

Expanding our understanding of ovarian cancer risk: the role of incomplete pregnancies

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Abstract

Background

Parity is associated with decreased risk of invasive ovarian cancer; however, the relationship between incomplete pregnancies and invasive ovarian cancer risk is unclear. This relationship was examined using 15 case-control studies from the Ovarian Cancer Association Consortium (OCAC). Histotype-specific associations, which have not been examined previously with large sample sizes, were also evaluated.

Methods

A pooled analysis of 10,470 invasive epithelial ovarian cancer cases and 16,942 controls was conducted. Odds ratios and 95% confidence intervals for the association between incomplete pregnancies and invasive epithelial ovarian cancer were estimated using logistic regression. All models were conditioned on OCAC study, race/ethnicity, age, and education level, and adjusted for number of complete pregnancies, oral contraceptive use, and history of breastfeeding. The same approach was used for histotype-specific analyses.

Results

Ever having an incomplete pregnancy was associated with a 16% reduction in ovarian cancer risk (OR=0.84, 95% CI = 0.79 to 0.89). There was a trend of decreasing risk with increasing number of incomplete pregnancies (two-sided $P_{trend} < .001$). An inverse association was observed for all major histotypes; it was strongest for clear cell ovarian cancer.

Conclusions

Incomplete pregnancies are associated with a reduced risk of invasive epithelial ovarian cancer. Pregnancy, including incomplete pregnancy, was associated with a greater reduction in risk of clear cell ovarian cancer, but the result was broadly consistent across histotypes. Future work should focus on understanding the mechanisms underlying this reduced risk.

Parity is associated with a decreased risk of ovarian carcinoma (cancer) in a dose-dependent manner [1-3]. Compared to nulliparous women, women with one birth have an approximate 24% (95% CI = 12% to 34%) decrease in risk and women with two or more births have an approximate 42% (95% CI = 35% to 49%) risk reduction [1].

However, the association between incomplete pregnancies (induced and spontaneous abortions) and ovarian cancer risk is unclear. Some studies [4-7] and one pooled analysis of six population-based case-control studies [8] have reported a decreased risk. However, a number of studies have reported a null association [9-15] and one reported an increased risk [16] but there was no adjustment for any potential confounders in this study. Whether the association might differ by histotype has not been adequately studied due to limited numbers. Since different histotypes likely represent distinct diseases with different risk factors [17], understanding the association by histotype may provide insight into their etiologies.

Given the equivocal literature, we evaluated the relationship between incomplete pregnancies and ovarian cancer risk using data from 15 case-control studies with data on incomplete pregnancies from the Ovarian Cancer Association Consortium (OCAC); some data from two of these studies have been published previously [10, 12]. We have included 10,470 women with ovarian cancer and 16,942 controls. This is the largest analysis of this relationship, allowing us to consider histotype-specific associations with sufficient sample sizes.

Methods

Study Populations

We included data from 15 case-control studies (14 population-based and one clinic-based) in the OCAC. These studies were conducted in the United States (n=10) [3, 18-26], the United Kingdom (n=1) [27], Europe (n=3) [28-30], and Australia (n=1) [31]. Each study received institutional review board approval and written informed consent was provided by all women included in this analysis. Eligible cases had a pathologically confirmed invasive epithelial ovarian cancer.

Statistical Analysis

A complete pregnancy was defined as any pregnancy that lasted six months or longer. This variable was created by summing the number of live births lasting 6+ months and the number of still births (defined as pregnancies lasting 6+ months, including late term pregnancy terminations). An incomplete pregnancy was defined as the number of reported pregnancies minus the number of complete pregnancies. It is possible that a small number of pregnancies lasted <6 months, but resulted in live births; these pregnancies were included in the incomplete pregnancy category based on their duration.

