

Oral contraceptive use and reproductive factors and risk of ovarian cancer in the European Prospective Investigation into Cancer and Nutrition

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BACKGROUND: It is well established that parity and use of oral contraceptives reduce the risk of ovarian cancer, but the associations with other reproductive variables are less clear.

METHODS: We examined the associations of oral contraceptive use and reproductive factors with ovarian cancer risk in the European Prospective Investigation into Cancer and Nutrition. Among 327 396 eligible women, 878 developed ovarian cancer over an average of 9 years. Hazard ratios (HRs) and 95% confidence intervals (CIs) were estimated using Cox proportional hazard models stratified by centre and age, and adjusted for smoking status, body mass index, unilateral ovariectomy, simple hysterectomy, menopausal hormone therapy, and mutually adjusted for age at menarche, age at menopause, number of full-term pregnancies and duration of oral contraceptive use.

RESULTS: Women who used oral contraceptives for 10 or more years had a significant 45% (HR, 0.55; 95% CI, 0.41–0.75) lower risk compared with users of 1 year or less (*P*-trend, <0.01). Compared with nulliparous women, parous women had a 29% (HR, 0.71; 95% CI, 0.59–0.87) lower risk, with an 8% reduction in risk for each additional pregnancy. A high age at menopause was associated with a higher risk of ovarian cancer (>52 vs ≤45 years: HR, 1.46; 95% CI, 1.06–1.99; *P*-trend, 0.02). Age at menarche, age at first full-term pregnancy, incomplete pregnancies and breastfeeding were not associated with risk.

CONCLUSION: This study shows a strong protective association of oral contraceptives and parity with ovarian cancer risk, a higher risk with a late age at menopause, and no association with other reproductive factors.

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In developed countries, ovarian cancer is the sixth most common malignancy and cause of cancer death in women (American Cancer Society, 2007). Some reproductive factors are associated with the risk of ovarian cancer, with evidence for a protective association of high parity and oral contraceptive use (Negri *et al*, 1991; Whittemore *et al*, 1992; Hankinson *et al*, 1995; Beral *et al*, 2008). However, the evidence that other reproductive variables, such as breastfeeding, incomplete pregnancies, age at menarche and age at menopause, are associated with risk is weak and inconsistent, and mostly comes from case-control studies (Riman *et al*, 2004).

The aim of this study was to evaluate the association between oral contraceptive use and reproductive factors with ovarian cancer risk in a large prospective European study. A secondary aim was to examine whether these associations differed by participant characteristics such as age at enrolment, body mass index (BMI) and other factors.

MATERIALS AND METHODS

Source and study population

The European Prospective Investigation into Cancer and Nutrition (EPIC) includes approximately 370 000 women and 150 000 men and was designed to investigate dietary and lifestyle determinants of cancer. The participants were recruited between 1992 and 2000 in 23 centres in 10 European countries (Denmark, France, Germany, Greece, Italy, The Netherlands, Norway, Spain, Sweden and the United Kingdom). The cohort population and data collection procedures have been described in detail elsewhere (Riboli *et al*, 2002). Approval for the study was obtained from the local ethics committees in the participating countries and the internal review board of the International Agency for Research on Cancer.

Incident cancer cases were identified through linkage to population cancer registries in Denmark, Italy, The Netherlands, Norway, Spain, Sweden and the UK, or using a combination of methods including linkage to health insurance records, cancer and pathology registries, and active follow-up of study participants or their next of kin in France, Germany and Greece.

Of the approximately 370 000 women enrolled in the cohort, women were excluded if they had prevalent cancer ($n=19\,707$), if they had incomplete follow-up data ($n=2\,205$), if they had a bilateral ovariectomy ($n=10\,500$), if they did not return the baseline questionnaire ($n=509$), if they never menstruated ($n=61$), if they had missing information on oral contraceptive use and all reproductive history variables ($n=7\,589$), or if they were diagnosed with a non-epithelial ovarian cancer ($n=26$). Of the final analytic cohort of 327 396 women, 878 developed epithelial ovarian cancer from the date of recruitment until the end of follow-up (31 December 2003 to 20 December 2006, according to centre). The cancer diagnosis was confirmed by histology for 77.6% of the cases, by clinical examination for 13.8% and the remaining 8.6% by self-report, autopsy or death certificate. In all, 47% of tumours were of a serous histology, 10% were mucinous, 10% endometrioid, 4% clear cell and 1% undifferentiated; the remaining 28% had missing, undefined or not otherwise specified histologies. Of the 878 cases, 70 were of low malignant potential (borderline tumours); exclusion of these cases did not change the risk estimates, and they were therefore included in the final analysis.

Exposure and covariate assessment

Women were asked at the baseline questionnaire whether they had ever used oral contraceptives, their duration of use up until the time of recruitment, and the age at first use. Information on age at

menarche and menopause, numbers of full-term pregnancies (defined as the sum of live and stillbirths), incomplete pregnancies (defined as induced or spontaneous abortions) and age at the first full-term pregnancy was also collected. Information on breastfeeding was collected for the first three full-term pregnancies and the last one. The duration of breastfeeding was calculated as the sum for all pregnancies for which we had information. For women with more than four pregnancies and who had breastfed for all the pregnancies for which we had information, the duration of breastfeeding was taken to be the number of pregnancies multiplied by the mean of breastfeeding duration of each child. Menopausal status was defined according to information on menstruation status, hysterectomy, ovariectomy, use of exogenous hormones and age, details of which are provided elsewhere (Dossus *et al*, 2010). The cumulative duration of menstrual cycles among postmenopausal women was defined as the time between age at menarche and age at menopause minus the cumulative duration of full-term pregnancies (calculated as the number of full-term pregnancies times 0.75) and oral contraceptive use.

