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Reproductive and hormonal factors in relation to survival and platinum resistance among ovarian cancer cases

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Background: Ovarian cancer survival is poor, particularly for platinum-resistant cases. The previous literature on pre-diagnostic reproductive factors and ovarian cancer survival has been mixed. Therefore, we evaluated pre-diagnostic reproductive and hormonal factors with overall survival and, additionally, platinum-chemotherapy resistance.

Methods: We followed 1649 invasive epithelial ovarian cancer cases who were enrolled between 1992 and 2008 for overall mortality within the New England Case-Control Study and abstracted chemotherapy data on a subset ($n = 449$). We assessed pre-diagnostic reproductive and hormonal factors during in-person interviews. We calculated hazard ratios (HRs) using Cox-proportional hazards models.

Results: We observed 911 all-cause deaths among 1649 ovarian cancer cases. Self-reported endometriosis and longer duration of hormone therapy use were associated with improved survival (HR: 0.72; 95% confidence interval (CI): 0.54–0.94 and HR, ≥ 5 years vs never: 0.70; 95% CI: 0.55–0.90, respectively). Older age at menopause and menarche were associated with worse survival (HR, ≤ 50 vs > 50 years: 1.23; 95% CI: 1.03–1.46 and HR, 13 vs < 13 years: 1.24; 95% CI: 1.06–1.44, respectively). We observed no association between oral contraceptive use, parity and tubal ligation, and overall survival. No significant associations were observed for any of the reproductive and hormonal factors and platinum resistance.

Conclusions: These results suggest that pre-diagnostic exposures such as endometriosis and HT use may influence overall survival among ovarian cancer patients.

Ovarian cancer is the deadliest gynaecological malignancy, accounting for an estimated 14 240 deaths in US in 2016 (Siegel *et al*, 2016). Among women with ovarian cancer, only 45% will survive for 5 years after diagnosis, primarily because 60% of women are diagnosed at an advanced disease stage (Howlader *et al*,

2015). Furthermore, $\sim 80\%$ of women will eventually relapse after first-line platinum and taxane-based chemotherapy (Howlader *et al*, 2015; NCI, 2015), and relapse within 6 months of ending treatment (platinum resistance) is associated with worse outcomes (Markman and Bookman, 2000; Jayson *et al*, 2014).

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Thus, identifying factors associated with survival and chemoresistance may elucidate pathways involved in ovarian carcinogenesis and progression that could be explored in future research.

Increasing age, advanced disease stage, and poor tumour differentiation have been consistently associated with worse ovarian cancer survival (Baldwin *et al*, 2012; Anuradha *et al*, 2014; Urban *et al*, 2016). However, the literature has been mixed on the relationship between reproductive ovarian cancer risk factors and overall survival (Poole *et al*, 2016). One recent study noted improved survival for ovarian cancer patients with endometriosis (Melin *et al*, 2011); however, a 2014 meta-analysis of smaller studies reported no association after adjustment for covariates (Kim *et al*, 2014). Tubal ligation has been associated with an increased risk of ovarian cancer death in two small studies (Naik *et al*, 2000; Zhang and Holman, 2012), but not in larger studies (Mascarenhas *et al*, 2006; Nagle *et al*, 2008; Robbins *et al*, 2009). Use of menopausal hormone therapy (HT) before diagnosis was associated with a survival advantage in one study (Besevic *et al*, 2015), but not in other studies (Mascarenhas *et al*, 2006; Nagle *et al*, 2008; Wernli *et al*, 2008; Felix *et al*, 2015). Inconsistencies across studies may be driven by small sample sizes.

In this study, we used the large, population-based New England Case-Control (NECC) study to examine the association between pre-diagnostic reproductive and hormonal factors and overall survival among 1649 ovarian cancer cases. We had detailed characterisation of many pre-diagnosis exposures as well as data on tumour characteristics and treatment. In addition, given the particularly poor survival among patients with platinum resistance, we evaluated associations of reproductive and hormonal factors with platinum resistance among 449 ovarian cancer cases who were treated with platinum therapy and had information on relapse during the study interval.

MATERIALS AND METHODS

Study population. The NECC Study is a population-based study of ovarian cancer conducted in Eastern Massachusetts and New Hampshire. Data included in this analysis come from three enrolment phases (1992–1997, 1998–2002, 2003–2008). Details of enrolment into the three study phases have been described previously (Vitonis *et al*, 2011). Briefly, 3957 women diagnosed with incident ovarian cancer in Eastern Massachusetts or New Hampshire were identified through hospital tumour boards and statewide cancer registries. Exclusion criteria for the ovarian cancer cases included: < 18 years old, moved, had no phone, did not speak English, died, or their physician declined permission to contact them. Of the ovarian cancer cases identified, 78% were eligible and 2203 enrolled in the study. Each participant provided a signed informed consent and the study was approved by the institutional review boards at Brigham and Women's Hospital and Dartmouth Medical School.

