A prospective study of postmenopausal hormone use and ovarian cancer risk

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The relationship between postmenopausal hormone use (PMH) and ovarian cancer risk is unclear, particularly for specific hormone formulations, but recent studies suggest that there is a positive association. We conducted a prospective observational study with 82,905 postmenopausal women, including 389 ovarian cancers, in the Nurses’ Health Study from 1976 to 2002. Compared with never users of PMH, both current and past users of ≥5 years had a significantly elevated risk of ovarian cancer (RR = 1.41, 95% confidence interval [CI] 1.07–1.86 and relative risk [RR] = 1.52, 95% CI 1.01–2.27, respectively). Examined by hormone type in continuous years, use of unopposed estrogen was associated with a significant increase in the risk of epithelial ovarian cancer (P for trend < 0.001; RR for 5-year increment of use = 1.25, 95% CI 1.12–1.38). Use of estrogen plus progestin (RR for 5-year increment of use = 1.04, 95% CI 0.82–1.32) was not significantly associated with ovarian cancer risk. Generally, results were similar for serous tumours (RR for 5-year increment of unopposed estrogen use = 1.23, 95% CI 1.07–1.40) and slightly stronger for endometrioid tumours (RR for 5-year increment of unopposed estrogen use = 1.53, 95% CI 1.20–1.94). Recency of use was not significantly associated with ovarian cancer risk, but statistical power was limited here.

Keywords: hormone; ovarian cancer; postmenopausal; epidemiology

Ovarian cancer is the fifth most common cause of cancer mortality among women in the United States (American Cancer Society, 2006), and yet few truly modifiable factors have been established. Postmenopausal hormone (PMH) use has been examined as a potential risk factor for ovarian cancer in several studies, but reviews (IARC Working Group on the Evaluation of Carcinogenic Risks to Humans et al., 1999; Riman et al., 2004; Farquhar et al., 2005) and meta-analyses (Garg et al., 1998; Coughlin et al., 2000) have found studies to be inconsistent, as did the US Preventive Services Task Force review of higher-quality studies (USPSTF, 2005). Recently, unopposed estrogen use has been positively associated with ovarian cancer risk or mortality in several cohort studies (Rodriguez et al., 2001; Lacey et al., 2002, 2006; Folsom et al., 2004). Although estrogen plus progestin use also has been examined in multiple studies (Lacey et al., 2002, 2006; Riman et al., 2002; Sit et al., 2002), only one cohort study reported a substantial number of cases among long-duration estrogen plus progestin users, finding a significant increased risk of ovarian cancer (Lacey et al., 2006).

We evaluated the association between PMH use and ovarian cancer in the prospective Nurses’ Health Study (NHS) over 26 years of follow-up; we examined duration, recency of use, and PMH type for all ovarian tumours, as well as by histologic tumour type.

MATERIALS AND METHODS

Study cohort

The NHS began in 1976, when 121,701 female registered nurses in 11 US states completed a self-administered, mailed questionnaire. At enrolment, participants were 30–55 years old. Subsequently, follow-up questionnaires were mailed biennially to obtain updated exposure and disease information. Information on deaths was obtained through the post office, relatives and linkages with the National Death Index. Through 2002, these methods yielded a follow-up rate of 93.7% of potential person-years. The study was approved by the Institutional Review Board of Brigham and Women’s Hospital.

Study population

The study population was restricted to postmenopausal women. A validation study in the NHS found self-reported menopause to have high reproducibility (Colditz et al., 1987). Women whose menopausal status was missing, or who reported a hysterectomy without bilateral oophorectomy, contributed person-time from the age at which natural menopause occurred for 90% of the cohort (54 years for current smokers, 56 years for past or never smokers).
In 1976, there were 24,443 postmenopausal women in the NHS. Participants were excluded if they reported radiation as the reason for menopause (n = 209), a bilateral oophorectomy (n = 8,506), or a diagnosis of cancer other than non-melanoma skin cancer (n = 514) before the start of follow-up. Women missing exposure or covariate information (n = 1,074) were excluded (details below), leaving 14,140 eligible women in the baseline population.

Women subsequently entered the study population as they became postmenopausal, provided that radiation or bilateral oophorectomy was not the cause of menopause. Participants were censored at the earliest of: (1) development of ovarian cancer, (2) report of any cancer other than non-melanoma skin cancer, (3) death, or (4) the end of the study period, 6/1/2002. Person-time with missing exposure or covariate information also was excluded. From 1976 to 2002, 82,905 postmenopausal women accumulated a total of 966,017 person-years.

