Gynecologic Oncology xxx (2016) xxx–xxx

Contents lists available at ScienceDirect

Gynecologic Oncology

journal homepage: www.elsevier.com/locate/ygyno

# Increased risk of borderline ovarian tumors in women with a history of pelvic inflammatory disease: A nationwide population-based cohort study

Christina B. Rasmussen [a], Allan Jensen [a], Vanna Albieri [b], Klaus K. Andersen [b], Susanne K. Kjaer [a,c,*]

[a] Virus, Lifestyle and Genes, Danish Cancer Society Research Center, Copenhagen, Denmark
[b] Statistics, Bioinformatics and Registry, Danish Cancer Society Research Center, Copenhagen, Denmark
[c] Department of Gynecology, Rigshospitalet, University of Copenhagen, Copenhagen, Denmark

## HIGHLIGHTS

- Few studies have investigated the association between pelvic inflammatory disease and risk of borderline ovarian tumors.
- Pelvic inflammatory disease increases the risk of serous borderline ovarian tumors.
- No association between pelvic inflammatory disease and mucinous borderline ovarian tumors

## ARTICLE INFO

*Article history:*
Received 30 May 2016
Received in revised form 11 August 2016
Accepted 15 August 2016
Available online xxxx

*Keywords:*
Borderline ovarian tumor
Pelvic inflammatory disease
Inflammation
Risk factor
Cohort study

## ABSTRACT

*Objective.* Some studies suggest that pelvic inflammatory disease (PID) is a potential risk factor for ovarian cancer. However, only few studies have investigated the association between PID and risk of borderline ovarian tumors. We conducted a population-based cohort study to investigate the association between PID and risk of borderline ovarian tumors.

*Methods.* Using various nationwide Danish registries we identified all women in Denmark during 1978–2012, who were born during 1940–1970 ($n$ = 1,318,925). Of these, 81,263 women were diagnosed with PID in the study period, and 2736 women had a borderline ovarian tumor (1290 serous and 1344 mucinous). Hazard ratios (HRs) and 95% confidence intervals (CIs) for the association between PID and risk of borderline tumors were estimated using Cox regression models with adjustment for potential confounders.

*Results.* A history of PID was associated with an increased risk of borderline ovarian tumors (HR = 1.39; 95% CI: 1.19–1.61). However, histotype-specific analyses revealed significant variation in risk as PID was only associated with an increased risk of serous borderline tumors (HR = 1.85; 95% CI: 1.52–2.24), but not with mucinous borderline tumors (HR = 1.06; 95% CI: 0.83–1.35).

*Conclusions.* PID is associated with an increased risk of serous borderline tumors. Further research on the potential underlying biological mechanisms and on the identification of the subset of women with PID who are at increased risk of serous borderline tumors is warranted.



## 1. Introduction

Borderline ovarian tumors constitute a subset of ovarian tumors accounting for approximately 10–30% of non-benign ovarian tumors [1]. They are characterized by morphological features intermediate between benign and malignant, but lack stromal invasion [2]. However, they have the potential to spread beyond the ovary and recur [3]. Compared with ovarian cancer, borderline tumors occur at a younger age, in an earlier stage and have a more favorable prognosis [4]. Although borderline ovarian tumors, also referred to as tumors of low malignant potential, were implemented separately in the FIGO classification of ovarian tumors in 1971 [5], there has been a continued debate whether these tumors represent a separate disease entity unrelated to ovarian cancer or are precursors of ovarian cancer. Consequently, studies investigating risk factors for ovarian cancer have either excluded borderline tumors or grouped them together with ovarian cancer. However, in

* Corresponding author at: Virus, Lifestyle and Genes, Danish Cancer Society Research Center, Strandboulevarden 49, DK-2100 Copenhagen, Denmark.
*E-mail address:* susanne@cancer.dk (S.K. Kjaer).

http://dx.doi.org/10.1016/j.ygyno.2016.08.318
0090-8258/

studies investigating borderline tumors separately, many well-established risk factors for ovarian cancer have been similarly associated with risk of borderline tumors [6–8].

Inflammation has been suggested to be involved in the pathogenesis of ovarian cancer, and therefore an association between pelvic inflammatory disease (PID) and risk of ovarian cancer has been proposed [9]. PID is defined as an infection-induced inflammation of the upper genital tract (i.e. the uterus, fallopian tubes, ovaries and surrounding pelvic peritoneum) caused by an ascending infection from the lower genital tract [10]. While studies investigating the association between PID and risk of ovarian cancer have revealed inconsistent results [11–19], the association with borderline ovarian tumors is sparsely investigated as most of the studies either excluded borderline tumors or only provided results for ovarian cancer and borderline tumors combined. Only two case-control studies [16,17] and one pooled analysis [20]—also including the aforementioned two case-control studies—have reported separate results for borderline ovarian tumors, and all reported an increased risk among women with a history of PID. However, in these studies, information on PID was self-reported with the potential for recall bias and misclassification.

The limited evidence regarding a potential association between PID and risk of borderline ovarian tumors and the methodological limitations of previous studies underscores the need for further research on this topic. We therefore conducted a large nationwide registry-based cohort study with up to 35 years of follow-up with the aim of investigating the association between PID and risk of borderline tumors using data on PID that is not self-reported. We conducted analyses for borderline ovarian tumors overall and according to histotype. In addition, we also explored the effect of timing of PID and number of PID episodes.