We categorized women as ever or never having an incomplete pregnancy as well as according to the number of incomplete pregnancies (0, 1, 2+). The number of complete pregnancies (0, 1, 2, and 3+), duration of oral contraceptive use (never, <1, 1 to <5, 5 to <10, 10+ years), duration of breastfeeding (never, <12 months, 12 to <24 months, 24+ months), race/ethnicity (non-Hispanic White, Hispanic White, Black, Asian, and other), age (in five-year categories from <30 to 80+ years) and education level (less

than high school, high school, some college, college graduate) were considered important *a priori* confounders and were included in every model.

Additional potential confounders were added to the model described above one at a time and the impact on the incomplete pregnancy-ovarian cancer association was evaluated. These variables included a personal history of endometriosis (yes/no), body mass index (BMI; <18.5, 18.5-<25, 25-<30, 30+ kg/m²), age at menarche (continuous), a first-degree family history of ovarian cancer (yes/no), tubal ligation (yes/no), and a previous diagnosis of a cancer other than non-melanoma skin cancer (yes/no). None of these variables materially affected the incomplete pregnancy-ovarian cancer relationship and were not included in the final model.

To evaluate the association between incomplete pregnancies and risk of ovarian cancer, we first conducted logistic regression and calculated odds ratios (ORs) and 95% confidence intervals (CIs) for each OCAC study site; all models were conditioned on race/ethnicity, age, and education level and adjusted for number of complete pregnancies, oral contraceptive use and breastfeeding (all fitted as described above). Because we did not observe heterogeneity in the study-specific effect estimates, we pooled the individual-level data across the 15 OCAC studies and used logistic regression as described above with the addition of conditioning on OCAC study site. This pooled approach was also used for histotype-specific analyses. Tests for trend were carried out using a grouped ordinal variable both with and without the reference group included. Multinomial logistic regression was used to evaluate whether the results across histotypes were different from each other.

Individuals with missing data (8% of controls and 6% of cases) for any of the variables included in the model were dropped from the analysis. All p values quoted are 2-sided and considered statistically significant if $P < .05$.

In addition to the usual standard joint analysis of complete (0, 1, 2, 3+) and incomplete (0, 1, 2+) pregnancies assuming a multiplicative relationship of their ORs, we also evaluated whether there was a statistical or qualitative departure from multiplicativity. The statistical assessment was carried out by fitting an interaction term between complete and incomplete pregnancies. The qualitative assessment was carried out by modeling complete and incomplete pregnancies as a single variable having 12 levels with nulligravid women as the reference group. To qualitatively assess whether there was evidence of a departure from multiplicativity, we calculated the difference between what was observed from the standard joint analysis to the model with a single variable.

Meta-Analysis

We identified 13 published reports encompassing 18 independent datasets [4-16]. Three of the reports [13-15] excluded nulligravid women so their results for incomplete pregnancies are in part a comparison of the effect of incomplete pregnancies to ever having a complete pregnancy and cannot be compared to ours or to those of the other published papers. One study did not adjust for any confounders [16]. Two of the studies from the published literature [10, 12] are subsets of data included in the present OCAC analysis (AUS and NEC); the remaining seven reports [4-9, 11] were included in a meta-analysis with the individual OCAC study results. Meta-

analysis was carried out following the methods described by Higgins and Thompson [32]. Fixed effects results are presented as these were very close to the random effects results.

Results

The 15 studies included 10,470 ovarian cancer cases and 16,942 controls. Among the cases, 32.3% reported ever having had an incomplete pregnancy compared to 38.0% of the controls. Table 1 shows the number of ovarian cancer cases and controls by OCAC study site and the percentages of participants with an incomplete pregnancy. The number of control women and those with ovarian cancer by number of incomplete pregnancies (overall and by histotype) are shown in Supplementary Table 1.

There was a statistically significant inverse association between ever having had an incomplete pregnancy and ovarian cancer overall (OR=0.84, 95% = CI 0.79 to 0.89, $P<.001$; $P_{heterogeneity}$ across studies=.59) (Figure 1). This inverse association was observed in 11 of the 15 studies with results from four studies reaching statistical significance; the results for the remaining four studies were null (with ORs ranging from 0.95 to 1.04). The results from all studies were compatible with the overall OR of 0.84 (Figure 1).

