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Endometriosis and risks for ovarian, endometrial and breast cancers: A nationwide cohort study

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HIGHLIGHTS

- The risks for ovarian-, endometrial and breast cancer among 45,790 women with endometriosis were studied.
- We found an increased risk for endometrioid- and clear-cell ovarian cancer in women with endometriosis.
- We observed that endometriosis was associated with an excess risk for endometrial cancer, primarily type 1.
- The risk for breast cancer was only increased in women where endometriosis was first diagnosed at ≥50 years of age.

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ABSTRACT

Objective. A growing body of evidence suggests that endometriosis increases the risk for ovarian cancer, but it is less well studied whether the excess risk is confined to certain histotypes. Furthermore, it is not fully resolved if endometriosis is associated with endometrial- and breast cancer. The aim was to study overall- and histotype-specific risks for these hormone-dependent cancers in women with endometriosis.

Methods. In the Danish National Patient Register, we identified 45,790 women with a clinical diagnosis of endometriosis during 1977–2012. We linked the cohort to the Danish Cancer Register and calculated standardized incidence ratios (SIRs) with corresponding 95% confidence intervals (CIs).

Results. Endometriosis was associated with increased risks for ovarian cancer (SIR 1.34; 95% CI: 1.16–1.55), due primarily to endometrioid (SIR 1.64; 95% CI: 1.09–2.37) and clear-cell types (SIR 3.64; 95% CI: 2.36–5.38). An excess risk was also observed for endometrial cancer (SIR 1.43; 95% CI: 1.13–1.79), primarily of type 1 (SIR 1.54; 95% CI: 1.20–1.96); and the risk for breast cancer was increased among women aged ≥50 years at first diagnosis of endometriosis (SIR 1.27; 95% CI: 1.12–1.42).

Conclusions. The results corroborate previous findings of increased risks for endometrioid and clear-cell ovarian cancer in women with endometriosis. As the first cohort study to date, we observed a significantly increased risk for endometrial cancer in women with a diagnosis of endometriosis. The increased breast cancer risk among women with endometriosis diagnosed at ≥50 years of age should be studied further.

1. Introduction

Endometriosis is a common gynecological inflammatory disease in women of reproductive age, with a prevalence of 6–10% in the general female population [1]. It is characterised by growth of endometrial tissue outside the uterine cavity, mainly on the pelvic peritoneum but also on the ovaries and in the rectovaginal septum and more rarely in the pericardium, pleura and brain [1]. Endometriosis can cause pelvic inflammation, adhesions, infertility and chronic pain [1]. Although it is considered to be a benign condition, endometriosis shares features with invasive cancer, including cell invasion, unrestrained growth, the ability to form new blood vessels and a decrease in the number of cells undergoing apoptosis [2].

In 1925, Sampson first proposed that ovarian cancer can arise from endometriosis. Subsequently, most epidemiological studies have shown increased risks for ovarian cancer among women with endometriosis [3–5], although not all [6]. The increased risk may be confined to specific histotypes of ovarian cancer, primarily endometrioid and clear-cell ovarian tumours [5–7]. It is biologically plausible that endometriosis is associated with increased risks for endometrial and breast cancer, but the results of studies on associations between endometriosis and risks for these cancers are inconclusive [4,8]. Most of the previous studies

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are limited by self-reporting of endometriosis diagnoses, small numbers or restriction to hospitalised patients. While several epidemiological studies have explored whether the risk is confined to specific histotypes of ovarian cancer, these were primarily of case–control design. Furthermore, to our knowledge, only one study investigated the association between endometriosis and endometrial cancer risk according to histotype [9]. The risk of women with endometriosis for breast cancer has not yet been studied according to histotype.

We used data on a nationwide cohort of Danish women with endometriosis diagnosed during 1977–2012 to further assess the association between a diagnosis of endometriosis and subsequent risks for ovarian, endometrial and breast cancer. This register-based cohort study is one of the largest to date on this topic.

2. Methods

2.1. Study population

We identified a register-based cohort of women with a diagnosis of endometriosis in Denmark between 1977 and 2012. Data were retrieved from the Danish National Patient Register, a nationwide register that comprises all hospital admissions for somatic conditions in Denmark since January 1977 and outpatient and emergency services since 1995. All records in this register contain the personal identification number, date of admission or first visit, diagnoses (ICD-8 or ICD-10 codes) and surgical procedures (coded according to the Danish Classification of Surgical Procedures and Therapies in 1977–1995 and the Classification of Surgical Procedures from 1996 onwards). We included all first diagnoses of endometriosis (Danish version of the International Classification of Diseases (ICD), ICD-8 625.3, during 1977–1993 and ICD-10 N80 during 1994–2012) in both hospitalised patients and outpatients and identified a total of 45,934 women during the study period. In the Danish National Patient Register all diagnoses of endometriosis are clinical diagnoses made by a medical doctor. The diagnoses are initially registered in patient journals and subsequently reported to the register. According to the Danish Society for Obstetrics and Gynecology, laparoscopy (with or without biopsy) is the golden standard diagnostic examination for peritoneal and deep infiltrating endometriosis diagnosis in Denmark, if the diagnosis cannot be verified from a gynecological examination alone. However, endometriomas may also be diagnosed using an ultrasound scan. The same types of diagnostic examinations are used for both in- and outpatients [10].

