Combined oral contraceptive use before the first birth and epithelial ovarian cancer risk

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Background: Combined oral contraceptive (COC) use reduces epithelial ovarian cancer (EOC) risk. However, little is known about risk with COC use before the first full-term pregnancy (FFTP).

Methods: This Canadian population-based case–control study (2001–2012) included 854 invasive cases/2139 controls aged X 40 years who were parous and had information on COC use. We estimated odds ratios (aORs) and 95% confidence intervals (CI) adjusted for study site, age, parity, breastfeeding, age at FFTP, familial breast/ovarian cancer, tubal ligation, and body mass.

Results: Among parous women, per year of COC use exclusively before the FFTP was associated with a 9% risk reduction (95% CI = 0.86–0.96). Results were similar for high-grade serous and endometrioid/clear cell EOC. In contrast, per year of use exclusively after the FFTP was not associated with risk (aOR = 0.98, 95% CI = 0.95–1.02).

Conclusions: Combined oral contraceptive use before the FFTP may provide a risk reduction that remains for many years, informing possible prevention strategies.

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Combined oral contraceptive (COC) use is an established factor that consistently reduces the risk for epithelial ovarian cancer (EOC; Beral et al., 2008). Less is known about the association between EOC risk and COC use with respect to the timing of full-term births. Increasing parity reduces EOC risk (Hankinson and Danforth, 2006), but it is difficult to tease apart the independent effects of COC use and parity. The total number of ovulatory years between menarche and menopause has been used, but this does not address the timing of COC use with respect to full-term births. Studies of breast cancer (Schlesselman, 1989; Romieu et al, 1990; Kahlenborn et al, 2006) and endometrial cancer (Cook et al, 2014) have reported a long-term effect with the use of COCs before the
**Table 1. Characteristics of invasive, epithelial ovarian cancer cases and controls, parous women only, OVAL-BC, 2002–2012**

| Characteristics                                      | Cases, N = 854 | Controls, N = 2139 |
|------------------------------------------------------|----------------|---------------------|
| **Age (years)**                                      |                |                     |
| 40–49                                                | 113 (13)       | 423 (20)            |
| 50–59                                                | 272 (32)       | 773 (36)            |
| 60–69                                                | 278 (33)       | 670 (31)            |
| >70                                                  | 191 (22)       | 273 (13)            |
| **Race**                                             |                |                     |
| White                                                | 711 (83)       | 1877 (88)           |
| Chinese/Japanese                                     | 35 (4)         | 57 (3)              |
| Other Asian                                          | 24 (3)         | 44 (2)              |
| Others                                               | 54 (6)         | 96 (4)              |
| Unknown                                              | 30 (4)         | 64 (3)              |
| **Education**                                        |                |                     |
| High school or less                                  | 357 (42)       | 755 (35)            |
| Vocational school                                    | 216 (25)       | 573 (27)            |
| University                                           | 280 (33)       | 809 (38)            |
| Unknown                                              | 1 (1)          | 2 (1)               |
| **BMI (kg m\(^{-2}\))**                             |                |                     |
| <25                                                  | 406 (48)       | 1015 (47)           |
| 25–29.9                                              | 274 (32)       | 682 (32)            |
| 30–34.9                                              | 101 (12)       | 278 (13)            |
| >35                                                  | 73 (9)         | 161 (8)             |
| Unknown                                              | 0 (0)          | 3 (<1)              |
| **Smoking**                                          |                |                     |
| Never                                                | 409 (48)       | 1046 (49)           |
| Current                                              | 95 (11)        | 156 (7)             |
| Former                                               | 350 (41)       | 937 (44)            |
| **Family history breast and/or ovarian cancer**      |                |                     |
| No                                                   | 673 (79)       | 1767 (83)           |
| Yes                                                  | 163 (19)       | 328 (15)            |
| Unknown                                              | 18 (2)         | 44 (2)              |
| **Menopausal status and HT**                         |                |                     |
| Pre-menopausal                                       | 170 (20)       | 584 (27)            |
| Peri, post-menopausal                                |                |                     |
| No HT                                                | 399 (47)       | 933 (44)            |
| Oestrogen only                                       | 131 (15)       | 252 (12)            |
| Oestrogen plus progesterone only                     | 101 (12)       | 252 (12)            |
| Other HT                                             | 53 (6)         | 114 (5)             |
| Unknown                                              | 0 (0)          | 4 (<1)              |
| **COC**                                              |                |                     |
| No (never or <6 months)                              | 452 (39)       | 506 (20)            |
| Yes                                                  | 692 (61)       | 2007 (80)           |
| **Duration breastfeeding (months)**                  |                |                     |
| Never                                                | 229 (27)       | 424 (20)            |
| >10                                                  | 386 (45)       | 872 (41)            |
| ≥10                                                  | 237 (28)       | 838 (39)            |
| Unknown                                              | 2 (<1)         | 5 (<1)              |
| **Hysterectomy**                                     |                |                     |
| No                                                   | 631 (74)       | 1683 (79)           |
| Yes                                                  | 221 (26)       | 454 (21)            |
| Unknown                                              | 2 (<1)         | 2 (<1)              |
| **Tubal ligation**                                   |                |                     |
| No                                                   | 582 (68)       | 1335 (62)           |
| Yes                                                  | 272 (32)       | 802 (37)            |
| Unknown                                              | 0 (0)          | 2 (<1)              |