Information on anthropometric data, physical activity, smoking status, education level, self-reported diabetes mellitus, simple hysterectomy (with ovarian conservation) and unilateral ovariectomy status was also collected from the baseline questionnaire. Weight and height were measured at recruitment, except for part of the Oxford cohort, the Norwegian cohort, and approximately two-thirds of the French cohort, among whom weight and height were self-reported. Body mass index was calculated as weight in kilograms divided by height in metres squared. A combined physical activity index was calculated, which incorporated occupational and recreational activities.

Statistical analysis

Hazard ratios (HRs) and their 95% confidence intervals (CIs) for ovarian cancer were estimated using Cox proportional hazards models with age as the underlying time scale. Entry and exit time was defined as the woman's age at recruitment and age at ovarian cancer diagnosis or censoring (death, lost to follow-up or end of follow-up), respectively. All models were stratified by EPIC recruitment centre and age at enrolment (≤ 50 , 51–53, 54–56, 57–59, 60–62, 63–65, > 65 years). The proportionality of hazards was verified based on the slope of the Schoenfeld residuals over time, which is equivalent to testing that the log HR function is constant over time (Schoenfeld, 1982). Linear trends were tested by entering appropriate ordinal variables into the model, the coefficients of which were evaluated by the Wald test.

All models were adjusted for potential risk factors for ovarian cancer, including tobacco smoking status (never, former, current), BMI (continuous), unilateral ovariectomy (no, yes), simple hysterectomy (no, yes), menopausal hormone therapy (never, former, current use: oestrogen only, oestrogen plus progestin, other formulation), and further mutually adjusted for age at menarche (< 12 , 12, 13, 14, ≥ 15 years), age at menopause (premenopausal, perimenopausal, postmenopausal: ≤ 45 , 46–50, 51–52, > 52 years; based on fourths of the distribution in the controls), number of full-term pregnancies (0, 1, 2, 3, ≥ 4) and duration of oral contraceptive use (never, ever: ≤ 1 , 2–4, 5–9, ≥ 10 years), as applicable. Only the fully adjusted statistical models are presented in the text, because the centre and age-stratified models yielded almost identical estimates. For each covariate, missing values were assigned to separate categories, where appropriate; an analysis that excluded individuals with missing values for these covariates produced similar results and is not presented here. Further adjustments for physical activity, diabetes mellitus and education yielded almost identical results and are not presented.

To examine whether the oestrogen dose in oral contraceptive formulations influenced the risk, the analyses were stratified by

calendar year of first oral contraceptive use. The oral contraceptives prescribed before 1970 were typically high-dose preparations, whereas those prescribed between 1970 and 1980 were typically medium dose and by 1980 most prescriptions were for low-dose preparations (Piper and Kennedy, 1987; Thorogood and Villard-Mackintosh, 1993).

Analyses were also performed by ovarian cancer histology, EPIC-participating country and according to other factors including: age at recruitment (at the median, <50 vs ≥ 50), BMI (at the median, <24 vs ≥ 24 kg m⁻²), smoking status (ever vs never), parity (parous vs nulliparous), menopausal status (postmenopausal vs pre/perimenopausal) and menopausal hormone therapy at recruitment (ever vs never use and current vs never use). Tests for interaction were carried out by using the relevant exposure variables, indicator variables for the potentially modifying factors, and product terms of the two variables. Sensitivity analyses were run after excluding ovarian cancer cases that developed in the first 2 years of follow-up or after excluding participants with a history of simple hysterectomy and/or unilateral ovariectomy at baseline. The statistical significance of the interaction terms was evaluated by the Wald test. All *P*-values (*P*) were two-sided and all analyses were performed using STATA version 11 (College Station, TX, USA).

RESULTS

After recruitment into the study, 878 cases of ovarian cancer were diagnosed during 2.9 million person-years of follow-up, over an average of 9 years (Table 1). The mean age at recruitment and diagnosis for the ovarian cancer cases was 55 and 60 years, respectively. In all, 59% of the cohort reported ever use of oral contraceptives (Table 1), 9% of which were current users. Ever use of oral contraceptive was lowest in Greece (10%) and highest in Germany (82%). The median duration of oral contraceptive use was 5 years but women in Greece, Italy and Spain had considerably shorter durations. Eighty percent of the cohort reported having had a full-term pregnancy, 28% reported ever having an incomplete pregnancy and 82% reported that they had ever breastfed. The overall mean ages at menarche and menopause were 13 and 50 years, respectively, without any notable variation by country.

Oral contraceptive use

Compared with never users of oral contraceptives, ever users had a significantly lower risk of ovarian cancer in the age and centre-stratified model (HR, 0.84; 95% CI, 0.72–0.98), and that remained very similar after additional adjustment for smoking status, BMI, unilateral ovariectomy, simple hysterectomy, menopausal hormone therapy, age at menarche, age at menopause and number of full-term pregnancies (HR, 0.86; 95% CI, 0.73–1.00; Table 2). Increasing duration of oral contraceptive use was associated with a progressive reduction in risk; women who used oral contraceptives for 10 or more years had a 45% (HR, 0.55; 95% CI, 0.41–0.75) lower risk compared with users of 1 year or less, which corresponded to a 13% (HR, 0.87; 95% CI, 0.82–0.93) lower risk per 5 years of use (*P*-trend, <0.01). There was no association between age at first use of oral contraceptives and risk of ovarian cancer (Table 2), either before or after adjusting for duration of oral contraceptive use (data not shown).

