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Parity, infertility, oral contraceptives, and hormone replacement therapy and the risk of ovarian serous borderline tumors: A nationwide case-control study

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HIGHLIGHTS

- Parity and use of oral contraceptives are both highly protective factors in development of an ovarian serous borderline tumor
- Infertility and use of hormone replacement therapy are risk factors for developing an ovarian serous borderline tumor
- An ovarian serous borderline tumor and serous ovarian cancer seem to share some similar risk factors

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ABSTRACT

Objective. Few studies have examined the risk of an ovarian serous borderline tumor (SBT) associated with parity, infertility, oral contraceptives (OCs), or hormone replacement therapy (HRT), which was the study aim.

Methods. This nationwide case-control study included all women with an SBT diagnosis in Denmark, 1978–2002. SBTs were confirmed by centralized expert pathology review. For each case, 15 age-matched female controls were randomly selected using risk-set sampling. Cases and controls with previous cancer (except for non-melanoma skin cancer) and controls with bilateral oophorectomy or salpingo-oophorectomy were excluded. Conditional logistic regression was used to estimate adjusted odds ratios (ORs) and 95% confidence intervals (CIs).

Results. We found a strongly decreased risk of SBTs among parous women which decreased with increasing number of children ($p < 0.01$). Older age at first birth also decreased the SBT risk ($p = 0.03$). An increased SBT risk was associated with infertility (OR = 3.31; 95% CI: 2.44–4.49), which was present both among parous and nulliparous women. HRT use increased the SBT risk (OR = 1.32; 95% CI: 1.02–1.72), whereas OC use decreased the risk (OR = 0.40; 95% CI: 0.26–0.62).

Conclusions. Our nationwide study with expert histopathologic review of all SBTs showed that parity, infertility, use of HRT, and use of OCs, respectively, were strongly associated with the risk of SBTs. This is the first study to report a strong and significantly decreased SBT risk associated with OC use and a significantly increased risk with infertility, and HRT use. This supports that SBTs and serous ovarian cancer share similar risk factors.

1. Introduction

Ovarian cancer is the most lethal gynecologic cancer in the developed world [1]. The most common histologic subtype is serous ovarian cancer, which most often has a poor prognosis [2]. An ovarian serous borderline tumor (SBT) is a non-invasive tumor suspected to be a precursor for some types of serous ovarian cancer [3]. Despite being non-

Abbreviations: CI, confidence interval; ICD, International Classification of Disease; ICD-O-3, ICD for Oncology, 3rd Edition; OR, odds ratio; SBT, ovarian serous borderline tumor.

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invasive, however, an SBT is able to spread beyond the ovaries as implants, which can be non-invasive or invasive [4]. In contrast to serous ovarian cancer, an SBT is usually diagnosed in women 10–15 years younger and as localized disease, resulting in a significantly better prognosis [2]. Previous studies suggest that ovarian borderline and invasive tumors, such as SBTs and serous ovarian cancer, may share a similar risk factor profile, although the literature is inconsistent [5].

Parity and oral contraceptive (OC) use are well-established protective factors for serous ovarian cancer [6,7]. Likewise, a possible protective effect of parity on the development of an SBT has been suggested in some studies [5,8,9] and indicated in others [10–12], whereas the protective effect of OC use related to SBTs has not been consistent in the available literature [5,8–12]. In contrast to parity and OC use, infertility and use of hormone replacement therapy (HRT) have been found

Table 1
Overview of case-control studies examining relevant risk factors for ovarian serous borderline tumors.

