Ovarian cancer and hormone replacement therapy in the Million Women Study

Million Women Study Collaborators*

Summary
Background Ovarian cancer is the fourth most common cancer in women in the UK, with about 6700 developing the malignancy and 4600 dying from it every year. However, there is limited information about the risk of ovarian cancer associated with the use of hormone replacement therapy (HRT).

Methods 948 576 postmenopausal women from the UK Million Women Study who did not have previous cancer or bilateral oophorectomy were followed-up for an average of 5·3 years for incident ovarian cancer and 6·9 years for death. Information on HRT use was obtained at recruitment and updated where possible. Relative risks for ovarian cancer were calculated, stratified by age and hysterectomy status, and adjusted by area of residence, socioeconomic group, time since menopause, parity, body-mass index, alcohol consumption, and use of oral contraceptives.

Findings When they last reported HRT use, 287 143 women (30%) were current users and 186 751 (20%) were past users. During follow-up, 2273 incident ovarian cancers and 1591 deaths from the malignancy were recorded. Current users were significantly more likely to develop and die from ovarian cancer than never users (relative risk 1·20 [95% CI 1·09–1·32; p=0·0002] for incident disease and 1·23 [1·09–1·38; p=0·0006] for death). For current users of HRT, incidence of ovarian cancer increased with increasing duration of use, but did not differ significantly by type of preparation used, its constituents, or mode of administration. Risks associated with HRT varied significantly according to tumour histology (p<0·0001), and in women with epithelial tumours the relative risk for current versus never use of HRT was greater for serous than for mucinous, endometroid, or clear cell tumours (1·53 [1·31–1·79], 0·72 [0·52–1·00], 1·05 [0·77–1·43], or 0·77 [0·48–1·23], respectively). Past users of HRT were not at an increased risk of ovarian cancer (0·98 [0·88–1·1] and 0·97 [0·84–1·1], respectively, for incident and fatal disease). Over 5 years, the standardised incidence rates for ovarian cancer in current and never users of HRT were 2·6 (2·4–2·9) and 2·2 (2·1–2·3) per 1000, respectively—ie, one extra ovarian cancer in roughly 3300 users; death rates were 1·6 (1·4–1·8) and 1·3 (1·2–1·4) per 1000, respectively—ie, one extra ovarian cancer death in roughly 3300 users.

Interpretation Women who use HRT are at an increased risk of both incident and fatal ovarian cancer. Since 1991, use of HRT has resulted in some 1300 additional ovarian cancers and 1000 additional deaths from the malignancy in the UK.

Introduction Ovarian cancer is the fourth most common cancer in women in the UK, with some 6700 developing the malignancy and 4600 dying from it every year.1–3 Published results on the relation between use of hormone replacement therapy (HRT) and the subsequent risk of developing ovarian cancer are inconclusive.4–20 The reported findings vary across studies, with some investigators reporting a significantly increased risk of fatal11 and incident12–15,18,20 ovarian cancer in users of HRT. However, most previous studies lacked statistical power, since they included relatively few affected women who had also used HRT. To investigate the effect of HRT on women’s risk of developing and dying from ovarian cancer, we present results from a large cohort study in the UK, in which about half the postmenopausal women had used HRT.19

Methods
Data collection and follow-up During 1996–2001, 1·3 million women who had been invited for screening for breast cancer completed the first study questionnaire, which asked, among other things, about social, demographic, and lifestyle factors, including the use of HRT.21 A second questionnaire was sent to participants between 1999 and 2004, about 3 years after recruitment, to update information on use of HRT and other factors, and 64% responded. Questions about the use of HRT asked both at recruitment and resurvey included: ever, current, and past use; age at first and last use; total duration of use; and the name and duration of the proprietary preparation last used. All participants gave written consent to take part in the study, and the Oxford and Anglia Multi-Centre Research Ethics Committee approved the study.

