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SHORT REPORT

Risk for breast cancer among women with endometriosis

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Although several risk factors are common to endometriosis and breast cancer, the results of observational studies of an association have so far been inconsistent. We evaluated the relationship between endometriosis and breast cancer on the basis of data on selected cancers and medical histories from the Danish nationwide cancer and hospital registries used in a large case–cohort study. A total of 114,327 women were included in the study of whom 1,978 women had received a diagnosis of endometriosis and 16,983 had had a diagnosis of breast cancer between 1978 and 1998. Of the women with endometriosis, 236 subsequently received a diagnosis of breast cancer. The crude overall rate ratio for breast cancer after endometriosis was 1.00 and after adjustment for reproductive factors, calendar-period, bilateral oophorectomy and benign breast disease, the rate ratio was 0.97 (95% confidence interval, 0.85–1.11). The risk for breast cancer increased with age at diagnosis of endometriosis, so that women in whom endometriosis was diagnosed at a young age (approximately <40 years) had a reduced risk for breast cancer and women in whom endometriosis was diagnosed at older ages (approximately ≥40 years) tended to have an increased risk for breast cancer. The reduced risks observed among young women may reflect their exposure to drugs with antiestrogenic effects. The increased risk associated with endometriosis among postmenopausal women may be due to common risk factors between postmenopausal endometriosis and breast cancer or an altered endogenous estrogen.

Key words: endometriosis; breast cancer; record linkage case–cohort

A woman's lifetime exposure to endogenous estrogens is an established risk factor for breast cancer.[1] It is conceivable that a woman's cumulative exposure to endogenous estrogens is influenced by medical conditions related to hormonal abnormalities that she might have had during her reproductive life.

Endometriosis is an estrogen-related, gynecological disorder with an estimated prevalence of 2.5–3.5% in women of reproductive age.[2,3] The condition is characterized by the presence of endometrial tissue in ectopic foci outside the uterus, which can result in chronic pelvic pain, delayed pregnancy and infertility. The cause of endometriosis is unclear, but maintenance of the disease is dependent on the presence of estrogen,[3] as reflected in the characteristics and risk factors related to the condition. Endometriosis is more common among nulliparous than parous women and is rarely seen in women with anovulatory cycles. It presents after menarche and usually regresses after the menopause. Postmenopausal cases of endometriosis are primarily seen in connection with obesity or use of hormone replacement therapy (HRT).[4] Treatment with *e.g.*, danazol or gonadotropin-releasing hormone (GnRH) agonists, which suppress endogenous estrogen production, has proven effective in relieving the symptoms associated with endometriosis. The latter treatment is prescribed mainly to premenopausal women.

Although endometriosis and breast cancer appear to have common risk factors such as endogenous estrogen, reproductive characteristics, obesity and use of HRT, which indirectly support an association between the 2 diseases, the results of observational studies of the association between endometriosis and breast cancer are inconsistent.[5–10] Two cohort studies based on hospital records of patients with endometriosis showed an increased risk for breast cancer,[6,7] while 4 other studies based on selfreports of endometriosis did not confirm such an association.[5,8–10] To clarify further the relationship between breast cancer and endometriosis, we used data from a large population-based case–cohort study with data from Danish registers and designed to examine associations between various medical conditions and breast, ovary and endometrial cancer.

Material and methods

Breast cancer cases and subcohort

The initial study population consisted of all women born in Denmark after 1936 and alive on January 1, 1978, defined as the base line. The women were identified through the Central Population Register, which was started in 1968, from their personal identification number. This number, which is unique to every Danish citizen, incorporates sex and date of birth and permits accurate linkage of information between registers. The Central Population Register also includes dates of death and emigration. All women were linked to the files of the Danish Cancer Registry, which has reported incidence data on cancer in Denmark since 1943 with a modified version[11] of the International Classification of Diseases, 7th Revision (ICD-7). Women in whom invasive breast cancer was diagnosed before January 1, 1978 (baseline) were excluded from the initial study population to ensure that endometriosis occurred before breast cancer.