Case outcomes. A gynaecological pathologist reviewed the pathology reports for all cases to classify ovarian tumours by histology (serous, endometrioid, mucinous, clear cell, other), grade (1, 2, 3), and FIGO stage (I, II, III, IV). Among a subset of women ($n = 881$) diagnosed at Brigham and Women's Hospital, Boston, MA, USA and Massachusetts General Hospital, Boston, MA, USA, we abstracted data on chemotherapy, residual disease, and ovarian cancer recurrence. Information was collected on first-line adjuvant chemotherapy, including each chemotherapy drug the woman received and the therapy start and end dates. Medical records up to July 2015, when available, were searched for evidence of ovarian cancer recurrence. Information was also collected on the size of residual disease after the initial debulking surgery and response to chemotherapy (complete, partial, poor/limited, stable disease,

unknown/other). Women were considered optimally debulked if they had < 2 cm of residual disease remaining after their initial surgery. Date of death for cases was collected primarily through the Social Security Death Index and also from voter and census data and obituaries.

Assessment of pre-diagnostic exposure and covariate information.

During in-person interviews, participants recalled detailed information on lifestyle, reproductive factors, medical history, and body size at least 1 year prior to diagnosis. In analyses on parity, pregnancies lasting 6 months or longer were included. Age at first birth was calculated using the date of the first pregnancy minus date of birth, whereas age at last birth was calculated using the date of the last pregnancy. Women were classified as having menstrual cycle irregularity if they never had regular menstrual cycles. Women reported each oral menopausal HT they had used including the type and duration of use, except in phase 1 of the study, which was excluded from this analysis. Self-reported endometriosis included endometriosis discovered as a cause of infertility. Women were classified as postmenopausal before their diagnosis if (1) their periods had stopped naturally, or (2) they had a hysterectomy or medical menopause and were older than 60 years. Women were classified as having uncertain menopause status if (1) they had a hysterectomy without an oophorectomy and were not yet 60 years old, or (2) their periods were still occurring due to HT use. Age at menopause was considered only for women who reported that their periods had stopped naturally. Ovulatory years were calculated as the age at natural menopause (or current age for premenopausal women) minus age at menarche with subtraction of OC duration and 1 year for each pregnancy. Finally, body mass index (BMI) was calculated as weight in kilograms divided by height in metres squared.

Statistical analyses. We included 1649 invasive epithelial ovarian cancer cases in our main survival analyses. Cox-proportional hazards model was used to calculate hazard ratios (HRs) and 95% confidence intervals (CI) for the association of each reproductive and hormonal factor with overall death, with years since ovarian cancer diagnosis used as the time scale. Cases contributed person-time from the date of ovarian cancer diagnosis until death or the end of follow-up in February 2015. In the platinum-resistance analyses, we included 449 cases with a complete response to platinum-based chemotherapy and information on ovarian cancer recurrence. Logistic regression was used to calculate odds ratios (OR) and 95% CI for the association of each reproductive and hormonal factor with platinum resistance. Cases with a complete response to platinum-based chemotherapy and an ovarian cancer recurrence with 6 months of ending platinum-based chemotherapy were classified as platinum resistant. Cases with a complete response to platinum-based chemotherapy and no recurrence or a recurrence > 6 months after completing chemotherapy were considered non-platinum resistant (i.e., platinum sensitive).

Our initial statistical models adjusted for age at diagnosis (years), year of diagnosis, state of residence (MA, NH), menopausal status (premenopausal, postmenopausal, uncertain menopause status), smoking status (current, past, never), BMI (kg m^{-2}), OC use (ever, never), and parity (ever, never). We included reproductive factors in our initial models to account for possible confounding by pre-diagnostic factors as the association between reproductive and hormonal factors with survival among ovarian cancer cases is not clear. We then evaluated a second model additionally adjusting for tumour stage (I/II, III/IV), grade (1, 2, 3, unknown), histology (serous, endometrioid, mucinous, clear cell, other), and debulking status (optimal debulking, non-optimal debulking, unknown). The fully adjusted models further accounted for chemotherapy (no chemotherapy, platinum and taxol chemotherapy, chemotherapy other than platinum and taxol, unknown chemotherapy type) in the overall survival analysis.

We choose to adjust for prognostic characteristics, such as tumour histology, to assess if the associations observed were driven by the characteristics of the tumour that developed or were independent of these factors. In the platinum analysis, histology was collapsed into serous *vs* non-serous.

For the overall survival analysis, we performed a number of sensitivity analyses which included restricting to high-grade serous cases, excluding cases with stage IV disease, and restricting to cases with stage III disease. As the cause of death was not known for the majority of women, we restricted to the first 5 years of follow-up as most deaths are likely to be due to ovarian cancer during this time period. We tested for effect modification by study phase (1992–1997, 1998–2002, 2003–2008), age at diagnosis (≤ 50 years *vs* > 50 years), and histology (serous *vs* non-serous) using a likelihood ratio test. In addition, as we observed strong associations for endometriosis, menstrual cycle irregularity, age at menarche, and age at natural menopause with overall survival, we stratified by tumour histology, grade, and stage.

