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A cohort study of 49 933 women with surgically verified endometriosis - increased incidence of breast cancer below the age of 40

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Conflicts of Interest statement

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ABSTRACT

Introduction: The association between endometriosis and breast cancer is unclear. We assessed the risk of breast cancer in women with surgically verified endometriosis, with special focus on the age at cancer diagnosis, time from endometriosis diagnosis and breast cancer histology. **Material and Methods*:*** All women with first endometriosis associated diagnoses occurring concomitantly with relevant surgical codes during 1987-2012 were retrieved from the Finnish Hospital Discharge Register in Finland. Breast cancers diagnosed after the endometriosis diagnosis were identified from the Finnish Cancer Registry. The Finnish female population served as the reference. The endometriosis cohort consisted of 49 933 women (23 210 cases of ovarian, 20 187 peritoneal and 2372 deep infiltrating endometriosis). The outcome measure was the standardized incidence ratio (SIR) with 95% confidence interval (95%CI) of breast cancer calculated for the whole cohort and for the subtypes of endometriosis, stratified by the age at breast cancer diagnosis, histology, and time from endometriosis diagnosis. **Results:** The overall risk of breast cancer (1555 cases) was similar to the reference population (SIR 0.99; 95%CI 0.94 to 1.03), did not differ in types of endometriosis, and was similar for ductal and lobular breast cancer. However, the SIR of breast cancer was increased in the age group of 20-29 years (4.44; 95%CI 2.22 to 7.94), and in the age group of 30-39 years (1.28; 1.03 to 1.57). The risk of *in situ* breast cancer (170 cases) was increased in the entire endometriosis cohort (1.25; 1.07-1.44). **Conclusions:** The overall risk of breast cancer in women with surgically verified endometriosis was similar to that of general population. However, the risk of breast cancer at young age was increased. Young women with surgically verified endometriosis represent highly symptomatic patients with more frequent surgeries and additional therapies that might also contribute to the risk of breast cancer.

Keywords

Breast cancer, endometriosis, ovarian endometriosis, peritoneal endometriosis, deep infiltrating endometriosis

Abbreviations

FHDR	Finnish Hospital Discharge Register
SIR	standardized incidence ratio
CI	confidence incidence
ICD	International Classification of Diseases

Key message

Risk of breast cancer is increased in women less than 40-years of age with surgically verified endometriosis.

INTRODUCTION

Endometriosis is a chronic inflammatory disease of the female pelvis affecting 6-10% of fertile-age women, resulting in increased morbidity including pelvic pain and subfertility.[1] The risk factors relate to increased exposure to menstruation, such as early menarche, short menstrual cycle length, and longer menstrual duration, as well as reduced parity.[1] The etiology is uncertain, but it includes genetic, environmental and immunological abnormalities.[2] A key feature of ectopic endometriotic implants is their capacity for autonomic estrogen production.[3] In clinical practice, endometriosis is divided into three different subgroups, i.e., ovarian, peritoneal and deep infiltrating endometriosis. The pathogenesis of these entities might differ.[4]

Breast cancer is the most common cancer and cause of cancer death in women worldwide.[5] General risk factors include genetic factors, reproductive, hormonal and life-style related factors such as nulliparity, early menarche or late menopause, current or recent use of oral contraceptives or combined menopausal hormone therapy, obesity, physical inactivity and excess alcohol consumption.[6]

Previous studies assessing the relationship between endometriosis and breast cancer have reported conflicting results. Some recent large studies have suggested that the risk of breast cancer among endometriosis patients is increased [7-9], whereas several other studies reported no such risk[10-15] Moreover, a cross-sectional study from North America found a decreased prevalence.[16]

We have previously assessed the risk of gynecological and non-gynecological cancers according to the type of endometriosis.[17 18] We found that the overall risk of breast cancer in women with surgically verified endometriosis was similar to that of the Finnish female population.[17] Moreover, the risk did not differ according to the type of endometriosis. However, as breast cancer is the most common cancer among fertile-aged women and a concern to all women we further explored the risk of breast cancer according to age at breast cancer diagnosis, time from endometriosis diagnosis as well as breast cancer histology (i.e. ductal and lobular) and separately for breast carcinoma *in situ*.

