SHORT COMMUNICATION

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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 ⩾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.

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

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Table 1. Characteristics of invasive, epithelial ovarian cancer cases and controls, parous women only, OVAL-BC, 2002–2012

	Cases, N = 854		Controls, N = 2139	
Characteristics	**N**	**%**	**N**	**%**
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
Yes, duration (years)				
<5	367	32	918	37
5–10	185	16	564	22
⩾10	128	11	504	20
Unknown	12	1	21	1
Parity				
1	389	46	1080	50
2	288	34	736	34
⩾3	177	21	323	15
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
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.

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, <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 FTTP (⩽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 exclusively after the FFTP were mutually exlcusive, 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 and after the FFTP (aOR = 0.45, 95% CI = 0.34–0.59; per year of use: aOR = 0.94, 95% CI = 0.91–0.98) as well as exclusive use before the FFTP (aOR = 0.56, 95% CI = 0.42–0.75; per year of use: aOR = 0.91, 95% CI = 0.86–0.96) was associated with a reduced risk for EOC. Similarly, both before and after the FFTP as well as use exclusively before the FFTP was associated with a reduced risk for both high-grade serous (aOR = 0.50, 95% CI = 0.35–0.72 and aOR = 0.49, 95% CI = 0.35–0.70, respectively) and endometrioid/clear cell (aOR = 0.52, 95% CI = 0.29–0.92 and aOR = 0.47, 95% CI = 0.27–0.83, respectively) EOC. In contrast, COC use exclusively after the first birth was associated with a smaller reduction in EOC risk (aOR = 0.78, 95% CI = 0.61–1.01) that was suggestive but there was no association with increasing duration (per year of use aOR = 0.98, 95% CI = 0.95–1.02). When the risk estimate for exclusive use before the FFTP was compared (via contrasts) with the risk estimate for exclusive use after, the aORs were found to be significantly different (*P*-value, <0.01) (Table 2).

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.

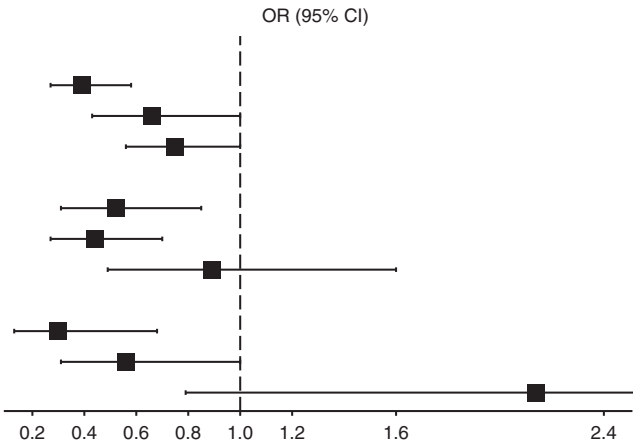
Table 2. Risk for epithelial ovarian cancer among parous women associated with exclusive use of combination oral contraceptives (COCs) before and after the first full-term pregnancy (FFTP), overall and by histotype

			All epithelial cancer				Histotype-specific							
							Serous (high grade)				Endometrioid/clear cell			
	Controls *N* = 1574		Cases *N* = 720		OR[a]	95% CI	Cases *N* = 375		OR[a]	95% CI	Cases *N* = 113		OR[a]	95% CI
	N	%	*N*	%			*N*	%			*N*	%		
COC use														
No	427	27	323	45	1.00	referent	179	48	1.00	referent	46	41	1.00	referent
Yes, exclusive use														
Before and after FFTP	535	25	119	14	0.45	(0.34, 0.59)	64	15	0.50	(0.35, 0.72)	28	20	0.52	(0.29, 0.92)
Before FFTP	703	45	186	26	0.56[b]	(0.42, 0.75)	85	23	0.49[b]	(0.35, 0.70)	38	34	0.47[b]	(0.27, 0.83)
After FFTP	444	28	211	29	0.78[b]	(0.61, 1.01)	111	30	0.76[b]	(0.56, 1.04)	29	26	0.73[b]	(0.41, 1.30)
Yes, duration of use (years)														
Before and after FFTP														
<5	153	7	46	5	0.62	(0.42, 0.92)	28	6	0.75	(0.46, 1.20)	11	8	0.79	(0.35, 1.64)
5–<10	183	9	36	4	0.39	(0.26, 0.59)	22	5	0.46	(0.27, 0.76)	7	5	0.29	(0.11, 0.67)
⩾10	197	9	37	4	0.36	(0.24, 0.54)	14	3	0.33	(0.17, 0.59)	10	7	0.56	(0.24, 1.18)
Unknown	2	<1	0	0			0	0			0	0		
per year of use[c]					0.94	(0.91, 0.98)			0.95	(0.90, 1.00)			0.91	(0.83, 0.99)
Exclusively before FFTP														
<5	397	25	121	17	0.61	(0.45, 0.83)	52	14	0.50	(0.34, 0.74)	26	23	0.56	(0.30, 1.04)
5–<10	193	12	51	7	0.57	(0.37, 0.85)	27	7	0.62	(0.37, 1.03)	7	6	0.33	(0.12, 0.81)
⩾10	112	7	13	2	0.22	(0.11, 0.42)	5	1	0.18	(0.06, 0.44)	5	4	0.35	(0.10, 0.99)
Unknown	1	<1	1	<1			1	<1			0	0		
per year of use[c]					0.91	(0.86, 0.96)			0.92	(0.86, 0.99)			0.92	(0.83, 1.01)
Exclusively after FFTP														
<5	270	17	128	18	0.84	(0.63, 1.12)	67	18	0.80	(0.56, 1.15)	17	15	0.70	(0.36, 1.35)
5–<10	107	7	48	7	0.74	(0.49, 1.10)	24	6	0.67	(0.39, 1.11)	7	6	0.84	(0.31, 2.01)
⩾10	62	4	32	4	0.76	(0.47, 1.22)	19	5	0.82	(0.45, 1.43)	4	4	0.68	(0.18, 1.97)
Unknown	5	<1	3	<1			1	<1			1	1		
per year of use[c]					0.98	(0.95, 1.02)			0.98	(0.94, 1.04)			0.97	(0.88, 1.07)

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.
[c]Among COC users only.

