

Impact of parity on the incidence of ovarian cancer subtypes: a population-based case–control study

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ABSTRACT

Background: Parity is known to have a protective effect as regards ovarian cancer, but its effect on the different histological subtypes of ovarian cancer is not well known. The impact of parity on the incidence of ovarian cancer subtypes was studied.

Material and methods: All Finnish women diagnosed 1994–2013 with ovarian cancer for the first time were included. Altogether, 5412 cases of ovarian cancer were identified in the Finnish Cancer Registry and stratified according to morphology into serous, mucinous, endometrioid, clear cell and others. Five age-matched controls were randomly selected for each case from the Finnish National Population Registry. Data on postmenopausal hormonal therapy were derived from the Registry of Prescribed drugs and used as cofactors. Multivariate conditional logistic regression for matched case-control data was used to examine the associations between parity parameters and ovarian cancer risk.

Results: Parous women had lower risk than nulliparous women in getting ovarian cancer of any type under age of 55 years. The odds ratio (OR) for serous cancer was 0.65 (95% confidence interval 0.56–0.77), for mucinous cancer 0.66 (0.52–0.83), for endometrioid cancer 0.52 (0.40–0.68), for clear-cell cancer 0.30 (0.19–0.46) and for other types 0.59 (0.43–0.80). In women aged 55 or older, the respective ORs were 0.86 (0.75–0.99), 0.78 (0.57–1.07), 0.61 (0.47–0.79), 0.44 (0.29–0.66) and 0.74 (0.57–0.95), adjusted for hormone therapy. Number of childbirths was associated with a trend toward reduction of risk, especially in serous and clear-cell cancers. Higher age at first birth was associated with higher risk of clear-cell cancer but otherwise age at first or last birth did not have an impact on the incidence of cancer subtypes.

Conclusions: Childbirths decrease the risk of all histologic subtypes of epithelial ovarian cancer in women in premenopausal and postmenopausal age.

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Introduction

Ovarian cancer is the most lethal gynecologic cancer, with more than 150 000 deaths worldwide annually [1]. Although multiple carcinogenetic mechanisms have been hypothesized, including incessant ovulation, hormonal stimulation and chronic inflammation, the etiology of ovarian cancer is still not well understood. Epithelial cancer accounts for about 90% of all malignant ovarian tumors [2]. It can be divided into five major histological subtypes: serous (50%), mucinous (5–14%), endometrioid (10–25%), clear cell (4–5%) and transitional-cell (1–2%) tumors.

Recent evidence from histopathological and genetic studies suggests that the different histological subtypes of ovarian cancer may have distinct, possibly extra-ovarian, origins. For example, many high-grade serous tumors may arise from precursor lesions within the Fallopian tubes, while endometrioid and clear-cell tumors may develop from endometriosis [3].

Previous studies on the role of reproductive risk factors in the etiology of ovarian cancer have shown that increasing parity decreases the risk of this disease, especially that of epithelial cancer [4]. Pregnancy is associated with significant changes in the metabolic and hormonal state. Circulating levels of sex steroids during pregnancy are 10–100 times higher than in nonpregnant women, which influences many functions of reproductive and other organs. Cell differentiation, proliferation and apoptosis may explain differences in cancer incidence between parous and nulliparous women [5,6]. Infertility has been associated with an increased risk of ovarian cancer [6–8].

Many factors, including the use of oral contraceptives and smoking show variation in their risk effects to different ovarian cancer histotypes [3]. The association between the risk of ovarian cancer and postmenopausal hormone therapy (HT) is controversial [9–11] and varies by the histological type [12].

There is a limited number of studies that have examined the effects of childbirth on the incidence of different subtypes of ovarian cancer and taken into account the impact of HT. We therefore aimed to assess the risk of different epithelial histological types of ovarian cancer in relation to parity in both pre- and postmenopausal women, with adjustment for HT in postmenopausal women.

Material and methods

Study population

Our study includes all Finnish women who were diagnosed for the first time with ovarian cancer in 1994–2013. Altogether, 5412 cases of ovarian cancer were identified in the Finnish Cancer Registry (FCR; Table 1). Data recorded at the FCR are collected from hospitals, pathology and hematology laboratories, physicians and dentists, and death certificates [13]. We extracted information on ovarian cancer histology from the FCR and classified cases into serous, mucinous, endometrioid, clear cell and other cancers. The category 'other cancers' included adenocarcinomas, carcinosarcomas, mesonephromas, carcinoid tumors, yolk sac tumors, transitional cell carcinomas, mixed mesenchymal sarcomas and non-specified tumors. The morphological codes of cancer used by the FCR until 2007 were based on the Manual of Tumor Nomenclature Coding (MOTNAC), after which the codes were converted to and used as morphology codes of ICD-O-3 [14] (Supplementary Table 1).