Women who reported one incomplete pregnancy had a 14% decreased risk (OR=0.86, 95% CI = 0.81 to 0.92) and women who reported two or more incomplete pregnancies had a 20% decreased risk (OR=0.80, 95% CI = 0.74 to 0.87; Table 2). Having an incomplete pregnancy was also associated with decreased risk of ovarian cancer among women who had never had a complete pregnancy (Table 3, column

headed “Observed Model”). Among women who had no complete pregnancies, having one incomplete pregnancy was associated with a 16% decreased risk of ovarian cancer (OR=0.84, 95% CI = 0.72 to 0.99; Table 3, column headed “Observed Model”).

Similarly, for women who had no complete pregnancies and two incomplete pregnancies, a 31% decreased risk was observed (OR=0.69, 95% CI = 0.57 to 0.83).

When we more finely categorized incomplete pregnancies (0, 1, 2, 3, 4+), there was a 34% decreased risk in the 4+ group (OR=0.66, 95% CI = 0.54 to 0.80; $P=.049$ for trend among those with at least one incomplete pregnancy). The inverse association with incomplete pregnancy was seen for each histotype; the 2+ incomplete pregnancies ORs show that the magnitude of the association was weakest for high-grade serous (OR=0.93, 95% CI = 0.84 to 1.03) and strongest for clear cell (OR=0.39, 95% CI = 0.28 to 0.53; Table 2). The association between having 2+ incomplete pregnancies and clear cell ovarian cancer was statistically significantly different from that observed with high-grade serous, low-grade serous, mucinous and endometrioid cancers ($P<.05$ for all comparisons).

The magnitude of the decreased risk for an incomplete pregnancy was weaker than that for a complete pregnancy. The reduction in risk for a single incomplete pregnancy compared to a single complete pregnancy was 14% compared to 25%. We modeled all joint categories of having 0, 1, 2 or 3+ complete pregnancies and 0, 1 or 2+ incomplete pregnancies, taking nulligravid women as the reference group. This analysis showed that the assumption of a multiplicative relationship provided a close estimate of the joint estimate of complete and incomplete pregnancies (Table 3). Similarly, no

departure from multiplicativity was observed in a model with an interaction term between complete and incomplete pregnancies ($P>.05$)

Of the ten published reports that are comparable to our OCAC analysis, five reported a decreased risk [4-8], including the pooled analysis [8], four reported no association [9-12], and one reported an increased risk [16], however there was no adjustment for potential confounders in this study. Two of the null studies [10, 12] are subsets of data included in the present OCAC analysis. One of these studies (AUS) shows an inverse association in the present analysis, whereas the other (NEC) continues to be null (Figure 1). Meta-analysis of the existing comparable published studies (excluding the AUS and NEC published studies as well as the study that did not adjust for any confounders) with the results from the individual OCAC studies yielded a pooled odds ratio of 0.87 for ever having an incomplete pregnancy (95% CI = 0.81 to 0.92, $P<.001$; $P_{heterogeneity}=.13$).

Discussion

We have carried out a comprehensive analysis of the relationship between incomplete pregnancies and risk of invasive ovarian cancer in a large number of women with ovarian cancer and controls from 15 OCAC studies. We found a statistically significant reduced risk of ovarian cancer among women who have had an incomplete pregnancy. Eleven of the 15 studies showed an inverse association, and the results from all studies were compatible with each other. The published literature is also consistent with our findings. This inverse association was present for each histotype, but most apparent for clear cell cancer.

