Epidemiologic factors that predict long-term survival following a diagnosis of epithelial ovarian cancer

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Background: Various epidemiologic factors have been shown to influence the risk of ovarian cancer development. Given the high fatality associated with this disease, it is of interest to evaluate the association of prediagnostic hormonal, reproductive, and lifestyle exposures with ovarian cancer-specific survival.

Methods: We included 1421 patients with invasive epithelial ovarian cancer diagnosed in Ontario, Canada. Clinical information was obtained from medical records and prediagnostic exposure information was collected by telephone interview. Survival status was determined by linkage to the Ontario Cancer Registry. Proportional hazards regression was used to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) for ovarian cancer-specific mortality associated with each exposure. Analyses were stratified by histologic subtype to further investigate the associations of risk factors on ovarian cancer-specific mortality.

Results: After a mean follow-up of 9.48 years (range 0.59–20.32 years), 655 (46%) women had died of ovarian cancer. Parity (ever) was associated with a significant 29% decreased mortality risk compared with nulliparity (HR = 0.71; 95% CI 0.54–0.93; P = 0.01). There was a borderline significant association between ever use of oestrogen-containing hormone replacement therapy (HRT) and mortality (HR = 0.79; 95% CI 0.62–1.01; P = 0.06). A history of cigarette smoking was associated with a significant 25% increased risk of death compared with never smoking (HR = 1.25; 95% CI 1.01–1.54; P = 0.04). Women with a greater cumulative number of ovulatory cycles had a significantly decreased risk of ovarian cancer-specific death (HR = 0.63; 95% CI 0.43–0.94; P = 0.02). Increasing BMI (kg m^{-2}) 5 years before diagnosis was associated with an increased risk of death (HR = 1.17; 95% CI 1.07–1.28; P = 0.0007). Other hormonal or lifestyle factors were not significantly associated with ovarian cancer-specific mortality.

Conclusions: Parity, ovulatory cycles, smoking, and BMI may affect survival following the diagnosis of ovarian cancer. Whether or not oestrogen-containing HRT use is beneficial for survival requires further evaluation.

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Cancer of the ovary is the most fatal gynaecologic malignancy and is the fifth leading cause of cancer related death among women in Canada and the United States (Sopik *et al*, 2015). Although the pathogenesis of ovarian cancer is not clearly understood, proposed mechanisms include the 'incessant ovulation hypothesis,' whereby factors that suppress or interrupt ovulation protect against ovarian cancer (Fathalla, 1971; Ness *et al*, 2000; Fleming *et al*, 2006). Other proposed mechanisms of ovarian cancer carcinogenesis include stimulation by hormonal exposures, inflammation mechanisms, and retrograde transportation of endogenous or exogenous carcinogens through the fallopian tubes (Cramer *et al*, 1982; Cramer and Xu, 1995; Risch, 1998; Ness and Cottreau, 1999; Shan and Liu, 2009). These hypotheses are supported by epidemiologic findings of ovarian cancer risk reduction with events that interrupt or suppress ovulation (e.g., pregnancy and oral contraceptive use; Whittemore *et al*, 1992; Danforth *et al*, 2007; Beral *et al*, 2008; Luan *et al*, 2013), reduce inflammation (e.g., aspirin or non-aspirin NSAID use, tubal ligation; Trabert *et al*, 2014), whereas exposures that increase inflammation (e.g., endometriosis; Pearce *et al*, 2012; Terry *et al*, 2013) or hormonal exposure (e.g., exogenous hormone use) are associated with an increased risk (Zhou *et al*, 2008).

The prognosis of ovarian cancer is poor with a mean 5-year survival of 45% and 15–25% among stage III/IV patients (Sopik *et al*, 2015). Clinical factors that influence survival include stage at detection, volume of disease, success in optimal debulking, histologic subtype, tumour grade, and response to chemotherapy (Barakat *et al*, 2009; du Bois *et al*, 2009; Chang and Bristow, 2012). The influence of additional lifestyle factors such as body mass index (BMI) have been inconsistent as some evidence suggests higher BMI is associated with adverse prognosis and increased ovarian cancer mortality (Poole *et al*, 2016); however, these findings contrast previous reports of no association between body size and ovarian cancer survival (Kotsopoulos *et al*, 2012; Zhou *et al*, 2014). In a recent previous study, we found that the most important prognostic factor was the absence of residual tumour following primary debulking surgery, irrespective of other tumour characteristics (Kotsopoulos *et al*, 2016). Given that the mortality associated with ovarian cancer has changed little in recent years, it is of interest to evaluate whether or not epidemiologic factors associated with risk of ovarian cancer may also influence outcome from this fatal disease.