Cohort members, in whom breast cancer, ovary cancer and endometrial cancer were diagnosed between January 1, 1978 and December 31, 1998, the period of follow-up, were identified on their tumor code and date of diagnosis. In the present analysis, only women with breast cancer (ICD-7: 170)[11] were considered as cases, providing us with a case group of 16,983 women. Uterine and ovarian cancers are considered elsewhere.[12] From the study cohort we randomly selected a subcohort of 99,812 women, representing 4 times the number of cases of breast cancer, ovary cancer and endometrial cancer for women born 1937–1951 and 6 times the number of cases born after 1951. More detailed information on the selection procedure has been provided elsewhere.[12] Of the 16,983 women with breast cancer, 2,468 were also members of the subcohort. All breast cancer cases and members of the subcohort were included in the risk analysis.

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TABLE I – REPRODUCTIVE AND MEDICAL CHARACTERISTICS OF 16,983 BREAST CANCER PATIENTS AND 97,344 WOMEN IN THE REMAINING SUB-COHORT, INCLUDING ASSOCIATED RATE RATIOS (RRs) OF BREAST CANCER WITH 95% CONFIDENCE INTERVALS (CIs)

Characteristics	Breast cancer patients		Remaining subcohort		Adjusted RR[1]	95% CI
	No.	%	No.	%		
Parity						
Nulliparous	2,043	12.0	10,535	10.8	0.92[2]	0.87–0.98
1	3,077	18.1	15,558	16.0		
2–3	10,978	64.7	64,556	66.3	0.92[3]	0.90–0.94
4+	885	5.2	6,695	6.9		
Age at birth of first child						
<20	1,820	12.2	11,575	13.3		
20–24	6,810	45.5	41,544	47.9		
25–29	4,574	30.6	24,738	28.5	1.12[4]	1.10–1.14
30–34	1,355	9.1	6,913	8.0		
35	381	2.6	2,039	2.3		
Benign breast disease						
Yes	1,378	8.1	4,769	4.9	2.48	2.32–2.64
No	15,605	91.9	92,575	95.1		
Bilateral oophorectomy						
Yes	11	0.1	183	0.2	0.61	0.33–1.14
No	16,972	99.9	97,161	99.8		

[1]Mutually adjusted for the other risk factors in the table and for age and calendar year of follow-up.–[2]Rate ratio for one birth at age 25 years *vs.* nulliparous.–[3]Rate ratio per more than one birth.–[4]Rate ratio per 5-year increment in age at birth of first child.

Hospitalization for endometriosis

We linked data on breast cancer cases and subcohort members to the Danish Hospital Discharge Register, which has diagnostic information on 99% of all hospital admissions at nonpsychiatric hospitals in Denmark since 1977 and all outpatient visits since 1995.[13] In this Register, each hospital visit gives rise to a record that contains the personal identification number of the patient and information on the hospital department, date of admission and discharge or date of outpatient visit, surgical procedures performed during the visit, and up to 20 discharge diagnoses. The diagnoses were coded according to the Danish version of the International Classification of Diseases, 8th Revision (ICD-8)[14] during 1977–1993 and ICD-10[15] from 1994 onward. Surgical interventions were coded according to the Danish Classification of Surgical Procedures and Therapies during 1977–1995,[16] and Classification of Surgical Procedures from 1996.[17] All records on study subjects with a diagnosis of endometriosis (ICD-8, 625.3; ICD-10, N80) during the period 1977–1998 were identified. For patients who had more than one visit with this diagnosis, only the first record was retained, giving the date of diagnosis defined as the date of first hospital admission or outpatient visit for this disease. Moreover, all records with a diagnosis of benign breast disease (ICD-8, 610; ICD-10, N60) and records indicating bilateral oophorectomy were identified together with the date of diagnosis defined as date of discharge. The numbers and dates of birth of the offspring of all the women with breast cancer and subcohort members were obtained from the files of the Central Population Register to adjust for possible confounding from reproductive events.