Five control women were randomly selected from the National Population Registry (NPR) for each case of ovarian cancer, matched by date of birth. Women who had emigrated or died before the index date, i.e. the date of ovarian cancer diagnosis of the case, or women with ovarian cancer were not eligible as controls. The NPR also provided information on the dates of birth of biological children of the cases

and controls. We also linked the controls in the Care Register for Health Care (HILMO) of the Finnish Institute for Health and Welfare and excluded those who had undergone oophorectomy, salpingectomy or sterilization before the index date ($n=1074$). Altogether, 26 022 control women were included in the study. The characteristics of cases and controls are shown in Table 1.

Exposure to postmenopausal HT

Data on the use of postmenopausal HT was obtained from the nationwide Prescription Registry of the Social Insurance Institution of Finland. This registry contains data on regular purchases of HT since 1994. Medication for HT is available only with a doctor's prescription and is automatically registered. Purchase of estradiol (E) plus the levonorgestrel-releasing intrauterine system (E+LNG-IUS) at the age of 45 or older was taken into account as postmenopausal HT in our study because such device is normally used for more than five years. For other HT regimens, only purchases at the age of 50 or older were regarded.

Postmenopausal HT use before the index date was categorized into E only, E+continuous progestin, E+monthly progestin, E+progestin every 3 months and E+LNG-IUS. Progestin therapy combined with E was defined as continuous when oral or transdermal E was combined daily with progestin. In sequential progestin therapy, progestin was combined with E for 10–14 days at 1- to 3-month intervals. E+LNG-IUS therapy consisted of oral or transdermal estradiol added to low-dose levonorgestrel released by an intrauterine device.

Statistical methods

Multivariate conditional logistic regression for matched case-control data was used to examine the associations between

Table 1. Characteristics of ovarian cancer cases and controls.

	Cases		Controls ^a	
	N	%	N	%
Total	5412	100.0	26 022	100.0
Histology				
Serous	2862	52.88	13 713	52.70
Mucinous	767	14.17	3723	14.31
Endometrioid	755	13.95	3635	13.97
Clear-cell tumor	285	5.27	1369	5.26
Other ^b	743	13.73	3582	13.77
Age				
<55 years	2159	39.9	10 452	40.2
55+ years)	3253	60.1	15 570	59.8
Hormone therapy				
Total	2118	39.1	9958	38.3
Estradiol-only therapy (50+ years)	556	10.3	2688	10.3
Estradiol + continuous progestin therapy (50+ years)	627	11.6	2926	11.2
Estradiol + monthly progestin therapy (50+ years)	734	13.6	3373	13.0
Progestin therapy in every 3 months (50+ years)	126	2.3	606	2.3
Estradiol + LNG-IUS ^c (45+ years)	75	1.4	365	1.4

N: number of cancer cases.

^aFive control women without ovarian cancer were randomly selected from the National Population Registry for each case of ovarian cancer.

^bAdenocarcinomas, carcinosarcomas, mesonephromas, carcinoid tumors, yolk sac tumors, transitional cell carcinomas, mixed mesenchymal sarcomas and non-specified tumors.

^cLevonorgestrel-releasing intrauterine system (LNG-IUS).

parity parameters and ovarian-cancer risk. Relative risks are reported as odds ratios (ORs) with 95% confidence intervals (95% CIs). The variables used in the models were parity (0, 1, 2, 3, 4, 5+), age at first birth (<20, 20–24, 25–29, 30+ years), and age at last birth (<30, 30–34, 35–39, 40+ years). In addition to these variables, in analyses of risk of ovarian cancer diagnosed in age 55 or higher, the durations of use of each category of HT (<1 year, 1–5 years, 5+ years) were included as covariates in the logistic regression models. Since the average age of menopause in Finland is 51–52 years and effects of HT on ovarian cancer risk are only seen at least after 3 years of HT use [13], it is unlikely that we would see any effect before the age of 55.

All calculations were carried out using R statistical software.