MATERIAL AND METHODS

In this historic register-based cohort study all first diagnoses of endometriosis, either main or subsidiary, were identified from the Finnish Hospital Discharge Registry when existing concomitantly with a relevant procedural code for the first time from 1987 to 2012. The Finnish Hospital Discharge Registry has national coverage and includes personal identity codes, codes for diseases according to the International Classification of Diseases (ICD), procedure codes according to the Nordic Medico-Statistical Committee Classification of Surgical Procedures (NCSP) and dates for each hospital visit and surgery. The ICD codes are set by the physician in charge of the patient and chosen for each hospital visit based on their clinical relevance. The registry includes records both from public and private hospitals, and also outpatient surgeries from 1994 onwards. The index day was the discharge day of the first hospital visit. The cohort formation, its description and the quality assessment have been published previously.[19]

Information on the incident histologically verified carcinoma *in situ* and breast cancers in the endometriosis cohort were assessed by linkage to the Finnish Cancer Registry using the personal identity codes, which are available for all permanent residents in Finland. This registry includes information on the date of carcinoma *in situ* and cancer diagnosis and

topography and morphology of all malignancies diagnosed in Finland since 1953 allowing also analyses by histology and stage of the disease.[20] The breast tumor hormone receptor status is not registered. The follow-up started on the index day and ended either on the day of emigration, death, or December 31st, 2014 whichever came first. The data on emigrations and deaths were retrieved from the Finnish Population Register Centre.

The endometriosis cohort consisted of 49 933 women who were assigned to sub-cohorts of ovarian (n=23 210), peritoneal (n=20 187), deep infiltrating (n=2372), mixed (n=1120) and "other/unknown" endometriosis (n=3044) according to the site of endometriosis using the diagnostic codes from ICD versions 9 and 10 assigned at the index procedure (Supporting Information Table S1). First, the categories of ovarian and deep infiltrating endometriosis were retrieved. The combination of both ovarian and deep infiltrating endometriosis formed the sub-cohort of mixed endometriosis. Second, the category of peritoneal endometriosis was selected. Third, those not stratified into previous four categories formed the sub-cohort of "other/unknown" endometriosis. The categories of ovarian, deep infiltrating, and mixed endometriosis could also include additional diagnoses of peritoneal endometriosis and/or other/unknown endometriosis. The sub-cohort of peritoneal endometriosis could also include additional diagnoses of other/unknown endometriosis but not ovarian, deep infiltrating, nor mixed endometriosis.[19] Cases with adenomyosis as the only diagnosis were excluded, as histological data to confirm the diagnoses were not available. We focused on the three main sub-cohorts: ovarian, peritoneal and deep infiltrating endometriosis.

Statistical analyses

Women were divided to age groups by ten years intervals (20-29, 30-39, 40-49, 50-59, 60-69, ≥70). Person-years of follow-up were calculated by five-year age categories and calendar periods, and by time since the index day (<0.5, 0.5-4.9, 5-9.9, ≥10 years). The expected number was defined by multiplying the accumulated person-years of follow-up in each stratum by breast cancer incidence rate in the corresponding Finnish female population. The standardized incidence ratio (SIR) was calculated as the ratio between the observed and the expected number of cancers. The 95% confidence intervals (95%CI) for the SIR were defined on the assumption that the number of observed cases followed a Poisson distribution. In the stratified analyses the same calculations were performed according to the histology (ductal/lobular/*in situ carcinoma*) and stage of the breast cancer (localized/non-localized) and presented according to age groups and time since index day.

