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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-

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years in the ovarian cancer analyses to 552,244 (86%), and censoring for hysterectomy reduced the number of person-years in the endometrial cancer analyses to 308,680 (48%) (Table 1). The median age at ovarian cancer diagnosis was 55.4 years (10th percentile = 44.2, 90th percentile = 70.6), 59.0 years (10th percentile = 49.0, 90th percentile = 69.1) at endometrial cancer- and 57.6 years (10th percentile = 44.9, 90th percentile = 71.3) at breast cancer diagnosis.

3.1. Endometriosis and risks for ovarian, endometrial and breast cancer overall

Women with endometriosis had statistically significantly increased risks for ovarian (SIR 1.55; 95% CI: 1.35–1.77), endometrial (SIR 2.13; 95% CI: 1.77–2.55) and breast cancer (SIR 1.05; 95% CI: 1.00–1.11) in comparison with that of the general female population (Table 1). To account for the possibility that some cancers might have been present at the time of diagnosis of endometriosis, we performed analyses in which cancers diagnosed during the first year after a diagnosis of endometriosis were excluded. In these analyses, the risks for ovarian cancer (SIR 1.34; 95% CI: 1.16–1.55) and in particular endometrial cancer (SIR 1.43; 95% CI: 1.13–1.79) were attenuated (Table 1). All the results presented subsequently are for the analyses in which cancers and person-years in the first year after a diagnosis of endometriosis were excluded.

For ovarian cancer, statistically significantly increased risks were observed after 1–4 years (SIR 1.51; 95% CI: 1.00–2.18) and 5–9 years of follow-up (SIR 1.78; 95% CI: 1.30–2.37) but not ≥10 years after the first diagnosis of endometriosis. In addition, the risk was statistically significantly increased in all calendar periods, especially in the most recent calendar period, 2005–2012 (SIR 2.79; 95% CI: 1.39–4.99). When age at first diagnosis of endometriosis was taken into account, the highest risk was that of women who received a diagnosis after the age of 50 years (SIR 2.27; 95% CI: 1.61–3.10) (Table 2).

The risk for endometrial cancer increased with time since first diagnosis of endometriosis and was statistically significant after ≥10 years of follow-up (SIR 1.51; 95% CI: 1.15–1.95). An excess risk for endometrial cancer was also observed among women with a diagnosis of endometriosis before 1995 (SIR 1.48; 95% CI: 1.13–1.90) but not in the later calendar year periods. No convincing association between age at first diagnosis of endometriosis and risk for endometrial cancer was observed (Table 2).

No association was observed between endometriosis and risk for breast cancer in relation to time since first diagnosis or calendar period of endometriosis. The risk was, however, statistically significantly increased among women with endometriosis diagnosed at age ≥ 50 years (SIR 1.27; 95% CI: 1.12–1.42) (Table 2).

3.2. Endometriosis and risks for specific histotypes of ovarian, endometrial and breast cancer

For ovarian cancer, increased risks were observed only for endometrioid (SIR 1.64; 95% CI: 1.09–2.37) and clear-cell (SIR 3.21; 95% CI: 2.01–4.85) tumours (Table 3). A statistically significantly increased risk was observed for type 1 endometrial tumours (SIR 1.54; 95% CI: 1.20–1.96), whereas the risk for type 2 tumours was not greater than expected, based on four observed cases. Of the breast cancers diagnosed among women in our cohort, 74% were ductal tumours and 13% were lobular tumours. After a diagnosis of endometriosis, a modestly increased risk for the lobular subtype of breast cancer was observed; however, the estimate did not reach statistical significance (SIR 1.14; 95% CI: 0.98–1.33).

We estimated the SIRs for the histological types of ovarian cancer according to time since endometriosis and age at first diagnosis of endometriosis (Table 4). An increased risk for endometrioid tumours was observed ≥10 years after a diagnosis of endometriosis. For clear-cell tumours, statistically significantly increased risks were observed 5–9 years and ≥10 years after a diagnosis of endometriosis. Among women aged ≥50 years at first diagnosis of endometriosis, the risk for serous ovarian tumours was increased, whereas the risk for clear-cell tumours was increased in all age groups at first endometriosis diagnosis.