Postmenopausal hormone use

PMH use was assessed in every questionnaire. In 1976, users reported their total duration of use. As 72% of users of a known type reported use of unopposed estrogen in 1978 (when such details were first collected), PMH use in 1976 was classified as unopposed estrogen. This classification probably resulted in a small amount of misclassification of other types of PMH; however, in a sensitivity analysis, we also re-coded PMH use in 1976 to other/unknown type of hormone.

Ovarian cancer

Incident cases of ovarian cancer were identified through responses to biennial questionnaires or death certificates and confirmed by medical record review. From 1976 to 2002, there were 760 reported cases of postmenopausal ovarian cancer. We were unable to obtain medical records for 71 (9.3%) and did not confirm the diagnosis upon medical record review for 135 (17.8%) women. Of the 554 confirmed cases, 492 were epithelial tumours (88.8%). After applying exclusion criteria (e.g., prior diagnosis of another cancer), we were left with 389 cases of primary epithelial ovarian cancer. Histologic type, as coded from pathology reports by a gynecologic pathologist (JLH), had the following distribution: 233 serous/poorly differentiated (hereafter referred to as serous), 60 endometrioid, 35 mucinous, 19 clear-cell and 42 other/unknown subtype. Of the 389 cases, 353 were invasive and 36 were of low malignant potential (18 serous, 15 mucinous, 2 endometrioid and 1 clear cell).

Covariates

Age and time period were used as stratification variables in the Cox proportional hazards models. Based on previous literature, the following covariates were forced into the multivariate models: duration of oral contraceptive use (continuous), parity (continuous), tubal ligation (yes/no), age at natural menopause (continuous) and age at menarche (<12, 12, 13, 14, >15 years). The complete case method (restricting the analysis to participants with data on the exposure and all covariates) was used, except that women with a hysterectomy were included; the population was restricted to women with natural menopause in secondary analyses.

In addition, the following potential confounders were not included in the final models: vigorous physical activity, smoking, alcohol consumption, caffeine intake, lactose/galactose consumption, perineal talc use, breastfeeding, simple hysterectomy, use of non-steroidal anti-inflammatory medications other than aspirin and family history of breast cancer. Data on family history of ovarian cancer, first collected in 1992, was evaluated as a potential confounder by examining its distribution across PMH categories in 1992. Fat intake and body mass index (BMI) were not considered confounders because they were not associated with postmenopausal ovarian cancer in previous NHS analyses (Bertone et al, 2002; Fairfield et al, 2002). However, BMI and having an intact reproductive system (no tubal ligation or hysterectomy) were evaluated as potential effect modifiers.

Data analysis

Multivariate Cox proportional hazards regression models were used to estimate RRs and 95% CIs. The association with ovarian cancer was examined for status of PMH use (never, past and current), total duration and time since last use. In addition, analyses were performed by type-specific duration in continuous years, simultaneously including all PMH types in the models (unopposed estrogen, estrogen plus progestin, other PMH). Results have not been presented for the ‘other PMH’ group because it represents a heterogeneous group of hormones, including non-conjugated estrogens, patch hormones, and vaginal hormones, as well as person-time for which hormone type was not reported.

Primary analyses included all tumours (invasive and low malignant potential), but sensitivity analyses restricted cases to invasive tumours. Separate analyses were performed for serous and endometrioid tumour subtypes, but owing to small numbers, those for mucinous tumors (n = 35) were adjusted only for age, and clear cell tumors (n = 19) were not evaluated.

RESULTS

Description of the study population

Population characteristics are presented for 1992 (Table 1), the approximate midpoint of the study, and the first year in which family history of ovarian cancer was collected. The mean age among study participants in 1992 was 61.2 years. The average duration of hormone use was longer among current unopposed estrogen users than current estrogen plus progesterin users (9 vs 6 years, respectively). Compared to never users, PMH users were more likely to have used oral contraceptives or had a simple hysterectomy. As expected, current users of unopposed estrogen were substantially more likely to have had a hysterectomy than current users of estrogen plus progesterin. Correspondingly, tubal ligation was more common among users of estrogen plus progesterin than users of unopposed estrogen. The distribution of other risk factors was generally similar across PMH classifications. There was no substantial variation by family history of ovarian cancer across exposure groups.