The inverse association for an incomplete pregnancy was weaker than that of a complete pregnancy. The biologic mechanism(s) underlying the association between complete and incomplete pregnancies and ovarian cancer is not clear. The original mechanism proposed for the association with parity was thought to be through the cessation of recurrent breakdown and repair of the ovarian surface epithelium as a result of ovulation suppression during pregnancy [33]. However, given that the ovarian surface epithelium is no longer believed to be the site of origin for most high-grade serous ovarian cancers (the most common histotype), this can only provide a small part of the explanation. It has also been suggested that stopping ovulation reduces the exposure of fallopian tube fimbria, endosalpingiosis, and endometriosis, the presumed cells of origin of most ovarian cancers, to inflammatory follicular fluid from within the ovary [34]. In our analysis, the OR for an incomplete pregnancy (0.86) is approximately what would be expected based on an OR for a complete pregnancy (0.75) given the difference in duration. Thus our results suggest that the effects of an incomplete pregnancy are no less than would be expected based on the duration of the pregnancy. More research is needed to elucidate the mechanism through which pregnancy is protective for ovarian cancer.

Reporting bias is a potential concern in case-control studies. However, one might expect controls to be less likely to report incomplete pregnancies than cases, which has been observed in previous breast cancer case-control studies [36], and such a scenario would produce a positive association between incomplete pregnancy and ovarian cancer risk, rather than the inverse association we observed. In addition, there is the possibility that women may be more likely to report induced abortions as spontaneous

due to stigma, but because our data focused on any type of incomplete pregnancy, the effect of this type of misreporting is likely to be mitigated. There are two cohort studies that have examined the incomplete pregnancy-ovarian cancer relationship; these studies would be free of differential reporting bias. One did observe a positive association with four or more incomplete pregnancies [9], but this was not observed in the other cohort study which found a protective effect overall and particularly for three or more incomplete pregnancies [5], which is in line with our results. Also, two previously published studies carried out in China where there may be less stigma surrounding the reporting of incomplete pregnancies given its past one-child policy found an inverse association [4, 7]. Lastly, because the incomplete pregnancy variable is calculated from the total number of pregnancies and the number of pregnancies lasting six months or longer, it is possible that a few pregnancies lasting less than six months resulted in a live birth. In our analysis, such births were included in the incomplete pregnancy group; this is unlikely to affect our results because such births are very uncommon and given their duration, they may be more likely to mirror the association with incomplete pregnancies.

Considering the evidence from all of the studies on incomplete pregnancies, having an incomplete pregnancy appears to be associated with decreased risk of ovarian cancer. Interestingly, this inverse association with incomplete pregnancies has also been observed in endometrial cancer [38], which shares similar risk factors with ovarian cancer. Future research should focus on understanding the mechanisms underlying the reduced risk associated with complete and incomplete pregnancies to shed light on ovarian cancer etiology.

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Data Availability: The data underlying this article will be shared upon approval of a data request form by the Ovarian Cancer Association Consortium Data Access Coordinating Committee and with appropriate human subjects approval and data transfer agreements.

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Table 1. Number of ovarian cancer cases and controls with the percent of women ever having an incomplete pregnancy in parentheses by OCAC study site