The reduced risk of ovarian cancer associated with ever use of oral contraceptives was similar within each category of calendar year of first use (1960s or earlier: HR, 0.83; 95% CI, 0.68–1.01; 1970s: HR, 0.80; 95% CI, 0.63–1.01; 1980s or later: HR, 0.90; 95% CI, 0.69–1.16). The risk associated with increasing duration of oral contraceptive use did not vary significantly by ovarian cancer histology, country, age at recruitment, smoking status or parity

(data not shown). However, there was some evidence that this association varied by BMI (Table 3; *P*-interaction, 0.01), with a stronger inverse association in women with a BMI <24 kg m⁻² (≥ 10 vs ≤ 1 year of use: HR, 0.38; 95% CI, 0.25–0.59; *P*-trend, <0.01) compared with women with a BMI of 24 kg m⁻² or more (HR, 0.80; 95% CI, 0.52–1.23; *P*-trend, 0.24). This association was also stronger in pre/perimenopausal women (Table 3; ≥ 10 vs ≤ 1 years of use: HR, 0.41; 95% CI, 0.26–0.63; *P*-trend, <0.01) than in postmenopausal women (HR, 0.76; 95% CI, 0.49–1.17; *P*-trend, 0.14; *P*-interaction, 0.02).

Parity and other reproductive variables

Compared with nulliparous women, women who had children had a 29% (HR, 0.71; 95% CI, 0.59–0.87) lower risk of ovarian cancer (Table 4), with a progressive reduction in risk with each additional pregnancy. Compared with women with one full-term pregnancy, women with four or more full-term pregnancies had a 23% lower risk (HR, 0.77; 95% CI, 0.57–1.04), which corresponded to an 8% (HR, 0.92; 95% CI, 0.85–0.99) lower risk per full-term pregnancy (*P*-trend, 0.03). Compared with nulliparous women, women with four or more full-term pregnancies had a 38% lower risk (HR, 0.62; 95% CI, 0.46–0.83; *P*-trend, <0.01). Age at first full-term pregnancy, ever having had an incomplete pregnancy and breastfeeding were not associated with risk (Table 4).

The risk of ovarian cancer was not associated with age at menarche or menopausal status (Table 4), although age at menopause was significantly positively associated with risk (>52 vs ≤ 45 years: HR, 1.46; 95% CI, 1.06–1.99). The estimated cumulative duration of menstrual cycles was also associated with a higher risk (>36 vs ≤ 27 years: HR, 1.57; 95% CI, 1.16–2.13; *P*-trend, <0.01). A one-year increase in menstrual lifespan corresponded to a 2% higher risk (HR, 1.02; 95% CI, 1.01–1.04). However, when women who were diagnosed with ovarian cancer within the first 2 years of follow-up were excluded from the analysis (194 cases), the associations of age at menopause (>52 vs ≤ 45 years: HR, 1.40; 95% CI, 0.98–2.00; *P*-trend, 0.12) and menstrual lifespan (>36 vs ≤ 27 years: HR, 1.37; 95% CI, 0.98–1.93; *P*-trend, 0.01) with risk of ovarian cancer were attenuated.

None of the associations between reproductive factors and risk of ovarian cancer differed by ovarian cancer histology, country, age, BMI, smoking status, menopausal status or menopausal hormone therapy (data not shown). In addition, sensitivity analyses that excluded participants with a history of simple hysterectomy and/or unilateral ovariectomy at recruitment yielded almost identical estimates.

DISCUSSION

This large prospective study confirms the strong protective association of oral contraceptive use and parity on risk of ovarian cancer. No significant associations with risk were found for age at menarche, age at first full-term pregnancy, incomplete pregnancies or breastfeeding.

There is strong evidence that oral contraceptive use reduces ovarian cancer risk; a collaborative pooled analysis of 45 epidemiological studies (13 prospective and 32 case-control studies) reported a relative risk of 0.73 (95% CI, 0.70–0.76) for ever vs never users of oral contraceptives (Beral *et al*, 2008). That study also showed a progressive decline with increasing duration of use (10–14 years vs <1 year: HR, 0.56; 95% CI, 0.50–0.62) of a magnitude similar to our findings. The pooled analysis also showed that, although the risk is attenuated with increasing time since last use, the protective effect of oral contraceptives on ovarian cancer remains for many years after cessation of use (Beral *et al*, 2008). However, we were unable to examine this association because many EPIC centres did not collect information