Ethical approval

We obtained approval from the ethics committee of the Hospital District of Helsinki and Uusimaa (238/13/03/03/2013) before initiation of this study. Permissions by the National Institute for Health and Welfare (THL/546/5.05.00.2014), and the Population Register Centre (D1794/410/14) were also obtained for the register data and their linkages.

RESULTS

There were altogether 838 685 person-years of follow-up during 1987-2014 with mean follow-up time was 16.8 years. Six percent of the person-years accumulated in age categories under 30 years, 60% under 50 years and 14% in ages over 60 years (Table 1). The sub-cohorts of ovarian and peritoneal endometriosis represented 89% of all person-years. The median age on the index day was 36.4 years.

The overall incidence of breast cancer was similar to that in the Finnish female population in the entire endometriosis cohort (1555 observed cases, SIR 0.99; 95%CI 0.94 to 1.03) and in all sub-cohorts of endometriosis (Table 2, Supporting Information Table S2). An increased risk of breast cancer was seen in the 20 to 29 -year-olds (SIR 4.44; 95%CI 2.22 to 7.94, 11 cases), and in the 30-39 -year-olds (1.28; 1.03 to 1.57, 90 cases). Moreover, a slightly decreased risk of breast cancer was observed among the 50 to 59 -year-old women (0.92; 0.85 to 0.99) (Table 2).

Eleven women with endometriosis had the diagnosis of breast cancer at the age of less than 30 years (Table 3). The SIR of localized breast cancer in the 20-29 -year-olds was 5.80 (95%CI 2.13 to 12.6, 6 cases) while that of non-localized disease was 3.15 (0.86 to 8.07, 4 cases). The corresponding numbers among the 30-39 -year-olds were 1.50 (1.09 to 2.02, 43 cases) and 1.12 (0.81 to 1.51, 42 cases).

In the stratified analyses the SIR of the breast cancer diagnosis increased 0.5-4.9 years after the endometriosis diagnosis in the whole cohort (1.15; 1.01 to 1.29), and especially in the sub-cohort of peritoneal endometriosis (1.30; 1.06 to 1.56). (Table 2)

The SIR for ductal histology was 0.97 (0.91 to 1.02) and for lobular histology 0.99 (0.87 to 1.11). However, the SIR for ductal histology was increased in the 20-29 -years-olds (4.17;

1.91 to 7.92, 9 cases). The overall incidence of *in situ* carcinoma of the breast (n=170) was increased in women with endometriosis (1.25; 1.07 to 1.44). The risk of *in situ* carcinoma was highest in the age group of 50-59 years (1.35; 1.08 to 1.66, 85 cases). (Table 2)

DISCUSSION

We observed that women with surgically verified endometriosis do not have an overall increased risk of breast cancer. The risk did not differ according to the type of endometriosis either. The distribution of ductal and lobular histology of breast cancer did not differ from the reference population. However, we found an increased incidence of breast cancer among the 20-39 -year-olds. The incidence of carcinoma *in situ* of the breast was increased.

The non-elevated overall incidence of breast cancer among women with endometriosis has been shown in several previous studies with different study designs and ascertainments of the diagnosis of endometriosis.[10-14] A large British cohort study published in 2018 found no association between breast cancer and endometriosis among women receiving infertility treatment with assisted reproductive technologies.[15] In contrast, an increased incidence of breast cancer has been observed in recent study with histologically proven endometriosis.[9]

The differences in the overall incidence of breast cancer between different subtypes of endometriosis were small in our study. In two previous Nordic studies, the risk of breast cancer has also been assessed in relation to the site of endometriosis (ovarian, pelvic, uterine and other endometriosis).[7 11] The Swedish study found an increased risk of breast cancer with pelvic (SIR 1.8; 95%CI 1.2 to 2.6) and uterine (SIR 1.4; 95%CI 1.1 to 1.7) but not with ovarian endometriosis.[7] The Danish study did not find altered risks of breast cancer in any of the different locations of endometriosis.[11]