4. Discussion

Using data from a cohort of >45,000 Danish women with endometriosis, we found a higher risk for ovarian cancer overall than that in the general female population of Denmark. Histological type-specific analyses showed that the increase was present only for endometrioid and clear-cell tumours. The risks for endometrial and breast cancer were also increased, although the latter was confined to women with endometriosis diagnosed at age ≥ 50 years.

Our finding of an increased risk for ovarian cancer overall after a diagnosis of endometriosis confirms the results of the vast majority of previous epidemiological studies [5,7,13–17]. Further, the magnitude of our risk estimate for ovarian cancer overall (SIR = 1.34) is comparable to that obtained by Kim et al. [5], who reported an 80% increased risk in a meta-analysis based on cohort studies. Our results also show that the association with endometriosis differs according to histological type of ovarian cancer. The increased risks for endometrioid and clear-cell tumours and the lack of association with serous and mucinous tumours are consistent with the findings of previous studies [5–7], including the meta-analysis of Kim et al. [5] and a Danish case–cohort study by Brinton et al. [7] based on data from the Danish registers but for a shorter study period (1977–1998) than ours. Pearce et al. [18] used pooled data from 13 case–control studies and found increased risks for low-grade serous ovarian tumours, endometrioid tumours and clear-cell tumours among women with self-reported endometriosis. As tumour grade is not registered in the Danish Cancer Register, we were unable to investigate the association between endometriosis and risk for serous tumours according to grade.

A number of biological explanations have been suggested for an association between endometriosis and ovarian cancer, but the precise steps in malignant transformation of endometriosis are not fully understood [5,19]. It has been suggested that endometriosis-associated ovarian cancer is an entity of its own with a number of specific characteristics, including an earlier age at diagnosis than ovarian cancers not caused by endometriosis [20–22]. Inflammatory and immunological factors are suggested to be of importance in the malignant process. Both endometriosis and ovarian cancer lead to a predominance of Th1 cytokines, which play an important role in endometriosis by facilitating infiltration of ectopic endometrium and in invasion and metastasis of ovarian cancer [19]. Also, the hormonal consequence of endometriosis is an oestrogen-rich environment and progesterone resistance in endometriotic tissue. These locally altered hormone levels

Table 1
Standardized incidence ratios (SIRs) and 95% confidence intervals (CIs) for ovarian, endometrial and breast cancers among Danish women with endometriosis diagnosed in 1977–2012.

Cancer site	Total follow-up					Follow up ≥1 year after first diagnosis of endometriosis				
	PY	MFU (P10–P90) (years)	O	E	SIR (95% CI)	PY	MFU (P10–P90) (years)	O	E	SIR (95% CI)
Ovary	592,741	10.75 (0.26–29.33)	221	142.64	1.55 (1.35–1.77)	552,244	11.85 (2.11–29.07)	186	138.31	1.34 (1.16–1.55)
Endometrium	337,829	4.10 (0.01–22.73)	118	55.34	2.13 (1.77–2.55)	308,680	8.83 (1.35–25.86)	77	53.82	1.43 (1.13–1.79)
Breast	686,339	13.00 (2.53–30.22)	1452	1377.46	1.05 (1.00–1.11)	641,403	12.67 (2.34–29.42)	1397	1335.17	1.05 (0.99–1.10)

PY = person–years. MFU = median follow-up. P10 = 10th percentile. P90 = 90th percentile. O = observed. E = expected.

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Table 2
Standardized incidence ratios (SIRs) with 95% confidence intervals (CIs) for ovarian, endometrial and breast cancers among Danish women with endometriosis diagnosed 1977–2012 by time, calendar period and age at first diagnosis of endometriosis. Cancers and person–years in the first year after a diagnosis of endometriosis were excluded.