Multivariate results

Results from the age-adjusted and multivariate models were nearly identical, indicating minimal confounding by other risk factors (Table 2). Neither current (RR = 1.24, 95% CI 0.97–1.59) nor past (RR = 1.00, 95% CI 0.77–1.31) use of PMH was significantly associated with ovarian cancer risk compared with never use. For serous tumours, current use of PMH was associated with a significant increase in risk (RR = 1.43, 95% CI 1.04–1.96) compared to never use. Risk was non-significantly increased for endometrioid tumours for current (RR = 1.61, 95% CI 0.85–3.05) and past (RR = 1.68, 95% CI 0.85–3.33) use compared with never use. Results were similar when models were restricted to invasive tumours (data not shown).

When analyses were stratified by total duration of PMH use (<5 and ≥5 years), increased risk was observed among both current (RR = 1.41, 95% CI 1.07–1.86) and past (RR = 1.52, 95% CI 1.01–
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Table 1  Age and age-standardised characteristics by postmenopausal hormone use and hormone type in the Nurses’ Health Study, 1992

| PMH status | Never user (n = 20 853) | Past user (n = 10 053) | Current user (n = 16 831) | Estrogen only (n = 4 315) | Estrogen+Progestin (n = 7 394) |
|------------|------------------------|------------------------|---------------------------|--------------------------|-------------------------------|
| Age, mean, years | 50 49 50 49 50 | 60 62 | 58 |
| Duration of PMH use, mean, years | 0 3 | 7 | 9 | 6 |
| Duration of OC use (%) | | | | | |
| Never | 66 58 | 55 | 54 | 52 |
| < 3 years | 18 23 | 22 | 23 | 22 |
| ≥ 3 years | 17 20 | 23 | 23 | 26 |
| Parity | | | | | |
| Parous women (%) | 94 93 | 93 | 94 | 93 |
| Mean no. of children (among parous) | 3 3 | 3 | 3 | 3 |
| Familya history of ovarian cancer (%) | 3 3 | 2 | 3 | 3 |
| Had a simple hysterectomy (%) | 5 12 | 19 | 47 | 2 |
| Had a tubal ligation (%) | 13 14 | 14 | 10 | 17 |
| Age at menarche, mean, years | 13 13 | 13 | 13 | 13 |
| Age at natural menopause, mean, years | 50 49 | 50 | 49 | 50 |

Abbreviations: PMH, postmenopausal hormone; OC, oral contraceptive. aCharacteristics are presented for the 47 737 nurses who met the study eligibility criteria in 1992; all factors except age were age-standardised in 5-year intervals. bMother or sister had ovarian cancer according to nurse’s response to questionnaire.

Table 2  Use of postmenopausal hormones and epithelial ovarian cancer risk, all cases combined and by histologic type

| All epithelial ovarian tumours | Never user | Past user | Current user |
|-------------------------------|------------|-----------|--------------|
| No. of cases | 167 | 88 | 134 |
| Person-years | 455 200 | 210 778 | 300 039 |
| Age-adjusted RR (95% CI) | 1.00 (referent) | 1.00 (0.77, 1.31) | 1.23 (0.97, 1.57) |
| Multivariateb RR (95% CI) | 1.00 (referent) | 1.00 (0.77, 1.31) | 1.24 (0.97, 1.59) |
| Serous tumours | | | |
| No. of cases | 96 | 51 | 86 |
| Multivariateb RR (95% CI) | 1.00 (referent) | 0.98 (0.69, 1.40) | 1.43 (1.04, 1.96) |
| Endometrioid tumours | | | |
| No. of cases | 21 | 16 | 23 |
| Multivariateb RR (95% CI) | 1.00 (referent) | 1.68 (0.85, 3.33) | 1.61 (0.85, 3.05) |

Abbreviations: RR, relative risk; CI, confidence interval. aResults by histologic type are presented for serous/poorly differentiated and endometrioid tumours only due to small numbers for the other histologic types. bAdjusted for: age, parity, duration of oral contraceptive use, tubal ligation, age at natural menopause, age at menarche.

The increased risk observed with continuous years of unopposed estrogen use was generally similar for serous tumours (RR for 5-year increment of unopposed estrogen use = 1.23, 95% CI 1.07 – 1.40) and slightly stronger for endometrioid tumours (RR for 5-year increment of unopposed estrogen use = 1.53, 95% CI 1.20 – 1.94), although there was a limited number of cases for the endometrioid analysis. When mucinous tumours were examined in age-adjusted analyses, point estimates suggested that past (RR = 0.72, 95% CI 0.30 – 1.76) and current (RR = 0.72, 95% CI 0.31 – 1.67) users had a reduced risk compared with never users, although results were not significant and based on few cases.