In sensitivity analyses for the platinum-resistance analysis, we included all ovarian cancer cases treated with platinum chemotherapy and with a known end date of their treatment irrespective of their response to the platinum treatment. In these sensitivity analyses, we included a third model with additional adjustment for maintenance therapy (no, yes, unknown).

All analyses were performed using SAS version 9.3 (SAS Institute, Cary, NC, USA). *P*-values were two-sided and considered statistically significant if < 0.05 .

RESULTS

Study population. Among 1649 invasive epithelial ovarian cancer cases, we observed 911 all-cause deaths over an average follow-up of 7.6 years (s.d. 5.9 years). The average age at diagnosis among cases that died was 58 years compared with 52 years among cases who survived during follow-up (Table 1). Cases who died were less likely to report pre-diagnostic OC use (47 *vs* 59%) and more likely to be parous (75 *vs* 64%). In addition, women who died were more likely to be diagnosed with high-grade (72 *vs* 42%), and serous (76 *vs* 37%) tumours compared with women who did not die during follow-up.

Among the 449 ovarian cancer cases included in the platinum-resistance analysis (Table 1), 47 (10.5%) had a recurrence within the first 6 months of ending platinum-based chemotherapy (platinum resistant). The majority of platinum-resistant cases, 79%, had a serous tumour compared with only 54% of platinum-sensitive cases. In addition, platinum-resistant cases were more likely to be older, have a high-grade tumour, be parous and be postmenopausal at diagnosis compared with platinum-sensitive cases.

Overall survival. Pre-diagnostic parity and tubal ligation were significantly positively associated with overall survival before adjusting for tumour characteristics; however, after adjustment for tumour histology in particular, the associations were substantially attenuated (Table 2). Further, pre-diagnostic induced abortion was not significantly associated with survival, but women with at least one miscarriage had a 17% (95% CI: 1.00–1.36) increased risk of death compared with women who never reported a miscarriage. In the fully adjusted analyses, increasing age at menarche was associated with an increased risk of death with a HR of 1.24 (95% CI: 1.06–1.44) for an age at menarche of 13 years *vs* < 13 years. In addition, women who were older than 50 years at natural menopause before diagnosis had a 23% (95% CI: 1.03–1.46) increased risk of death compared with women who were 50 years or younger at menopause. There was a significant relationship between menstrual cycle irregularity and overall survival (HR: 0.73;

95% CI: 0.54–0.99). Women who reported ever having pre-diagnostic endometriosis were 29% (95% CI: 0.54–0.94) less likely to die after their ovarian cancer diagnosis compared with women without endometriosis. Although pre-diagnostic postmenopausal use of HT was not associated with overall death (HR: 0.89; 95% CI: 0.73–1.08), longer duration of HT use was associated with a decreased risk of death (HR: 0.79; 95% CI: 0.55–0.90 for > 5 years *vs* never). No significant associations were observed for pre-diagnostic breastfeeding, oral contraceptive use, or ovulatory years as well as age at first and last birth and IUD use with overall survival (data not shown).

Stratified analyses. There was significant heterogeneity between age at menarche and histology (Table 3). The increased risk of death for women with an age at menarche > 13 years compared with < 13 years was only observed among women with high-grade serous, endometrioid, and clear cell ovarian tumours and not among women with low-grade serous tumours (*P*-heterogeneity = 0.01). Although based on a small sample size, the reduced risk of death among women with endometriosis and never regular menstrual cycles was consistent across tumour histology (*P*-heterogeneity = 0.27 and 0.20, respectively). The HRs for endometriosis, menstrual cycle irregularity, age at natural menopause, and age at menarche did not vary by FIGO stage at diagnosis (data not shown).

Sensitivity analyses. In sensitivity analyses, there were no significant interactions between any of the exposures and study phase (data not shown). There was a significant interaction between menopausal status and tumour histology (*P*-heterogeneity = 0.02), although menopausal status was not significantly associated with risk of death for serous or non-serous tumours. In addition, we observed significant interactions of age at diagnosis with parity, menopausal status and menstrual cycle irregularity (*P*-heterogeneity < 0.04). For example, there was a significant inverse association with death for parity among women aged > 50 years (HR: 0.81; 95% CI: 0.67–0.98), but not ≤ 50 years (HR: 1.08; 95% CI: 0.79–1.47). Conversely, the inverse association for menstrual cycle irregularity was only observed among women aged ≤ 50 years (data not shown).

Overall, associations were slightly stronger among women interviewed within 1 year of diagnosis, except for endometriosis, age at natural menopause, and 5 or more years of HT use, which were in the same direction as the full analysis but no longer significant. Similarly, results were generally stronger in analyses restricted to the first 5 years of follow-up (data not shown), including a significant association for ovulatory years (HR, top *vs* bottom quartile: 1.32; 95% CI: 1.01–1.73). Results were substantially unchanged when excluding stage IV disease or restricting to stage III tumours, but slightly attenuated, although in the same direction, when restricting to high-grade serous tumours (data not shown).