Every study participant is routinely followed-up for death, emigration, and cancer registration, by being flagged on the National Health Service Central Registers. The registers regularly provide study investigators with information on the date of any such event in participants, and code the underlying cause of death and cancer site with the tenth revision of the International Classification of Diseases (ICD10), as well as providing the ICD10-O morphology codes for incident cancers.22 The main endpoints for these analyses were incident and fatal malignant ovarian cancer (ICD10 C56). The malignant cancers were further classified as epithelial (including tumours coded as clear cell malignancy and 4600 dying from it every year. However, there is limited information about the risk of ovarian cancer associated with the use of hormone replacement therapy (HRT).
Articles

Characteristics of the study population according to last reported use of HRT

<table>
<thead>
<tr>
<th>HRT use</th>
<th>Never (n=474 682)</th>
<th>Past (n=186 751)</th>
<th>Current (n=287 143)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Characteristics</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean age at entry (SD)</td>
<td>57.9 (4.9)</td>
<td>57.0 (4.3)</td>
<td>56.1 (4.1)</td>
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<tr>
<td>Upper third of socioeconomic group (n, %)</td>
<td>151 426 (32.1%)</td>
<td>63 777 (34.3%)</td>
<td>100 143 (35.1%)</td>
</tr>
<tr>
<td>Mean parity (SD)</td>
<td>2.1 (1.3)</td>
<td>2.2 (1.2)</td>
<td>2.1 (1.2)</td>
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<td>Past use of oral contraceptives (n, %)</td>
<td>223 216 (47.4%)</td>
<td>115 935 (62.6%)</td>
<td>188 452 (66.2%)</td>
</tr>
<tr>
<td>Mean, body-mass index, kg/m² (n)</td>
<td>25.9 (4.9)</td>
<td>25.9 (4.5)</td>
<td>25.1 (4.3)</td>
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<tr>
<td>Strenuous physical activity &gt;once/week (n, %)</td>
<td>171 134 (37.6%)</td>
<td>71 814 (39.6%)</td>
<td>112 731 (40.5%)</td>
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<tr>
<td>Mean alcohol intake, g/day (SD)</td>
<td>4.4 (7.3)</td>
<td>6.4 (7.6)</td>
<td>6.9 (7.9)</td>
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<td>Current smoker (n, %)</td>
<td>87 315 (19.9%)</td>
<td>35 615 (20.2%)</td>
<td>57 242 (21.0%)</td>
</tr>
<tr>
<td>Hysterectomy (n, %)</td>
<td>61 470 (13.0%)</td>
<td>38 004 (20.4%)</td>
<td>81 978 (28.6%)</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Follow-up for ovarian cancer</th>
<th></th>
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<tbody>
<tr>
<td>Woman-years of follow-up for incidence (1000s)</td>
<td>25 150</td>
<td>943 8</td>
<td>153 7</td>
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<tr>
<td>Number of incident ovarian cancers</td>
<td>11 42</td>
<td>391</td>
<td>740</td>
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<tr>
<td>Woman-years of follow-up for death (1000s)</td>
<td>3 285 0</td>
<td>125 5 2</td>
<td>19 77</td>
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<tr>
<td>Number of ovarian cancer deaths</td>
<td>819</td>
<td>275</td>
<td>497</td>
</tr>
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</table>

Table: Characteristics of the study population according to last reported use of HRT
follow-up at 48 months since last contact; (2) censoring at the earliest of either 48 months or Dec 31, 2002; and (3) using information obtained at recruitment only.

Women were categorised by duration of current use reported at last contact, and the actual average duration of current HRT use at the time of diagnosis for women who developed ovarian cancer was estimated; the estimates assumed that, before the cancers were diagnosed, the proportion of current users ceasing use every year was the same as for current users who did not develop cancer, and that among the continuing users, their average duration of use increased by 1 year for each year of follow-up until cancer diagnosis. (Based on reports by women who completed the second study questionnaire before 2003 and did not develop cancer, an estimated 8% of current users ceased use every year: 7% for users of oestrogen-only HRT, and 9% for users of oestrogen-progestagen and for other HRT preparations.26)

When results are presented in the form of plots, the relative risks and their corresponding CIs are represented by squares and lines, with the area of every square inversely proportional to the variance of the logarithm of the corresponding relative risk. The area of the squares thus provides an appropriate indication of the amount of statistical information involved.

Standardised incidence rates for ovarian cancer in the study population are calculated per 1000 women over a 5-year period; never-users of HRT are taken as the standard, and incidence rates in users are standardised by age, hysterectomy status, region of residence, socioeconomic status, time since menopause, parity, body-mass index, and past use of oral contraceptives. The number of ovarian cancers attributed to the use of HRT in the UK was estimated by applying the incidence rates obtained here to the prevalence of HRT use in the UK from 1991 to 2005 (Joanna Watson, personal communication).