	Ovary			Endometrium			Breast		
	O	E	SIR (95% CI)	O	E	SIR (95% CI)	O	E	SIR (95% CI)
Time since endometriosis (years)									
1–4	28	18.59	1.51 (1.00–2.18)	6	5.99	1.00 (0.37–2.18)	207	185.34	1.12 (0.97–1.28)
5–9	46	25.84	1.78 (1.30–2.37)	12	8.77	1.37 (0.71–2.39)	272	254.15	1.07 (0.95–1.21)
≥10	112	93.87	1.19 (0.98–1.44)	59	39.06	1.51 (1.15–1.95)	918	895.66	1.02 (0.96–1.09)
Calendar period of endometriosis									
<1995	142	114.56	1.24 (1.04–1.46)	61	41.33	1.48 (1.13–1.90)	1085	1036.86	1.05 (0.99–1.11)
1995–2004	33	19.81	1.67 (1.15–2.34)	11	10.48	1.05 (0.52–1.88)	254	244,19	1.04 (0.92–1.18)
2005–2012	11	3.94	2.79 (1.39–4.99)	5	2.01	2.48 (0.80–5.79)	58	54.12	1.07 (0.81–1.39)
Age at first endometriosis (years)									
<30	15	11.80	1.27 (0.71–2.10)	4	6.44	0.62 (0.17–1.59)	118	115.85	1.02 (0.84–1.22)
30–39	60	41.65	1.44 (1.10–1.85)	34	18.76	1.81 (1.26–2.53)	374	393.73	0.95 (0.86–1,05)
40–49	72	67.65	1.06 (0.83–1.34)	26	21.20	1.23 (0.80–1.80)	627	606.13	1.03 (0.96–1,12)
≥50	39	17.22	2.27 (1.61–3.10)	13	7.43	1.75 (0.93–2.99)	278	219.46	1.27 (1.12–1.42)

O = observed. E = expected.

are thought to stimulate endometriosis itself and affect the occurrence of ovarian cancer by promoting neoplastic characteristics in ovarian endometriosis [1,19,23]. As endometrioid ovarian tumours are stimulated by oestrogen, it is likely that the oestrogen-rich environment facilitates malignant transformation of this tumour type. Clear-cell ovarian tumours are not affected by oestrogens because they exhibit very low oestrogen receptor expression and the development of this tumour type is considered to be related to oxidative stress due to free iron from endometriomas [5,24]. In addition, a number of genes, including *PTEN*, *ARID1A*, *KRAS* and *CTNNB1/β-catenin*, have been shown to be mutated in endometriosis-associated ovarian cancers [25]. According to a dualistic model of ovarian carcinogenesis, endometrioid and clear-cell ovarian tumours are both clinically indolent type 1 ovarian cancer tumours, which are proposed to evolve through precursor lesions or borderline tumours [26]. The genetic mutations in endometriosis-associated ovarian cancers are thought to result in histological changes in endometriotic tissue, first leading to an intermediary stage known as atypical endometriosis and finally to invasive ovarian cancer [25].

Our results show that women with endometriosis have a 40% increased risk for endometrial cancer, while most previous studies found no convincing association [7,9,13,14,27]. Only one previous study, a case–control study by Zuccetto et al. [28], also showed a statistically significantly increased risk for endometrial cancer after endometriosis. Another case–control study, by Borgfeldt and Andolf [15], found a statistically significantly decreased risk. To our knowledge, only one previous study, a case–control study by Rowlands et al. [9], investigated the association between endometriosis and endometrial cancer risk by histological type; however, they found no indication that the risk varied by type. The majority of the endometrial tumours observed in our study (67/71) were type 1, and we found a 54% increased risk for this tumour type. As only four cases were type 2, we were unable to draw a firm conclusion about any difference in the association between endometriosis and histological types of endometrial cancer.

