

# RAPID APPRAISAL

**Name of Trial:** Ovarian cancer and hormone replacement therapy in the Million Women Study.

**Reference:** Lancet 2007; published online April 19. DOI:10.1016/S0140-6736(07)60534-0.

**Question:** Does hormone replacement therapy (HRT) increase the risk of ovarian cancer?

**Summary:** This study shows that the use of HRT for more than five years is associated with small increases in the risks of developing and dying from ovarian cancer. However, no residual risk was associated with women who had taken HRT in the past or for those who took HRT for less than five years. The associated risks of ovarian cancer and HRT should not be viewed in isolation. HRT remains an effective therapy for the short-term relief of menopausal symptoms in the majority of women but the minimum effective dose should be used for the shortest duration possible. Women who wish to start HRT should discuss the known risks and benefits of treatment with their doctor. Those currently on HRT should have regular health check-ups and their need to continue HRT should be re-assessed at least annually.

### ***Did the study ask a clearly focussed question?***

**Yes** - This study was designed to evaluate the effect of hormone replacement therapy (HRT) on women's risks of developing and dying from ovarian cancer.<sup>1</sup> The primary outcomes were the relative risk of incidence and death from ovarian cancer, adjusted for age, hysterectomy status, social, demographic and lifestyle factors.

### ***Was the study design appropriate?***

**Yes** - This study used data from the Million Women Study, a large population-based prospective cohort study of UK women aged 50 to 64 years investigating the relationship between the use of HRT and the risks of various conditions, particularly breast cancer.<sup>2</sup> Information on HRT use and social and demographic factors were obtained at recruitment using a questionnaire. Questions about the use of HRT included: ever, current, and past usage; age at first and last use; total duration of use; and the name and duration of the proprietary preparation last used. Of the 1.3 million women who completed the first questionnaire, 948,576 postmenopausal women who did not have previous cancer (except non-melanoma skin cancer), or bilateral oophorectomy, and for whom data on use of HRT were available were included in this analysis. A second questionnaire was sent to participants about three years after recruitment to update information on use of HRT and other factors. The incidence of ovarian cancer and death from ovarian cancer was compared between current, past, or never users of HRT.

### ***Were participants appropriately allocated to intervention and control groups?***

**Yes** - Participants were initially classified as either current, past, or never users of HRT using information provided at recruitment, and

contributed data to the appropriate category up to the date that they completed the second study questionnaire. Participants were re-classified whenever possible using updated information on HRT use and menopausal status reported on the second questionnaire.

### ***Were participants, staff and study personnel 'blind' to participants study group?***

**Yes** - All information on HRT use was recorded before a diagnosis of cancer was made. The National Health Service Central Register (NHSCR) recorded and coded information on the underlying cause of death and morphology of incident cancers before it was supplied to the study investigators. The sponsors of the study (Cancer Research UK, the NHS Breast Screening Programme, and the Medical Research Council) had no role in the study design, data interpretation, preparation of the report, or decision to publish.

### ***Were all of the participants who entered into the trial accounted for at its conclusion?***

**No** - Updated information on HRT use and menopausal status was only available for around two-thirds of those who returned the second study questionnaire. However, various sensitivity analyses were conducted to assess the effects of any potentially out of date information on the results.

### ***Were the participants followed up and data collected in the same way?***

**Yes** - Every participant was routinely followed-up for death, emigration, and cancer registration using the NHSCR. The registers provided information on the date of any such event, and the World Health Organisation International Classification of Diseases code for the underlying cause of death and cancer site as well as morphology codes for

incident cancers. Participants were followed for an average of 5.3 years for incident ovarian cancer and 6.9 years for death.

### ***Was the study large enough?***

**Yes** – The Million Women Study was designed to have sufficient statistical power to detect a relative risk (RR) for mortality from ovarian cancer of 0.81 to 1.20 in current users compared to never users of HRT, and an RR for developing ovarian cancer of 0.76 to 1.26 in current users of five or more years duration compared to never users, at the 95% significance level with 80% power (based on national mortality rates for 1996 in England and Wales).<sup>2</sup>

### ***How are the results presented and what is the main result?***

The results are presented as plots of RR for ovarian cancer with their corresponding 95% confidence intervals [CI], stratified by age, and hysterectomy status, and adjusted by area of residence, socioeconomic status, time since menopause, parity, body-mass index, alcohol consumption, and past oral contraceptive use. Standardised incident rates for ovarian cancer per 1000 women over a five year period are presented; non users are taken as the standard and incident rates standardised as above.