Role of the funding source
The sponsors of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results
948 576 postmenopausal women with no previous cancer or bilateral oophorectomy were included in the analyses. Their average age at recruitment was 57-2 years. At the time of last contact 473 894 women (50% of the total) had ever used HRT and 287 143 (30%) were current users. When demographic, social, health, and lifestyle characteristics of the never, past, and current users were compared, the groups did not differ appreciably in most respects (table). 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 study population was followed-up for cancer incidence over 5 million woman-years, an average of 5-3 years per woman, during which time 2273 incident ovarian cancers were notified by the National Health Service Central Registers. Women who developed ovarian cancer were diagnosed an average of 2.4 (SD 1-6) years after the date that use of HRT was last reported, with a median year of diagnosis of 2000 (with 89% diagnosed...
between 1997 and 2003). Compared with never users of HRT, ever-users had a slightly increased risk of ovarian cancer (relative risk 1·11 [95% CI 1·02–1·21], p=0·02). Figure 1 shows findings on the incidence of ovarian cancer in never, past, and current users of HRT. Compared with never-users, the risk of ovarian cancer is significantly increased in current users (1·20 [1·09–1·32], p=0·0002) but not in past users (0·98 [0·88–1·11], p=0·7) and the difference between current and past users is significant (test for heterogeneity p=0·01).

Among current users of HRT at the time of last contact, 85 931 (30%) were using oestrogen-only HRT, 169 273 (59%) were using oestrogen-progestagen combinations, and 31 939 (11%) were using other or unknown preparations. Of the current users who developed ovarian cancer, the estimated duration of use of HRT at the time of diagnosis was 7·7 years overall, slightly longer for oestrogen-only HRT (9·2 years) than for oestrogen-progestagen combinations (6·9 years) or other or unknown types (7·0 years). The risk of ovarian cancer did not differ significantly between these three groups of HRT users (p=0·3) or between women using oestrogen-only and combined preparations (p=0·1).

Past users who developed ovarian cancer had ceased use of HRT an average of 5·6 (SD 4·3) years before they were diagnosed with the malignancy. The relative risks were not significantly increased, and were close to 1·0 for women who had ceased use of HRT less than 5 years previously (1·01 [0·87–1·18]) and for those who ceased 5 or more years previously (0·95 [0·78–1·16]). Nor were the relative risks significantly related to the duration of use (1·02 [0·89–1·17] for women who had used HRT for less than 5 years, and 0·96 [0·80–1·17] for duration of 5 years or more).

The results shown in figure 1 are stratified by age and hysterectomy status, and also adjusted by region, socioeconomic status, time since menopause, parity, body-mass index, alcohol consumption, and use of oral contraceptives, where appropriate. Totals are not always the same because of missing values.

Results for current users compared with never users varied little when sensitivity analyses were done: when analyses were based solely on information reported at recruitment, the relative risk was 1·18 (1·07–1·30); censoring follow-up at 48 months yielded a relative risk of 1·20 (1·08–1·33); and censoring at the earliest of 48 months or Dec 31, 2002, yielded an estimate of 1·21 (1·07–1·36).

Figure 2 shows results for current users compared with never-users of HRT, according to the pattern of use. The risk of incident ovarian cancer increased with increasing duration of HRT use (test for trend, p=0·04) and the relative risk was 1·31 (1·12–1·53) for 10 or more years of use (12·3 years of use, on average). The relative risk of

Figure 3: Relative risk of ovarian cancer in current compared with never users of HRT, by various characteristics of the study participants

Relative risks are for HRT users compared with never-users, stratified by age and hysterectomy status, and adjusted by region of residence, socioeconomic group, time since menopause, parity, body-mass index, alcohol consumption, and use of oral contraceptives, where appropriate. Totals are not always the same because of missing values.

*Estimated duration of use of HRT among cases at time of diagnosis of ovarian cancer.
ovarian cancer tended to be greater with longer use of both oestrogen-only and oestrogen-progestagen HRT, and there were no significant differences in the relative risks between preparations with different oestrogenic and progestagenic constituents, between oral and transdermal therapies, or between preparations with progestagens given continuously or sequentially (figure 2).