Results

Parity and ovarian cancer risk

Serous cancer was the dominant type of epithelial ovarian cancer among both pre- and postmenopausal women. It was observed in 266 nulliparous and 741 parous women under the age of 55 (<55), and in 291 nulliparous and 1564 parous women in the age of 55 or higher (55+). In ages <55, the parous women had a reduced risk of serous ovarian cancer (OR 0.65, 95%CI 0.56–0.77), as compared with nulliparous women, and the risk decreased as the number of births increased (Table 2). Similarly, parous women aged 55+ had a reduced risk of serous ovarian cancer (OR 0.86, 95% CI 0.75–0.99), and the risk decreased with increasing parity (Table 3). Age at first or last birth did not significantly affect the risk of serous ovarian cancer at any age.

The risk of mucinous cancer in age <55 was reduced in parous compared with nulliparous women (OR 0.66, 95% CI 0.52–0.83), but the risk did not markedly change with an

Table 2. Multivariate conditional logistic regression analysis for the parity, age at first birth and age at last birth as predictors of serous and mucinous ovarian cancer diagnosed among women aged <55 years.

Variable	Serous			Mucinous		
	N	OR	95%CI	N	OR	95%CI
Parity^a						
Nulliparous	266	1.00	Ref.	136	1.00	Ref.
Parous	741	0.65	0.56–0.77	310	0.66	0.52–0.83
Number of children^b						
1	221	1.00	Ref.	80	1.00	Ref.
2	330	0.78	0.64–0.96	146	1.00	0.72–1.39
3	140	0.64	0.48–0.85	59	0.87	0.57–1.34
4	32	0.42	0.27–0.66	13	0.70	0.34–1.42
5+	18	0.64	0.35–1.16	12	0.91	0.41–2.00
Age at first birth^b						
<20	117	1.00	Ref.	55	1.00	Ref.
20–24	288	0.88	0.69–1.12	100	0.65	0.44–0.96
25–29	206	0.82	0.62–1.08	84	0.67	0.44–1.03
30+	130	0.72	0.50–1.05	71	0.90	0.52–1.54
Age at last birth^b						
<30	410	1.00	Ref.	172	1.00	Ref.
30–34	212	1.13	0.89–1.43	91	1.10	0.77–1.56
35–39	105	1.25	0.91–1.71	40	0.86	0.52–1.41
40+	14	0.64	0.36–1.24	7	0.70	0.28–1.72

N: number of cancer cases; OR: odds ratio; 95%CI: 95% confidence interval.

^aThe model only included parity.

^bThe model included number of children, and age at first and last birth.

increasing number of births (Table 2). There was no significant difference in risk of mucinous cancer in ages 55+ between parous and nulliparous women (Table 3). Age at first or last birth did not affect the OR at any age.

The OR for endometrioid ovarian cancer was significantly decreased in parous women <55 years of age (OR 0.52, 95% CI 0.40–0.68, Table 4), with a significant decrease observed with increasing parity (p for linear trend 0.04). Similarly in older women, there was a significant difference in risk between parous and nulliparous women (OR 0.61, 95% CI 0.47–0.79), and the risk was significantly lower among

Table 3. Multivariate conditional logistic regression analysis for the predictors of serous and mucinous ovarian cancer diagnosed among women aged 55+ years.

Variable	Serous			Mucinous		
	N	OR	95%CI	N	OR	95%CI
Parity^a						
Nulliparous	291	1.00	Ref.	64	1.00	Ref.
Parous	1564	0.86	0.75–0.99	257	0.78	0.57–1.07
Number of children^b						
1	412	1.00	Ref.	76	1.00	Ref.
2	691	0.85	0.73–0.98	109	0.75	0.51–1.10
3	326	0.77	0.63–0.93	49	0.63	0.38–1.04
4	91	0.56	0.42–0.74	10	0.39	0.17–0.86
5+	44	0.56	0.38–0.81	13	0.87	0.39–1.95
Age at first birth^b						
<20	221	1.00	Ref.	37	1.00	Ref.
20–24	754	1.08	0.91–1.28	114	0.90	0.58–1.38
25–29	426	1.02	0.83–1.25	70	1.04	0.63–1.72
30+	163	0.88	0.66–1.18	36	1.18	0.58–2.41
Age at last birth^b						
<30	945	1.00	Ref.	142	1.00	Ref.
30–34	399	1.09	0.93–1.27	79	1.08	0.72–1.62
35–39	180	0.97	0.78–1.21	30	0.96	0.54–1.71
40+	40	0.82	0.57–1.19	6	0.42	0.16–1.09

N: number of cancer cases; OR: odds ratio; 95%CI: 95% confidence interval.