Platinum resistance. Among women who had a complete response to platinum-based chemotherapy, no significant associations were observed with platinum resistance (Table 4). Although non-significant, ORs for age at menarche (OR, ≥ 13 *vs* < 13 years: 1.42; 95% CI: 0.75–2.71), age at natural menopause (OR, > 50 *vs* ≤ 50 years: 1.54; 95% CI: 0.68–3.48), and endometriosis (OR: 0.33; 95% CI: 0.07–1.50) are all in the same direction as the hazard estimates for the overall survival analysis. Overall the sensitivity analyses including all ovarian cancer cases irrespective of their response to platinum treatment were similar to the main results for cases with a complete response (Supplementary Table 1), with the exception of menopausal status. Postmenopausal women were at greater risk of platinum resistance compared with premenopausal women (OR: 2.27; 95% CI: 1.06–4.84).

Table 1. Characteristics of NECC invasive epithelial ovarian cancer cases for the survival analysis (N = 1649) and the platinum-resistance analysis (N = 449)

	Overall survival				Platinum-resistance analysis			
	Alive (n = 738)		Deaths (n = 911)		Platinum sensitive (n = 402)		Platinum resistant (n = 47)	
	N	%	N	%	N	%	N	%
Ever OC use	432	59	429	47	223	55	28	60
Ever parous	470	64	687	75	252	63	37	79
Tubal ligation	76	10	142	16	42	10	9	19
Ever smoked	228	31	385	42	107	27	14	30
Postmenopausal	355	48	623	68	219	54	35	74
Uncertain menopause	57	8	60	7	28	7	4	9
Ever breastfed ^a	234	50	296	43	131	52	20	54
Endometriosis	102	14	57	6	55	14	2	4
Ever HT use ^b	134	38	213	37	86	39	15	43
Grade								
1	171	23	47	5	44	11	0	0
2	167	23	146	16	83	21	7	15
3	313	42	657	72	233	58	38	81
Unknown	72	10	51	6	40	10	2	4
Missing	15	2	10	1	2	1	0	0
Histology								
Serous	273	37	695	76	216	54	37	79
Endometrioid	245	33	81	9	99	25	2	4
Mucinous	74	10	21	2	15	4	1	2
Clear cell	83	11	31	3	38	9	3	6
Other	63	9	83	9	34	8	4	9
Chemotherapy ^c								
No chemotherapy	132	18	91	10	—	—	—	—
Platinum + taxol	272	37	413	45	368	92	44	94
Other chemotherapy	34	5	98	11	34	8	3	6
Unknown chemo type	300	41	309	34	—	—	—	—
	Mean	S.d.	Mean	S.d.	Mean	S.d.	Mean	S.d.
Age at diagnosis	52.3	11.2	58	10.4	54.2	11.3	57.7	10.1
Length of follow-up ^d	12.3	4.5	3.8	3.7	8.6	4.6	3.0	2.5
Years of OC use ^e	4.7	4.8	3.8	4.2	3.9	4.1	3.7	4.6
Number of children ^a	2.3	1.2	2.7	1.3	2.4	1.3	2.6	1.1
Age at natural menopause	48.7	5.0	49	5.1	49.0	4.8	49.9	5.7
Age at menarche	12.5	1.5	12.6	1.5	12.4	1.3	12.6	1.5
Ovulatory years	28.7	8.3	31.3	6.9	30.1	7.5	32.5	8.4
Years of HT use ^f	8.4	15.9	8.3	12.7	9.5	13.8	5.0	5.0

Abbreviations: NECC = New England Case-Control Study; OC = oral contraceptive; HT = hormone therapy.

^aAmong parous.

^bAmong postmenopausal women.

^cOther chemotherapy category includes platinum without taxol.

^dMean number of years until death or censoring in overall survival analysis and mean number of months until recurrence or censoring in platinum-resistance analysis.

^eAmong OC users.

^fAmong ever HT users.

DISCUSSION

In one of the largest studies to date, we investigated the association between pre-diagnostic reproductive and hormonal factors and overall survival among 1649 ovarian cancer cases in the NECC Study with careful control for reproductive, tumour, and treatment characteristics. Endometriosis, menstrual cycle irregularity, and longer duration of HT use were associated with improved survival whereas spontaneous miscarriage, older age at menarche, and older age at natural menopause were associated with a worse prognosis. Consistent with the majority of previous research we did not observe any associations between survival and OC use, parity,

breastfeeding, tubal ligation, and ovulatory years (Jacobsen *et al*, 1993; Kjaerbye-Thygesen *et al*, 2006; Mascarenhas *et al*, 2006; Nagle *et al*, 2008; Yang *et al*, 2008; Robbins *et al*, 2009; Zhang and Holman, 2012; Besevic *et al*, 2015). In the first analysis of its kind, we did not observe any significant associations between reproductive and hormonal factors with platinum resistance, although power was limited by a smaller sample size of only 449 ovarian cancer cases with complete response to platinum chemotherapy.

Endometriosis has been consistently associated with an increased risk of ovarian cancer, particularly for endometrioid and clear cell tumours (Pearce *et al*, 2012). Interestingly, in our study, we observed a 29% decreased risk of death among ovarian cancer cases with self-reported endometriosis before diagnosis.