On the contrary to our study a recent register-based study from Denmark found an increased risk of breast cancer in women with first diagnosis of endometriosis at ≥50 years of age (SIR 1.27; 1.12 to 1.42).[13] Moreover, a previous partially overlapping Danish register-based study reported that the risk of breast cancer was decreased if the endometriosis diagnosis had been made at <40 years of age but increased along with increasing age at the first endometriosis diagnosis.[11] A Swedish register-based study found an increased risk of breast cancer (SIR 1.28; 1.13 to 1.45) when endometriosis diagnosis had been made between 50-60 years of

age.[10] In contrast, a prospective study from the USA reported that the risk of breast cancer was not increased in premenopausal or postmenopausal women with endometriosis.[14]

Early onset breast cancer is rare, and therefore, the absolute excess risk based on our study is small: in the age group of 20 to 29 -year-olds, the relative risk of 4.4 would translate into eight breast extra cancers among 10 000 women with endometriosis followed-up for five years. In the age group of 30 to 39 -year-olds, the corresponding number would be five.

The reasons for the increased risk of breast cancer among young women with surgically diagnosed endometriosis is uncertain. Similar risk factors for both endometriosis and young-age breast cancer might in part explain our finding. The known risk factors of early onset breast cancer, such as family history and known genetic predisposition, explain only approximately 10% of young-age breast cancer cases.[21] However, we speculate that genetic factors predisposing to breast cancer might be more frequent among women with endometriosis at early age. Other possible risk factors for breast cancer in young women include low body mass index and use of oral contraceptives.[21] The women operated for endometriosis at a young age are also likely to be highly symptomatic and therapies used in addition to surgery for symptom control, such as hormonal treatments and analgesics, might differently affect the risk of breast cancer in these women compared to older women with less symptoms. [22 23] Recent meta-analyses indicated a slightly increased risk of breast cancer associated with current or recent use of hormonal contraceptives (risk ratio for current users 1.3; 95%CI 1.1 to 1.5 and for ever-users 1.1; 95%CI 1.0 to 1.2) [24 25] The use of progestin-only contraceptives has also been linked with breast cancer.[26 27] In Finland, oral contraceptives and progestins are widely used in the treatment of endometriosis. In our study, data on hormonal therapies were not available, and therefore, the effect of hormonal therapies could not be estimated. According to the abovementioned facts, we speculate that in our study the SIRs would be lower if we could have adjusted for hormonal therapies.

Breast cancer occurring at a young age is known to be aggressive and commonly diagnosed at a non-localized stage.[21] The proportion of non-localized stage young-age breast cancer in our data was however lower than in the breast cancer patients of similar age in the reference population, as indicated by the higher SIR for a localized than for a non-localized stage of the breast cancer. We speculate that endometriosis patients attend medical care and are examined

more often and therefore breast cancers of young women with endometriosis are diagnosed earlier than in the reference population.

The risk of breast cancer was slightly decreased among 50-59 -year old women with endometriosis (0.9-fold, 95%CI 0.9 to 1.0). On the other hand, the SIR of *in situ* cancers was increased in the age group of 40 to 59 -year-olds. Endometriosis patients at 40 years of age or older might receive breast imaging examinations more frequently than the average female population. This may lead to increased detection of *in situ* cancers and their timely treatment, resulting in decreased risk of breast cancer.

A strength of our study is in the high-accuracy of the registers. [20 28] The cohort data from the Finnish Hospital Discharge Registry, cancer data from the Finnish Cancer Registry, and the data on deaths and emigrations from the Finnish Population Register Centre were reliably linked using the unique personal identity codes available in all registries. Additional strengths of the study are the 27 years long study period with almost 840 000 person-years and more than 1500 breast cancer cases. The large cohort size and the surgically verified diagnoses of endometriosis gave us the possibility to assess the breast cancer risks for various subtypes of endometriosis. Still, the sub-cohort of deep infiltrating endometriosis is too small for reliable conclusions; deep infiltrating endometriosis is rare, and the definition of the disease entity was established only in the 1990s. Furthermore, our follow-up does not properly extend into the oldest age groups – there were only 48 breast cancer cases in age groups of 70 years or more – and therefore our results on breast cancer risk in old age remain uninformative.