Various studies have evaluated roles of hormonal, reproductive, and lifestyle factors on the prognosis of ovarian cancer; however, findings have been inconclusive and many analyses were limited by a small number of patients, relatively short follow-up periods, and other methodologic concerns (recently reviewed in Poole *et al*, 2016). Using a large sample of patients with ovarian cancer, many followed for a decade or more, we evaluated the association between prediagnostic epidemiologic factors and long-term ovarian cancer-specific mortality.

MATERIALS AND METHODS

Study population. The current study uses information from a large series of unselected ovarian cancer patients diagnosed in Ontario, Canada. Detailed information about the study design and data collection has been previously published (Zhang *et al*, 2011; McLaughlin *et al*, 2013; Narod *et al*, 2013). Briefly, all residents between the ages of 20 and 79 years with diagnoses of new invasive epithelial ovarian cancer from January 1995 to December 1999 and from January 2002 to December 2004 were identified through the Ontario Cancer Registry (OCR) (Zhang *et al*, 2011; McLaughlin *et al*, 2013; Narod *et al*, 2013). Of the 3168 initially eligible patients, genetic testing was performed on 1421 (45%), as previously described, and these are the subjects included in the present study

(Zhang *et al*, 2011). The mean time between date of diagnosis and date of genetic testing was 1.83 years. All of the women provided written informed consent and the study was approved by the institutional review boards of the University of Toronto and Yale University.

Pathology review and outcome data. For each patient, the investigators reviewed pathology records to determine eligibility and tumour histology. Medical records were reviewed to obtain information about clinical staging, treatments received, and treatment outcomes. Extent of residual disease following primary debulking surgery was coded as 'yes' (presence of any residual disease) or 'no' (zero residual disease). Survival status was determined both by periodic chart review at local hospitals and computerised linkage to the records of the OCR that provides information on fact, date, and cause of death. The OCR, which began in 1964, contains highly complete information on cancer incidence, mortality, and survival in Ontario. We used vital status and cause of death obtained from a linkage performed with data in the OCR on 1 May 2015. For the purpose of this analysis, cause of death was coded as ovarian cancer or other.

Assessment of epidemiologic risk factors and covariates. Information on known and suspected ovarian cancer risk factors and demographic information was collected by telephone interview with a standardised-script questionnaire. Specifically, detailed data were obtained for age at menarche, age at menopause, parity, breastfeeding (number of months), oral contraceptives use, oestrogen-containing hormone replacement therapy (HRT), infertility treatment, smoking history, tubal ligation, intrauterine device (IUD) use, family history of breast or ovarian cancer, and endometriosis. The cumulative number of ovulatory cycles for each woman was estimated using the following equations: (1) if premenopausal: ovulatory cycles $= 12 \times$ (current age $-$ age at menarche $-$ years of oral contraceptive use $-$ (parity $\times$ 0.77) $-$ years of breastfeeding); (2) if postmenopausal, current age was replaced with age at menopause (surgical or natural). Participants also reported their current weight and height, height and weight at age 21 years, and weight 5 years before their diagnosis. Body mass index at various ages was calculated in units of $kg\,m^{-2}$ using the reported current height. To avoid the influence of disease status on body weight, we calculated BMI ($n = 1316$) in units of $kg\,m^{-2}$ using reported current height but weight 5 years in the past. The mean number of months elapsed from date of diagnosis to the date of interview was 22.0 months (range 0.1–79 months).

Statistical analysis. Differences between clinical, demographic, and other characteristics were compared according to cause of death at the end of follow-up using the χ^2 test or t-test, as appropriate. The primary outcome in this analysis was ovarian cancer-specific survival defined as the duration from the date of diagnosis until the date of death from ovarian cancer. Survival was censored at death from another cause or 1 May 2015, the most recent limit of available death-certificate information (if patient was still alive). We performed a left-truncated survival analysis to account for the time elapsed between the date of diagnosis and the date of ascertainment (i.e., enrolment for genetic testing). This method of adjustment has been previously shown to reduce the extent of survivorship bias present in the current study population (Narod *et al*, 2013). Proportional hazards models were used to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) associated with the epidemiologic risk factors. The base model (model 1) was adjusted for age at diagnosis (continuous), histologic subtype (serous, mucinous, endometrioid, clear cell, and other (mixed histology and epithelial not otherwise specified)), and stage (I, II, III, IV). Twenty-seven patients had missing information on tumour stage, and thus the total number of ovarian cancer cases in model 1 was 1394. Model 2 adjusted for the covariates in model 1

as well as for residual disease status (yes or no), in which 588 participants had missing information, and thus the total number of ovarian cancer cases in model 2 was 833. Each exposure variable of interest was added to the models one at a time. Proportional hazards assumptions were assessed with Schoenfeld and Martingale residuals (Allison, 1995). The statistical significance of interaction terms between histologic subtypes and various exposures were determined using the likelihood ratio test. Stratified analyses were conducted for significant interaction terms to further investigate the role of histological subtype on various exposures. Analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC, USA) and all P-values are two sided.