A

FFTP age	COC use	Cases, *N*	Controls, *N*	OR	95% CI
<24	Before + After	60	265	0.39	(0.27, 0.58)
	Before FFTP	54	159	0.66	(0.43, 1.00)
	After FFTP	168	380	0.75	(0.56, 1.00)
25–29	Before + After	48	186	0.52	(0.31, 0.85)
	Before FFTP	64	291	0.44	(0.27, 0.70)
	After FFTP	30	51	0.89	(0.49, 1.60)
>30	Before + After	11	84	0.30	(0.13, 0.68)
	Before FFTP	68	253	0.56	(0.31, 1.00)
	After FFTP	13	13	2.14	(0.79, 5.90)



B

Parity	COC use	Cases, *N*	Controls, *N*	OR	95% CI
1	Before + After	95	400	0.40	(0.28, 0.55)
	Before FFTP	150	527	0.47	(0.34, 0.65)
	After FFTP	117	216	0.80	(0.57, 1.12)
2	Before + After	68	329	0.43	(0.28, 0.64)
	Before FFTP	102	392	0.57	(0.38, 0.84)
	After FFTP	87	173	0.77	(0.52, 1.14)
⩾3	Before + After	24	135	0.49	(0.28, 0.84)
	Before FFTP	36	176	0.67	(0.40, 1.11)
	After FFTP	94	228	0.80	(0.56, 1.16)

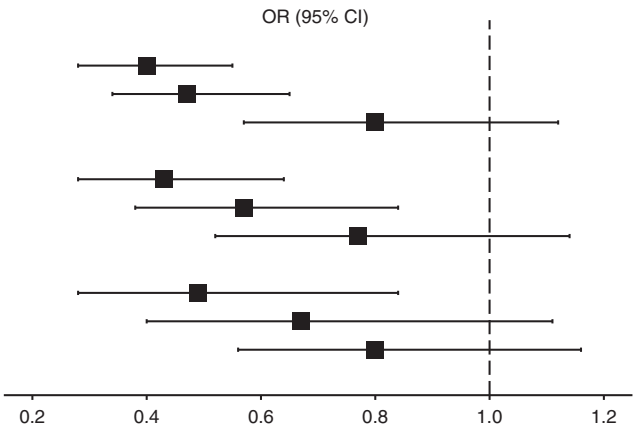


Figure 1. Combined oral contraceptive use with respect to the FFTP by age at first birth (A) and by number of births (parity) (B) among parous women. The aORs are adjusted for the following: study site (Alberta, BC before 2005, BC after 2005); age (40–49, 50–59, 60–69, ⩾70 years); parity in Panel **A** only (1, 2, ⩾3); age at FFTP in Panel **B** only (⩽24, 25–29.9, 30–34.9, ⩾35 years); breastfeeding (never, ever); first degree female family history of breast or ovarian cancer (no, yes); tubal ligation (no, yes); BMI (<25, 25–29.9, 30–34.9, ⩾35 kg m^{-2}).

CONCLUSION

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 indicating 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 FTTP 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.

Consistent with our findings, other studies have reported that any use of COCs before age 20 years (Ness *et al*, 2000; Kumle *et al*, 2004; Beral *et al*, 2008; Lurie *et al*, 2008) or 25 years (Bosetti *et al*, 2002) is associated with a reduced EOC risk of 29–50% many years later. Ours is the first study to assess COC use exclusively before and after the FFTP to evaluate the timing of COC use with pregnancy.

Although the more immediate effects of COC use on biological end points such as hormone levels, gene expression, and ovulation are well documented, the long-term effects on EOC risk are largely attributed to fewer ovulations during reproductive life (Fathalla, 1971), with the assumption that the timing of ovulation reduction does not matter. Our results could be due, in part, to fewer ovulations because of COC use, but it is not clear why use before the FFTP would have such a strong, lasting impact on EOC risk. In breast cancer, the elevated risk noted with COC use before the FFTP has been hypothesised to be related to the carcinogenic susceptibility of undifferentiated breast tissue at this time (Romieu *et al*, 1990), and in endometrial cancer the reduction in risk with early COC use is unknown but may be related to a lasting effect on hormone levels that reduce cellular proliferation (Chan *et al*, 2007). Whether such mechanisms are also applicable to a long-lasting reduction in EOC risk is not clear. Regardless of the tissue of origin for EOC (fallopian tube, endometrium, ovary, etc.), our results suggest that the timing of ovulation reduction is important, and that there may be other long-term mechanisms for an EOC risk reduction beyond ovulation that manifest before the FFTP.

Study strengths include the population-based design; large sample size; restriction to first primary, histologically confirmed invasive EOC; detailed information on parity; assessment of contemporary histotypes (Köbel *et al*, 2014); high prevalence of COC use; and, restriction to parous women with adjustment for parity, thus minimising confounding by parity. Limitations include: no COC name/dosage information; cases recalling past COC use more fully than controls (but that would bias risk estimates to the null value); relatively low response percentage

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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