Table 1 Participant characteristics at recruitment among women in the EPIC cohort by country, means or medians (s.d. or inter-quartile ranges) and percentages

| Characteristic | All (n = 327 396) | Denmark (n = 27 958) | France (n = 67 504) | Germany (n = 27 586) | Greece (n = 14 459) | Italy (n = 29 857) | Netherlands (n = 26 259) | Norway (n = 35 800) | Spain (n = 23 975) | Sweden (n = 20 418) | UK (n = 53 580) |
|--|----------------------|-------------------------|------------------------|-------------------------|------------------------|-----------------------|-----------------------------|------------------------|-----------------------|------------------------|--------------------|
| Number of cases | 878 | 92 | 192 | 56 | 32 | 73 | 64 | 76 | 52 | 87 | 154 |
| Age at recruitment, years | 50.4 (9.7) | 56.2 (4.4) | 52.1 (6.6) | 48.3 (8.9) | 52.4 (12.6) | 49.9 (8.1) | 50.1 (11.7) | 47.6 (4.3) | 47.5 (8.4) | 55.3 (8.0) | 47.3 (14.4) |
| Body mass index (kg m ⁻²) | 24.9 (4.4) | 25.6 (4.4) | 23.0 (3.4) | 25.6 (4.7) | 28.5 (5.2) | 25.6 (4.3) | 25.1 (4.2) | 24.4 (3.8) | 28.1 (4.7) | 25.1 (4.2) | 24.2 (4.2) |
| Current smokers (%) | 19.7 | 31.4 | 8.8 | 18.6 | 17.5 | 26.3 | 28.0 | 31.7 | 19.4 | 24.6 | 11.0 |
| Unilateral ovariectomy (%) | | | | | | | | | | | |
| Yes | 3.4 | 6.0 | 3.5 | 5.2 | 1.8 | 4.3 | 5.6 | NR | 2.9 | NR | 3.1 |
| No | 77.7 | 92.9 | 91.9 | 94.7 | 97.8 | 95.3 | 92.5 | NR | 97.0 | NR | 93.5 |
| Missing | 18.9 | 1.1 | 4.6 | 0.1 | 0.4 | 0.4 | 1.9 | NR | 0.1 | NR | 3.4 |
| Hysterectomy (%) | | | | | | | | | | | |
| Yes | 7.9 | 11.4 | 7.6 | 12.5 | 3.1 | 5.5 | 15.3 | 4.7 | 3.3 | NR | 10.0 |
| No | 82.6 | 88.5 | 89.6 | 87.5 | 96.9 | 94.3 | 84.6 | 70.9 | 96.6 | NR | 88.7 |
| Missing | 9.5 | 0.1 | 2.8 | 0 | 0 | 0.2 | 0.1 | 24.4 | 0.1 | NR | 1.3 |
| Oral contraceptive use (%) | | | | | | | | | | | |
| Ever | 58.9 | 58.2 | 61.6 | 81.7 | 9.8 | 41.4 | 73.8 | 64.1 | 42.9 | 51.1 | 66.5 |
| Never | 40.6 | 40.8 | 38.2 | 18.2 | 90.2 | 58.4 | 26.1 | 35.9 | 57.0 | 48.2 | 32.0 |
| Missing | 0.5 | 1.0 | 0.2 | 0.1 | 0 | 0.2 | 0.1 | 0 | 0.1 | 0.7 | 1.5 |
| Duration (years) of OC use ^a | 5 (2–10) | 6 (2–12) | 5 (2–10) | 10 (5–30) | 1 (1–3) | 2 (1–5) | 10 (5–15) | 3 (1–7) | 2 (1–5) | 7 (3–14) | 6 (3–10) |
| Age at first OC use (years) ^a | 25.4 (6.7) | 27.7 (5.7) | 28.6 (6.5) | NR | 26.5 (6.0) | 28.3 (6.8) | 25.6 (7.3) | 22.4 (4.1) | NR | 26.5 (7.3) | 22.0 (5.8) |
| FTP (%) ^b | | | | | | | | | | | |
| Ever | 79.6 | 88.3 | 83.7 | 85.4 | 89.5 | 86.9 | 48.7 | 91.5 | 88.6 | 78.9 | 66.9 |
| Never | 13.6 | 11.4 | 8.8 | 14.4 | 10.3 | 13.1 | 6.9 | 8.5 | 10.5 | 9.1 | 31.3 |
| Missing | 6.8 | 0.3 | 7.5 | 0.2 | 0.2 | 0 | 44.4 | 0 | 0.9 | 12.0 | 1.8 |
| Number of FTP ^c | 2.3 (1.0) | 2.2 (0.9) | 2.3 (0.9) | 2.0 (0.9) | 2.4 (1.1) | 2.1 (0.9) | 2.7 (1.3) | 2.4 (0.9) | 2.7 (1.3) | 2.2 (1.0) | 2.3 (1.0) |
| Age at first FTP (years) ^c | 24.9 (4.4) | 23.8 (4.2) | 24.9 (4.0) | 24.3 (4.4) | 24.2 (4.7) | 25.8 (4.3) | 25.6 (4.0) | 24.1 (4.5) | 24.7 (3.9) | 24.7 (4.6) | 26.0 (4.7) |
| Incomplete pregnancy (%) ^d | | | | | | | | | | | |
| Ever | 27.7 | 40.7 | 35.6 | 37.0 | 58.2 | 36.8 | 14.6 | NR | 24.6 | 15.9 | 23.4 |
| Never | 44.1 | 50.7 | 49.9 | 51.8 | 35.0 | 53.0 | 34.7 | NR | 65.0 | 54.2 | 47.6 |
| Missing | 28.2 | 8.6 | 14.5 | 11.2 | 6.8 | 10.2 | 50.7 | NR | 10.4 | 29.9 | 29.0 |
| Breastfeeding (%) ^e | | | | | | | | | | | |
| Ever | 81.8 | 91.7 | 69.5 | 84.4 | 87.3 | 83.5 | 81.0 | 92.8 | 88.7 | 69.6 | 80.7 |
| Never | 14.7 | 6.8 | 27.9 | 15.3 | 11.3 | 16.0 | 18.4 | 5.7 | 10.8 | 3.6 | 13.7 |
| Missing | 3.5 | 1.5 | 2.6 | 0.3 | 1.4 | 0.5 | 0.6 | 1.5 | 0.5 | 26.8 | 5.6 |
| Breastfeeding duration ^e | 6 (3–13) | 7 (4–12) | 5 (2–7) | 3 (1–8) | 11 (4–24) | 7 (3–12) | 5 (2–9) | 12 (6–19) | 9 (4–16) | 8 (4–13) | 7 (2–15) |
| Age at menarche (years) | 13.1 (1.5) | 13.7 (1.6) | 12.9 (1.4) | 13.2 (1.5) | 13.2 (1.7) | 12.6 (1.5) | 13.3 (1.6) | 13.3 (1.4) | 12.9 (1.6) | 13.5 (1.5) | 12.9 (1.6) |
| Age at menopause (years) ^f | 50 (46–52) | 50 (47–52) | 50 (48–53) | 50 (46–52) | 49 (45–52) | 50 (47–52) | 50 (46–52) | 48 (46–50) | 50 (46–52) | 50 (47–52) | 50 (45–52) |
| Menopausal status (%) | | | | | | | | | | | |
| Premenopausal | 35.2 | 7.6 | 26.9 | 47.9 | 38.8 | 40.9 | 34.3 | 35.3 | 56.6 | 7.2 | 50.7 |
| Perimenopausal | 19.3 | 19.4 | 26.1 | 13.3 | 7.2 | 16.1 | 18.2 | 35.3 | 9.8 | 25.7 | 10.6 |
| Postmenopausal | 45.5 | 73.0 | 47.0 | 38.8 | 54.0 | 43.0 | 47.5 | 29.4 | 33.6 | 67.1 | 38.7 |
| Total menstrual lifespan ^g | 33 (27–37) | 32 (25–36) | 35 (30–38) | 30 (22–35) | 33 (29–37) | 35 (31–38) | 30 (23–35) | 32 (28–35) | 33 (30–36) | 33 (27–36) | 33 (27–37) |