RESULTS

Characteristics of the 1421 women diagnosed with invasive epithelial ovarian cancer are displayed in Table 1 by cause of death. An average of 9.48 years (range 0.59–20.32 years) of follow-up elapsed. Women who died of ovarian cancer had a shorter mean follow-up period, were older on average, and more likely to be diagnosed with serous, stage III, or stage IV tumours compared with women who did not die of ovarian cancer ($P < 0.0001$). Among women with information on the extent of residual disease following primary debulking surgery ($n = 833$; 59%), those who died of ovarian cancer were more likely to have residual disease compared with patients who were still alive ($P < 0.0001$). With respect to reproductive and hormonal exposures, women who died of ovarian cancer during the follow-up period were less likely to have used oral contraceptives, more likely to have used HRT, had higher mean parity, and higher mean number of ovulatory cycles compared with participants who did not die of ovarian cancer ($P < 0.04$). Women who died of ovarian cancer were more likely to have a history of cigarette smoking, a higher BMI 5 years before diagnosis, and were more likely to carry an inherited BRCA1 or BRCA2 mutation ($P < 0.04$). No other significant differences were found between the two groups of women.

We next evaluated the role of various epidemiologic exposures on the prognosis of ovarian cancer (Tables 2 and 3). Table 2 summarises the HRs and 95% CIs for ovarian cancer-specific survival by various reproductive and hormonal factors. Model 1 adjusted for age, tumour histology, and grade ($n = 1394$) and model 2 was further adjusted for residual disease status ($n = 833$). Parity was associated with decreased ovarian cancer-specific mortality compared with nulliparity ($HR_{Model\ 1} = 0.82$; 95% CI 0.66–1.02; $P = 0.07$) and reached significance after further adjusting for residual disease ($HR_{Model\ 2} = 0.71$; 95% CI 0.54–0.93; $P = 0.01$). In the same way, after additionally adjusting for residual disease, women with a greater cumulative number of ovulatory cycles had a significantly decreased risk of death from ovarian cancer (>439.42 cycles $vs \leqslant 322.28$ cycles $HR_{Model\ 2} = 0.63$; 95% CI 0.43–0.94; $P = 0.02$). No significant associations between the other reproductive or hormonal characteristics and mortality were observed in this cohort of ovarian cancer patients.

Associations between various lifestyle and family history characteristics and ovarian cancer survival are displayed in Table 3. Women who reported a history of cigarette smoking had increased ovarian cancer-specific mortality compared with never smokers ($HR_{Model\ 1} = 1.16$; 95% CI 0.99–1.36; $P = 0.08$) and this association was stronger in the model that further adjusted for residual disease status ($HR_{Model\ 2} = 1.25$; 95% CI 1.01–1.54; $P = 0.04$). Moreover, increasing BMI 5 years before diagnosis by 5-unit increments was associated with an increased risk for ovarian cancer-specific mortality, both in model 1 ($HR_{Model\ 1} = 1.11$; 95% CI 1.03–1.19; $P = 0.006$) and model 2 ($HR_{Model\ 2} = 1.17$; 95% CI 1.07–1.28; $P = 0.0007$). Similarly, obesity (BMI $\geqslant 30\,kg\,m^{-2}$)

