Relationship of Benign Gynecologic Diseases to Subsequent Risk of Ovarian and Uterine Tumors

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Abstract

Objective: **Although endometriosis and uterine leiomyomas are common conditions, the extent to which either is associated with certain types of malignancies remains uncertain.**
Methods: **Using record linkage techniques, we assessed the relationships between hospital and outpatient admissions for endometriosis or leiomyomas and the development of ovarian and uterine cancers in Denmark between 1978 and 1998. Based on a population-based cohort exceeding 99,000 women, including 2,491 ovarian cancers, 860 borderline ovarian tumors, and 1,398 uterine cancers, we derived relative risks (RR) and 95% confidence intervals (95% CI) associated with overall and histology-specific tumor risks after adjustment for calendar time and reproductive characteristics.**
Results: **Endometriosis seemed to predispose to the development of ovarian cancer, with the association restricted to endometrioid or clear cell malignancies. Five or more years after the diagnosis of endometriosis, the RRs (95% CIs) were 2.53 (1.19-5.38) for endometrioid (7 exposed cases) and 3.37 (1.24-9.14) for clear cell (4 exposed cases) malignancies. Uterine leiomyomas were associated with increases in the risk of uterine malignancies, particularly sarcomas, where the RRs (95% CIs) were 20.80 (11.32-38.22) for women with 1 to 4 years of follow-up (11 exposed cases) and 5.70 (2.27-14.32) for those with more extended follow-up (5 exposed cases).**
Conclusion: **In combination with clinical, pathologic, and molecular data, our results support that some endometriotic lesions may predispose to clear cell and endometrioid ovarian cancers. Uterine leiomyomas also showed a strong connection with subsequent uterine sarcomas, although it was difficult to decipher whether this reflected detection bias, shared risk factors, or an etiologic relationship.** (Cancer Epidemiol Biomarkers Prev 2005;14(12):2929–35)

Introduction

Studies have suggested that women with certain common benign gynecologic diseases, such as endometriosis and uterine leiomyoma, may experience increased risks of developing malignant tumors. These observations have important public health implications, given that endometriosis may affect 7% to 15% of all reproductive age women (1), whereas leiomyomas may occur in as many as 70% of White and 80% of Black women by the time they reach age 50 years (2). Although the significance of understanding the cancer risk presented by these common diseases is accepted, clarifying the associations has proven challenging. First, many cases of endometriosis or leiomyomas are unrecognized, especially when asymptomatic. Second, in some instances, the diagnosis of these benign diseases may lead to increased testing and detection of cancers that would otherwise go undetected (detection bias). However, in other instances, patients may undergo hysterectomy and/or oophorectomy for these benign indications, thereby eliminating their future cancer risk. To date, most studies of these relationships have been retrospective, raising issues of recall bias (spurious reporting of endometriosis or leiomyomas among women affected with cancer) and preventing accurate estimates of risks over time.

Clinical investigations (3-12) and recent case-control (13, 14) and retrospective cohort (15-17) studies have found that women with endometriosis face an ~2-fold increased risk of developing ovarian cancers. However, it is uncertain how this risk varies with follow-up time; one study found elevated risks of ovarian cancer even ≥10 years following a diagnosis of endometriosis (16). It also remains unclear whether the predisposition toward ovarian cancer applies to all histologies or is limited to endometrioid and clear cell carcinoma as suggested in some small clinical series (5, 7, 10, 11). Similarly, limited data from clinical reports suggest that leiomyomas occur more frequently in women undergoing hysterectomy for endometrial carcinoma (18-22) and perhaps sarcomas (19). These concerns are supported by at least one case-control study showing that women with leiomyomas are at an ~3-fold increased risk of developing subsequent uterine malignancies (23).

We conducted an investigation in Denmark in which we linked hospital discharge and outpatient admission histories with cancer registry data to assess the relationship between benign gynecologic diseases and subsequent cancer risk. Our ability to evaluate diagnoses listed in medical records before the diagnosis of cancer, the large population size, and the lengthy period for which data were available enabled us to assess issues unresolved by previous investigations, including overall effects of gynecologic diseases on the risk of subsequent ovarian and uterine cancer risk and whether effects vary by follow-up time and histologic tumor type.