In analyses restricted to women exclusively using one hormone formulation, unopposed estrogen use of five or more years was associated with an increased risk compared with never use (RR = 2.04, 95% CI 1.41 – 2.97), whereas estrogen plus progesterin use of five or more years was not (RR = 0.93, 95% CI 0.47 – 1.83) (Table 5). However, there were only ten cases among estrogen plus progesterin users of ≥ 5 years. Results were similar for unopposed estrogen use among women reporting a hysterectomy and estrogen plus progesterin use among women with intact uteri (data not shown).

Time since last use was not significantly associated with risk. Neither users who quit within the previous three years (RR = 1.04, 95% CI 0.71 – 1.53) nor those who stopped over three years ago (RR = 0.86, 95% CI 0.60 – 1.22) were at a significantly increased risk of ovarian cancer. Based on the significant association observed with duration, a recency effect would most likely be seen primarily among long-term users. Although limited by small numbers, when we examined the effects of recency and duration together, point estimates suggested an increase in risk among users of five or more years that decreased over time (RR = 1.62 among the most recent quitters and RR = 1.35 among those who quit over 3 years ago, with 17 and 11 cases respectively).

No substantial differences were observed when stratifying on BMI (< 25, 25 – 29, ≥ 30 kg m–2) or an intact reproductive system (i.e., no prior hysterectomy or tubal ligation) (data not shown). Results were also similar among women reporting natural menopause, although the association with unopposed estrogen use was slightly stronger (RR = 1.40 for a 5-year increment of use, 95% CI 1.09 – 1.80).
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Table 3  Total duration of postmenopausal hormone use and risk of epithelial ovarian cancer; all cases combined and by histologic typea

| All epithelial ovarian tumours | Never user | <5 years use | ≥5 years use | Current user |
|-------------------------------|------------|--------------|--------------|--------------|
| No. of cases | 167 | 57 | 31 | 40 | 94 |
| Person-years | 455,200 | 164,558 | 46,220 | 129,669 | 170,370 |
| Age-adjusted RR (95% CI) | 1.00 (referent) | 0.87 (0.64, 1.18) | 1.50 (1.01, 2.22) | 1.00 (0.70, 1.43) | 1.38 (1.06, 1.82) |
| Multivariateb RR (95% CI) | 1.00 (referent) | 0.88 (0.64, 1.19) | 1.52 (1.01, 2.27) | 1.01 (0.70, 1.44) | 1.41 (1.07, 1.86) |
| Serous tumours | 96 | 32 | 19 | 23 | 63 |
| No. of cases | 1.00 (referent) | 0.83 (0.55, 1.25) | 1.60 (0.95, 2.68) | 1.09 (0.68, 1.75) | 1.66 (1.17, 2.36) |
| Multivariateb RR (95% CI) | 1.25 (1.12, 1.38) | 1.04 (0.82, 1.32) | 1.30 (0.99, 1.67) | 0.99 (0.73, 1.38) | 1.16 (0.84, 1.61) |
| Endometrioid tumours | 21 | 9 | 7 | 8 | 15 |
| No. of cases | 1.00 (referent) | 1.25 (0.56, 2.80) | 3.59 (1.41, 9.14) | 1.38 (0.59, 3.25) | 1.86 (0.89, 3.91) |
| Multivariateb RR (95% CI) | 1.25 (1.12, 1.38) | 1.04 (0.82, 1.32) | 1.30 (0.99, 1.67) | 0.99 (0.73, 1.38) | 1.16 (0.84, 1.61) |

Abbreviations: RR, relative risk; CI, confidence interval. aResults by histologic type are presented for serous/poorly differentiated and endometrioid tumours only due to small numbers for the other histologic types. bAdjusted for age, parity, duration of oral contraceptive use, tubal ligation, age at natural menopause and age at menarche.