Figure 3 shows results according to various characteristics of the women studied. There were no significant differences in the relative risk of ovarian cancer in current users of HRT compared with never users according to age, socioeconomic status, parity, past use of oral contraceptives, body-mass index, physical activity, or alcohol and tobacco consumption. The higher relative risk among current users who had had a hysterectomy than among current users who had not had a hysterectomy, although significant (p=0.03), is partly due to the longer duration of HRT use by women who had had a hysterectomy (9·3 vs 6·9 years).

According to the ICD10-O codes, 95% of the malignant ovarian cancers were epithelial; only 2% were non-epithelial, and the remaining 3% were not specified as either (figure 4). The relative risk for current versus never-use of HRT did not differ significantly between epithelial and non-epithelial tumours (p=0·09); however, the relative risk of epithelial tumours varied significantly according to tumour histology (p<0·0001) and was greater for serous than for mucinous, endometroid, or clear cell tumours (1·53 [1·31–1·79], 0·72 [0·52–1·00], 1·05 [0·77–1·43] and 0·77 [0·48–1·23], respectively). About 10% of the serous tumours were of low malignant potential, and the relative risk for current versus never-use of HRT was 1·85 (1·15–2·96) for such tumours, not significantly different to the corresponding relative risk for other serous tumours (1·49 [1·26–1·79]). Nor did the relative risks vary significantly across other histological subtypes of serous tumours. About half the mucinous tumours were of low malignant potential, and the HRT-associated relative risk for such tumours (0·80 [0·50–1·26]) did not differ significantly from the risk for other mucinous tumours (0·66 [0·42–1·03])

Study participants were followed-up for death for a total of 6·5 million woman-years, an average of 6·9 years per woman. During this period, 1991 deaths were attributed to ovarian cancer. Figure 5 shows results for fatal ovarian cancer, according to HRT use reported at the time of last contact (but before any incident ovarian cancer was diagnosed). The findings for fatal ovarian cancer were broadly similar to those for incident disease, in that women who were current users of HRT at the time of last contact had a significantly higher mortality than never users (1·23 [1·09–1·38], p=0·0006) but past users did not (0·97 [0·84–1·11]). Although the current users at the time of last contact were at an increased risk of fatal cancer, the risk did not vary significantly between the types of HRT last used. Included among the current users of other preparations were 22 344 users of tibolone, and their relative risks for incident and fatal ovarian cancer were 1·07 (0·81–1·41) and 1·16 (0·84–1·60), respectively, not significantly different to the risk associated with use of other types of HRT (tests for heterogeneity, p=0·09 and p=0·2, respectively).

Crude incidence and mortality rates for ovarian cancer in the study population as a whole were 2·2 and 1·3, respectively, per 1000 women over 5 years. In never users of HRT the standardised rates were 2·2 (2·1–2·3) and 1·3 (1·2–1·4), respectively, and in current users the corresponding rates were 2·6 (2·4–2·9) and 1·6 (1·4–1·8), respectively. If the differences between never users and current users are due to HRT, these results imply that, over a 5-year period, use of HRT resulted in about one extra case of ovarian cancer in every 2500 users and one extra death from the malignancy in every 3300 users. Applying these rates to figures on the use of HRT in the UK from 1991 to 2005, HRT use since 1991 is estimated to have resulted in about 1300 additional cases of ovarian cancer and about 1000 additional deaths from the malignancy.

Ovarian, endometrial, and breast cancer account for 39% of all incident cancers registered and 25% of all fatal cancers in women in the UK.24 Use of HRT affects the risk of endometrial and breast cancer, with combined oestrogen-progestagen treatment causing a greater increase in breast cancer than oestrogen-only preparations,25 and the converse being true for endometrial cancer.24 Figure 6 shows the standardised incidence rates for ovarian, endometrial, and breast cancer in never-users of HRT and in current users of oestrogen-only and combined HRT in the study population. Taking all three cancers together, the total incidence of cancer is substantially higher in current users (31 per 1000 over 5 years) than never users of HRT (19 per 1000 over 5 years; p<0·0001). Breast cancer is more common than either ovarian or endometrial cancer, and when the incidence of all three cancers is added together, the total is dominated by breast cancer, and is significantly higher in current users of oestrogen-progestagen (35 per 1000 over 5 years) than oestrogen-only HRT (26 per 1000 over 5 years; p<0·0001).
Discussion