OCAC Site	Geographic Location	Diagnosis Years	Controls*	Cases*	High-Grade Serous*	Low-Grade Serous*	Mucinous*	Endometrioid*	Clear Cell*
AUS	Australia	2001-2006	1445 (35.4)	1104 (30.0)	596 (32.9)	46 (39.1)	44 (28.3)	131 (27.5)	86 (17.4)
CON	Connecticut, USA	1999-2003	421 (38.2)	300 (29.0)	150 (31.3)	6 (16.7)	17 (23.5)	58 (32.8)	26 (26.9)
DOV	Washington, USA	2002-2009	1845 (41.5)	1140 (35.9)	559 (40.8)	17 (70.6)	33 (48.5)	184 (25.0)	87 (29.9)
GER	Germany	1993-1998	527 (23.3)	225 (20.9)	83 (25.3)	15 (13.3)	25 (28.0)	26 (15.4)	6 (16.7)
HAW	Hawaii, USA	1993-2008	1103 (39.9)	709 (30.9)	279 (35.1)	11 (54.6)	71 (39.4)	117 (21.4)	82 (20.7)
HOP	Western Pennsylvania, Northeast Ohio, Western NY, USA	2003-2009	1802 (33.3)	622 (31.0)	331 (31.1)	22 (31.8)	37 (24.3)	94 (30.9)	45 (22.2)
MAL	Denmark	1994-1999	1552 (41.8)	543 (32.8)	225 (35.1)	90 (32.2)	50 (34.0)	75 (32.0)	42 (11.9)
NCO	North Carolina, USA	1999-2008	1050 (38.0)	840 (32.6)	399 (31.3)	47 (31.9)	45 (40.0)	135 (34.8)	87 (21.8)
NEC	New Hampshire, Eastern Massachusetts, USA	1992-2008	2079 (37.6)	1419 (30.8)	783 (35.9)	45 (33.3)	91 (35.2)	315 (31.1)	68 (20.6)
NJO	New Jersey, USA	2002-2009	442 (36.0)	224 (33.5)	103 (36.9)	9 (33.3)	12 (41.7)	31 (38.7)	30 (20.0)
POL	Poland	2000-2004	516 (46.1)	209 (42.8)	59 (37.3)	2 (100.0)	15 (40.0)	29 (41.4)	7 (42.9)
STA	Northern California, USA	1997-2002	567 (43.4)	495 (35.4)	224 (40.6)	25 (36.0)	42 (38.1)	61 (26.2)	49 (24.5)
UCI	California, USA	1995-2005	298 (36.2)	384 (34.6)	177 (39.0)	16 (31.3)	28 (32.1)	70 (40.0)	36 (27.8)
UKO	United Kingdom	2006-2009	786 (21.8)	439 (16.2)	191 (18.3)	13 (0.0)	43 (18.6)	74 (13.5)	43 (18.6)
USC	Los Angeles, CA, USA	1993-2008	2509 (43.2)	1817 (35.3)	870 (37.4)	74 (27.0)	161 (39.8)	230 (30.9)	116 (26.7)
		Total†:	16942 (38.0)	10470 (32.3)	5029 (35.0)	438 (32.9)	714 (35.2)	1630 (29.3)	810 (22.7)

* Total number (percentage reporting an incomplete pregnancy).

† The sum of high-grade serous, low-grade serous, mucinous, endometrioid and clear cell is lower than the total number of cases due to some cases not being classified as one of those five histotypes.

Table 2. Association between ovarian cancer risk and incomplete and complete pregnancies by histotype

No. of Incomplete and Complete Pregnancies	<u>All Cases</u>	<u>High-Grade Serous</u>	<u>Low-Grade Serous</u>	<u>Mucinous</u>	<u>Endometrioid</u>	<u>Clear Cell</u>
	OR* (95% CI)	OR* (95% CI)	OR* (95% CI)	OR* (95% CI)	OR* (95% CI)	OR* (95% CI)
Incomplete Pregnancies						
0	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
1	0.86 (0.81 to 0.92)	0.94 (0.87 to 1.03)	0.90 (0.70 to 1.15)	0.94 (0.77 to 1.15)	0.77 (0.66 to 0.89)	0.68 (0.55 to 0.84)
2+	0.80 (0.74 to 0.87)	0.93 (0.84 to 1.03)	0.68 (0.49 to 0.95)	0.77 (0.59 to 1.00)	0.71 (0.59 to 0.84)	0.39 (0.28 to 0.53)
P_{trend} w/ ref [†] :	<.001	.09	.02	.06	<.001	<.001
P_{trend} w/o ref [†] :	.15	.55	.32	.27	.91	.012
Complete Pregnancies						
0	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
1	0.75 (0.68 to 0.83)	0.93 (0.81 to 1.06)	0.69 (0.48 to 1.00)	0.68 (0.50 to 0.92)	0.59 (0.49 to 0.71)	0.49 (0.38 to 0.64)
2	0.59 (0.54 to 0.65)	0.81 (0.72 to 0.91)	0.49 (0.35 to 0.70)	0.54 (0.41 to 0.71)	0.38 (0.32 to 0.46)	0.27 (0.21 to 0.35)
3+	0.51 (0.47 to 0.57)	0.70 (0.62 to 0.79)	0.45 (0.31 to 0.66)	0.50 (0.37 to 0.67)	0.28 (0.23 to 0.34)	0.19 (0.15 to 0.26)
P_{trend} w/ ref [†] :	<.001	<.001	<.001	<.001	<.001	<.001
P_{trend} w/o ref [†] :	<.001	<.001	.015	.040	<.001	<.001