A limitation of this study is the lack of possibility to adjust the results for important potential confounding factors that might bias the SIRs of our study. The decreased parity or late onset of first pregnancy among women with endometriosis could increase the risk of breast cancer. The body mass index is decreased in women with endometriosis, which might lead to an increased incidence of breast cancer in premenopausal and a decreased incidence of breast cancer in postmenopausal women.[29 30] Furthermore, data on hormonal therapies, a cause of possible bias in the study, were unavailable. We speculate that hormone replacement therapy is likely to be used less often due to the risk of endometriosis recurrence and therefore postmenopausal women with endometriosis might have decreased risk of breast cancer.

CONCLUSION

The overall incidence of breast cancer was not increased in women with surgically verified endometriosis nor was the risk increased in any of the specific types of endometriosis. The increased incidence of breast cancer in young women with endometriosis warrants further studies.

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Supporting Information legends

Table S1. Types of endometriosis and the possible additional diagnosis of endometriosis.

Table S2. Breast cancers and carcinoma *in situ* lesions of the breast among women with endometriosis, by the type of endometriosis and by dynamic age at follow-up: observed number of cases (O), standardized incidence ratios (SIR) and 95% confidence intervals (CI).

Legends to the tables

Table 1. Number of women with surgically verified endometriosis by age in the beginning of the follow-up, and numbers of person-years by dynamic age at follow-up.

Table 2. Breast cancers and carcinoma *in situ* lesions of the breast among women with endometriosis, by time since endometriosis diagnosis and by dynamic age at follow-up: observed number of cases (O), standardized incidence ratios (SIR) and 95% confidence interval (CI).

Table 3. Details of women with endometriosis and subsequent breast cancer diagnosed under 30 years of age.

Table 1. Number of women with surgically verified endometriosis by age in the beginning of the follow-up, and numbers of person-years by dynamic age at follow-up.

Age (years)	Number of women at endometriosis diagnosis	Person-years, by years since endometriosis diagnosis				
		< 0.5	0.5 – 4.9	5 – 9.9	≥ 10	Whole follow-up
10-19	525	228	440	8	0	676
20-29	12 685	6135	35 577	9048	452	51 212
30-39	18 027	9027	79 485	66 145	31 458	186 115
40-49	15 286	7766	75 103	77 531	102 746	263 145
50-59	2985	1580	25 218	53 628	140 137	220 562
60-69	339	178	2392	7125	90 754	100 449
≥70	86	45	564	1067	14 850	16 526
Total	49 933	24 959	218 780	214 550	380 397	838 685

Table 2. Breast cancers and carcinoma *in situ* lesions of the breast among women with endometriosis, by time since endometriosis diagnosis and by dynamic age at follow-up: observed number of cases (O), standardized incidence ratios (SIR) and 95% confidence interval (CI).