Types 1 and 2 endometrial cancers differ in a number of characteristics. Type 1 tumours are endometrioid and are oestrogen-sensitive. They constitute 80–85% of all endometrial cancers and occur mainly in younger, obese and perimenopausal women. Type 2 endometrial cancers are oestrogen-independent, mainly high-grade serous or clear-cell, have a worse prognosis and occur most frequently in older women [29,30]. It has long been recognised that oestrogens without sufficient progesterone increases the risk for type 1 endometrial cancer, while progesterone has a protective effect for this cancer type [31]. The endometriotic tissue produces biologically significant quantities of both local oestrogens and progesterone via an abnormally active steroidogenic cascade; however, there is evidence suggesting that the eutopic endometrium exhibits progesterone resistance [31]. This may somehow be linked to the positive association between endometriosis and type 1 endometrial cancer observed in our study. In addition, mutations in the same gene as that observed in endometriosis-associated ovarian cancers, loss of *ARID1A*, has also frequently been identified in endometrial cancer of endometrioid histology and has been found to correlate with uterine endometrioid tumour progression from low to high grade, suggesting a common genetic cause for endometriosis and endometrial cancer of endometrioid histology [25].

Several factors associated with endometriosis affect breast cancer risk, as both conditions are hormone-related [23]. We observed a 27% increased risk for breast cancer among women aged ≥50 years at first diagnosis of endometriosis. Most previous studies found no convincing evidence of an association between endometriosis and breast cancer overall [13,15,32–34], but two found that endometriosis patients were at increased risk for breast cancer [14,35]. A previous Danish register-based study, by Bertelsen et al. [33], which partly overlapped with our study, showed that women aged ≥50 years at first diagnosis of endometriosis had a significantly increased risk for breast cancer; however, in contrast to our results, they found a decreased risk for breast cancer among women aged <40 years at diagnosis of endometriosis. Bertelsen et al. [33] hypothesised that the difference is due to the fact that both the aetiological factors and the type of treatment differ with the age of endometriosis patients. Thus, the increased risk for breast cancer of women aged ≥50 years at first diagnosis of endometriosis may be due at least partly to obesity and use of hormone replacement therapy, which are associated with both endometriosis and breast cancer in postmenopausal women. With regard to type of treatment, endogenous oestrogen suppression is used primarily for younger women, and

Table 3
Standardized incidence ratios (SIRs) with 95% confidence intervals (CIs) for specific histotypes of ovarian, endometrial and breast cancer among Danish women with endometriosis diagnosed in 1977–2012. Cancers and person–years in the first year after a diagnosis of endometriosis were excluded.

Histotype of cancer	O	E	SIR (95% CI)
Ovarian			
Serous	70	66.80	1.05 (0.82–1.32)
Mucinous	10	13.41	0.75 (0.36–1.37)
Endometrioid	28	17.09	1.64 (1.09–2.37)
Clear-cell	25	6.87	3.64 (2.36–5.38)
Endometrial			
Type 1	67	43.41	1.54 (1.20–1.96)
Type 2	4	3.78	1.06 (0.28–2.71)
Breast			
Ductal	1034	997.28	1.04 (0.97–1.10)
Lobular	176	153.82	1.14 (0.98–1.33)

O = observed. E = expected.

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Table 4
Standardized incidence ratios (SIRs) with 95% confidence intervals (CIs) for histotypes of ovarian cancer among Danish women with endometriosis diagnosed in 1977–2012, by time since and age at first diagnosis of endometriosis. Cancers and person–years in the first year after a diagnosis of endometriosis were excluded.