Abbreviations: EPIC = European Prospective Investigation into Cancer and Nutrition; FTP = full-term pregnancy; NR = not reported; OC = oral contraceptive. ^aAmong ever OC users only. ^bA FTP is defined as a live or stillbirth. ^cAmong women with a FTP only. ^dAn incomplete pregnancy is defined as an induced or spontaneous abortion. ^eAmong women with a FTP who ever breastfed only; in months. ^fAmong postmenopausal women only. ^gCalculated in years as (age at menopause – age at menarche – duration of OC use – cumulative duration of FTP) in postmenopausal women only.

on the age at last oral contraceptive use, and it is possible that the stronger inverse associations observed for the duration of oral contraceptive use and ovarian cancer risk among lean and pre/perimenopausal women in our study population might, in part, reflect a shorter time since last use among these women. Our results also suggest that the dose of oestrogen contained in oral contraceptives has a negligible impact on the association with ovarian cancer risk, as shown by similar estimates in risk according to calendar year of first oral contraceptive use, and which is consistent with the findings from the pooled analysis (Beral *et al*, 2008).

A protective association between parity and ovarian cancer risk has been observed in most previous studies (Negri *et al*, 1991; Whittemore *et al*, 1992; Hankinson *et al*, 1995; Vachon *et al*, 2002; Tung *et al*, 2003; Moorman *et al*, 2009). The current study suggests

that there is a quite large reduction in risk with the first child, with progressive lower risks with each additional full-term pregnancy. Our finding of no association between age at first full-term pregnancy and ovarian cancer risk is consistent with most studies (Kvale *et al*, 1988; Booth *et al*, 1989; Gwinn *et al*, 1990; Risch *et al*, 1994; Hankinson *et al*, 1995; Purdie *et al*, 1995; Riman *et al*, 2002; Vachon *et al*, 2002; Braem *et al*, 2010), although some have reported a reduction in risk with an early age at first full-term pregnancy (Adami *et al*, 1994; Albrektsen *et al*, 1996; Mogren *et al*, 2001; Titus-Ernstoff *et al*, 2001; Whiteman *et al*, 2003; Pike *et al*, 2004). Our finding of no association between number of incomplete pregnancies and ovarian cancer risk is consistent with some studies (Kvale *et al*, 1988; Booth *et al*, 1989; Risch *et al*, 1994; Purdie *et al*, 1995; Titus-Ernstoff *et al*, 2001), although others have found a reduced risk with more incomplete pregnancies, but

smaller in magnitude than the reduction observed for full-term pregnancies (Negri *et al*, 1991; Whittemore *et al*, 1992; Riman *et al*, 2002; Pike *et al*, 2004; Zhang *et al*, 2004).