Table 1. Baseline characteristics of study population by ovarian cancer-specific survival			
Characteristic	Did not die of OC, $n = 766$	Died of OC, $n = 655$	*P*-value
Follow-up (years), mean (s.d.)	12.90 (5.58)	5.48 (3.58)	<0.0001
Age at diagnosis, mean (s.d.)	54.86 (11.62)	59.84 (11.02)	<0.0001
Tumour characteristics			
Histology, n (%)			<0.0001
Serous	329 (43.0%)	454 (69.3%)	
Mucinous	90 (11.8%)	25 (3.8%)	
Endometrioid	218 (28.5%)	80 (12.2%)	
Clear cell	70 (9.1%)	25 (3.8%)	
Other	59 (7.7%)	71 (10.8%)	
Stage, n (%)			<0.0001
I	225 (29.8%)	29 (4.6%)	
II	165 (21.8%)	82 (12.9%)	
III	297 (39.3%)	402 (63.0%)	
IV	69 (9.1%)	125 (19.6%)	
Residual disease, n (%)			<0.0001
No residual disease	208 (48.5%)	92 (22.8%)	
Residual disease	221 (51.5%)	312 (77.2%)	
Reproductive/hormonal factors			
Oral contraceptive use (ever), n (%)	438 (60.5%)	314 (52.3%)	0.003
Duration of oral contraceptive use (years), mean (s.d.)	2.96 (4.23)	2.62 (4.22)	0.18
Oestrogen HRT (ever), n (%)	162 (22.3%)	163 (27.3%)	0.04
Tamoxifen use (ever), n (%)	4 (1.5%)	4 (2.3%)	0.72
Infertility (female only), n (%)	29 (4.0%)	17 (2.9%)	0.39
Fertility treatment (ever), n (%)[a]	22 (3.1%)	17 (2.8%)	0.82
Endometriosis, n (%)	39 (5.4%)	33 (5.6%)	0.93
Parity, mean (s.d.)[b]	2.45 (1.26)	2.71 (1.42)	0.002
Age at first birth, mean (s.d.)[b,c]	24.73 (4.87)	24.55 (4.76)	0.56
Breastfed (ever), n (%)[b]	341 (58.8%)	275 (57.5%)	0.68
Duration of breastfeeding (months), mean (s.d.)[b]	6.33 (11.78)	7.17 (13.57)	0.29
Age at menarche, mean (s.d.)	12.90 (1.52)	12.98 (1.58)	0.32
Age at natural menopause, mean (s.d.)	49.75 (4.10)	49.27 (4.02)	0.12
IUD use (ever), n (%)	111 (15.4%)	100 (16.8%)	0.50
Tubal ligation, n (%)	158 (21.8%)	151 (25.2%)	0.15
Number of ovulatory cycles, mean (s.d.)	379.90 (109.20)	396.1 (113.20)	0.03
Lifestyle factors/family history characteristics			
Smoking (ever), n (%)	333 (45.9%)	316 (52.7%)	0.01
BMI 5 years before diagnosis, mean (s.d.)	25.62 (5.28)	26.24 (5.72)	0.04
BRCA1/2 mutation, n (%)	75 (9.8%)	102 (15.6%)	0.001
First-degree relatives with history of breast cancer, n (%)	138 (18.4%)	128 (20.2%)	0.39
First-degree relatives with history of ovarian cancer, n (%)	52 (6.9%)	52 (8.2%)	0.36

Abbreviations: BMI = body mass index; HRT = hormone replacement therapy; IUD = intrauterine device; OC = ovarian cancer.
[a]Fertility treatment included one or more of Clomid, Serophene, Pergonal, Metrodin, Profasil, Lupron, Leuprolide, or other fertility medication.
[b]Among parous women only.
[c]Age at first birth based on year of birth, not exact date because of data limitations.

5 years before diagnosis was associated with an increased risk for ovarian cancer-specific mortality after additionally adjusting for residual disease ($HR_{Model\ 2} = 1.34$; 95% CI 1.02–1.76; $P = 0.04$).

Analyses were stratified by histologic subtype to further investigate the associations of risk factors on distinct subtypes, although these analyses were limited by the small number of cases in the subgroups and we did not adjust for residual disease status. The impact of smoking on death was stronger for women with a mucinous tumour (HR = 2.52; 95% CI 1.01–6.33; $P = 0.05$) vs a serous (HR = 1.12; 95% CI 0.92–1.36; $P = 0.28$) or an endometrioid

Table 2. Association between reproductive and hormonal exposures and ovarian cancer-specific survival