Note: OR=odds ratio, CI=confidence interval.

* Model included both incomplete and complete pregnancies, conditioned on OCAC study site, age, race, and education level, and adjusted for oral contraceptive use and breastfeeding.

[†] P_{trend} w/ ref includes the reference group; P_{trend} w/o ref excludes the reference group and represents the trend among exposed women.

Table 3. Evaluation of the multiplicative relationship between ovarian cancer and incomplete and complete pregnancies

No. of Complete Pregnancies	No. of Incomplete Pregnancies	Expected Model 1 [†]	Observed Model **	Difference
		OR _{joint(model1)}	OR _{joint(model2)} (95% CI)	OR _{joint(model1)} - OR _{joint(model2)}
0	0	1.00	1.0	
	1	0.86	0.84 (0.72 to 0.99)	0.02
	2+	0.80	0.69 (0.57 to 0.83)	0.11
1	0	0.75	0.76 (0.67 to 0.85)	-0.01
	1	0.65	0.63 (0.54 to 0.75)	0.02
	2+	0.60	0.55 (0.46 to 0.67)	0.05
2	0	0.59	0.59 (0.53 to 0.65)	0.00
	1	0.51	0.47 (0.41 to 0.53)	0.04
	2+	0.47	0.51 (0.44 to 0.60)	-0.04
3+	0	0.51	0.49 (0.44 to 0.54)	0.02
	1	0.44	0.47 (0.41 to 0.57)	-0.03
	2+	0.41	0.42 (0.36 to 0.49)	-0.01

Note: OR=odds ratio, CI=confidence interval.

[†] Expected Model 1 calculated as OR_{complete}* OR_{incomplete}, using OR estimates from Table 2 and assuming multiplicativity, e.g., expected OR for 2 complete and 1 incomplete = 0.59 * 0.86 = 0.51.

** Observed Model included a single variable with all combinations of incomplete and complete pregnancy categories (total 12 categories).

Figure Title and Legend:

Figure 1. Association between incomplete pregnancy and ovarian cancer by study site.

US: United States; OR: Odds Ratio; CI: Confidence Interval

SITE	OR(95%CI)
Studies in US	
NEC (1992-2008)	0.95 (0.82-1.11)
USC (1993-2008)	0.75 (0.66-0.86)
HAW (1993-2008)	0.77 (0.62-0.96)
UCI (1995-2005)	1.04 (0.72-1.52)
STA (1997-2002)	0.79 (0.59-1.05)
CON (1999-2003)	0.85 (0.58-1.24)
NCO (1999-2008)	0.79 (0.64-0.97)
DOV (2002-2009)	0.86 (0.73-1.02)
NJO (2002-2009)	1.00 (0.81-1.23)
HOP (2003-2009)	1.00 (0.65-1.54)
Studies in Europe	
GER (1993-1998)	0.87 (0.58-1.32)
MAL (1994-1999)	0.76 (0.61-0.94)
POL (2000-2004)	0.90 (0.63-1.28)
UKO (2006-2009)	0.78 (0.54-1.12)
Study in Australia	
AUS (2001-2006)	0.84 (0.70-1.01)
Overall	0.84 (0.79-0.89)