Breastfeeding was not significantly associated with ovarian cancer risk in this study population, and although this is consistent with several studies (Booth *et al*, 1989; Purdie *et al*, 1995; Titus-Ernstoff *et al*, 2001; Riman *et al*, 2002; Pike *et al*, 2004), the cumulative duration of breastfeeding was relatively short in our study (upper category: >13 months), and we cannot rule out the

possibility of a protective association with a longer duration (e.g., >18 or >24 months) as seen in some other studies (Gwinn *et al*, 1990; Whittemore *et al*, 1992; Danforth *et al*, 2007; Jordan *et al*, 2010). The association between age at menarche and menopause and the risk of ovarian cancer has been extensively studied, although the findings have generally been weak and not statistically significant (Kvale *et al*, 1988; Gwinn *et al*, 1990; Whittemore *et al*, 1992; Hankinson *et al*, 1995; Purdie *et al*, 1995; Schildkraut *et al*, 2001; Titus-Ernstoff *et al*, 2001; Riman *et al*, 2002; Pike *et al*, 2004; Jordan *et al*, 2005; Braem *et al*, 2010). The current study shows that although there is no association between age at menarche and risk, a late age at menopause and the cumulative duration of menstrual cycles are both positively associated with ovarian cancer risk. If the number of menstrual cycles is important in the development of ovarian cancer, as has been suggested (Pike *et al*, 2004), it is likely that a difference of 1 or 2 years in the age at menarche will not contribute sufficiently to the lifetime number of menstrual cycles compared with larger differences in age at menopause, parity and oral contraceptive use. However, the increased risk in ovarian cancer observed with age at menopause was restricted to women in the highest category (52 years or older), and it is possible that this increased risk is partially a result of reverse causation, whereby older women may mistake bleeding from a sub-clinical cancer as menses. Indeed, after excluding the first 2 years of follow-up, the risk associated with a relatively late age at menopause was slightly attenuated and no longer statistically significant.

The exact mechanisms through which oral contraceptives and parity may reduce risk are not known, although several hypotheses have been proposed. These include inhibition of ovulation (Fathalla, 1971), exposure to low concentrations of gonadotropins (Stadel, 1975; Cramer and Welch, 1983), reduced retrograde transportation of contaminants from the vagina or growth factors from the uterus (Harlow *et al*, 1992; Cramer and Xu, 1995) and exposure to high progesterone concentrations (Risch, 1998; Lau *et al*, 1999; Syed *et al*, 2001; Riman *et al*, 2004; Mukherjee *et al*, 2005). In particular, pregnancy leads to anovulation, reduces gonadotropin secretion, increases progesterone levels and temporarily interrupts the retrograde transportation. Similarly, combined oral contraceptives suppress the midcycle gonadotropin surge with a consequent inhibition of ovulation. The increase in risk with a late age at menopause supports the incessant ovulation and the retrograde transportation hypotheses, but is not readily compatible with the gonadotropin stimulation and progesterone deficiency hypotheses (Riman *et al*, 2002).

Table 2 HR and 95% CI for oral contraceptive use and ovarian cancer risk in the EPIC cohort

| Variable | Cases/ non-cases | Age- and centre- stratified HR (95% CI) | Multivariable- adjusted HR (95% CI) ^a |
|--|---------------------|--|--|
| OC use | | | |
| Never | 453/132 622 | 1.00 (ref.) | 1.00 (ref.) |
| Ever | 418/192 401 | 0.84 (0.72–0.98) | 0.86 (0.73–1.00) |
| Duration of OC use, years ^b | | | |
| ≤1 | 96/35 185 | 1.00 (ref.) | 1.00 (ref.) |
| 2–4 | 109/41 341 | 1.04 (0.78–1.37) | 1.05 (0.79–1.38) |
| 5–9 | 83/41 723 | 0.79 (0.59–1.07) | 0.80 (0.59–1.08) |
| ≥10 | 90/57 246 | 0.56 (0.42–0.76) | 0.55 (0.41–0.75) |
| P-trend | | <0.01 | <0.01 |
| Per 5 years | | 0.88 (0.82–0.94) | 0.87 (0.82–0.93) |
| Age at first OC use ^b | | | |
| <25 | 115/75 496 | 1.00 (ref.) | 1.00 (ref.) |
| 25–29 | 81/34 282 | 1.03 (0.75–1.42) | 1.04 (0.76–1.44) |
| 30–34 | 73/20 495 | 1.34 (0.92–1.94) | 1.36 (0.94–1.97) |
| ≥35 | 55/15 838 | 1.21 (0.78–1.87) | 1.20 (0.78–1.86) |
| P-trend | | 0.23 | 0.23 |

Abbreviations: CI = confidence interval; EPIC = European Prospective Investigation into Cancer and Nutrition; HR = hazard ratio; OC = oral contraceptive; ref. = reference. ^aFrom a Cox proportional hazards model stratified by EPIC-participating centre and age at recruitment, and adjusted for smoking status (never, former, current), body mass index (kg m^{-2} , continuous), unilateral ovariectomy (no, yes), simple hysterectomy (no, yes), menopausal hormone therapy (never, former, current use: oestrogen-only, oestrogen plus progestin, other formulation), age at menarche (<12, 12, 13, 14, ≥15 years), number of full-term pregnancies (0, 1, 2, 3, ≥4) and age at menopause (premenopausal, perimenopausal, postmenopausal: ≤45, 46–50, 51–52, >52 years). ^bAmong ever OC users only.