Table 4  Continuous years of estrogen and estrogen plus progestin use and risk of epithelial ovarian cancer; all cases combined and by histologic type

| All ovarian tumours | Continuous RR converted to 5-year increment |
|---------------------|------------------------------------------|
|                      | Estrogen only | Estrogen plus progestin |
| Casesa              | 137 | 82 |
| Age-adjusted RR (95% CI) | 1.23 (1.11, 1.35) | 1.05 (0.82, 1.33) |
| Multivariateb RR (95% CI) | 1.25 (1.12, 1.38) | 1.04 (0.82, 1.32) |
| Serous tumours | 89 | 49 |
| Casesa              | 1.23 (1.07, 1.40) | 1.12 (0.84, 1.51) |
| Multivariateb RR (95% CI) | 1.53 (1.20, 1.94) | 1.04 (0.53, 2.03) |
| Endometrioid tumours | 23 | 15 |
| Casesa              | 1.53 (1.20, 1.94) | 1.04 (0.53, 2.03) |

Abbreviations: RR, relative risk; CI, confidence interval; PMH, postmenopausal hormone. aResults by histologic type are presented for serous/poorly differentiated and endometrioid tumours only due to small numbers for the other histologic types. bSome participants (and therefore cases) contribute to multiple categories simultaneously because they used estrogen only, estrogen plus progestin and/or other PMH formulations. cAdjusted for age, parity, duration of oral contraceptive use, tubal ligation, age at natural menopause and age at menarche.

DISCUSSION

In this prospective study, we observed a positive association between long duration of PMH use and ovarian cancer risk, regardless of whether use was current or past. More specifically, duration of unopposed estrogen use was positively associated with risk, whereas estrogen plus progestin use was not; the association was stronger for endometrioid tumours, although numbers were small.

In a collaborative re-analysis of 12 case–control studies, no association was found with duration of PMH use in either hospital-based (OR = 0.90 for a 5-year increment of use, P = 0.37) or population-based (OR = 1.10 for a 5-year increment of use, P = 0.21) studies (Whitemore et al, 1992). Meta-analyses (Garg et al, 1998; Coughlin et al, 2000) and certain case–control studies (Weiss et al, 1992; Riman et al, 2002) also failed to find a significant trend with duration of use, although some found a positive association (Risch, 1996) or suggested a positive trend (Kaufman et al, 1989; Bosetti et al, 2001).

Recently, four prospective studies found that longer durations of PMH use were associated with ovarian cancer risk or death (Rodriguez et al, 2001; Lacey et al, 2002; Folsom et al, 2004; Lacey et al, 2006). In two, ovarian cancer risk (Lacey et al, 2006) and mortality (Rodriguez et al, 2001) were increased among unopposed estrogen users of ≥10 years but not among users of <10 years; elevations in mortality were similar for current and past long-duration users (Rodriguez et al, 2001). Two other cohort studies observed increases in risk with shorter durations of use: in the Breast Cancer Detection Demonstration Project (BCDDP, n = 329 cases), unopposed estrogen use was significantly associated with risk (RR = 1.40 for 5 years use, converted from a 1-year estimate), with similar results for recent and former long-duration users (Lacey et al, 2002). In another prospective study, current users of unopposed estrogens for >5 years had a significantly elevated risk (RR = 2.53, 95% CI 1.44–4.45, n = 16 cases); although risk was not increased among long-duration past users, there were only four cases (Folsom et al, 2004). Findings from recent case–control studies also generally support a positive association with long-duration PMH use (Glud et al, 2004; Mills et al, 2004; Pike et al, 2004; Riman et al, 2004; Moorman et al, 2005).

We found a strong association with duration of PMH use and risk among current and past users of five or more years duration. With both duration and status of use (never, past, current) in the same model, only duration was statistically significant (data not shown). Overall, the significant increase in risk appeared to be driven largely by duration rather than by status of use. This contrasts with breast cancer PMH findings, where the increased risk is confined to current users (Colditz et al, 1995; Collaborative Group on Hormonal Factors in Breast Cancer, 1997; Beral et al, 2003), although the comparison is limited by the relative paucity of data on recency effects for ovarian cancer.

Only recently have studies had sufficient case numbers to evaluate associations for estrogen and progestin use. A Swedish case–control study (n = 655 cases) found that use of estrogen plus sequential progestin was associated with an increased risk, whereas estrogen plus continuous progestin was not (Riman et al, 2002). However, results from the women’s health initiative (WHI), a randomized clinical trial of estrogen plus continuous progestin (n = 32 cases), were consistent with an increase in risk (RR = 1.58, 95% CI 0.77–3.24), although not statistically significant (Anderson et al, 2005). Another cohort study found an increased risk associated with both sequential (RR = 3.09, 95% CI 1.68–5.68;
n = 13 cases) and continuous (RR = 1.82, 95% CI 1.03–3.23; n = 15 cases) estrogen plus progestin use of ≥5 years in women without a hysterectomy (Lacey et al, 2006).