	OC deaths/n^a	HR model 1[b]	95% CI	P-value	OC deaths/n^c	HR model 2[d]	95% CI	P-value
Age at diagnosis	638/1394	1.25	1.17, 1.35	<0.0001	404/833	1.19	1.09, 1.31	0.0002
Histology								
Serous	439/758	1.00	Ref.	Ref.	280/468	1.00	Ref.	Ref.
Mucinous	25/115	0.50	0.33, 0.76	0.001	20/67	1.26	0.90, 1.76	0.18
Endometrioid	80/298	0.58	0.45, 0.75	<0.0001	45/164	1.16	0.66, 2.01	0.61
Clear cell	24/94	0.62	0.41, 0.95	0.03	17/50	0.85	0.55, 1.32	0.48
Other	70/129	0.87	0.67, 1.12	0.27	42/84	1.34	0.75, 2.40	0.33
Stage								
I	29/254	1.00	Ref.	Ref.	18/173	1.00	Ref.	Ref.
II	82/247	2.82	1.84, 4.33	<0.0001	59/142	4.09	2.37, 7.04	<0.0001
III	402/699	6.38	4.28, 9.51	<0.0001	288/455	8.73	5.18, 14.72	<0.0001
IV	125/194	9.17	5.95, 14.13	<0.0001	39/63	11.44	6.23, 21.02	<0.0001
Tumour characteristics								
Residual disease								
No	92/300	1.00	Ref.	Ref.	92/300	1.00	Ref.	Ref.
Yes	312/533	1.64	1.28, 2.11	0.0001	312/533	1.64	1.28, 2.11	0.0001
Reproductive/hormonal factors								
Age at menarche (years), continuous	585/1297	1.02	0.96, 1.07	0.58	369/762	1.04	0.97, 1.11	0.30
Age at menarche (years)								
≤12	219/489	1.00	Ref.	Ref.	146/301	1.00	Ref.	Ref.
13	179/409	0.97	0.79, 1.18	0.74	109/231	1.00	0.77, 1.29	0.98
14	100/221	0.91	0.72, 1.16	0.44	60/123	1.03	0.76, 1.39	0.87
>14	87/178	1.10	0.85, 1.41	0.47	54/107	1.13	0.83, 1.56	0.44
Parity, continuous[e]	465/1037	1.04	0.97, 1.11	0.26	289/611	1.04	0.95, 1.13	0.41
Parity[e]								
1	73/190	1.00	Ref.	Ref.	52/111	1.00	Ref.	Ref.
2	178/407	1.19	0.90, 1.56	0.22	108/244	0.92	0.66, 1.28	0.61
>3	214/440	1.13	0.86, 1.49	0.37	129/256	0.96	0.69, 1.34	0.82
Parity, never/ever								
Nulliparous	99/218	1.00	Ref.	Ref.	64/126	1.00	Ref.	Ref.
Parous	487/1084	0.82	0.66, 1.02	0.07	305/638	0.71	0.54, 0.93	0.01
Age at first birth (years), continuous[e]	408/909	1.00	0.98, 1.02	0.94	250/520	1.01	0.98, 1.03	0.70
Age at first birth[e]								
<20	54/117	1.00	Ref.	Ref.	33/68	1.00	Ref.	Ref.
20–30	306/685	0.90	0.67, 1.20	0.45	187/387	0.96	0.66, 1.40	0.84
>30	48/107	0.99	0.67, 1.46	0.94	30/65	1.02	0.62, 1.68	0.94
Breastfed[e]								
Never	197/434	1.00	Ref.	Ref.	124/256	1.00	Ref.	Ref.
Ever	268/603	1.07	0.89, 1.28	0.49	165/355	0.96	0.76, 1.21	0.71
Duration of breastfeeding (months), continuous[e]	465/1037	1.00	1.00, 1.01	0.50	285/605	1.01	1.00, 1.01	0.27
Duration of breastfeeding (months)[e]								
0	192/427	1.00	Ref.	Ref.	121/252	1.00	Ref.	Ref.
1–6	122/286	1.03	0.82, 1.30	0.78	82/180	0.91	0.68, 1.20	0.50
>6	144/313	1.11	0.90, 1.38	0.34	82/173	1.04	0.79, 1.38	0.77
Oral contraceptive use								
Never	284/568	1.00	Ref.	Ref.	167/328	1.00	Ref.	Ref.
Ever	302/732	1.00	0.83, 1.20	0.99	203/437	1.16	0.92, 1.47	0.20
Duration of oral contraceptive use (years), continuous	482/1096	1.00	0.98, 1.02	0.99	308/648	1.02	0.99, 1.04	0.27
Duration of oral contraceptive use (years)								
0	268/570	1.00	Ref.	Ref.	164/336	1.00	Ref.	Ref.
1–5	119/307	1.00	0.80, 1.25	0.98	79/185	1.06	0.81, 1.41	0.66
>5	96/219	1.08	0.84, 1.38	0.55	65/127	1.23	0.91, 1.67	0.18
Oestrogen HRT								
Never	424/977	1.00	Ref.	Ref.	280/577	1.00	Ref.	Ref.
Ever	160/322	0.90	0.75, 1.09	0.28	89/187	0.79	0.62, 1.01	0.06
Tamoxifen use								
Never	164/414	1.00	Ref.	Ref.	82/183	1.00	Ref.	Ref.
Ever	3/7	2.54	0.77, 8.38	0.13	3/4	3.57	0.99, 12.93	0.05
Fertility treatment								
Never	570/1258	1.00	Ref.	Ref.	359/741	1.00	Ref.	Ref.
Ever	16/38	0.89	0.54, 1.47	0.64	11/20	1.24	0.67, 2.29	0.50
Endometriosis								
No	551/1219	1.00	Ref.	Ref.	349/716	1.00	Ref.	Ref.
Yes	31/70	1.27	0.88, 1.83	0.21	17/38	1.10	0.67, 1.81	0.71

Table 2. (Continued)