In this large cohort study, use of HRT by postmenopausal women was associated with a significantly increased risk of both incident and fatal ovarian cancer. In women who were current users of HRT at the time of last contact, the risk of ovarian cancer increased with increasing duration of use, but did not vary significantly according to the hormonal constituents, the mode of administration, or the type of HRT regimen. Nor did the relative risks vary appreciably by socioeconomic status, reproductive history, previous use of oral contraceptives, body-mass index, or alcohol and tobacco consumption. The risk associated with current use of HRT did vary, however, by tumour histology, with the greatest risk seen for serous ovarian tumours. Women who had stopped taking HRT had a similar risk of ovarian cancer to that in women who had never used HRT.

To ensure non-differential ascertainment of exposure and of cancer incidence and deaths in the study population, all information on HRT use is recorded before the diagnosis of cancer, and the National Health Service Central Registers record and code information on all incident cancers and deaths before notifying this to the study investigators. Current use of HRT reported at recruitment showed 97% agreement with general practitioner prescription records. We classified tumour histology using the International Classification of Diseases morphology codes provided by the cancer registries in the UK to the National Health Service Central Registers and, although no independent review was done, there is no reason to expect differential reporting of tumour histology by pathologists across the UK by women’s use of HRT.

Our results on the relation between HRT and the subsequent risk of ovarian cancer are broadly consistent with previous reports, but there is limited scope for direct comparisons across studies because the classifications tended to vary from one study to another. Across the nine studies (including this one) that quoted a relative risk for ovarian cancer in current (or recent) users of HRT compared with never users, the findings did not vary significantly (figure 7). The numbers of cases are relatively small in the other studies and, since the average duration of HRT use might well differ from one study to another, the risk estimates are not strictly comparable. All results shown in figure 7 are for incident ovarian cancer, except for one study, which has only published results for fatal disease. In that study, the relative risk in current and recent users versus never users was $1.51$ ($1.16–1.96$), not significantly different to our estimate of $1.23$ ($1.09–1.38$) for fatal ovarian cancer. Comparison of the effect of type and duration of use of HRT across studies is difficult, since definitions vary. To investigate such associations in a systematic way will need the pooling of all available information, both published and unpublished, using similar definitions across studies, and an international collaboration has now been set up to do this.

Our finding that the excess risk of ovarian cancer in current users of HRT varied significantly according to tumour histology is difficult to interpret at present. Two of the eight other studies shown in figure 7, and eight other studies that did not present results in current or recent HRT users, reported on some aspect
of HRT use in relation to certain histological groupings of ovarian cancer. However, there is little consistency in the exposure categories for which results were reported, further limiting the scope for comparisons between equivalent groups. The international pooling of data that is now planned should help clarify the role of HRT for tumours of different histology.

Because the ovarian cancers included in these analyses were diagnosed, on average, 2.4 years after use of HRT was last reported, some women’s use at the time of diagnosis would be misclassified. However, over 2.4 years comparatively few current, past, and never users would have changed from one category to another. Based on the re-survey of women who did not develop cancer during follow-up, before 2003 an estimated 1% of the never users at recruitment became current users each year, 4% of the past users became current users each year, and 8% of the current users ceased use every year, and most of the woman-years of follow-up preceded 2003. With such small changes in HRT use over the follow-up period, comparisons of the risk of ovarian cancer in current versus never users should be underestimated only slightly as a result of misclassification of women’s HRT use. Our sensitivity analyses support that conclusion, in that even stringent censoring of follow-up to keep misclassification at a minimum, yielded a relative risk estimate of 1.21 for current versus never use of HRT, similar to the estimate of 1.20 obtained without such censoring; and if we underestimated only slightly as a result of ovarian cancer in current versus never users should be underestimated only slightly as a result of misclassification of women’s HRT use. Our sensitivity analyses support that conclusion, in that even stringent censoring of follow-up to keep misclassification at a minimum, yielded a relative risk estimate of 1.21 for current versus never use of HRT, similar to the estimate of 1.20 obtained without such censoring; and if we underestimated only slightly as a result of misclassification by not updating any information on HRT use after recruitment, a slightly lower estimate, of 1.18, was obtained.

