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Hormone Replacement Therapy May Increase Ovarian Cancer Risk

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February 13, 2015

Hormone replacement therapy (HRT) was significantly associated with an increased risk for ovarian cancer in postmenopausal women, according to an extensive meta-analysis from the Collaborative Group on Epidemiological Studies of Ovarian Cancer.

"The findings that ovarian cancer risk is greatest in current users of hormone therapy, falls after use ceases, and varies by tumour type, strongly suggest a causal relationship," the researchers write. They project that if the association is causal, one additional ovarian cancer will occur for every 1000 users among women who take HRT for 5 years, starting near age 50 years, and one extra ovarian cancer death will happen for every 1700 users.

In the United States and the United Kingdom, 6 million women take HRT, and a similar number do so in other nations. HRT guidelines from the World Health Organization, European Union, and United States do not cite a link to elevated risk for ovarian cancer. UK guidelines state that ovarian cancer risk may rise with long-term use.

Most studies that have examined a possible link between HRT for and ovarian cancer risk have been small and/or retrospective and many remain unpublished. Therefore, to access sufficient numbers to test an association while controlling for recall bias, the authors of the current study analyzed published and unpublished individual participant data collected since 1998. They report the results of their analysis in an article published online February 13 in the *Lancet*.

The primary analysis included prospective studies that recorded how recent HRT use was and how long women took hormones, up to 4 years after cessation of the therapy. For sensitivity analyses, the reserachers considered both prospective and retrospective studies.

The team included 52 of the 58 epidemiological studies identified, including 17 prospective and 35 retrospective studies. Case participantspatients were postmenopausal women with ovarian cancer, and control patientparticipants were postmenopausal women without cancer who still had their ovaries. Participants were matched for study, age group, and body mass index and were adjusted for parity, use of oral contraceptives, and age at menopause.

Overall, the meta-analysis included information on 21,488 postmenopausal women with ovarian cancer.

Of the cases, 12,110 were from prospective studies and 6601 (55%) of them had had HRT, for a median duration of 6 years, with a mean diagnosis year of 2001. Only 2702 (29%) of the

case participants in the retrospective studies had used HRT, with median duration of 4 years, and a mean year of diagnosis was 1992.

The researchers found that women who use HRT, even for a short duration, were approximately 20% more likely to have developed ovarian cancer than women who never used HRT (relative risk [RR] 1.20 [95% confidence interval (CI), 1.15 - 1.26; $P < .0001$] for prospective studies; RR, 1.14 [95% CI, 1.10 - 1.19; $P < .0001$] for all studies).

The more recent the therapy, the greater the risk. In the prospective studies, the risk was greatest among women who were taking HRT when last asked (RR, 1.41; 95% CI, 1.32 - 1.50; $P < .0001$). This elevation in risk held even among women who had been using HRT for less than 5 years at the time of their diagnosis (median duration 3 years; RR, 1.43; 95% CI, 1.31 - 1.56; $P < .0001$).

Women who had stopped HRT recently but were within 5 years of last use at the time of their cancer diagnoses had a 23% increased relative risk (95% CI, 1.09 - 1.37; $P = .0006$).

The longer the time since last use of HRT, the lower the cancer risk, although having used HRT for at least 5 years (median duration 9 years) was still associated with 10% increased relative risk more than 5 years later (median time since last use 10 years; RR, 1.10; 95% CI, 1.01 - 1.20; $P = .02$). The sensitivity analyses were consistent with the results from prospective studies.

Elevated risk was seen for the more prevalent serous and endometrioid ovarian cancers compared with the rarer mucinous and clear cell ovarian cancers. This specificity for cancer subtype supports causality, the researchers write.

The increased risk for ovarian cancer corresponded to both estrogen-only HRT and estrogen-progestogen combinations.

Alcohol use, smoking, body size, oral contraceptive use, age of HRT start, hysterectomy, and family history of breast or ovarian cancer did not account for the increased risk.

A limitation of the study is that it did not assess dose, which might be an important consideration because lowest dose is advised, write Nicolas Wentzensen, MD, PhD, and Britton Trabert, PhD, from the Division of Cancer Epidemiology and Genetics at the National Cancer Institute in Bethesda, Maryland, in an accompanying comment.

Dr Wentzensen and Dr Trabert review the association between estrogen use and endometrial cancer and increase in breast cancer risk with estrogen-progestogen use. Dr Wentzensen and Dr Trabert point out that regulatory decisions concerning HRT and cancer were based largely on the Women's Health Initiative trial, which did not consider ovarian cancer, and that observational studies considering ovarian cancer suggested increased risk associated with long-term HRT.

The findings of the meta-analysis "support the addition of ovarian cancer

to the list of adverse effects associated with hormone therapy use," Dr Wentzensen and Dr Trabert write. However, they caution that the results might not strongly influence risk assessment for ovarian cancer because the cancer is much rarer than breast cancer. Avoidance

of HRT could reduce ovarian cancer mortality because of the effect on the serous subtype, they conclude.

The authors and commentators have disclosed no relevant financial relationships.

Lancet. Published online February 13, 2015.

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Cite this article: Hormone Replacement Therapy May Increase Ovarian Cancer Risk. *Medscape*. Feb 13, 2015.