	Serous			Mucinous			Endometrioid			Clear-cell		
	O	E	SIR (95% CI)	O	E	SIR (95% CI)	O	E	SIR (95% CI)	O	E	SIR (95% CI)
Time since endometriosis(years)												
1–4	13	7.69	1.69 (0.90–2.89)	3	2.30	1.30 (0.26–3.81)	5	2.36	2.12 (0.68–4.95)	2	0.97	2.07 (0.23–7.48)
5–9	15	11.24	1.33 (0.75–2.20)	3	3.02	0.99 (0.20–2.90)	4	3.35	1.19 (0.32–3.05)	8	1.41	5.69 (2.45–11.22)
≥10	42	47.87	0.88 (0.63–1.19)	4	8.09	0.49 (0.13–1.27)	19	11.38	1.67 (1.00–2.61)	15	4.49	3.34 (1.87–5.51)
Age at first endometriosis (years)												
<30	5	5.55	0.90 (0.29–2.10)	1	1.61	0.62 (0.01–3.46)	1	1.43	0.70 (0.01–3.90)	4	0.62	6.45 (1.73–16.51)
30–39	24	20.20	1.19 (0.76–1.77)	3	4.49	0.67 (0.13–1.95)	8	5.39	1.48 (0.64–2.93)	10	2.27	4.40 (2.11–8.09)
40–49	22	33.01	0.67 (0.42–1.01)	5	6.01	0.83 (0.27–1.94)	14	8.34	1.68 (0.92–2.82)	8	3.32	2.41 (1.04–4.75)
≥50	19	8.04	2.36 (1.42–3.69)	1	1.30	0.77 (0.01–4.27)	5	1.93	2.59 (0.83–6.03)	3	0.65	4.62 (0.93–13.51)

O = observed. E = expected.

definitive surgery, such as hysterectomy, is commonly used in older women. We did not, however, observe a lower risk for breast cancer among younger women, and further investigation on this topic is warranted.

The strengths of this population-based cohort study include the large number of cancer cases and the long follow-up. Further, because of the unique Danish personal identification numbers, which permit accurate linkage between registries, virtually no women were lost to follow-up. This, in combination with the possibility of censoring for gynecological surgery, allowed us to calculate the true number of person-years at risk for the analysis of each cancer site. Most of the previous studies were based on self-reporting of a diagnosis of endometriosis. By using data from the Danish National Patient Register, we retrieved information on all clinical diagnoses of endometriosis in Denmark between 1977 and 2012. We were also able to investigate the associations with cancer for both in- and outpatients in Denmark, however, the latter were only included from 1995 onwards. As endometriosis was diagnosed in >25% of the patients as outpatients, we were able to include more women and hence obtain more precise risk estimates. Further, as endometriosis is diagnosed at hospital in the vast majority of women in Denmark, the results are generalizable to the general population. As health personnel may be aware of a potential association between endometriosis and gynecological cancers, women with endometriosis might have received more medical surveillance than women in the background population, which would result in surveillance bias. However, even after we excluded the first year of follow-up from our analyses (when the possibility of surveillance bias is highest), we still observed increased risks for all the cancers included, and the risks for ovarian and endometrial cancer relative to those of the general female population remained increased for 5–10 years.

Although our study cohort comprised many patients, some subgroup analyses were limited by small sample sizes. Comparisons of cancer incidence in endometriosis patients and women in the general population took age and calendar year into account, but we were unable to adjust for other potential confounders, such as parity, which might have slightly confounded our results. Even though we had a relatively long follow-up period, the median age at end of follow-up was below the usual peak age for ovarian-, endometrial- and breast cancer (early 60s), which might slightly have weakened our risk estimates. Our risk estimates might be slightly underestimated, as the background comparison population included the women in this study cohort as well as women with undiagnosed endometriosis and women with endometriosis diagnosed and treated by general practitioners and private gynecologists.

In conclusion, our study shows that women aged ≥50 years at first diagnosis of endometriosis are at increased risk for endometrioid and clear-cell ovarian cancers, type 1 endometrial cancer and breast cancer for women ≥50 years at first endometriosis diagnosis. Our finding of increased risks for certain histotypes of ovarian cancer adds to the consistent results of previous studies. As the first cohort study to date, we found a statistically significantly increased risk for endometrial cancer in endometriosis patients which persisted for ≥10 years, after a diagnosis of endometriosis. As breast cancer is highly prevalent, the observed increase in risk of women with endometriosis diagnosed at a late age should be studied further. Research should also be conducted on correct identification of the subgroup of women with endometriosis who are at high risk for cancer.

Conflict of interest

All authors have read and understood Gynecologic Oncology policy on declaration of interests and all authors declare no competing financial interests.

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