In contrast, a cohort study in Norway found no association with use of estrogen plus progestin (RR = 1.5, 95% CI 0.9–2.6; n = 23 cases) (Bakken et al, 2004), and nor did the BCDDP study. Data suggested that unopposed estrogen, followed by estrogen plus progestin, was associated with risk; however, the effects of the different hormones could not be disentangled (Lacey et al., 2002). In our study, when simultaneously including terms for years of unopposed estrogen, estrogen plus progestin and other PMH use, only unopposed estrogen use was significantly associated with risk; results were consistent among users of a single hormone type. However, duration of estrogen plus progestin use was on an average shorter than use of unopposed estrogen, and the upper confidence limits were similar to those observed for unopposed estrogen use. Further studies about long-duration estrogen plus progestin use are therefore needed, given its more recent introduction to the market, particularly those focused on sequential or continuous hormone regimens.

Among the few analyses by histologic type, one suggested that PMH use might specifically increase risk of endometrioid tumours (Weiss et al, 1998). This prospective study either have not examined tumour subtype (Rodriguez et al, 2001; Anderson et al, 2003; Bakken et al, 2004; Folsom et al, 2004; Lacey et al, 2006) or had incomplete information on histology (Lacey et al, 2002). Despite limited power, in our study, the association with unopposed estrogen use appeared slightly stronger for endometrioid tumours. In age-adjusted analyses, point estimates suggested PMH use might decrease the risk of mucinous tumours, consistent with epidemiologic and biologic data (Lacey et al, 1997), and unopposed estrogen use increases the risk of endometrioid cancer (Fraser et al, 1998). Mucinous tumours are classified as those that resemble colonic or endocervical epithelium (Kumar et al, 1997). PMH use has been associated with decreased colon cancer risk (Nelson et al, 2002) but not with altered cervical cancer risk (Weiss and Hill, 1996).

The mechanism by which PMH might affect ovarian cancer risk is unknown. One theory posits that high levels of gonadotropins increase risk, implying that PMH use might decrease risk by reducing these levels (follicle-stimulating hormone (FSH) and leutinising hormone (LH)), but as the declines associated with PMH use are small, the benefits might be outweighed by estrogen-induced proliferation of ovarian cells (Cramer and Welch, 1983; Fraser et al, 1998); it has been estimated that as many as 60% of ovarian tumours are estrogen receptor-positive (Cunat et al, 2004).

Breast cancer research also suggests that estrogen may be directly genotoxic (Ho, 2003). Although it is premature to conclude that estrogen plus progestin use is unassociated with ovarian cancer risk, particularly given the conflicting findings, research on ovariating macaques suggests that progesterone offsets the effect of unopposed estrogen use by increasing apoptosis in the ovary (Rodriguez et al, 1998), possibly by altering levels of TGF-β, a regulator of apoptosis (Rodriguez et al, 2002). The progesterone in these animal studies may have different effects from the progestins commonly used in PMH formulations, but a mechanism is suggested, given that progesterone receptors are normally found in ovarian epithelium (Risch, 1998).

Our analysis has several strengths. The NHS is one of only a few prospective studies of PMH use and ovarian cancer, and associations could be examined by hormone type. Information on exposures and confounders is updated through biennial questions, and follow-up of the cohort is high. The nurses are a relatively homogenous group, with similar education and access to health care, reducing concerns about confounding. Although family history of ovarian cancer was first collected in 1992, this did not vary substantially across exposure. Histologic tumour type was coded by a gynecologic pathologist and was available for most cases.

Nurses’ Health Study (NHS) participants are not a representative sample of the general population. While it is unlikely that the observed associations would differ in other women, studies covering different race/ethnicity and socioeconomic status are warranted. Generalisability may also be limited by the variations in PMH formulations across countries. We had limited power to look at non-oral formulations of PMH, which are more commonly used outside the US (Ho, 2003). Small numbers prevented evaluation of different regimens of estrogen plus progestin and limited the analysis of recency of use.

In conclusion, we found that use of PMH was positively associated with risk of epithelial ovarian cancer. With other recent studies, our findings suggest that women should be counselled about the potential long-term increase in ovarian cancer risk with extended use of unopposed estrogen. Evidence is insufficient to say whether estrogen plus progestin or very short durations of unopposed estrogen use are associated with risk. Available findings indicate that ovarian cancer is one of several conditions that should be considered by women when weighing the risk and benefits of PMH use.

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