At the time of last contact 30% (287,143) of women were currently using HRT, 20% (186,751) were past users, and 50% (474,682) had never used HRT. During the follow-up period there were 2,273 incident ovarian cancers and 1,591 deaths from ovarian cancer. Women who were current users of HRT (average estimated HRT use 7.7 years) had a statistically significant increased risk of developing ovarian cancer (RR 1.20 [95% CI 1.09-1.32],  $p=0.0002$ ) and death from ovarian cancer (RR 1.23 [95% CI 1.09-1.38],  $p=0.0006$ ) than those who had never used HRT. The risk of developing ovarian cancer significantly increased with duration of use (RR 1.24 [1.09-1.41] for five to nine years, and RR 1.31 [1.12-1.53] for more than ten years, respectively,  $p=0.04$  for trend), but did not differ significantly by type of HRT used or the method of administration. The use of HRT for less than five years was not associated with an increased risk of developing ovarian cancer (RR 1.05 [0.90-1.23]). Past use of HRT (average 3.3 years of HRT use) was also not associated with an increased risk of ovarian cancer (RR 0.98 [0.88-1.11], and 0.97 [0.84-1.11] for incidence and death, respectively).

Over five years, the standardised incidence and mortality rates for ovarian cancer in women who had never used HRT were 2.2 [2.1-2.3] and 1.3 [1.2-1.4] per 1,000 respectively; and in current users they were 2.6 [2.4-2.9] and 1.6 [1.4-1.8] per 1000. These correspond to absolute increased risks of 0.04% and 0.03%, respectively. The increased risks associated with HRT are better reported in absolute numbers rather than relative

risks or percentages. If the differences between never users and current users can be attributed to HRT, these results imply that over a five-year period the use of HRT resulted in approximately one extra case of ovarian cancer in every 2,500 users, and one extra death from the malignancy in every 3,300 users. The authors of the study conclude that if this association is causal, then the use of HRT since 1991 has resulted in an additional 1,300 cases of ovarian cancer and 1,000 extra deaths from the malignancy in the UK. However, it should be stressed that the latter are estimates only based on less than seven years of data.

### ***How precise are the results?***

This was a large well-conducted cohort study. Baseline characteristics with respect to demographic, social, health and lifestyle characteristic were largely similar among the three groups. The main differences were that never users were less likely than past and current users to have had a hysterectomy (13%, 20% and 29%, respectively) and to have used oral contraceptives (47%, 63% and 66%, respectively). The primary outcome measures of incidence and death from ovarian cancer were highly statistically significant with relatively narrow confidence intervals that do not approach zero. Three different sensitivity analyses were conducted to assess the effects of potential misclassification of women's HRT use on the results. Even when misclassification of HRT use was increased by using information obtained only at recruitment the primary outcome results were not significantly affected.

### ***Can the results be applied to the local population?***

**Yes** - The Million Women Study represents around a quarter of all women aged 50 to 64 in the UK.<sup>3</sup> This study involved nearly 950,000 women in that age group. The women were followed up for an average of almost seven years. Around a third of them were taking HRT and a fifth had taken it in the past.

### ***Does HRT increase the risk of ovarian cancer?***

**Yes** - This study shows that the use of HRT for more than five years is associated with small increases in the risk of developing ovarian cancer and dying from the malignancy (absolute increases in risk 0.04% and 0.03%, respectively). However, the use of HRT for less than five years did not increase this risk.<sup>1</sup> The associated risks of ovarian cancer and HRT should not be viewed in isolation. HRT remains an effective therapy for the short-term relief of menopausal symptoms in the majority of women but the minimum effective dose should be used for the shortest duration possible.<sup>4</sup> Women who wish to start HRT should discuss the known risks and benefits of treatment with their doctor. Women currently on HRT should have

regular health check-ups and their need to continue HRT should be re-assessed at least annually.<sup>4</sup> Due to the associated risks; HRT is not

the first choice treatment for the long-term prevention of osteoporosis in women over the age of 50 years.<sup>4</sup>

## REFERENCES

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