	OC deaths/n^a	HR model 1[b]	95% CI	P-value	OC deaths/n^c	HR model 2[d]	95% CI	P-value
Age at natural menopause (years), continuous	341/692	0.98	0.96, 1.01	0.11	208/403	0.98	0.94, 1.01	0.14
Age at natural menopause								
⩽47	97/175	1.00	Ref.	Ref.	55/99	1.00	Ref.	Ref.
>47–50	118/228	0.89	0.68, 1.17	0.41	78/138	0.94	0.66, 1.34	0.74
>50–52	61/147	0.78	0.56, 1.07	0.12	36/87	0.74	0.48, 1.14	0.17
>52	65/142	0.75	0.55, 1.03	0.08	39/79	0.69	0.45, 1.05	0.08
Menopausal status at diagnosis								
Premenopausal	131/370	1.00	Ref.	Ref.	89/211	1.00	Ref.	Ref.
Postmenopausal	449/907	1.01	0.77, 1.32	0.97	278/542	0.96	0.69, 1.35	0.83
IUD use								
Never	487/1090	1.00	Ref.	Ref.	306/638	1.00	Ref.	Ref.
Ever	98/206	1.09	0.87, 1.36	0.45	63/122	1.06	0.80, 1.40	0.71
Tubal ligation								
Never	438/998	1.00	Ref.	Ref.	276/581	1.00	Ref.	Ref.
Ever	148/302	1.08	0.89, 1.31	0.43	94/183	0.98	0.77, 1.25	0.87
Number of ovulatory cycles								
⩽322.28	95/228	1.00	Ref.	Ref.	61/130	1.00	Ref.	Ref.
>322.28–389.52	105/230	0.87	0.65, 1.16	0.35	65/134	0.82	0.58, 1.18	0.29
>389.52–439.42	101/225	0.78	0.58, 1.05	0.10	62/133	0.74	0.50, 1.08	0.12
>439.42	102/225	0.82	0.60, 1.11	0.20	65/143	0.63	0.43, 0.94	0.02

Abbreviations: CI = confidence interval; HR = hazard ratio; HRT = hormone replacement therapy; IUD = intrauterine device; OC = ovarian cancer; ref. = reference value.
[a]There were a total of $n = 1394$ in model 1 because 27 participants had missing information on tumour stage.
[b]Adjusted for age at diagnosis (continuous), histology (serous, mucinous, endometrioid, clear cell, other), and stage (I, II, III, IV).
[c]There were a total of $n = 833$ in model 2 because 588 participants had missing information on residual disease after debulking surgery.
[d]Adjusted for model 1 and residual disease (no residual disease, any residual disease).
[e]Among parous women only.

(HR = 0.92; 95% CI 0.58–1.45; $P = 0.71$) tumour. The interaction was not statistically significant (P–interaction = 0.13). Increasing BMI (per 5-unit increase) was associated with increased mortality for women diagnosed with a serous (HR = 1.09; 95% CI 1.00–1.19; $P = 0.05$) and endometrioid (HR = 1.18; 95% CI 0.98–1.43; $P = 0.09$) tumour, but was not significantly associated with death among women with a mucinous tumour (HR = 1.14; 95% CI 0.72–1.81; $P = 0.56$) (P–interaction = 0.02). None of the other risk factors associations varied by histologic subtype.

DISCUSSION

The goal of the current study was to evaluate associations between reproductive, hormonal, and lifestyle factors before diagnosis of epithelial ovarian cancer on survival among 1394 women. After accounting for known clinical prognostic factors (i.e., age, tumour histology, grade, and presence of residual disease), we observed that parity and greater number of ovulatory cycles were associated with better prognosis, whereas higher BMI and a history of smoking had a significant adverse effect. No other reproductive and hormonal factors were significantly associated with outcome, although we observed a borderline decreased risk of death with use of oestrogen-containing HRT. Some of the associations varied by histologic subtype, although our stratified analyses were limited by small numbers in the subgroups. Collectively, these findings suggest that although various exposures may be associated with ovarian cancer development (e.g., oral contraceptive use), the majority of these have little impact on long-term ovarian cancer outcomes.

Poole et al (2016) recently conducted an extensive review of the published literature on the prognostic associations of reproductive, hormonal, and lifestyle factors for ovarian cancer Many of the early studies included small numbers of cases, did not have information on ovarian cancer-specific survival, and did not adjust for important confounders, particularly residual disease status. The

authors of the review concluded that overall the data were sparse, and whereas reproductive or hormonal factors were likely not strong predictors of outcome, body size was among the most studied and represented a lifestyle factor that may favourably influence prognosis. Since this review, one additional work evaluated the association of reproductive and hormonal factors on survival, in data from the New England Case-Control Study of Ovarian Cancer that included prediagnostic information on 1649 ovarian cancer patients and 911 all-cause deaths and reported improved survival for endometriosis and for HRT use (Shafrir et al, 2016).