All Danish inhabitants are assigned a unique personal identification number at birth, which contains their date of birth and sex. The number is used throughout Danish society, including public health registries, and ensures accurate linkage of information among registries. Using the personal identification numbers as the key identifier, we linked the cohort of women with endometriosis to the Central Population Register to obtain information on vital status and emigration. Women with an invalid personal identification number (n = 107) and women who had emigrated before a diagnosis of endometriosis (n = 37) were excluded, leaving 45,790 eligible women in the study cohort for the analysis of endometriosis and risk for breast cancer. For the analysis of ovarian cancer, we excluded a further 434 women who had undergone bilateral oophorectomy (operation codes 60,120 and 60,320 during 1977–1995 and KLAE20-21 and KLAF10-11 during 1996–2012) on the same date or before the date of diagnosis of endometriosis, leaving 45,356 eligible women for this analysis. For the analysis of endometrial cancer, we excluded 2006 women who had a hysterectomy (operation codes 61000, 61020, 61040-050 and 61100 during 1977–1995 and KLCC10-11, KLCC20, KLCD00-01, KLCD04, KLCD10-11, KLCD30-31, KLCD40, KLCD96-97, KLEF13 and KMCA33 during 1996–2012) on the same date or before the date of diagnosis of endometriosis, leaving 43,784 women in this analysis. The study was approved by the Danish Data Protection Board.

2.2. Ascertainment of cancer cases

We linked all 45,790 women with a diagnosis of endometriosis to the Danish Cancer Register by their personal identification numbers. This nationwide register contains information on all incident cases of malignant neoplasms identified in the Danish population since 1943. Until 2003, the register was based on paper notification forms from the diagnosing hospitals and supplemented by linkage to the Death Certificate Register and the Danish National Patient Register to ensure completeness. Since 2004, the register has been based entirely on recordings from several Danish health registries, mainly the Danish National Patient Register and the Pathology Register. All cancer cases were retrieved according to ICD-7 from 1943 to 1977 and ICD-10 from 1978 onwards, as follows: ovarian cancer (ICD-7 = 175; ICD-10 = C56, C570–C574), endometrial cancer (ICD-7 = 172–174; ICD-10 = C54–C55, C58) and breast cancer (ICD-7 = 170; ICD-10 = C50). Since 1978, all incident cancer cases have also been classified according to the International Classification of Diseases of Oncology, 3rd edition (ICD-O-3 morphology codes), and this classification system was used to classify the specific histotypes of cancer. Ovarian cancers were classified as serous (84,413, 84,603, 84,613, 90,143), mucinous (84,703, 84,713, 84,803, 84,813, 90,153), endometrioid (83,803, 83,813, 85,703, 89,333, 89,803) or clear-cell tumours (83,103, 83,133, 84,903). Endometrial cancer was classified as type 1 (81,403, 81,433, 82,103, 82,303, 83,803, 83,813, 84,303, 84,703, 84,803, 84,813, 85,603 and 85,703) or type 2 tumours (80,203, 80,213, 80,503, 82,463, 82,603, 83,103, 84,403, 84,413, 84,503, 84,603, 84,613, 89,333, 89,343, 89,503); and breast cancers were classified as ductal (85,003) or lobular tumours (85,203).

Women with endometriosis were followed for cancer from the first date of admission for inpatients or the date of first visit for outpatients until the date of death, date of gynecological surgery (date of bilateral oophorectomy for ovarian cancer and date of hysterectomy for endometrial cancer), date of emigration or 31 December 2012, whichever came first. Ovarian, endometrial or breast cancer was diagnosed in 483 women on the same date or before the diagnosis of endometriosis. These malignancies were not included in the analyses, but the women remained in the cohorts as they were still at risk for other cancers.

2.3. Statistical analyses

Standardized incidence ratios (SIR) with corresponding 95% confidence intervals (CIs) were computed as the ratio between the observed number of cancers in each analysis group and the expected number. The expected numbers of cancers were calculated by multiplying the accumulated person-years of observation by cancer incidence rates in the general female population of Denmark in 5-year age groups and calendar periods. The SIRs and 95% CIs were calculated on the assumption that the observed number of cancer cases followed a Poisson distribution [11], and the CIs were calculated by Byar's approximation [12]. Analyses were stratified by time since first endometriosis diagnosis (1–4 years, 5–9 years and ≥10 years), calendar period of endometriosis diagnosis (<1995, 1995–2004 and 2005–2012) and age at endometriosis diagnosis (<30 years, 30–39 years, 40–49 years and ≥50 years). For histotype-specific analyses, ovarian cancer was classified as serous, mucinous, endometrioid or clear-cell; endometrial cancer was classified as type 1 or type 2; and breast cancer was classified as ductal or lobular.

3. Results

The large majority of women included in the analyses were aged 25–49 years at diagnosis, and approximately three quarters of the women received their diagnosis of endometriosis as inpatients. The analysis with breast cancer as the outcome on follow-up beyond the first year after endometriosis included 641,403 person-years of follow-up. Censoring for bilateral oophorectomy reduced the number of person-