^aThe model included parity and hormonal therapy use.

^bThe model included number of children, age at first and last birth and hormonal therapy use.

Table 4. Multivariate conditional logistic regression analysis for the predictors of endometrioid and clear-cell ovarian cancer diagnosed among women aged <55 years.

Variable	Endometrioid			Clear cell		
	N	OR	95%CI	N	OR	95%CI
Parity^a						
Nulliparous	109	1.00	Ref.	51	1.00	Ref.
Parous	213	0.52	0.40–0.68	70	0.30	0.19–0.46
Number of children^b						
1	55	1.00	Ref.	33	1.00	Ref.
2	110	1.10	0.74–1.63	29	0.42	0.21–0.83
3	39	0.81	0.47–1.39	6	0.19	0.06–0.61
4	6	0.37	0.14–0.99	2	0.24	0.04–0.51
5+	3	0.38	0.10–1.47	0	—	—
Age at first birth^b						
<20	24	1.00	Ref.	12	1.00	Ref.
20–24	110	2.02	1.22–3.33	32	0.79	0.33–1.90
25–29	47	1.22	0.69–2.18	12	0.38	0.12–1.20
30+	32	1.13	0.52–2.42	14	0.53	0.13–2.20
Age at last birth^b						
<30	125	1.00	Ref.	46	1.00	Ref.
30–34	59	0.99	0.63–1.57	18	1.03	0.42–2.51
35–39	26	1.09	0.59–2.02	3	0.32	0.07–1.43
40+	3	0.45	0.12–1.63	3	1.37	0.25–7.62

N: number of cancer cases; OR: odds ratio; 95%CI: 95% confidence interval.

^aThe model only included parity.

^bThe model included number of children, and age at first and last birth.

Table 5. Multivariate conditional logistic regression analysis for the predictors of endometrioid and clear-cell ovarian cancer diagnosed among women aged 55+ years.

Variable	Endometrioid			Clear-cell		
	N	OR	95%CI	N	OR	95%CI
Parity^a						
Nulliparous	101	1.00	Ref.	46	1.00	Ref.
Parous	332	0.61	0.47–0.79	118	0.44	0.29–0.66
Number of children^b						
1	95	1.00	Ref.	46	1.00	Ref.
2	134	0.66	0.48–0.93	46	0.57	0.34–0.98
3	68	0.62	0.41–0.94	17	0.58	0.27–1.24
4	24	0.72	0.40–1.30	6	0.44	0.15–1.31
5+	11	0.51	0.23–1.11	3	0.79	0.16–3.80
Age at first birth^b						
<20	40	1.00	Ref.	12	1.00	Ref.
20–24	167	1.45	0.99–2.13	61	2.15	1.02–4.53
25–29	93	1.65	1.05–2.58	28	2.43	0.98–5.99
30+	32	0.93	0.48–1.79	17	4.76	1.32–17.21
Age at last birth^b						
<30	201	1.00	Ref.	80	1.00	Ref.
30–34	86	0.99	0.70–1.40	24	0.50	0.24–1.15
35–39	33	0.95	0.57–1.56	10	0.29	0.11–0.79
40+	12	1.23	0.60–2.53	4	0.47	0.12–1.82

N: number of cancer cases; OR: odds ratio; 95%CI: 95% confidence interval.

^aThe model included parity and hormonal therapy use.

^bThe model included number of children, age at first and last birth and hormonal therapy use.

biparous and triparous women as compared with uniparous women (Table 5). Women diagnosed in age <55 who were 20–24 years at first birth had two-fold risk of endometrioid cancer compared with those of less than 20 years at first birth. Age at last birth did not affect the OR in either group.

The OR for clear-cell ovarian cancer was significantly reduced in parous women compared with nulliparous women (for age <55: OR 0.30, 95%CI 0.19–0.46, and for age 55+: OR 0.44, 95%CI 0.29–0.66). No significant trend in ORs was observed in relation to the number of births. An increase in the OR of clear-cell cancer was observed with increasing age at first birth in women aged 55+ (p for linear trend 0.04; Tables 4 and 5).