In the current study, parity per se (but not increasing parity or age at first birth) was associated with better prognosis in contrast to most previous studies that have generally shown no significant association between parity and survival (Besevic et al, 2015; Poole et al, 2016; Shafrir et al, 2016). Recent observational studies have shown that parity is associated with decreased risk of type I tumours (i.e., low-grade subtypes; Fortner et al, 2015) as well as with less aggressive subtypes (i.e., survived ⩾3 years; Poole et al, 2013). Thus, parity may be associated with the development of less aggressive subtypes and, subsequently, better outcome. However, because of our small sample size in stratified analyses, whether or not parity has an association with survival after tumour characteristics have been considered is uncertain.

Although of borderline significance, we also observed a survival benefit with ever use of oestrogen-containing HRT. We did not have specific information on combined HRT regimens (i.e., oestrogen and progesterone). Eight published observational studies have examined HRT use before diagnosis and survival. These studies ranged in size from 72 to 1649 patients, with only 3 studies adjusting for residual disease in their analysis (Poole et al, 2016; Shafrir et al, 2016). Findings have been inconclusive. In the largest of these studies, Shafrir et al (2016) reported a significant survival advantage among women with ⩾5 years of HRT use before diagnosis (HR for ⩾5 years vs never use = 0.79; 95% CI 0.55–0.90). The authors did not distinguish between types of hormonal preparations. In an analysis of the EPIC study ($n = 1025$ cases/511

Table 3. Association between lifestyle factors and family history and ovarian cancer-specific survival

	OC deaths/n^a	HR model 1[b]	95% CI	P-value	OC deaths/n^c	HR model 2[d]	95% CI	P-value
Lifestyle factors/family history								
Smoking, never/ever								
Never	274/661	1.00	Ref.	Ref.	159/372	1.00	Ref.	Ref.
Ever	312/640	1.16	0.99, 1.36	0.08	211/393	1.25	1.01, 1.54	0.04
BMI 5 years before diagnosis (kg m^{-2}), continuous (5-unit increases)	584/1294	1.11	1.03, 1.19	0.006	367/758	1.17	1.07, 1.28	0.0007
BMI 5 years before diagnosis (kg m^{-2})								
<18.5	10/20	1.10	0.58, 2.07	0.77	5/9	0.99	0.40, 2.42	0.97
18.5–<25	288/660	1.00	Ref.	Ref.	178/383	1.00	Ref.	Ref.
25–<30	179/388	1.10	0.92, 1.33	0.30	112/229	1.13	0.89, 1.44	0.31
⩾30	107/226	1.22	0.97, 1.52	0.08	72/137	1.34	1.02, 1.76	0.04
BRCA1/2 mutation								
No	539/1224	1.00	Ref.	Ref.	341/725	1.00	Ref.	Ref.
Yes	99/170	1.19	0.95, 1.48	0.13	63/108	1.05	0.80, 1.40	0.72
First-degree relative with breast cancer								
No	498/1105	1.00	Ref.	Ref.	317/668	1.00	Ref.	Ref.
Yes	123/257	1.05	0.86, 1.28	0.64	78/146	0.99	0.77, 1.28	0.95
First-degree relative with ovarian cancer								
No	568/1259	1.00	Ref.	Ref.	362/754	1.00	Ref.	Ref.
Yes	52/102	1.05	0.79, 1.40	0.73	32/59	1.03	0.71, 1.48	0.89

Abbreviations: BMI = body mass index; CI = confidence interval; HR = hazard ratio; OC = ovarian cancer; ref. = reference value.
[a]There were a total of $n = 1394$ in model 1 because 27 participants had missing information on tumour stage.
[b]Adjusted for age at diagnosis (continuous), histology (serous, mucinous, endometrioid, clear cell, other), and stage (I, II, III, IV).
[c]There were a total of $n = 833$ in model 2 because 588 participants had missing information on residual disease after debulking surgery.
[d]Adjusted for model 1 and residual disease (no residual disease, any residual disease).

ovarian cancer deaths), Besevic *et al* (2015) also reported a significant survival benefit among women with long-term use of HRT (HR for ⩾5 years *vs* never use = 0.70; 95% CI 0.50–0.99; P–trend = 0.04). However, this study did not take into account residual disease. Although the data from the larger studies suggest a survival advantage among women with histories of HRT use, these findings must be interpreted with caution given that a recent meta-analysis of 52 epidemiologic studies reported a significant increased risk of developing ovarian cancer with current use of HRT (oestrogen and oestrogen plus progesterone combinations) and increasing duration of use, particularly for serous and endometrioid subtypes (Collaborative Group on Epidemiological Studies of Ovarian Cancer *et al*, 2015).