Materials and Methods

Ascertainment of Cases and Selection of Population Subsample. From the Danish Cancer Register, 2,491 incident invasive ovarian cancers [International Classification of Diseases for Oncology (ICD-O) 183.0, behavior code 3], 860 borderline ovarian tumors (ICD-O 183.0, behavior code 1), and 1,398 uterine cancers (ICD-O 182.0, behavior code 3) were diagnosed between January 1, 1978 and December 31, 1998 among female residents of Denmark who were born after 1936

Received 6/1/05; revised 9/30/05; accepted 10/10/05.
Grant support: Intramural Research Program of the NIH, National Cancer Institute.
The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked advertisement in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.
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doi:10.1158/1055-9965.EPI-05-0394

(case group). A subsample of the population, randomly chosen from the Central Population Register (CPR), allowed efficient computing and little loss of statistical precision over the entire population. This subsample, selected using a two-stage sample design, comprised 99,812 women also born after 1936 and living in Denmark at study entry (January 1, 1978). During the first stage, a simple random sample of women was selected from the CPR based on birth year and the ninth digit of the CPR number, with digit values of 1, 2, and 3 selected for birth years 1937 to 1951; 5 and 6 selected for birth years 1952 to 1977; and 7 and 8 selected for birth years 1978 to 1991. At the second stage, the selection of women into the subsample was further narrowed according to the birth years of all breast, ovarian, and endometrial cancers and borderline ovarian tumors diagnosed during the study period; this enabled a generalized sample to be used for a variety of analyses, with breast cancer cases considered elsewhere. Specifically, four women per case were selected for each birth year between 1937 and 1951 and six women per case were selected for each birth year between 1952 and 1991. More women were drawn per case for the latter years, given that fewer women born between 1952 and 1991 developed cancer during the study period (1978-1998). The population subsample and the case groups of invasive ovarian cancers, borderline ovarian tumors, and endometrial cancers combined constituted the study cohort.

Identification of Benign Diseases and Exposures within the Study Cohort. Data related to hospital admissions from 1978 to 1998 and to outpatient visits from 1995 to 1998 were obtained for each woman through record linkage with the Hospital Discharge Register. Each admission record includes the personal identification number, date of admission (or date of outpatient visit), date of discharge surgical procedures, and up to 20 discharge diagnoses (24). Using these data, the first diagnosis of various diseases, including endometriosis (ICD-8 625.30-625.39; ICD-10 DN80) and uterine leiomyoma (ICD-8 218.99; ICD-10 DD25), was identified. Only discharge diagnoses were considered. The diagnosis date for each medical condition was defined as the date of hospital admission or outpatient visit. Diagnoses of obesity (ICD-8 277.99; ICD-10 DE66) were also identified in order for their independent influence on cancer risk to be evaluated. Records of relevant surgical procedures, including hysterectomy, bilateral/unilateral oophorectomy, and tubal ligation, were also identified, with the date of surgery defined as the first of the month following the date of hospital admission. Finally, cohort members were relinked to the files of the CPR to determine the number of children borne by each woman. Although the CPR lists the birth dates of all children for a given woman, it does not specify if any of her children were adopted. Therefore, the time interval between consecutive birth dates of children belonging to each woman was calculated to distinguish biological from adopted children. For two birth dates occurring <10 months apart, the first (or older) child was defined as adopted in our study.

Analysis. Women within the population subsample who were no longer at risk for uterine cancers, invasive ovarian cancers, or borderline ovarian tumors at study entry, either because they have undergone hysterectomy (n = 385) or bilateral oophorectomy (n = 41) or because they have been diagnosed with uterine (n = 7) or ovarian (n = 31) cancer before January 1, 1978, were excluded as appropriate. Cohort members were considered as having a medical condition if the date of diagnosis occurred before the censoring date. Censoring was marked either by death, emigration from Denmark, or surgical removal of the uterus or both ovaries depending on the outcome of interest. Each medical condition of interest was evaluated dichotomously (yes, no) as a time-dependent exposure. Time since diagnosis, which is the interval (in years) from the date of diagnosis until the date of censoring, was also examined to assess potential differences in risk with varying length of follow-up (<1, 1-4, and ≥5 years). A variety of time-dependent variables were considered as potential confounders, including calendar time (per 5 years), parity (yes, no), number of births, and age at first birth (per 5 years), with the data restructured for analysis using a counting process style of input in which a woman's entire observation period was split into smaller time interval each time any time-dependent variable changed in value. All women were followed from entry (January 1, 1978) until cancer diagnosis, any censoring event, or the end of the study (December 31, 1998), whichever occurred first.