Statistical analysis

For data analysis the case–cohort approach described by Barlow *et al.*[18] was used, in which cases are derived from the entire cohort, while the person-years at risk are estimated from the subcohort. This study design allowed for selection of all cases and generation of a subcohort by random selection of any proportion of the cohort. Women from the subcohort entered the study on January 1, 1978, and contributed person-years at risk until the censoring date defined as diagnosis of breast cancer, death, emigration, or December 31, 1998, whichever came first. Thus, if endometriosis occurred after a breast cancer diagnosis, the woman was considered as unexposed. Endometriosis occurring prior to the censoring date was evaluated as a time-dependent categorical exposure. The 2 potential confounders, benign breast disease and bilateral oophorectomy, were entered as categorical variables (yes/no). Three variables were established as indicators of confounding from reproductive status: parity (continuous variable), age at birth of first child (continuous variable), and parental status (categorical variable, mother yes/no). Endometriosis and the potential confounding variables were evaluated as time-dependent in STATA by splitting the observation period for each woman into smaller intervals whenever one of the variables changed between baseline and the censoring date. Current age was used as the time scale to ensure that the estimation procedure was based on comparisons of women of the same age. Calendar year of follow-up was entered as a continuous variable. Crude and adjusted rate ratios (RR) and 95% confidence intervals (CI) were calculated by weighted Cox regression. All analyses were conducted with SAS and STATA software systems.

Stratified analyses were conducted to assess whether breast cancer risk varied with age at diagnosis of endometriosis (<30, 30–39, 40–49, ≥50 years), site of origin of endometriosis (ovary, uterus and pelvis) and age at breast cancer diagnosis (<50, ≥50 years). Age at diagnosis of endometriosis and calendar year of endometriosis were also entered as linear variables. The analyses were repeated on the assumption of endometriosis as an exposure with a latency of 1 year. In a Cox regression analysis with the hazard ratio modeled as a function of age, the risk by time since a diagnosis of endometriosis is the inverse function of the risk by age at diagnosis of endometriosis.

Results

The 114,327 women included in the analysis accrued 2,031,811 person-years of follow-up (average 17.8 years; range 0–21 years). Table I provides information on women with breast cancer (the case group) and women without (the remaining subcohort). The RR for breast cancer associated with reproductive variables were all in the expected direction showing increasing RR for breast cancer with increasing age at birth of first child and decreasing number of births. Also as expected, more women with breast cancer had received a diagnosis of benign breast disease (adjusted RR, 2.48; 95% CI, 2.32–2.64) while fewer had undergone bilateral oophorectomy (adjusted RR, 0.61; 95% CI, 0.33–1.14).

Prior to the censoring date, endometriosis was diagnosed in 1,978 women at an average age of 40.6 years (range 16–60 years). Overall, 236 cases of endometriosis were diagnosed among the 16,983 women who subsequently developed breast cancer, while 1,742 were diagnosed with endometriosis among the remaining 97,344 women. These findings resulted in a crude RR for breast

TABLE II – RELATIONSHIP OF ENDOMETRIOSIS TO RISK FOR BREAST CANCER BY CALENDAR YEAR AND AGE OF DIAGNOSIS OF ENDOMETRIOSIS, SITE OF ORIGIN OF ENDOMETRIOSIS AND AGE AT BREAST CANCER DIAGNOSIS

