI: 1.15-2.05) with use longer than 10 years but not for continuous combined MHT.

A 2006 analysis of a cohort of US women[6] found an increased risk of ovarian cancer with use longer than 10 years. The risk was greatest among estrogen only users and sequential E+P users but was not increased in women who had undergone hysterectomy.

By far the two largest previous studies examining the relationship between MHT and ovarian cancer are The Million Women Study[7] and The Danish Sex Hormone Registry Study.[8]

The Danish prospective cohort study identified 2681 women with epithelial ovarian cancer and found an increased risk for the users of MHT (RR: 1.40, 95% CI: 1.30-1.58). Risk was not affected by the type of MHT or the duration of use and remained elevated for 2 years after ceasing therapy. No data was available for age at menopause, body mass index (BMI), family history, or the use of oral contraceptives. In the Million Women study,[7] 2273 ovarian cancers were identified. For the users of MHT, the risk was increased (RR: 1.20, 95%CI: 1.09-1.32). The risk was not affected by type or dose of MHT but was affected by the duration of use, there being no significant increase in risk until use exceeded 5 years. Past users were not at increased risk. The risk was increased for serous tumors but not for endometrioid, mucinous, or clear cell subtypes.

One large, prospective, randomized placebo-controlled trial has examined the link between MHT use and the risk of ovarian cancer.[9] After 5.6 years follow-up of 16,608 women in The Women's Health Initiative Clinical Trial, the risk was not significantly increased (RR: 1.58, 95% CI: 0.77-3.24).

WHERE DOES THIS LEAVE US?

It is clear from the data discussed above and from the recent meta-analysis[1] that when considering a possible link between MHT and risk of ovarian cancer, there remain a number of inconsistencies. To confidently attribute cause and effect for a risk as small as that suggested for MHT on ovarian cancer is testing the limits of meta-analysis and would require complete data. Unfortunately, despite the best efforts of the investigators, in this meta-analysis the data were incomplete. Two studies, The Million Women Study[7] and The Danish Sex Hormones Register Study[8] contributed 76% of the prospective data and one of these provided no information at all on oral contraceptive use, BMI, family history, neither age at menopause nor on women younger than 55, and the age group most likely to use MHT. All hysterectomized women <55 were excluded from the analyses and no information was available regarding an indication for the surgery. As estrogen only therapy is only prescribed for hysterectomized women, it is difficult to see how the investigators accurately calculated a risk for estrogen only therapy in the under 55 cohort. Data on the removal of fallopian tubes among women undergoing hysterectomy were unavailable.

It is also quite unusual to see a lower risk from retrospective, case- control studies, which usually amplify the risk. It is also unusual not to see an effect if the duration of therapy such as had been reported in some earlier studies. This may be a sign of possible detection bias.

In addition, not all confounders were identified or considered which may have affected final results. In a sub-analysis of the 17% of women for whom appropriate details were available, it was surprising to see no effect for commonly known risk factors for ovarian cancer.

Finally, the issue of detection bias (women receiving treatment are more likely to have had examinations and investigations than those not) was not considered.

Receptors for estradiol may be found on epithelial ovarian cancer cells thus providing some biological plausibility for a link between MHT and ovarian cancer. However the failure of this meta-analysis and earlier epidemiological studies to find any association between dose or duration of MHT and change in risk, argues against cause and effect, as does the overall inconsistency of effect on the different subtypes of epithelial ovarian cancer.

A number of established risk factors for ovarian cancer suggest that rather than estrogen itself being a risk factor, it may be more frequent ovulation, which is the culprit. Factors such as increased parity, breastfeeding, and the combined oral contraceptive all lead to less frequent ovulations and are also associated with a reduced lifetime risk of ovarian cancer. In support of this proposition, a recent study in poultry found that hens bred to lay eggs daily had a greater risk of ovarian cancer than hens, which did not, a finding possibly linked to the overexpression of oviduct-related genes.

This new meta-analysis has been a brave attempt to bring some clarity to the vexed question of whether or not there is an association between MHT use and the risk of ovarian cancer. That it has not succeeded, should not be seen as a failure but, rather, as an acknowledgment that the instruments used are not powerful enough to measure any possible tiny change in the risk of a rare condition.

What does this new study mean for women? It does not mean women should stop taking MHT. Rather, it is a reminder that the principal reason for taking MHT is the alleviation of troublesome menopausal symptoms. Considerations such as quality of life, protection against osteoporosis and cardiovascular disease, and risk of breast cancer far outweigh any risk of ovarian cancer and each individual woman should evaluate her own individual risk: benefit profile in consultation with her personal physician before deciding whether starting or continuing MHT, is the right choice for her.

The link between MHT and ovarian cancer remains unproven and consequently there should be no need for any change in clinical practice.

PRACTICE POINTS

- The link between MHT and ovarian cancer remains unproven.
- The principal indication for MHT use is alleviation of menopausal symptoms.
- Each woman should discuss her own individual risk factors before commencing or continuing MHT.
- Current evidence regarding MHT and ovarian cancer risk does not suggest a need for any change in clinical practice.

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Conflicts of interest
There are no conflicts of interest.

Prof. Rod Baber

Professor of Obstetrics and Gynaecology,
The University of Sydney, NSW, Australia
E-mail: Rodney.baber@sydney.edu.au

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