Using SUDAAN Release 8.0 (Research Triangle Institute, Research Triangle Park, NC), relative risks (RR) and 95% confidence intervals (95% CI) for ovarian, borderline ovarian, and uterine cancer associated with the diagnosis of either endometriosis or uterine leiomyomas were estimated by weighed Cox regression, with the hazard ratio modeled as a function of age. Following the stratified sampling design of this study, a weighting scheme was implemented to estimate risk based on the female population of Denmark of relevance for this investigation. Cases were assigned a weight of 1, given that all eligible cases were selected, and noncases were assigned weights according to their birth year. To account for the first stage of sampling, weights for each birth year were calculated by taking the inverse proportion of the number of values selected out of the total possible values of the ninth CPR digit. Therefore, birth years before 1952 and from 1952 onward were given sampling weights of 10/3 (3.33) and 10/2 (5.00), respectively. Sampling rates were then calculated by dividing the number of women selected into the subsample by the number of women in the CPR for each birth year as determined in the second stage of sampling. The applied weights were finally computed by multiplying the sampling weight by the inverse of the sampling rate for each birth year. Women in the subsample diagnosed with ovarian, borderline ovarian, or uterine tumors were defined as cases in analyses pertaining to their specific cancer(s) but as noncases in analyses pertaining to the other cancers studied.

Stratified analyses were also conducted to assess whether cancer risk associated with each medical condition differed by tumor histology as recorded via ICD-O tumor morphology codes within the Danish Cancer Registry. Ovarian carcinomas were grouped into six categories: (*a*) serous (codes 84413, 84603, and 84613; n = 932), (*b*) mucinous (codes 84703, 84713, 84803, and 84903; n = 344), (*c*) endometrioid (codes 83803 and 83813; n = 300), (*d*) germ cell (codes 90603, 90643, 90703, 90803, 90813, 91003, and 91013; n = 126), (*e*) clear cell (code 8313; n = 123), and (*f*) carcinosarcoma (codes 89503, 89513, and 89803; n = 19). Borderline ovarian tumors were categorized as serous (codes 84401, 84411, 84501, 84601, 84611, and 90141; n = 363) or mucinous (codes 84701, 84702, 84711, and 84801; n = 391). Uterine tumors were grouped into four categories: (*a*) common indolent types, including adenocarcinoma not otherwise specified, papillary adenocarcinoma, endometrioid carcinoma, mucinous adenocarcinoma, adenocarcinoma with squamous metaplasia (codes 81403, 81433, 82103, 82603, 83803, 84803, 85603, and 85703; n = 1,178); (*b*) sarcoma, including leiomyosarcoma, endometrial stromal sarcoma, sarcoma not otherwise specified, epithelioid leiomyosarcoma, adenosarcoma, rhabdomyosarcoma (codes 88003, 88903, 88913, 89003, 89303, and 89333; n = 137); (*c*) carcinosarcoma (codes 89503, 89513, and 89803; n = 19); and (*d*) aggressive types, including clear cell adenocarcinoma, serous cystadenocarcinoma, and papillary serous cystadenocarcinoma (codes 83103, 84413, and 84603; n = 18). Tumors that could not be classified into any of these histologic groups were omitted from these analyses. There were 647 ovarian cancers, 106 borderline ovarian tumors, and 46 uterine cancers that could not be classified into an analysis category.

Results

The characteristics of the cancer cases and the noncases are shown in Table 1. The average (SD) ages at diagnosis were 44.2 (9.8) years for the invasive ovarian cancer cases, 42.5 (10.1) years for the borderline ovarian cancer cases, and 49.7 (6.5) years for the uterine cancer cases (data not shown). All three groups of tumor patients were more often nulliparous than the noncases, and fewer were multiparous. There were less marked differences between the parous cancer cases and the comparison women according to ages at first birth, although patients with borderline ovarian tumors tended to be somewhat younger at their first births.

