Gynecologic Oncology 148 (2018) 86–90

Contents lists available at ScienceDirect

Gynecologic Oncology

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

Risk of borderline ovarian tumors among women with benign ovarian tumors: A cohort study

Sonia Guleria [a], Allan Jensen [a], Susanne K. Kjær [a,b,*]

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

HIGHLIGHTS

- Benign ovarian tumors increased the risk of borderline ovarian tumors.
- Age and time since diagnosis of first benign ovarian tumor were associated with risk.
- The risk was almost the same for different histotypes of borderline ovarian tumors.

ARTICLE INFO

Article history:
Received 25 August 2017
Received in revised form 6 November 2017
Accepted 17 November 2017
Available online 23 November 2017

Keywords:
Benign ovarian tumors
Borderline ovarian tumors
Ovarian cancer
Cohort study
Denmark

ABSTRACT

Objective. A growing number of studies suggest that some ovarian cancers can arise from benign and borderline ovarian tumors. However, studies on the association between benign and borderline ovarian tumors are lacking. We studied the overall- and histotype-specific risk of borderline ovarian tumors among women with a benign ovarian tumor.

Methods. This nationwide cohort study included all Danish women diagnosed with a benign ovarian tumor ($n = 139{,}466$) during 1978–2012. The cohort was linked to the Danish Pathology Data Bank and standardized incidence ratios (SIR) with 95% confidence intervals (CI) were calculated.

Results. Women with benign ovarian tumors had increased risks for subsequent borderline ovarian tumors (SIR 1.62, 95% CI 1.43–1.82), and this applied to both serous (SIR 1.69, 95% CI 1.39–2.03) and mucinous (SIR 1.75, 95% CI 1.45–2.10) histotypes of borderline ovarian tumors. The risk for borderline ovarian tumors was primarily increased for women diagnosed with a benign ovarian tumor before 40 years of age. The risk remained increased up to 9 years after a benign ovarian tumor diagnosis. Finally, the associations did not change markedly when analyzed for the different histotypes of benign (solid and cystic tumors) and borderline (serous and mucinous tumors) ovarian tumors.

Conclusions. Women with benign ovarian tumors have a long-term increased risk for borderline ovarian tumors. However, as all associations in this study were only adjusted for age and calendar period of diagnosis, more studies that are able to adjust for additional potential confounding variables are required to further understand these associations.

1. Introduction

Borderline ovarian tumors, also known as tumors of low malignant potential, are a distinct entity of ovarian tumors, which comprise 15–20% of all ovarian carcinomas [1]. Borderline ovarian tumors are considered an intermediate between benign ovarian tumors and ovarian cancer [2], and serous and mucinous histotypes comprise the vast majority (>96%) of borderline ovarian tumors [3]. In contrast to ovarian cancer, most borderline ovarian tumors do not invade the ovarian tissue, but can spread as implants outside the ovaries to the peritoneum. The overall 5-year survival for borderline ovarian tumors (97%) is markedly higher than for ovarian cancer (40%) [4,5].

During the last five decades, the incidence of borderline ovarian tumors has increased in the Scandinavian countries and is reported to be higher than in the other developed countries [1,3,6,7], which is most likely attributable to changes in associated risk factors and improvements in diagnostic procedures over time [3,8]. Obesity, tobacco smoking, polycystic ovarian syndrome, hormone therapy, infertility and fertility drugs increase the risk for borderline ovarian tumors,

* Corresponding author at: Unit of Virus, Lifestyle and Genes, Danish Cancer Society Research Center, Copenhagen, Denmark.
E-mail addresses: sonia@cancer.dk (S. Guleria), allan@cancer.dk (A. Jensen), susanne@cancer.dk (S.K. Kjær).

https://doi.org/10.1016/j.ygyno.2017.11.024
0090-8258/

while pregnancy, breast-feeding and use of oral contraceptives decrease the risk [9,10].

A growing number of studies have reported an increased risk of ovarian cancer among women with benign ovarian tumors and biological mechanisms involved in the transformation of benign ovarian tumors to ovarian cancers have been proposed [11–13]. In addition, it has also been suggested that borderline ovarian tumors may evolve from benign ovarian tumors [11], but to our knowledge, only two studies have examined this association: the study by Rossing et al. [11] reported a twofold increased risk for borderline ovarian tumors, while the study by Ness et al. [14] reported a fourfold increased risk for borderline ovarian tumors. Although both studies reported an increased risk of borderline ovarian tumors among women with benign ovarian tumors, they both face important limitations. The pooled analysis of eight case-control studies by Ness et al. [14] did not report the number of women with borderline ovarian tumors and suggested that the observed association may be due to multiple comparisons or surveillance bias. Further, the case-control study by Rossing et al. [11] had small sample size and the diagnosis of benign ovarian tumors was self-reported, giving rise to potential misclassification. Thus, the current knowledge on the association between benign and borderline ovarian tumors is very sparse and larger cohort studies are therefore warranted.

In the present study, we identified a nationwide cohort of women diagnosed with benign ovarian tumors during 1978–2012 from the Danish nationwide registers, and examined the associations between benign and borderline ovarian tumors, both overall and according to histotype.