Table 3 HR and 95% CI for duration of oral contraceptive use and ovarian cancer risk by BMI and menopausal status in the EPIC cohort

| Variable | BMI <24 kg m^{-2} | | BMI ≥24 kg m^{-2} | | Pre/perimenopausal | | Postmenopausal | |
|--|----------------------------|-----------------------------|----------------------------|-----------------------------|---------------------|-----------------------------|---------------------|-----------------------------|
| | Cases/ non-cases | HR (95% CI) ^a | Cases/ non-cases | HR (95% CI) ^a | Cases/ non-cases | HR (95% CI) ^b | Cases/ non-cases | HR (95% CI) ^b |
| Duration of OC use, years ^c | | | | | | | | |
| ≤1 | 52/17 673 | 1.00 (ref.) | 44/17 512 | 1.00 (ref.) | 54/22 645 | 1.00 (ref.) | 42/12 540 | 1.00 (ref.) |
| 2–4 | 58/22 652 | 0.93 (0.63–1.36) | 51/18 689 | 1.19 (0.79–1.79) | 58/28 756 | 0.88 (0.60–1.28) | 51/12 585 | 1.27 (0.84–1.92) |
| 5–9 | 38/23 922 | 0.57 (0.37–0.87) | 45/17 801 | 1.13 (0.73–1.74) | 38/29 806 | 0.55 (0.36–0.85) | 45/11 917 | 1.18 (0.77–1.81) |
| ≥10 | 39/30 969 | 0.38 (0.25–0.59) | 51/26 277 | 0.80 (0.52–1.23) | 41/37 013 | 0.41 (0.26–0.63) | 49/20 233 | 0.76 (0.49–1.17) |
| P-trend | | <0.01 | | 0.24 | | <0.01 | | 0.14 |
| P-interaction | | | | 0.01 | | | | 0.02 |
| Per 5 years | | 0.80 (0.71–0.89) | | 0.94 (0.86–1.02) | | 0.83 (0.75–0.92) | | 0.91 (0.84–1.00) |
| P-interaction (continuous) | | | | 0.02 | | | | 0.13 |

Abbreviations: BMI = body mass index; CI = confidence interval; EPIC = European Prospective Investigation into Cancer and Nutrition; HR = hazard ratio; OC = oral contraceptive; ref. = reference. ^aFrom a Cox proportional hazards model stratified by EPIC-participating centre and age at recruitment, and adjusted for smoking status (never, former, current), unilateral ovariectomy (no, yes), simple hysterectomy (no, yes), menopausal hormone therapy (never, former, current use: oestrogen-only, oestrogen plus progestin, other formulation), age at menarche (<12, 12, 13, 14, ≥15 years), number of full-term pregnancies (0, 1, 2, 3, ≥4) and age at menopause (premenopausal, perimenopausal, postmenopausal: ≤45, 46–50, 51–52, >52 years). ^bFrom a Cox proportional hazards model stratified by EPIC-participating centre and age at recruitment, and adjusted for smoking status (never, former, current), body mass index (kg m^{-2} , continuous), unilateral ovariectomy (no, yes), simple hysterectomy (no, yes), age at menarche (<12, 12, 13, 14, ≥15 years) and number of full-term pregnancies (0, 1, 2, 3, ≥4). ^cAmong ever OC users only.

Strengths of the present study include its prospective design and the wide distribution of oral contraceptive use and reproductive variables in different European studies. However, although EPIC is one of the largest studies to date to examine reproductive factors with ovarian cancer risk, there was limited statistical power to detect differences by histological subtypes of ovarian cancer. All analyses were adjusted for potential risk factors of ovarian cancer and further mutually adjusted for menstrual and reproductive variables, and which made little difference to the risk estimates suggesting that residual confounding is unlikely to influence our results. In particular, we lacked information on tubal ligation in EPIC but given the low prevalence of this procedure in Europe (Riman *et al*, 2002), the extent of potential confounding is expected to be minimal.

In conclusion, this study shows a strong protective association of oral contraceptive use and parity with risk of ovarian cancer, a higher risk with a late age at menopause, and no association with other reproductive factors in this large cohort of European women.

Table 4 HR and 95% CI for parity, other reproductive variables and ovarian cancer risk in the EPIC cohort