Table 2. Association between reproductive and hormonal factors and overall survival among invasive ovarian cancer cases in the NECC (N = 1649)

			Reproductive characteristics model ^a		Reproductive and tumour characteristics model ^b		Reproductive, tumour and treatment characteristics model ^c	
	Total (n)	Fatal cases (n)	HR	95% CI	HR	95% CI	HR	95% CI
Parity								
Nulliparous	492	224	1.00	(ref.)	1.00	(ref.)	1.00	(ref.)
Parous	1157	687	1.19	(1.02–1.40)	0.89	(0.76–1.05)	0.88	(0.75–1.04)
Nulliparous	492	224	1.00	(ref.)	1.00	(ref.)	1.00	(ref.)
1–2 children	683	370	1.17	(0.98–1.38)	0.90	(0.75–1.07)	0.88	(0.74–1.05)
3–4 children	386	254	1.21	(1.00–1.47)	0.87	(0.72–1.06)	0.87	(0.72–1.06)
5+ children	88	63	1.33	(0.99–1.79)	0.97	(0.72–1.31)	0.97	(0.72–1.31)
Breastfeeding^d								
Never	625	390	1.00	(ref.)	1.00	(ref.)	1.00	(ref.)
Ever	530	296	1.03	(0.88–1.21)	1.00	(0.85–1.17)	1.00	(0.85–1.17)
Oral contraceptive use								
Never	788	482	1.00	(ref.)	1.00	(ref.)	1.00	(ref.)
Ever	861	432	1.02	(0.88–1.18)	1.07	(0.92–1.23)	1.06	(0.91–1.23)
Never	788	482	1.00	(ref.)	1.00	(ref.)	1.00	(ref.)
< 1 years	187	104	1.07	(0.86–1.33)	1.18	(0.95–1.47)	1.16	(0.93–1.46)
1 to < 5 years	375	190	1.07	(0.89–1.28)	1.09	(0.91–1.31)	1.09	(0.91–1.31)
5 to < 10 years	193	96	1.00	(0.80–1.26)	1.03	(0.82–1.30)	1.01	(0.80–1.28)
10+ years	106	67	0.76	(0.54–1.06)	0.84	(0.60–1.17)	0.83	(0.60–1.16)
Tubal ligation								
Never	1431	769	1.00	(ref.)	1.00	(ref.)	1.00	(ref.)
Ever	218	142	1.24	(1.03–1.49)	1.01	(0.84–1.22)	1.03	(0.85–1.24)
Age at menarche^e								
< 13 years	801	422	1.00	(ref.)	1.00	(ref.)	1.00	(ref.)
13 years	502	290	1.15	(0.98–1.33)	1.25	(1.07–1.46)	1.24	(1.06–1.44)
> 13 years	339	194	1.10	(0.92–1.30)	1.22	(1.02–1.45)	1.20	(1.01–1.43)
Menopausal status at diagnosis^f								
Premenopausal	554	228	1.00	(ref.)	1.00	(ref.)	1.00	(ref.)
Postmenopausal	978	623	1.23	(0.97–1.56)	1.05	(0.83–1.33)	1.05	(0.83–1.33)
Age at natural menopause^g								
≤ 50 years	525	319	1.00	(ref.)	1.00	(ref.)	1.00	(ref.)
> 50 years	353	235	1.23	(1.04–1.47)	1.24	(1.04–1.47)	1.23	(1.03–1.46)
Ovulatory years^h								
< 26.5 years	366	150	1.00	(ref.)	1.00	(ref.)	1.00	(ref.)
26.5–< 32 years	357	203	1.19	(0.96–1.49)	1.10	(0.87–1.37)	1.11	(0.88–1.38)
32–35 years	314	183	1.16	(0.92–1.47)	1.09	(0.85–1.36)	1.08	(0.86–1.37)
> 35 years	387	240	1.20	(0.95–1.52)	1.14	(0.90–1.44)	1.15	(0.91–1.45)
Hormone therapy useⁱ								
Never	451	265	1.00	(ref.)	1.00	(ref.)	1.00	(ref.)
Ever	302	174	0.90	(0.74–1.10)	0.88	(0.73–1.08)	0.89	(0.73–1.08)
Never	451	265	1.00	(ref.)	1.00	(ref.)	1.00	(ref.)
< 5 years	142	85	1.04	(0.81–1.33)	1.21	(0.94–1.55)	1.21	(0.94–1.56)
≥ 5 years	160	89	0.80	(0.63–1.02)	0.70	(0.54–0.90)	0.70	(0.55–0.90)
Miscarriage and induced abortion								
Never	1104	588	1.00	(ref.)	1.00	(ref.)	1.00	(ref.)
Ever	545	323	1.14	(0.99–1.31)	1.11	(0.97–1.28)	1.10	(0.96–1.27)
Menstrual cycles								
Regular	1555	866	1.00	(ref.)	1.00	(ref.)	1.00	(ref.)
Irregular	94	45	0.81	(0.60–1.09)	0.74	(0.55–1.01)	0.73	(0.54–0.99)
Endometriosis								
Never	1490	854	1.00	(ref.)	1.00	(ref.)	1.00	(ref.)
Ever	159	57	0.60	(0.45–0.78)	0.72	(0.55–0.95)	0.72	(0.54–0.94)

Abbreviations: NECC = New England Case-Control Study; HR = hazard ratio; CI = confidence interval.