2. Materials and methods

2.1. Study population

A register-based cohort of women living in Denmark and diagnosed with a benign ovarian tumor during 1978–2012 was identified from the Danish National Patient Register. This register was established in 1977 and comprises detailed information on all hospital admissions since 1977 and emergency and outpatient visits since 1995 [15]. All records in the Danish National Patient Register contain the unique personal identification number, date of admission or first visit, diagnoses [coded using the Danish version of the International Classification of Diseases, ICD-8 codes (1977–1993) and ICD-10 codes (1994–2012)] and surgical procedures. For this study, we included 139,466 women with a main or secondary diagnosis of a benign ovarian tumor. Of these, 65,115 were classified as solid tumors (ICD-8 code 220.99 and ICD-10 codes D27.0, D27.1, D27.2, D27.8, D27.9) and 74,351 were classified as cystic tumors (ICD-8 codes 615.20, 615.21, 615.22, 615.28, 615.298 and ICD-10 codes N83.0, N83.1 and N83.2). Since 1968, all residents of Denmark are registered in the Civil Registration System and assigned a unique ten digit personal identification number called the CPR-number, which contains information on date of birth and gender of an individual [16]. This register also contains information on deaths and emigrations of the residents [16]. The data in the Civil Registration System are continuously updated, checked for errors and validated by the administrative system in Denmark [16]. We linked the study cohort of women with a diagnosis of benign ovarian tumor to this register, using the CPR-numbers as key identifiers, to identify deaths and emigrations. The study was approved by the Danish Data Protection Board.

2.2. Identification of borderline ovarian tumors

The study cohort of women with benign ovarian tumors was linked to the Danish Pathology Data Bank to identify all incident cases of epithelial borderline ovarian tumors. This register contains information on diagnoses from all Danish pathology departments since 1997. In addition, most pathology departments have also provided information to the Pathology Data Bank from 1978 to 1997, but data from this period are not entirely complete [17]. The data are recorded electronically in the Danish Pathology Data Bank based on National Board of Health guidelines. Furthermore, a steering committee comprising of pathologists from across the country ensures the data quality [17]. The register utilizes the Danish version of the Systematized Nomenclature of Medicine (SNOMED) to code the pathological diagnoses [17]. The borderline ovarian tumors were identified using the SNOMED topography codes for ovary (T86910, T86920, T86921, T86922 and T87) in combination with relevant SNOMED morphology codes (M84A01, M84411, M84601, M84611, M90141, M84701, M84702, M84711, M84801, M90151, M81202, M83101, M83131, M83801, M83811, M84501, M89501, M90001, M90131). The borderline ovarian tumors were further classified into one of the predominant histotypes: serous (M84A01, M84411, M84601, M84611, M90141) or mucinous (M84701, M84702, M84711, M84801, M90151).

All women in the study cohort were followed from the date of first benign ovarian tumor diagnosis until date of borderline ovarian tumor diagnosis, date of ovarian cancer (obtained from the Danish Cancer Register, ICD-10 codes C56, C570-C574), date of death, date of emigration, date of bilateral oophorectomy [obtained from the Danish National Patient Register, operation codes 60.120 and 60.320 (1977–1995) and KLAE20-21 and KLAF10-11 (1996–2012)] or December 31, 2012, whichever occurred first.

2.3. Statistical analysis

The associations between benign and borderline ovarian tumors (both overall and for the different histotypes of both tumor types) were assessed using standardized incidence ratios (SIRs) with corresponding 95% confidence intervals (CIs), which were calculated as the ratio of the observed and expected number of borderline ovarian tumors in each analysis group. The expected number of borderline ovarian tumors were calculated by multiplying the accumulated person-years of observation by borderline ovarian tumor incidence rates in the general female population of Denmark in 5-year age groups and calendar periods. The SIRs and the CIs were calculated on the assumption that observed number of borderline ovarian tumors followed a Poisson distribution [18] and the CIs were calculated by Byar's approximation [19].

The analyses were stratified for age at first benign ovarian tumor diagnosis (<30 years, 30–39 years and ≥40 years), calendar period of diagnosis (<1995 and 1995–2012) and time since first benign ovarian tumor diagnosis (1–4 years, 5–9 years, and ≥10 years). All statistical analyses were performed using SAS Enterprise Guide, version 7.1 (SAS Institute, Cary, NC, USA).

3. Results

Characteristics of the study cohort consisting of 139,466 women are shown in Table 1. Half of the women in the cohort (50.1%) were older than 40 years of age at the diagnosis of a benign ovarian tumor, and the majority (55.3%) were diagnosed after 1994. The cohort was followed for a total of 1,770,155 person-years, while exclusion of the first year of follow-up after a diagnosis of a benign ovarian tumor reduced the total follow-up period to 1,652,350 person-years.

Table 1
Characteristics of women in the study cohort.

Characteristics	Study population
Number of women	139,466
Age at benign ovarian tumor diagnosis, years (mean, P10-P90)	38.4 (22.0–57.0)
Age at borderline ovarian tumor diagnosis, years (mean, P10-P90)	44.6 (27.0–70.0)
Follow-up, years (median, P10-P90)	6.9 (0.8–19.0)
Person-years (total follow-up period, 1978–2012)	1,770,155

P10 = 10th percentile, P90 = 90th percentile.