One of the main differences between current and never-users of HRT was the proportion who had had a hysterectomy (29% and 13%, respectively, table). In women who do not use HRT, the incidence of ovarian cancer is lower in women who have had a hysterectomy than in women who have not, and appropriate adjustment for hysterectomy is, therefore, crucial when studying the relation between use of HRT and the subsequent risk of ovarian cancer.26 Stratification for hysterectomy as well as by age in our analyses ensured that no direct comparisons were made between the effect of HRT in women who have had a hysterectomy and women who have not. Although the relative risk of ovarian cancer associated with HRT use was somewhat greater in women with than without a hysterectomy, this difference was only marginally significant and could be due to chance. The longer duration of use of HRT by women who had had a hysterectomy than by women who had not (9·3 vs 6·9 years, figure 3) might have contributed to the higher HRT-associated relative risk in those who have had a hysterectomy; and the lower incidence rates among never-users who have had a hysterectomy might also be relevant. Although hysterectomy status was not updated, only 1% of women with a uterus had a hysterectomy in the 2.8 years after recruitment,29 suggesting that this is unlikely to have affected the main findings.

There was no obvious evidence of confounding by other factors in the effect of HRT on ovarian cancer. All analyses were stratified by age and prior hysterectomy and adjusted for region of residence, socioeconomic group, time since menopause, parity, body-mass index, alcohol consumption, and past use of oral contraceptives; and additional adjustment by smoking, physical activity, and age at first birth, did not materially alter the findings. Nor was there strong evidence that these factors modified the results (figure 3). Women were excluded from the analyses if they had cancer diagnosed previously, since this might affect both use of HRT and the subsequent incidence of ovarian cancer. Bilateral oophorectomy before recruitment was also a reason for exclusion, since this virtually eliminates women’s risk of developing ovarian cancer.

The mechanism of ovarian carcinogenesis is not well understood. Use of combined oral contraceptives, containing oestrogens and progestagens, substantially reduces the risk of ovarian cancer, and this persists long after use ceases.29 By contrast, the findings presented here show that use of HRT by postmenopausal women increases the risk of ovarian cancer, and that this excess risk disappears shortly after use ceases. Why preparations containing oestrogens and progestagens, albeit in different doses, should have qualitatively different effects on ovarian cancer risk in pre-menopausal compared with postmenopausal women is not clear. Among postmenopausal women, however, there are some similarities between the effect of HRT on ovarian cancer and on breast cancer, in that the risk of both types of cancer increases with increasing duration of use among current users, but returns to that observed in never-users soon after use ceases.39,40 Further evidence on the variation in hormone-associated risks across histological types of ovarian cancer might help clarify the mechanisms.

Ovarian cancer incidence and mortality rates in the study population over 5 years were 2·2 and 1·3, respectively, per 1000 women, similar to rates of 2·3 and 1·4, respectively, per 1000 women aged 50–69 years during 1998–2002 in the UK.7 Over 5 years, one extra ovarian cancer is estimated to have occurred in about 2500 HRT users and one extra death from the malignancy in about 3300 users. If this association is causal, use of HRT since 1991 has resulted in roughly 1300 extra cases of ovarian cancer and 1000 extra deaths from the malignancy in the UK.

The effect of HRT on ovarian cancer should not be viewed in isolation, especially since use of HRT also affects the risk of breast and endometrial cancer.25,26 In total, ovarian, endometrial, and breast cancer account for 39% of all cancers registered in women in the UK.22 The total incidence of these three cancers in the study population is 63% higher in current users of HRT than...
in never users (31 vs 19 per 1000 over 5 years, figure 6). Thus, when ovarian, endometrial, and breast cancer are taken together, use of HRT results in a material increase in the incidence of these common cancers.

**Acknowledgments**

We thank all the women who participated in the study, staff from the NHS Breast Screening Centres, Adrian Goodill for drawing the figures, and Joanna Watson for providing data for HRT use in the UK. This research was funded by Cancer Research UK, the NHS Breast Screening Programme, and the Medical Research Council. The funding sources did not influence the conduct of the study, the preparation of this report or the decision to publish.

**Contributors**

All members of the Analysis and Writing Committee took part in the design and implementation of the study, and approved the final report. Analysis and Writing Committee—Valerie Beral, Diana Bull, Jane Green, and Gillian Reeves.

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**References**