^aAdjusted for age at diagnosis, year of diagnosis, study center (NH, MA), menopause status (pre, post, uncertain), smoking status (never, current, former), parity (ever, never), OC use (ever, never), BMI (kg m⁻²).

^bAdjusted for same variables as reproductive characteristics model plus disease stage (I/II, III/IV), grade (1, 2, 3, missing), histology (serous, endometrioid, mucinous, clear cell, other), debulking status (not optimal, optimal, unknown).

^cAdjusted for same variables as the reproductive and tumour characteristics model plus chemotherapy (no chemotherapy, platinum + taxol, other chemotherapy, unknown chemotherapy type).

^dAmong parous women (n = 1152 for age at last and first birth, n = 1155 for breastfeeding).

^eAmong women with known age at menarche (n = 1642).

^fAmong women with known menopausal status (n = 1532).

^gAmong women with a natural menopause (n = 878).

^hCalculated as age at menopause (or current age, if premenopausal) minus age at menarche with additional subtraction of 1 year for each pregnancy and duration of OC use (n = 1424).

ⁱAmong postmenopausal women in the last two study phases (n = 753).

Table 3. Association between endometriosis and overall survival among invasive ovarian cancer cases by tumour histology and stage in the NECC (N = 1345)^a

	Reproductive and tumour characteristics model ^b			P ^{het} ^c
	High-grade serous HR (95% CI) (total n/fatal cases n)	Low-grade serous HR (95% CI) (total n/fatal cases n)	Endometrioid and clear cell HR (95% CI) (total n/fatal cases n)	
Age at menarche				
< 13 years	1.00 (ref.) (341/237)	1.00 (ref.) (90/63)	1.00 (ref.) (226/46)	0.01
≥ 13 years	1.44 (1.21–1.71) (395/310)	0.73 (0.48–1.11) (76/45)	1.30 (0.87–1.92) (212/65)	
Age at natural menopause				
≤ 50 years	1.00 (ref.) (277/210)	1.00 (ref.) (42/28)	1.00 (ref.) (108/33)	0.20
> 50 years	1.14 (0.91–1.42) (167/130)	1.43 (0.80–2.56) (43/34)	2.45 (1.33–4.50) (106/30)	
Endometriosis				
Never	1.00 (ref.) (687/517)	1.00 (ref.) (150/101)	1.00 (ref.) (364/99)	0.27
Ever	0.78 (0.54–1.12) (51/32)	0.39 (0.18–0.82) (17/8)	0.68 (0.37–1.24) (86/13)	
Menstrual cycles				
Regular	1.00 (ref.) (701/524)	1.00 (ref.) (156/103)	1.00 (ref.) (412/107)	0.80
Irregular	0.68 (0.45–1.02) (37/25)	0.83 (0.35–1.93) (11/6)	0.60 (0.24–1.49) (28/5)	

Abbreviations: NECC = New England Case-Control Study; HR = hazard ratio; CI = confidence interval.
^aExclude 95 mucinous cases, 63 serous tumours with unknown grade, and 146 other histology cases.
^bAdjusted for age at diagnosis, year of diagnosis, study centre (NH, MA), menopause status (pre, post, uncertain), smoking status (never, current, former), parity (ever, never), OC use (ever, never), BMI (kg m⁻²), disease stage (I/II, III/IV), grade (1, 2, 3, missing), histology (serous, endometrioid, mucinous, clear cell, other), and optimal debulking (not optimal, optimal, unknown).
^cP-value for heterogeneity calculated using a likelihood ratio test for the interaction between histology and the exposure of interest.

Although endometriosis-associated ovarian cancers (endometrioid, clear cell, and low-grade serous) are less aggressive than high-grade serous disease, our results suggested that the association was independent of tumour histology and disease stage, and remained after adjustment for debulking, tumour characteristics, and chemotherapy. Prior research in this area has been mixed. A recent meta-analysis of seven studies observed improved survival for women with endometriosis in univariate analyses, but the association was attenuated among the four studies that controlled for age and grade (Kim *et al*, 2014). More recent studies observed improved survival for women with endometriosis in univariate analyses, but not after adjusting for confounders (Garrett *et al*, 2013; Noli *et al*, 2013; Wang *et al*, 2013); however, the majority of these studies had small sample sizes, limiting power particularly in multivariate analyses. The largest study to date of endometriosis and survival was based within a Swedish registry and reported an improved prognosis among ovarian cancer patients with endometriosis (HR: 0.81; 95% CI: 0.65–1.01) (Melin *et al*, 2011). However, this association was attenuated with adjustment for tumour histology and stage among a small subset of the cases with tumour characteristics data ($n = 218$). With 1649 ovarian cancer cases, ours is the largest study to date to assess endometriosis and survival with adjustment for tumour characteristics. It is likely that inconsistencies for this association are largely driven by small sample sizes, supporting a consortial approach.