## 2. Material and methods

### 2.1. Study population

Since 1968, all Danish citizens have been assigned a unique personal identification number, which is used in all Danish health registries, thereby enabling unambiguous linkage of information between registries. The personal identification number is administered by the Civil Registration System, which also contains continuously updated information on vital status and emigration [21]. For the present study, we identified all women alive and living in Denmark during the study period from January 1, 1978 to December 31, 2012 by use of the Danish Civil Registration System. We restricted the population to women from the birth cohorts 1940–1970 ($n$ = 1,319,155). We applied this restriction to reduce misclassification of PID exposure among older women as they are more likely to have had PID before the National Patient Registry was established. Further, women born after 1970 would likely have inadequate follow-up to develop borderline tumors.

### 2.2. Assessment of PID exposure

Information on PID was obtained from the National Patient Registry, which was established in 1977 [22]. It holds information on all hospital contacts to Danish hospitals. Initially, only in-patient contacts were included, but since 1995, outpatient and emergency room contacts have been added. For each hospital contact, diagnoses and surgical procedures are registered. Diagnoses in the National Patient Registry have been coded according to the 8th revision of the International Classification of Diseases (ICD-8) during 1977–1993, and hereafter according to 10th revision of the International Classification of Diseases (ICD-10). Using the personal identification number as key identifier we linked the study cohort to the National Patient Registry to identify all women with PID diagnoses from January 1, 1978 to December 31, 2011. PID was defined as an infection of the upper genital tract, including endometritis, salpingitis, oophoritis, pelvic peritonitis and tubo-ovarian abscess (Supplementary Table S1).

### 2.3. Follow-up for borderline ovarian tumors

The study cohort was linked to the Pathology Data Bank to obtain information on women diagnosed with epithelial borderline ovarian tumors. The Pathology Data Bank holds information on all pathological diagnoses from all Danish Pathology Departments since 1997 [23]. Most Pathology departments have also transferred historical pathology data to the Pathology Data Bank, many as far back as the 1970′s. Pathological diagnoses are coded according to the Systematized Nomenclature of Medicine (SNOMED). We defined a borderline ovarian tumor as a SNOMED topography code for ovary combined with a SNOMED morphology code compatible with an epithelial borderline tumor, and these morphology codes were further used to divide borderline tumors into histotypes (Supplementary Table S1).

All women in the cohort were followed for development of epithelial borderline ovarian tumors from January 1, 1978 until date of death, bilateral oophorectomy, ovarian cancer, emigration or end of study (December 31, 2012), whichever occurred first. Women with ovarian cancer ($n$ = 220), borderline ovarian tumor ($n$ = 4) or bilateral oophorectomy ($n$ = 6) before entry into the cohort were excluded, leaving 1,318,925 women for analysis (Fig. 1). Women with synchronous ovarian cancer and borderline ovarian tumor (defined as ovarian cancer <1 year after a borderline tumor, $n$ = 16) were considered to have ovarian cancer only and were thus not counted as events.

### 2.4. Additional information and data sources

We also collected information on ovarian cancer and bilateral oophorectomy, which were used for censoring. Women with ovarian cancer were identified from the Danish Cancer Registry, which was established in 1943 [24]. It holds information on all incident cases of cancer in Denmark, and for gynecological cancers registration is estimated to be 98% complete [25]. In the Cancer Registry, cancers are coded according to the 7th revision of the International Classification of Disease (ICD-7) from 1943 to 1977, and according to the ICD-10 and the 3rd version of the International Classification of Diseases for Oncology (ICD-O-3) from 1978 and onwards (Supplementary Table S1). Information on bilateral oophorectomy was retrieved from the National Patient Registry and was coded according to the Danish Classification of Surgical Procedures and Therapies during 1977–1995, and thereafter according to the Nordic Classification of Surgical Procedures (Supplementary Table S1).

Potential confounders were chosen a priori and included parity status, endometriosis, tubal ligation and hysterectomy. We obtained information on parity status from the Fertility Database [26]. It contains data on number of live born children of all Danish women of reproductive age since 1980, and parity data is considered complete for all women born since 1945. From the National Patient Registry, we obtained information on endometriosis, tubal ligation and hysterectomy. The Danish Prescription Registry provided information on oral contraceptive use (Supplementary Table S1). The Prescription Registry holds information on all prescription drugs dispensed at Danish pharmacies since 1995, including date of dispensing and Anatomical Therapeutic Chemical (ATC) classification code [27].

### 2.5. Statistical analyses

Cox regression models were used to estimate hazard ratios (HRs) and corresponding 95% confidence intervals (CIs) for the association between PID and risk of borderline ovarian tumors. Analyses were conducted for borderline ovarian tumors overall and for histotypes separately. As borderline ovarian tumors are predominantly serous or mucinous, analyses according to histotype were conducted only for these two histotypes. All PID variables and other covariates were included as time-varying variables (i.e. women contributed person-time in the unexposed group until a diagnosis of PID and thereafter in the exposed

Please cite this article as: C.B. Rasmussen, et al., Increased risk of borderline ovarian tumors in women with a history of pelvic inflammatory disease: A nationwide population-based cohort study, Gynecol Oncol (2016), http://dx.doi.org/10.1016/j.ygyno.2016.08.318