	Age at breast cancer diagnosis					
	All ages		All ages 1-year latency[1]	<50 years		≥50 years	
	N	RR[2] (95% CI)	RR[2] (95% CI)	*N*	RR[2] (95% CI)	*N*	RR[2] (95% CI)
Endometriosis	236	0.97 (0.85–1.11)	0.91 (0.79–1.06)	139	0.91 (0.77–1.09)	97	1.05 (0.85–1.30)
Year of diagnosis of endometriosis[3]							
Per year	–	1.04 (1.02–1.07)	–	–	1.04 (1.01–1.08)	–	1.04 (1.00–1.09)
Per year adjusted for age at diagnosis	–	1.01 (0.98–1.05)	–	–	1.01 (0.97–1.06)	–	1.00 (0.93–1.08)
Age at endometriosis							
Per year[4]	–	1.05 (1.03–1.08)	–	–	1.06 (1.03–1.10)	–	1.06 (1.01–1.11)
Per year adjusted for year of diagnosis	–	1.04 (1.02–1.07)	–	–	1.06 (1.02–1.10)	–	1.06 (0.98–1.14)
<30 years	9	0.49 (0.25–0.96)	0.49 (0.25–0.97)	–	–	–	–
30–39 years	83	0.77 (0.61–0.96)	0.72 (0.57–0.92)	–	–	–	–
40–49 years	125	1.14 (0.95–1.36)	1.10 (0.90–1.34)	–	–	–	–
≥50 years	19	2.21 (1.36–3.60)	2.40 (1.43–4.01)	–	–	–	–
Site of origin of endometriosis[5]							
Ovary	88	0.92 (0.73–1.14)	0.84 (0.67–1.07)	–	–	–	–
Uterus	88	1.04 (0.83–1.30)	0.96 (0.76–1.22)	–	–	–	–
Pelvis	43	0.89 (0.62–1.17)	0.87 (0.63–1.20)	–	–	–	–

[1]Endometriosis considered as an exposure with a latency of 1 year.–[2]Rate ratio adjusted for parity, parental status, age at birth of first child, benign breast disease, bilateral oophorectomy and calendar year.–[3]Linear estimates for each year increase in calendar time.–[4]Linear estimates for each year increase in age.–[5]Women may appear in more than one category. Women with site of origin of endometriosis categorized as other and/or unspecified were not included in this analysis ($N = 41$).

cancer after endometriosis of 1.00. Adjustment for parental status, age at birth of first child, parity, benign breast disease, bilateral oophorectomy and calendar year did not change the neutral relationship between endometriosis and breast cancer appreciably (adjusted RR, 0.97; 95% CI, 0.85–1.11) (Table II).

The RR increased for each year of age and calendar year of first hospital contact with endometriosis. When mutually adjusted, the effect of age at endometriosis was largely unchanged, while the effect of calendar year almost disappeared (Table II). The risk estimates for categories of age at diagnosis of endometriosis went from a decreased risk to an increased risk for breast cancer at around the age of 40 (Table II). To evaluate a possible effect of increased screening for breast cancer after a diagnosis of endometriosis, the risk estimates were also calculated for a latency of 1 year. This did not change the results considerably. (Table II). No substantial variation in risk with site of origin of endometriosis or age at breast cancer diagnosis was noted (Table II).

Discussion

This study showed that women in whom endometriosis was diagnosed at young age (below approximately 40 years) tended to have a reduced risk for breast cancer, while women who received a diagnosis of endometriosis at older age (above approximately 40 years) tended to have an increased risk for breast cancer when compared to a random sample of women from the general population. This resulted in an overall neutral risk estimate for breast cancer associated with endometriosis.