The biological mechanism underlying the potential association between endometriosis and overall survival among ovarian cancer patients is unclear, but may involve differences in the immunological microenvironment within the peritoneal cavity of women with endometriosis (Gazvani and Templeton, 2002). In addition, ovarian tumours among women with endometriosis may be more likely to express progesterone receptors (PR) as endometriosis lesions have been reported to express PR (Attia *et al*, 2000). The expression of PR is associated with improved survival, particularly among endometrioid and high-grade serous ovarian cancer cases (Sieh *et al*, 2013). However, the expression of PR does not explain the decreased risk of death associated with endometriosis among clear cell tumours, which are generally PR negative (Hecht *et al*, 2009). Finally, endometriosis may affect survival through improved treatment outcomes. Although the association did not reach

statistical significance, most likely due to a small sample size, we did observe a non-significant decreased odds of platinum resistance among women who reported endometriosis. Future research should investigate the potential mechanisms through which endometriosis improves survival after an ovarian cancer diagnosis.

A recent pooled analysis of 52 epidemiological studies observed a significant increased risk of ovarian cancer with current HT use, particularly for serous and endometrioid tumours (Beral *et al*, 2015). Although HT increases risk of certain tumour subtypes, it may lead to less aggressive tumours, as we observed that longer duration of pre-diagnosis HT use was associated with a decreased risk of death. These results are similar to those observed in a large European cohort study (Besevic *et al*, 2015) that observed a 30% (95% CI: 0.50–0.99) decreased risk of death from ovarian cancer for 5 or more years of HT use. In addition, a smaller study noted a decreased risk of death with HT use among ovarian cancer patients who had optimal tumour debulking (Hein *et al*, 2013). In contrast, most smaller studies did not observe an association between pre-diagnostic HT use and survival, although they had limited power and few cases with longer duration of use (Mascarenhas *et al*, 2006; Nagle *et al*, 2008; Wernli *et al*, 2008; Zhang and Holman, 2012; Felix *et al*, 2015). Interestingly, similar associations of improved survival with HT use have been noted for breast cancer, with potential mechanisms including hormonal influences (Christante *et al*, 2008; Sener *et al*, 2009). Ovarian tumours that develop among long-term users of HT may be more likely to express PR, which as noted above has been associated with improved survival (Sieh *et al*, 2013). Better understanding the interplay between hormone exposure and ovarian tumour development may elucidate novel mechanistic pathways in survival. However, we cannot exclude the possibility that long-term HT users may be diagnosed with ovarian cancer at an earlier stage due to increased interaction with health care professionals compared with never HT users.

In our study, cases with an older age at menarche or an older age at natural menopause had worse survival. Interestingly, the association for older age at menarche and overall survival appeared to be strongest among women with high-grade serous, endometrioid and clear cell tumours but was null among women with low-grade serous tumours. Contrary to our findings, two studies have

Table 4. Association between reproductive and hormonal factors and platinum-resistance among invasive ovarian cancer cases with a complete response to first-line platinum chemotherapy in the NECC (n = 449)

			Reproductive characteristics model ^a		Reproductive and tumour characteristics model ^b	
	Total (n)	Platinum resistant (n)	OR	95% CI	OR	95% CI
Parity						
Nulliparous	160	10	1.00	(ref.)	1.00	(ref.)
Parous	289	37	1.80	(0.83–3.93)	1.26	(0.56–2.83)
Breastfeeding^c						
Never	137	17	1.00	(ref.)	1.00	(ref.)
Ever	151	20	1.24	(0.59–2.61)	1.48	(0.69–3.21)
Oral contraceptive use						
Never	198	19	1.00	(ref.)	1.00	(ref.)
Ever	251	28	1.42	(0.75–2.68)	1.41	(0.70–2.84)
Tubal ligation						
Never	398	38	1.00	(ref.)	1.00	(ref.)
Ever	51	9	1.65	(0.71–3.86)	1.27	(0.53–3.04)
Age at menarche^d						
< 13 years	234	22	1.00	(ref.)	1.00	(ref.)
≥ 13 years	214	25	1.28	(0.69–2.39)	1.42	(0.75–2.71)
Menopausal status at diagnosis^e						
Premenopausal	163	8	1.00	(ref.)	1.00	(ref.)
Postmenopausal	254	35	2.21	(0.70–7.00)	2.23	(0.69–7.23)
Age at natural menopause^f						
≤ 50 years	137	15	1.00	(ref.)	1.00	(ref.)
> 50 years	95	16	1.52	(0.70–3.30)	1.54	(0.68–3.48)
Ever HT use^g						
Never	141	19	1.00	(ref.)	1.00	(ref.)
Ever	97	13	0.94	(0.43–2.05)	0.98	(0.43–2.24)
Miscarriage and induced abortion						
Never	302	25	1.00	(ref.)	1.00	(ref.)
Ever	147	22	1.71	(0.90–3.23)	1.75	(0.90–3.40)
Menstrual cycles						
Regular	432	45	1.00	(ref.)	1.00	(ref.)
Irregular	17	2	1.32	(0.28–6.23)	0.96	(0.19–4.76)
Endometriosis						
Never	392	45	1.00	(ref.)	1.00	(ref.)
Ever	57	2	0.27	(0.06–1.17)	0.33	(0.07–1.50)