In addition, although we observed improved survival among women with the highest quartile of lifetime ovulatory cycles, this finding should also be interpreted with caution given that factors that suppress or interrupt ovulation (e.g., parity, oral contraceptive use) have consistently been shown to reduce risk of ovarian cancer (La Vecchia, 2016). In addition, we did not have information on menstrual irregularity and may have overestimated the lifetime ovulatory cycles and an inflated risk estimate (Moorman *et al*, 2002). Furthermore, others have generally shown no association with increasing ovulatory years or cycles (Nagle *et al*, 2008; Robbins *et al*, 2009; Besevic *et al*, 2015; Shafrir *et al*, 2016). In line with the published literature to date, we found no significant associations between any of the other prediagnostic reproductive or hormonal exposures and mortality (Poole *et al*, 2016; Shafrir *et al*, 2016).

Smoking is a risk factor for mucinous ovarian cancer (Wentzensen *et al*, 2016). In the current study, we observed that women who reported a history of smoking (at least 100 cigarettes in their lifetime) had a significant 25% increased risk of ovarian cancer death compared with women who never smoked ($P = 0.04$). The effect was stronger among women diagnosed with a mucinous tumour. Five studies have reported on smoking and ovarian cancer survival (range 130–676 cases) (Poole *et al*, 2016). Collectively, the

data suggest that recent or current smoking is associated with worse prognosis representing an important modifiable lifestyle factor that negatively affects outcome.

In the current study, increasing BMI was associated with a worse outcome, and the relationship was stronger among women with a serous or endometrioid tumour. These findings are in line with the majority of the published literature that have reported significant and adverse associations of adiposity with ovarian cancer prognosis (Poole *et al*, 2016), but the literature remains inconstant. Several reasons that may account for these discrepancies include small sample size, adjustment for important confounding factors such as residual disease, and the issue of assessing body size. Furthermore, our findings contrast our previous report of no association between body size and ovarian cancer survival within the same study population (Kotsopoulos *et al*, 2012). This latter discrepancy may be because of the shorter follow-up period in our earlier publication (7.4 *vs* 9.5 years).

Achieving no residual disease at surgical resection is likely the most important predictor of long-term survival (Chang *et al*, 2015). Among the patients in this study, we have recently published that women with no residual disease following primary debulking surgery experience significantly superior survival compared with patients with residual disease (Kotsopoulos *et al*, 2016). These observations support the notion that survival is optimised when residual disease is minimised through complete resection and chemotherapy (Narod, 2015).

The strengths and limitations of this study need to be considered. Despite the large number of unselected ovarian cancer patients, we were not sufficiently powered to conduct analyses stratified by histologic subtype for each exposure of interest. We did not consider comorbidities; however, we and others have shown that women with a diagnosis of ovarian cancer are likely to die of their disease. In our cohort, >80% of deaths were attributed to ovarian cancer (Kotsopoulos *et al*,

2016). In addition, the BMI calculation was based on self-reported weight and height; however, both measures have been shown to be highly valid and well-correlated with measured weight and height in previous studies (Kushi *et al*, 1988; Rimm *et al*, 1990). Furthermore, because of the length in time between diagnosis date and interview time, the potential for recall bias may impact our findings. Importantly, information on the extent of residual disease after primary debulking surgery (an important prognostic factor) was available for only 59% of the patients. However, we displayed our findings both with (model 2) and without (model 1) adjustment for this variable. In most instances, findings were strengthened in the fully adjusted model and a strength of this study was the ability to adjust for residual disease status, whereas previously published studies have not. Additional strengths of our study included the large number of unselected patients of epithelial ovarian cancer with detailed information on cause of death (ovarian cancer specific), as well as on tumour characteristics, allowing for a relatively well-powered and detailed analysis. We performed a left-truncated survival analysis whereby each subject only contributes person-years from the date of genetic testing, minimising the extent of survivorship bias that we have previously reported in our cohort (Narod *et al*, 2013).

In summary, our findings confirm that parity is associated with improved ovarian cancer survival, whereas BMI and smoking is associated with decreased survival. Whether or not postdiagnostic changes in exposures or lifestyle factors similarly affect survival is not known. Despite the well-described aetiologic roles of various hormonal and reproductive exposures on ovarian cancer risk, we observed no significant prognostic associations for the majority of these exposures. The findings from this study reiterate that once a woman is diagnosed with ovarian cancer, surgical debulking to achieve no residual disease likely has the most impact on her long-term survival.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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