Three case–control studies and one cohort study[5,8–10] showed no overall association between endometriosis and breast cancer. Two of these studies, a case–control study[9] and the cohort study[10] only included postmenopausal breast cancer cases and all the studies differed from ours by relying on selfreported endometriosis. Age at diagnosis of endometriosis was considered for pre and postmenopausal endometriosis in 2 of the case–control studies[5,8] with a tendency towards higher risk estimates associated with premenopausal endometriosis; however, the findings were not significant. Two cohort studies, both based on hospital records of endometriosis, showed overall increased risks for breast cancer after a diagnosis of endometriosis. Schairer *et al.*[6] found increased risk of breast cancer associated with endometriosis (standardized mortality RR, 3.2; 95% CI: 1.2–8.0), but their finding was restricted to women with endometriosis who had undergone surgery, and it was based on few observed cases of breast cancer. The study of Brinton *et al.*[7] is similar to ours in respect of the type of register data used and the underlying population (Swedish and Danish women, respectively). Nevertheless, they reported a standardized incidence RR of 1.27 (95% CI, 1.1–1.4) for breast cancer after a hospital diagnosis of endometriosis, and they found no apparent difference in risk according to age at diagnosis of endometriosis (before or after age 40). Brinton *et al.* compared the breast cancer incidence rates with those of the general population by estimating standardized incidence RR and they did not control for any confounders. Nevertheless, none of these factors is likely to explain the difference between their results and ours. Their hospital data went further back in time (1969–1983) than our data (1977–1998). They found that the risk of breast cancer slightly increased with calendar year of diagnosis of endometriosis, while we found no effect. Before 1988–1989 medical treatment of endometriosis consisted of oral contraceptives, danazol and gestagenes; after 1988–1989 GnRH analogues were included in the treatment regimen. The androgenic agent danazol and the GnRH agonists suppress endogenous estrogen and owing to their side effects they are not used for more than 6 months as treatment for endometriosis. Both drugs have been considered for treatment of breast cancer.[19,20] In addition, GnRH agonists have been suggested as chemoprevention of female cancers, including breast cancer[21] and women with endometriosis to whom GnRH agonists were prescribed might have been protected against breast cancer.

The type of treatment also varies with the age of the patient depending on the desire to become pregnant and menopausal status. Endogenous estrogen suppression used primarily for young women and more definitive surgery (*e.g.*, hysterectomy) reserved for older women, might result in different risks for the development of breast cancer.

The etiology of endometriosis in postmenopausal women may also differ from that in premenopausal women. Endometriosis in postmenopausal women is associated with known risk factors for postmenopausal breast cancer such as use of HRT[22] and obesity.[23] Thus, the reduced risk of women who receive a diagnosis of endometriosis at a young age may be related to treatment, while the increased risk among women who have endometriosis at an older age might be related to use of HRT or obesity. Furthermore, an altered endogenous estrogen level associated with endometriosis is likely to be more important among postmenopausal women, who have a naturally low level of endogenous estrogen, compared to premenopausal women.

Our study has the advantage of being based on nationwide hospital and cancer registries with nearly complete registration.[13,24] The quality of the outcome was notably high, as it was based on information derived from thorough notification procedures.[24,25] Use of the unique 10-digit personal identification numbers ensures unambiguous linkage of information from the different registers. When patients with a chronic disease such as endometriosis are identified through the Hospital Discharge Register, a sizeable proportion of cases are likely to be prevalent at the time of first known hospitalization with endometriosis. Mixing of prevalent and incident cases of endometriosis in our study may result in shorter time lag between endometriosis and breast cancer than in reality.

As patients in whom endometriosis was diagnosed and treated by general practitioners were not included, as well as patients registered with endometriosis at an outpatient visit before 1995, our results primarily relate to severe forms of endometriosis leading to hospitalization, which are likely to be treated by surgery or drugs that suppress or regulate endogenous estrogen. When we excluded the women with endometriosis at outpatient visits in 1995 or after, the results were unchanged. We were unable to obtain information about medical treatment or other potentially relevant covariates, such as obesity and use of HRT; however, we were able to adjust for parity, age at birth of first child, benign breast disease and bilateral oophorectomy.

In conclusion, we found that women who had endometriosis at a young age had a deficit of breast cancer, while those who had the condition at an older age had an excess of breast cancer. Common risk factors for postmenopausal endometriosis and breast cancer or a stronger effect of altered endogenous estrogen associated with endometriosis diagnosed in older women, who have a naturally low level of endogenous estrogen, might explain the excess of breast cancer in women diagnosed with endometriosis later in life. The reduced risk for breast cancer of young women might be related to the antiestrogenic effect of the drugs (Danazol, GnRH agonists), which are used to treat primarily younger women with endometriosis. If our results can be confirmed in other studies, the role of treatment and confounders such as use of HRT and obesity should be investigated.

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