Abbreviations: NECC = New England Case-Control Study; OR = odds ratio; CI = confidence interval; HT = hormone therapy.
^aAdjusted for age at diagnosis, year of diagnosis, study centre (NH, MA), menopause status (pre, post, uncertain), smoking status (never, current, former), parity (ever, never), OC use (ever, never), and BMI (kg m⁻²).
^bAdjusted for same variables as reproductive characteristics model plus disease stage (I/II, III/IV), grade (1, 2, 3, missing), histology (serous, endometrioid, mucinous, clear cell, other), optimal debulking (optimal, not optimal, unknown).
^cAmong parous women (n = 288 for breastfeeding).
^dAmong women with known age at menarche (n = 448).
^eAmong women with known menopausal status (n = 417).
^fAmong women with a natural menopause (n = 232).
^gAmong postmenopausal women in the last two study phases (n = 238).

reported improved survival with older age at menarche (Kjaerbye-Thygesen *et al*, 2006; Robbins *et al*, 2009), whereas the majority of studies observed no association (Jacobsen *et al*, 1993; Mascarenhas *et al*, 2006; Nagle *et al*, 2008; Yang *et al*, 2008; Zhang and Holman, 2012; Besevic *et al*, 2015). In addition, all other studies that have assessed age at menopause and survival among ovarian cancer cases have reported null findings (Jacobsen *et al*, 1993; Mascarenhas *et al*, 2006; Yang *et al*, 2008; Besevic *et al*, 2015). Given the overall weight of the evidence, it is likely that our results were due to chance.

Only one other study has assessed abortion and survival among ovarian cancer cases (Jacobsen *et al*, 1993). In contrast to our findings of an increased risk of death with at least one spontaneous miscarriage, Jacobsen *et al*, 1993 reported a protective effect on

survival for two or more abortions. However, this study did not distinguish between induced and spontaneous abortions making it difficult to directly compare with our results. In addition, we are the only study, as far as we know, that has assessed menstrual cycle irregularity and overall survival. We observed a better prognosis among women who reported menstrual cycle irregularity. Future research is needed to validate both the miscarriage and menstrual cycle irregularity findings in our analysis.

Our platinum-resistance analyses were limited by a small sample size. Only 10% of ovarian cancer cases with a complete response to platinum-based chemotherapy had a recurrence within 6 months of ending treatment. However, the observed direction of effects was similar to those observed in the analysis of overall survival. Although this may be due, in part, to the worse outcomes

for patients with platinum resistance, such research, in large datasets with detailed treatment and recurrence data, is crucial to identify the underlying pathways through which pre-diagnosis exposures may influence tumour aggressiveness and hence survival.

One limitation of our study is that we did not have information on cause of death; however, prior studies have shown that most deaths at least within the first 3 to 5 years after diagnosis are due to ovarian cancer (Poole *et al*, 2013; Besevic *et al*, 2015). Of the 554 deaths in the European Prospective Investigation into Cancer and Nutrition, 92% were due to ovarian cancer over a mean follow-up of 3.6 (s.d. = 3.2) years (Besevic *et al*, 2015). In analyses restricted to the first 5 years of follow-up, we observed similar results to the main findings. In addition, cases were interviewed a median of 8.9 months (min 0.8 months, max 45.4 months) after ovarian cancer diagnosis. Therefore, women with rapidly fatal cancers would be less likely to be included in the study. However, when we restricted analyses to women interviewed within 1 year of diagnosis the results were similar to the main findings. There were also a limited number of ovarian cancer cases who had a complete response to platinum-based chemotherapy thereby limiting power to observe associations between reproductive factors and platinum-resistance. Furthermore, as we have repurposed the NECC case-control study into a survival study, we lack information on post-diagnosis exposure information; however, we have detailed information on pre-diagnosis exposures and tumour characteristics (Poole *et al*, 2016). Finally, a large number of statistical tests were performed in this study, therefore there is the possibility that at least some of the results we have observed may be due to chance.

Our study was one of the largest studies to date to assess pre-diagnostic reproductive and hormonal factors, and overall survival. The large sample size allowed us to assess effect modification by histology and age at diagnosis. In addition, we had detailed pre-diagnostic exposure and covariate information collected through in-person interviews and pathology reports to abstract tumour characteristics. Furthermore, for over half of the study population we had access to detailed medical information including chemotherapy, debulking status, and response to chemotherapy enabling us to control for chemotherapy use and assess predictors of platinum resistance.

Among ovarian cancer cases we observed improved overall survival among women with pre-diagnostic endometriosis and long-term users of HT, which may be through changes in the hormonal or immunological milieu of these women. Future research should focus on understanding the mechanisms through which pre-diagnostic endometriosis and HT use may improve survival after an ovarian cancer diagnosis. In addition, further research is needed to validate our findings for spontaneous miscarriage and menstrual cycle irregularity.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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