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Risk of breast cancer in users of combined oestrogen-progestogen HRT compared with users of oestrogen alone

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Keywords

Hormone replacement therapy, oestrogen, oestrogen-progestogen, breast cancer

Introduction

Whilst it is clear that women using menopausal hormone replacement therapy (HRT) are at an increased risk of breast cancer, it is uncertain whether combined oestrogen-progestogen preparations increase risk beyond that associated with oestrogen alone.

Aims

To determine whether the risk of breast cancer in users of combined oestrogen-progestogen HRT is greater than that in users of oestrogen alone.

Comments

Recent results have suggested that the addition of progestogen might augment the effect of menopausal oestrogen therapy in increasing the risk of breast cancer. Up until relatively recently the bulk of menopausal hormone therapy use, particularly in the US, has been in the form of oestrogen alone, and data on the effects of combined oestrogen-progestogen preparations has therefore been limited. This study shows that in recent hormone users, the use of combined oestrogen-progestogen increases the risk of breast cancer above and beyond that associated with the use of oestrogen alone. The study could be criticised for including women with an unknown age at menopause and for combining invasive and non-invasive tumours. However, given the context of two other studies (Magnusson *et al*: Breast cancer risk following long-term oestrogen and oestrogen-progestin-replacement therapy. *Int J Cancer* 1999;**81**:339-344 [Abstract]; Colditz GA, Rosner B, for the Nurses Health Study Research Group: Use of estrogen plus progestin is associated with a greater increase in breast cancer risk than estrogen alone. *Am J Epidemiol* 1998, **147**[suppl]: 64S) also showing a significantly greater effect of combined oestrogen-progestogen therapy on breast cancer risk, compared with oestrogen alone, these results should be taken seriously. While more data are needed before firm conclusions can be reached, a disconcerting picture is emerging: for women with a uterus, longer term menopausal therapy with

oestrogen alone is accompanied by a substantial increase in the risk of endometrial cancer, and combined oestrogen-progestogen therapy is accompanied by a risk of breast cancer which is larger than previously thought.

Methods

A total of 46,355 women participating in the Breast Cancer Demonstration Detection Project (a US breast cancer screening programme) between 1973 and 1980 were recruited into a cohort study. Data were collected using telephone interviews and subsequent mailings of self-administered questionnaires in 1987-89 and 1993-95. The outcome of incident breast cancer was based on self-reporting or death certificate information. The risk of breast cancer in exclusive users of oestrogen-progestogen was compared to that in exclusive users of oestrogen alone, adjusting for age, age at menopause, education, mammographic screening and body mass index, although participants with an unknown age at menopause were included in most of the analyses.

Results

The mean duration of follow-up was 10.2 years and 473,687 person-years were accumulated. The mean age at commencement of follow-up was 58 years. During follow-up, 2082 cases of breast cancer were reported and pathology results were obtained for 1713 (82%); 1456 (85%) of these tumours were invasive. Compared to the risk for women who had never used HRT, the risk of breast cancer was elevated in women who had used oestrogen alone and oestrogen-progestogen within the previous four years (relative risk, 1.2 [95% confidence interval {CI} = 1.0-1.4] and 1.4 [95% CI = 1.1-1.8], respectively). The relative risk of breast cancer increased by 0.01 (95% CI = 0.002-0.03) for each year of oestrogen only use and by 0.08 (95% CI = 0.02-0.16), with each year of oestrogen-progestogen use among recent users, adjusted for age, education, age at menopause, body mass index, and mammographic screening. The test for heterogeneity between these estimates was statistically significant ($P = 0.02$). When women with an unknown age at menopause were excluded, the estimate for recent users for the increase in risk of breast cancer was 0.02 (95% CI = 0.002-0.04) in users of oestrogen alone and 0.06 (95% CI = -0.002 to 0.15) in users of oestrogen-progestogen, per year of use. The test for heterogeneity was no longer significant ($P = 0.23$).

The increase in risk with use of HRT was confined to women with a body mass index of 24.4 kg/m^2 or less; no increase in risk of breast cancer with use of oestrogen alone or oestrogen-progestogen combinations was evident in heavier women.

Discussion

Use of combined oestrogen-progestogen menopausal hormone therapy increases the risk of breast cancer to a greater extent than use of oestrogen alone. In keeping with other studies of HRT in general, this increase in risk is confined to recent or current users and is evident in lean but not heavier women. The association between HRT use and breast cancer risk was still seen when analyses were restricted to women who had undergone annual mammographic screening, suggesting that detection bias is unlikely to explain the relationship.

The exclusion of women with an unknown age at menopause (which represented about 20% of the data) did not change substantially the magnitude of the associations between oestrogen alone and oestrogen-progestogen therapy and breast cancer risk, although the loss of power meant that results were no longer statistically significant. Age at menopause was not considered a substantial confounder in these data. The study design meant that for some women, information on hormone use was reported on after the diagnosis of breast cancer. However, recall bias is unlikely to have materially affected results.

Additional information

An editorial accompanies this paper (Willett WC *et al*: Postmenopausal estrogens-opposed, unopposed, or none of the above. *JAMA* 2000,**283**:534-535).

References

1. Schairer C, Lubin J, Troisi R, Sturgeon S, Brinton L, Hoover R: Menopausal estrogen and estrogen-progestin replacement therapy and breast cancer risk. JAMA. 2000, 283: 485-491.