Dynamic age at follow-up (years)	Time since endometriosis diagnosis														
	< 0.5 year			0.5-4.9 years			5.0-9.9 years			≥ 10 years			Total		
	O	SIR	95%CI	O	SIR	95%CI	O	SIR	95%CI	O	SIR	95%CI	O	SIR	95%CI
Breast cancer															
20-29	0	0.00	0.00-14.5	7	4.18	1.68-8.60	4	7.69	2.10-19.7	0	0.00	0.00-130	11	4.44	2.22-7.94
30-39	2	0.64	0.08-2.30	37	1.33	0.93-1.82	36	1.43	1.00-1.97	15	1.08	0.61-1.78	90	1.28	1.03-1.57
40-49	11	1.00	0.50-1.79	114	1.01	0.83-1.20	112	0.91	0.75-1.08	194	1.16	1.01-1.33	431	1.04	0.95-1.14
50-59	4	0.98	0.27-2.51	80	1.19	0.95-1.48	116	0.77	0.64-0.92	389	0.93	0.84-1.02	589	0.92	0.85-0.99
60-69	0	0.00	0.00-7.07	13	1.74	0.92-2.96	23	0.94	0.60-1.41	350	0.97	0.87-1.07	386	0.98	0.89-1.08
≥70	0	0.00	0.00-28.4	0	0.00	0.00-2.22	2	0.61	0.10-2.02	46	0.89	0.65-1.19	48	0.86	0.63-1.14
Total	17	0.89	0.52-1.42	251	1.15	1.01-1.29	293	0.90	0.80-1.00	994	0.98	0.92-1.04	1555	0.99	0.94-1.03
Carcinoma *in situ*															
20-29	0	0.00	0.00-331	0	0.00	0.00-52.8	0	0.00	0.00-180	0	0.00	0.00-4155	0	0.00	0.00-36.0
30-39	0	0.00	0.00-29.5	3	2.53	0.52-7.40	0	0.00	0.00-3.19	0	0.00	0.00-5.22	3	0.95	0.20-2.76
40-49	1	1.66	0.04-9.26	4	0.59	0.16-1.50	13	1.60	0.85-2.73	22	1.67	1.05-2.52	40	1.39	1.00-1.89
50-59	0	0.00	0.00-11.1	9	1.55	0.71-2.94	23	1.64	1.04-2.46	53	1.23	0.92-1.61	85	1.35	1.08-1.66

60-69	0	0.00	0.00-105	0	0.00	0.00-6.69	1	0.49	0.01-2.73	37	1.06	0.75-1.46	38	1.01	0.72-1.39
≥70	0	0.00	0.00-787	1	14.3	0.36-79.6	0	0.00	0.00-24.6	3	0.96	0.20-2.81	4	1.19	0.33-3.06
Total	1	0.90	0.02-5.02	17	1.18	0.68-1.88	37	1.45	1.02-2.00	115	1.21	1.00-1.44	170	1.25	1.07-1.44

No cases of breast cancer or carcinoma *in situ* of the breast were found in the age group of 10-19 years (observed 0, expected <0.005).

Table 3. Details of women with endometriosis and subsequent breast cancer diagnosed under 30 years of age.

	Breast cancer						
						Follow-up after breast cancer diagnosis	
Type of endometriosis	**Latency**[1]	**Age**[2]	**Grade**	**Type**	**TNM**	**Recurrence (when**[3]**)**	**Total follow-up**[5]
Ovarian	2.4	26.7	II	ductal	T1N0M0	Yes (12.0)	24.9
Ovarian	5.6	28.6	II	ductal	T1N1MX	Yes (2.2)	4.3
Ovarian	5.7	28.9	III	ductal	T1N0MX	No	4.8
Peritoneal	0.7	28.2	III	ductal	T1N1M0	No	1.9
Peritoneal	1.8	26.8	N/A	N/A	N/A	N/A	11.3
Peritoneal	4.8	29.0	III	ductal	T1N1M0	No	8.4
Deep	3.4	27.9	III	ductal	T1N0M0	No	12.7
Deep	7.4	29.0	III	ductal	T1N0M0	No	2.9
Other	1.1	28.1	N/A	ductal	T1N0M0	Yes (2.7)[4]	4.9
Other	1.5	27.6	III	ductal	T3N1M0	No	15.2
Other	5.9	28.7	II	cribriform	T1N0MX	No	1.5

[1]Years between endometriosis diagnosis and breast cancer diagnosis.

[2]Age at breast cancer diagnosis (years).

[3] Recurrence (yes/no) during the follow-up and the time of possible recurrence.

[4] This person also died due to breast cancer 4.9 year after breast cancer diagnosis.

[5] Follow-up from breast cancer diagnosis until death or 31 Dec 2014 (years).

N/A – Not available