Reference Publishing year	Country Inclusion period	Study design Collection method of exposure data	No. of SBT cases	Centralized pathology review[a]	Exposure	No. of exposed SBT cases	Association		Adjusted for
							OR	95% CI	
Present study 2016	Denmark 1978–2002	Nationwide, population-based Register	885	Yes	Parity (ever/never)	560	0.61	0.52–0.73	Age, tubal ligation, salpingectomy, hysterectomy, endometriosis, pelvic inflammatory disease, infertility, parity. OC use was also adjusted for HRT use
					Age at first birth (per category older; <20, 20–24, 25–29, 30–34, ≥35 years)	560	$p = 0.03$[c]		
					Infertility (ever/never)	69	3.31	2.44–4.49	
					HRT use (ever/never)	95	1.32	1.02–1.72	
					OC use (ever/never)	32	0.40	0.26–0.62	
Huusom et al. 2006 [10]	Denmark 1995–1999	Population-based Interview	104	No	Childbirth (ever/never)	85	0.60	0.33–1.11	Age, breastfeeding, duration of OC use, smoking, intake of milk. Age at first birth and OC use was also adjusted for: childbirth, number of additional births, age at first birth
					Age at first birth (per 5 year older)	85	0.68	0.49–0.95	
					OC use (ever/never)	52	0.66	0.41–1.06	
Mills et al. 2005 [15]	USA 2000–2001	Population-based Interview	55	No	HRT use (ever/never[b])	18	1.71	0.84–3.46	Age, race/ethnicity, duration of OC use, breastfeeding
Mills et al. 2004 [12]	USA 2000–2001	Population-based Interview	55	No	Pregnant (ever/never)	–	0.65	0.27–1.55	Age, race/ethnicity, duration of OC use, breastfeeding
					Age at first birth (<25 vs. ≥ 25 years of age)	–	0.86	0.42–1.77	
					OC use (duration, per 5 year increase)	–	$p = 0.31$[c]		
Tung et al. 2003 [11]	USA 1993–1999	Population-based Interview	66	No	Pregnancy (ever/never)	–	0.6	0.3–1.3	Age, ethnicity, study site, education, OC use, tubal ligation, pregnancy status
					Fertility problems (yes/no)	–	1.2	0.6–2.4	
					OC use (ever/never)	–	0.7	0.4–1.3	
Riman et al. 2001 [5]	Sweden 1993–1995	Nationwide, population-based Questionnaire	110	Yes	Parity (ever/never)	90	0.44	0.26–0.75	Age, parity, body mass index, age at menopause, OC use, unopposed estrogens, estrogens with cyclic progestins, estrogens with continuous progestins (medium potency estrogens only). HRT use was also adjusted for low potency estrogens
					Age at first birth (per 5 year older)	90	$p = 0.08$[c]		
					Infertility evaluation (yes/no)	10	1.64[d]	0.81–3.29	
					HRT use (estrogen only, yes/no)	13	2.07	1.08–3.95	
					HRT use (estrogen and cyclic progestins, yes/no)	12	1.15	0.59–2.24	
					HRT use (estrogen and continuous progestins, yes/no)	6	0.59	0.23–1.53	
					OC use (yes/no)	47	1.40	0.87–2.26	
Modugno et al. 2001 [8]	USA 1994–1998	Hospital-based Interview	79	No	Full-term pregnancy (per live birth)	44	0.66	0.53–0.82	Age, number of live births, years of OC use, years of non-contraceptive estrogen use, months of breastfeeding, tubal ligation, hysterectomy, family history of ovarian and breast cancer, ethnicity
					Non-contraceptive estrogen use (per year of use)	8	0.98	0.86–1.10	
					OC use (per year of use)	60	0.91	0.85–0.98	
Risch et al. 1996 [9]	Canada 1989–1992	Population-based Interview	42	No	Full-term pregnancy (per pregnancy)	31	0.62	0.46–0.83	Age, number of full-term pregnancies, total years of OC use, average lactation/pregnancy, total years of non-contraceptive estrogen use, tubal ligation, hysterectomy, mother or sister with breast cancer
					OC use (per year of use)	21	0.86	0.77–0.96	

Abbreviations: CI, confidence interval; No., number; OR, odds ratio; —, not noted in article; SBT, ovarian serous borderline tumor; OC, oral contraceptive; HRT, hormone replacement therapy.

[a] Centralized pathology review was performed for all SBT cases.

[b] Never defined as <1 years use.

[c] *p*-value for trend.

[d] Exposed number of cases and OR are reported only for ovarian borderline tumors overall, however, the article notes similar results for all histologic subtypes.

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