| Variable | Cases/ non-cases | Age- and centre- stratified HR (95% CI) | Multivariable- adjusted HR (95% CI) ^a |
|--|---------------------|---|--|
| FTP^b | | | |
| Never | 133/44 328 | 1.00 (ref.) | 1.00 (ref.) |
| Ever | 689/259 740 | 0.70 (0.58–0.85) | 0.71 (0.59–0.87) |
| Number of FTP | | | |
| Never | 133/44 328 | 1.00 (ref.) | 1.00 (ref.) |
| 1 | 135/47 766 | 0.79 (0.62–1.01) | 0.80 (0.63–1.02) |
| 2 | 335/125 984 | 0.73 (0.59–0.89) | 0.74 (0.61–0.91) |
| 3 | 149/59 703 | 0.63 (0.49–0.80) | 0.64 (0.50–0.81) |
| ≥4 | 70/26 287 | 0.61 (0.45–0.82) | 0.62 (0.46–0.83) |
| P-trend | | <0.01 | <0.01 |
| Number of FTP^c | | | |
| 1 | 135/47 766 | 1.00 (ref.) | 1.00 (ref.) |
| 2 | 335/125 984 | 0.93 (0.76–1.14) | 0.94 (0.77–1.15) |
| 3 | 149/59 703 | 0.80 (0.63–1.02) | 0.81 (0.64–1.02) |
| ≥4 | 70/26 287 | 0.77 (0.57–1.04) | 0.77 (0.57–1.04) |
| P-trend | | 0.03 | 0.03 |
| Per FTP | | 0.92 (0.85–0.99) | 0.92 (0.85–0.99) |
| Age at first FTP (years)^c | | | |
| ≤20 | 97/38 591 | 1.00 (ref.) | 1.00 (ref.) |
| 21–23 | 170/69 656 | 0.91 (0.71–1.17) | 0.92 (0.72–1.19) |
| 24–25 | 145/50 567 | 1.05 (0.81–1.36) | 1.07 (0.82–1.39) |
| 26–30 | 208/73 523 | 1.03 (0.80–1.31) | 1.05 (0.81–1.34) |
| >30 | 64/26 419 | 0.91 (0.66–1.26) | 0.93 (0.67–1.29) |
| P-trend | | 0.79 | 0.69 |
| Incomplete pregnancy^d | | | |
| Never | 413/143 841 | 1.00 (ref.) | 1.00 (ref.) |
| Ever | 237/90 352 | 1.00 (0.85–1.18) | 1.00 (0.85–1.18) |
| Breastfeeding^e | | | |
| Never | 115/38 087 | 1.00 (ref.) | 1.00 (ref.) |
| Ever | 543/212 490 | 0.86 (0.69–1.06) | 0.86 (0.70–1.07) |
| Duration of breastfeeding, months^e | | | |
| ≤1 (Including never) | 176/58 968 | 1.00 (ref.) | 1.00 (ref.) |
| 2–6 | 205/85 202 | 0.83 (0.68–1.02) | 0.84 (0.68–1.03) |
| 7–12 | 134/50 185 | 0.90 (0.71–1.13) | 0.91 (0.72–1.14) |
| >13 | 139/54 475 | 0.87 (0.68–1.11) | 0.88 (0.69–1.13) |
| P-trend | | 0.38 | 0.45 |
| Age at menarche (years) | | | |
| <12 | 145/48 285 | 1.00 (ref.) | 1.00 (ref.) |
| 12 | 159/69 012 | 0.75 (0.60–0.94) | 0.76 (0.61–0.96) |
| 13 | 208/83 793 | 0.77 (0.62–0.96) | 0.79 (0.64–0.98) |
| 14 | 192/70 040 | 0.79 (0.64–0.99) | 0.82 (0.66–1.02) |
| ≥15 | 161/51 355 | 0.82 (0.65–1.04) | 0.85 (0.68–1.08) |

Table 4 (Continued)

| Variable | Cases/ non-cases | Age- and centre- stratified HR (95% CI) | Multivariable- adjusted HR (95% CI) ^a |
|--|---------------------|---|--|
| P-trend | | 0.29 | 0.46 |
| Per year | | 1.00 (0.95–1.04) | 1.00 (0.96–1.05) |
| Age at menopause (years)^e | | | |
| ≤45 | 75/23 730 | 1.00 (ref.) | 1.00 (ref.) |
| 46–50 | 172/46 885 | 1.14 (0.87–1.50) | 1.12 (0.84–1.49) |
| 51–52 | 75/19 790 | 1.11 (0.80–1.54) | 1.08 (0.77–1.52) |
| >52 | 120/22 831 | 1.51 (1.12–2.03) | 1.46 (1.06–1.99) |
| P-trend | | <0.01 | 0.02 |
| Per year | | 1.02 (1.00–1.05) | 1.02 (1.00–1.05) |
| Menopausal status | | | |
| Pre/perimenopausal | 331/178 107 | 1.00 (ref.) | 1.00 (ref.) |
| Postmenopausal | 547/148 411 | 0.92 (0.73–1.16) | 0.87 (0.69–1.10) |
| Total menstrual lifespan, years^f | | | |
| ≤27 | 75/25 330 | 1.00 (ref.) | 1.00 (ref.) |
| 28–32 | 71/22 627 | 1.05 (0.76–1.46) | 1.07 (0.77–1.49) |
| 33–36 | 121/28 006 | 1.42 (1.06–1.91) | 1.44 (1.07–1.95) |
| >36 | 135/27 225 | 1.56 (1.16–2.10) | 1.57 (1.16–2.13) |
| P-trend | | <0.01 | <0.01 |
| Per year | | 1.02 (1.01–1.04) | 1.02 (1.01–1.04) |

Abbreviations: CI = confidence interval; EPIC = European Prospective Investigation into Cancer and Nutrition; FTP = full-term pregnancy; HR = hazard ratio; ref. = reference. ^aFrom a Cox proportional hazards model stratified by EPIC-participating centre and age at recruitment, and adjusted for smoking status (never, former, current), body mass index (kg m⁻², continuous), unilateral ovariectomy (no, yes), simple hysterectomy (no, yes), menopausal hormone therapy (never, former, current use: oestrogen-only, oestrogen plus progestin, other formulation), duration of oral contraceptive use (never, ever: ≤1, 2–4, 5–9, ≥10 years), age at menarche (<12, 12, 13, 14, ≥15 years) and age at menopause (premenopausal, perimenopausal, postmenopausal: ≤45, 46–50, 51–52, >52 years). The models for incomplete pregnancy, age at menarche and menopause were further adjusted for number of FTPs (0, 1, 2, 3, ≥4). The model for menopausal status was not adjusted for menopausal hormone therapy and age at menopause. The model for total menstrual lifespan was not adjusted for age at menopause, age at menarche, duration of oral contraceptive use and number of FTPs. ^bA FTP is defined as a live or stillbirth. ^cAmong women with a FTP. ^dAn incomplete pregnancy is defined as an induced or spontaneous abortion. ^eAmong postmenopausal women only. ^fCalculated as (age at menopause – age at menarche – duration of oral contraceptive use – cumulative duration of FTP) in postmenopausal women only.

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