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Hormone therapy and ovarian cancer

In a nationwide prospective cohort study of Danish women who turned 50 years old between 1995 and 2002 [1], 909,946 women were eventually included in the analysis; 575,883 were never-users of HRT and 334,063 were ever-users. During an average follow-up of 8 years, there were 3068 ovarian cancers of which 2681 were epithelial tumors.
Ever-use of HRT was associated with an increased risk of ovarian cancer of 1.38 (95% confidence interval (CI) 1.26–1.51). The risk declined with years since last use and had disappeared after 2 years. The risk of epithelial ovarian cancer was 1.44 (95% CI 1.30–1.58). There was no significant difference between risk for users of estrogen-only therapy compared with combined estrogen plus progestin therapy and there was no significant difference in risk between those taking continuous or cyclic progestin. There was a non-significant trend to a lesser risk for women using transdermal estrogen compared to oral estrogen; however, the trend was reversed for transdermal compared to oral estrogen plus progestin therapy. There was no effect of dose or duration of therapy and no effect of age. The estimated absolute increase in risk of ovarian cancer for users of hormone replacement therapy (HRT) was 0.52 per 1000 woman-years compared to 0.40 per 1000 woman-years for non-users. This equates to one extra case per approximately every 8300 women taking HRT.

Comment

This large and interesting study maintains the uncertainty surrounding HRT and ovarian cancer risk. It finds no association between risk and either dose or duration of therapy, whilst cessation of therapy led to a rapid reduction in risk and indeed an apparent protective effect against ovarian cancer when users had ceased therapy for more than 6 years (relative risk (RR) 0.63; 95% CI 0.41–0.96).
Such rapid rises and falls cannot be attributed to a carcinogenic action of HRT and a promoter effect that is neither time- nor dose-dependent requires an inventive biological mind. Furthermore, time trends for risk, provided in the paper, are also inconsistent with an increasing risk with time for estrogen-only therapy, a decrease in time for cyclic combined therapy users and a decrease followed by an increase over 7 years for continuous combined therapy users.
Previous observational papers have similarly reported conflicting results, with several reporting a greater risk for estrogen-only therapy and a lesser or zero effect for estrogen plus progestin, whilst others do not. Most previous studies have shown a duration effect, with risk of ovarian cancer not raised before 4–5 years, but this too has been inconsistent.
The Women's Health Initiative randomized clinical trial [2] reported 32 cases of ovarian cancer in 16,608 women during a 5.2-year follow-up and suggested a trend towards an increase in risk of ovarian cancer amongst users of estrogen plus progestin therapy, but this trend did not achieve statistical significance (RR 1.58; 95% CI 0.77–3.24). Consistent with its previous record of over-estimation, the Million Women Study [3] estimated that the risk of ovarian cancer was 1 per 2500 hormone users compared to this more modest estimate from the present paper of 1 per 8300.
The strengths of this study are its size, the completeness of the records and careful statistical analysis. The weaknesses of this study are that, although large, it is a cohort study and subject to confounding biases. For example, there was no correction for age at menopause or for previous use of combined oral contraceptives, there was incomplete information about surgical procedures among older women, and no account was taken of the frequency of

clinical examinations of women in this study. Women using HRT are more likely to have regular pelvic examinations and ultrasound than non-HRT users and, as such examinations are the commonest means of diagnosing ovarian cancer, failure to have matching frequency of examination and thus detection bias could clearly confound the findings.

In conclusion, this interesting study does not really add anything new to our knowledge of HRT use and risk of ovarian cancer except to emphasize that any possible increase in risk is slight (1 in 8300).

The fact that previous individual studies, review articles and meta-analyses [4–6] have been inconsistent in their attribution of risk to estrogen or estrogen plus progestin therapy, to dose, mode of administration or length of therapy only serves to illustrate that observational studies, no matter how large, struggle to attribute actual risk when that risk is as small as is estimated here.

This information should not discourage clinicians from prescribing HRT in an appropriate way for relief of menopausal symptoms but reminds us all that a proper explanation of risks and benefits of therapy for each patient is essential.

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