Abbreviations: BMI = body mass index; COC = combined oral contraceptives; FFTP = first full-term pregnancy; HT = hormone therapy.

**Table 1. (Continued)**

| Characteristics                                      | Cases, N = 854 | Controls, N = 2139 |
|------------------------------------------------------|----------------|---------------------|
| **Age at FFTP (years)**                              |                |                     |
| <24                                                  | 561 (65)       | 1417 (66)           |
| 25–29                                                | 91 (11)        | 299 (14)            |
| >30                                                  | 196 (23)       | 402 (19)            |
| Unknown                                              | 6 (1)          | 21 (1)              |
| **Ever breastfed**                                   |                |                     |
| No                                                   | 229 (27)       | 424 (20)            |
| Yes                                                  | 625 (73)       | 1714 (80)           |
| Unknown                                              | 0 (0)          | 1 (<1)              |

first full-term pregnancy (FFTP) among parous women. We therefore investigated the EOC risk associated with COC use, focusing on COC use before the FFTP.

**MATERIALS AND METHODS**

This Canadian population-based case–control study has been previously described (Cook et al, 2016) including ethics approvals (Conjoint Health Research Ethics Board, Calgary, Alberta (AB) and Research Ethics Board, British Columbia (BC) Cancer Agency, Vancouver, BC) and written informed consent. Briefly, cases were identified from the population-based BC and AB cancer registries who were: age 20–79 years (40–79 in AB); diagnosed with first primary, incident, histologically confirmed EOC (invasive EOC in AB); and able to complete study in English. A total of 1505 cases (60% of 2522 eligible) completed the study. Eligible controls identified from provincial health rosters and a mammography screening program (Eheman et al, 2014) were: aged 20–79 years (40–79 in AB); able to complete study in English; and, had at least one ovary. A total of 2564 (53% of 4838 eligible) completed the study.

Risk factor information was ascertained through the diagnosis date (month/year) for cases and an assigned reference date (month/year) for controls based on an age-frequency match with cases. Respondents completed a self-administered questionnaire (BC before 2005) or a telephone interview (AB and BC after 2005). In additional to demographic, lifestyle, and medical/reproductive factors, women provided information on COC use, including dates or ages of use. Specific COC names were not ascertained. Histotypes were determined by re-review of haematoxylin and eosin slides according to contemporary criteria (Köbel et al, 2014) for 979 women (85.6%).

The analysis was restricted to those ≥40 years of age at diagnosis/reference date (1144 invasive cases and 2513 controls). Combined oral contraceptive use was evaluated as: non-use (never or <0.5 years) vs ever use (≥0.5 years); continuous duration (years, ever users only) and, as categorical duration (non-use, <0.5 years, 5–10, ≥10 years, and unknown). We used logistic regression to estimate adjusted odds ratios (aORs) and 95% confidence intervals (CIs) in R software (R Development Team, 2015). All variables in Table 1 were evaluated as potential confounders. Final aORs included matching variables (Alberta, BC before 2005, BC
after 2005, and 40–49, 50–59, 60–69, ≥70 years of age), parity (0, 1, 2, ≥3 or 1, 2, ≥3 when restricted to parous women), age at FFTP (<24, 25–29, ≥30 years), breastfeeding (never, ever), first degree family female breast or ovarian cancer (no, yes), tubal ligation (no, yes), and BMI (<25, 25–29.9, 30–34.9, ≥35 kg m⁻²). Other variables did not alter the estimated ORs by more than 10%.