The risk of other types of ovarian epithelial cancer was lower in parous than in nulliparous women (for age <55: OR 0.59, 95% CI 0.43–0.80; for age 55+: OR 0.74, 95% CI 0.57–0.95), and the risk seemed to decrease with increasing number of births (Supplementary Tables 2 and 3).

Effect of HT on ovarian cancer in postmenopausal women

The ORs for HT, derived from the multivariable model for women at age 55+, can be seen in Supplementary Tables 4–6. E only therapy increased the OR for serous ovarian cancer after five years of use (OR 1.32, 95% CI 1.08–1.62), while continuous or sequential EPT did not. A significant reduction in the risk of mucinous ovarian cancer was observed in women who had used E only therapy, and the risk decreased the longer the therapy lasted.

Discussion

The present results show that parous women had significantly lower incidence of all histological types of epithelial

ovarian cancer than nulliparous women both in premenopausal and postmenopausal ages.

It is well known that multiparity reduces the risk of ovarian cancer, especially that of epithelial cancer [2–5,15,16]. Our results support these observations as the parity decreased the risk of all epithelial cancer subtypes in women aged <55. The risk decrease was about 70% in clear-cell cancer and 40%–50% in the other subtypes. In women aged 55+, parous women also had reduced ORs, most strongly in clear-cell cancer. Furthermore, compared to women with one birth, increasing parity decreased the OR of especially serous cancer in both age groups and clear-cell cancer in premenopausal women. In the Million Women Study [3], parous women had an estimated 26% lower risk of ovarian cancer than nulliparous women and each additional birth was associated with an overall 6% reduction in ovarian cancer risk. Moreover, similarly to the present study in the study by Wentzensen *et al.* [1] the largest reduction in risk was observed in clear-cell tumors.

It has been speculated that the increased risk of clear-cell and endometrioid ovarian cancer in nulliparous women could be associated with infertility caused by endometriosis, as endometriosis has been linked to increased risk of clear cell and endometrioid cancers [3,17–19]. Unfortunately we did not have data on endometriosis of the cases and controls and therefore we were not able to assess the role of endometriosis in our results. Since severe endometriosis is relatively rare, its possible confounding effect on ovarian cancer risk is small. Other possible explanations for the reduced risk in parous women are that pregnancy and lactation act by interrupting the pro-inflammatory environment of incessant ovulation, by modifying the hormonal environment or by clearing pre-malignant cells from the ovary [3].

Earlier studies have shown conflicting results concerning whether or not there is an association between age at first or last birth and risk of ovarian cancer. In a study by Whiteman *et al.* [20], women who were 30 years of age or older at first or last birth had 30–50% lower risk of ovarian cancer than those aged less than 20 at first birth or 25 years at last birth. In a study by Yang *et al.* [21] a trend of increasing risk of ovarian cancer was observed with increasing age at first birth, but no consistent pattern of risk in relation to time since last birth and ovarian cancer was found in another study [22]. Thus, there is no final consensus on this issue yet. In the present study, age at first and last birth did not affect the incidence of ovarian epithelial cancer types at any age, except that of clear-cell cancer in women aged 55+, which increased along with increasing age at first birth.

As prolonged use of HT may affect the risk of epithelial ovarian cancer [9,13,23,24], we included HT in the models for ovarian cancer in ages 55+. We assumed that HT use started at the age of menopause cannot have marked effect on ovarian cancer risk before the age 55. We found that the OR for serous ovarian cancer was moderately increased after 5 years use of E only while the risk of mucinous cancer was decreased, and EPT did not alter the risk. These results are

largely similar to those from earlier studies on HT and ovarian cancer [2,12,25–27], indicating that the HT data used in our study were accurate.

Our study is based on nation-wide registries that are complete and reliable, and the large sample size ensured sufficient power of the study. The NPR provides accurate information on a very high proportion of childbirths of women born after the mid 1930s, and the FCR is virtually complete as regards cancer incidence since 1953 [14,15]. We did not have information on the family history of ovarian cancer. However, even if cancers in the family may affect parity and hence be a potential confounder, its effect is small because genetic ovarian cancer represents only about 5% of total ovarian cancer cases in Finland [28]. We did not have information on breastfeeding or use of hormonal contraceptives, which are known protective factors as regards ovarian cancer [29,30].

In conclusion, we were able to demonstrate that parity decreased the risk of main histological types of ovarian cancer even after adjustment for HT. The observations strengthen the importance of awareness of the beneficial health consequences associated with parity.

Disclosure statement

No potential conflict of interest was reported by the author(s).

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