Histotype-specific analyses were restricted to high-grade serous and combined endometrioid/clear cell, due to few cases of other histotypes. Because COC use exclusively before and after the FFTP was mutually exclusive, they were modelled simultaneously, allowing direct comparisons of the two risk estimates using contrasts (Montgomery, 2012).

**RESULTS**

Characteristics of parous cases and controls are described in Table 1. Combined oral contraceptive use was common among parous women, reported by 61% of cases and 80% of controls. With respect to the timing of COC use (Table 2), use of COCs before first birth and ovarian cancer risk

| COC use | All epithelial cancer | Histotype-specific |
|--------|-----------------------|--------------------|
|        | Controls N = 1574     | Cases N = 720 OR* 95% CI | Cases N = 375 OR* 95% CI | Cases N = 113 OR* 95% CI |
| No     | N %                   | N %                  | N %                  | N %                  |
| Yes, exclusive use |                      |                     |                     |                      |
| Before and after FFTP |                     |                     |                     |                      |
| Before FFTP |                     |                     |                     |                      |
| After FFTP |                     |                     |                     |                      |
| Yes, duration of use (years) |                   |                     |                     |                      |
| Before and after FFTP |                   |                     |                     |                      |
| S < 10 |                   |                     |                     |                      |
| ≥10   |                   |                     |                     |                      |
| Unknown |                   |                     |                     |                      |
| per year of use² |                   |                     |                     |                      |
| Exclusively before FFTP |                   |                     |                     |                      |
| S < 10 |                   |                     |                     |                      |
| ≥10   |                   |                     |                     |                      |
| Unknown |                   |                     |                     |                      |
| per year of use² |                   |                     |                     |                      |
| Exclusively after FFTP |                   |                     |                     |                      |
| S < 10 |                   |                     |                     |                      |
| ≥10   |                   |                     |                     |                      |
| Unknown |                   |                     |                     |                      |
| per year of use² |                   |                     |                     |                      |

Abbreviations: OR = odds ratio; 95% CI = 95% confidence interval.

*a* ORs adjusted for study site (Alberta, BC before 2005, BC after 2005), age (40–49, 50–59, 60–69, ≥70 years), parity (1,2, ≥3), age at FFTP (<24, 25–29, ≥30 years), breastfeeding (never, ever), first degree female family history of breast or ovarian cancer (no, yes), tubal ligation (no, yes), and BMI (<25, 25–29.9, 30–34.9, ≥35 kg m⁻²).

*b* P-value for difference in ORs, <0.01.

*a* Among COC users only.

When we stratified by age at FFTP, COC use before and after as well as exclusively before the FFTP was consistently associated with a reduction in EOC risk regardless of age at first birth, a consistency that was not seen with COC use exclusively after the FFTP (Figure 1), although some results were unstable. Similar results were noted when stratified by parity, although risk estimates were more similar for parity ≥3 (Figure 1).

The association of COC use and EOC risk for our entire study population (both parous and non-parous women combined) was consistent with the reported literature (Supplementary Tables 1–4). Any COC use was associated with a reduction in risk (aOR = 0.58, 95% CI = 0.49, 0.69). Among COC users, risk was most strongly reduced with longer durations of use overall, within more recent time since last use, and for younger ages at first use.
When we assessed the timing of COC use exclusively before the FFTP among parous women, we found a strong reduction in risk (~40%), which was almost as strong as the ~50% risk reduction seen with COC before and after the FFTP. Even for fairly short-term COC use (<5 years) before the FFTP there was a significant and substantial reduction in risk years later in parous women. This result is surprising, given that these women all experienced the reduction in risk associated with being parous, and given that the literature (Beral et al., 2008) and our own results for parous and non-parous women indicate that last use of COCs in the more distant past is associated with weaker reductions in risk. In contrast, the effect of such use after the FFTP was of lesser magnitude, despite the assumption that the cessation of ovulation in these women should have equivalent effects regardless of the timing of COCs.

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among the control women; and, possible residual confounding. In addition, COC use in this study represents formulations of COC available in the past, and current formulations may not have the same long-term effects.

In summary, the significant reduction in EOC risk observed with COC use before the FFTP among parous women is a novel and requires replication. Despite the consistently reported risk reduction in EOC with COCs, questions remain about the timing of use and the underlying biological mechanisms of long-term effects to guide future EOC risk prediction (Pearce et al., 2015) and directed chemoprevention strategies for high-risk women (Walker et al., 2015).

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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