Diagnoses of endometriosis preceding the diagnosis of a neoplasm were found in the medical records of 2.0% (n = 50) of the patients with ovarian cancers, 1.4% (n = 12) of the patients with borderline ovarian tumors, and 0.6% (n = 9) of the patients with uterine cancers (Table 2). The frequencies in the latter two case groups were comparable with that of the subsample, but the frequency of endometriosis in the group of patients who developed ovarian carcinoma was significantly higher than among the noncases (RR, 1.69; 95% CI, 1.27-2.25). There was, however, no evidence that risks increased with follow-up time, with the respective RRs (95% CIs) being 3.01 (1.25-7.25) for <1 year, 1.95 (1.15-3.31) for 1 to 4 years, and 1.49 (1.04-2.14) for ≥5 years between the diagnosis of endometriosis and the development of ovarian cancer.

The frequency of a prior diagnosis of uterine leiomyomas was 6.9% (n = 172) among patients diagnosed with ovarian carcinomas, 7.3% (n = 63) among the women diagnosed with borderline ovarian tumors, and 7.2% (n = 101) among patients diagnosed with uterine cancers; all rates were significantly in excess of the frequency seen in the noncases. The largest RR (95% CI) was seen for uterine cancers [3.63 (2.94-4.47)], with lesser risks seen for invasive ovarian cancers [1.36 (1.16-1.60)] and borderline ovarian tumors [1.84 (1.41-2.40)]. For all three tumors, the risks were highest for women followed for <1 year. However, for uterine cancer, the risk was also significantly elevated for those with 1 to 4 years of follow-up (RR, 2.90; 95% CI, 1.93-4.36).

Additional analyses assessed relationships of endometriosis and leiomyomas to different subtypes of invasive ovarian cancers as defined by histology (Table 3). A diagnosis of endometriosis was associated with a statistically significant risk exceeding 3-fold for endometrioid and clear cell ovarian cancers [respective RRs (95% CI), 3.37 (1.92-5.91) and 3.03 (1.23-7.44)], whereas risks associated with the most common histologic types of ovarian carcinomas, serous and mucinous, were not increased. For clear cell tumors, risk was highest among those with ≥5 years of follow-up after the initial diagnosis of endometriosis (RR, 3.37; 95% CI, 1.24-9.14). In contrast to these findings, leiomyomas were unrelated to most subtypes of ovarian cancer. The one exception was endometrioid tumors, where there was a marginally significant risk (RR, 1.57; 95% CI, 1.05-2.34), primarily reflecting an excess risk among subjects with <1 year of follow-up. Of the 126 women with ovarian germ cell tumors, none had endometrioisis and only 1 woman had a history of uterine leiomyoma, thus precluding estimation of risk for this histologic subtype with either condition. Risk for ovarian carcinosarcoma also could not be estimated given the limited number of women with such tumors (n = 19).

There were no strong links of a history of endometriosis with either serous or mucinous borderline ovarian tumors (Table 4). Subjects with <1 year of follow-up were at elevated risk (with the RR for serous tumors being statistically significant), but these risks were both based on small numbers of exposed subjects. A history of leiomyoma was associated with a significantly increased risk of serous borderline tumors (RR, 2.59; 95% CI, 1.80-3.72), with the excess risk primarily reflecting risks among subjects with <1 year of follow-up. Mucinous borderline tumors showed a relationship to leiomyomas only among subjects with <1 year of follow-up.

Relationships according to different histologies were also examined for uterine cancers (Table 5). Only risk estimates for common indolent types of uterine cancer and uterine sarcoma have been presented due to the small number of cases with carcinosarcoma (n = 19) and aggressive types of uterine cancer (n = 18). Endometriosis was related to both types of tumors only when short follow-up periods (<1 year) were involved. In contrast, a history of a uterine leiomyoma was associated with significantly increased risks of both common indolent uterine cancers (RR, 2.42; 95% CI, 1.86-3.16) and sarcomas of the uterus (24.83, 16.65-37.02). Patients whose diagnoses of leiomyomas

Table 1. Distribution of demographic and reproductive characteristics of the patients included in analyses of ovarian, borderline ovarian, and uterine tumors, Medical Conditions Linked Registry Study, Denmark

	Ovarian cancer analysis		Borderline ovarian tumor analysis		Uterine cancer analysis	
	Cases (n = 2,491)	Noncases (n = 99,421)	Cases (n = 860)	Noncases (n = 99,638)	Cases (n = 1,398)	Noncases (n = 99,172)
Birth year (%)						
1937-1941	34.1	30.7	19.8	30.7	47.7	30.7
1942-1946	28.9	29.0	24.9	29.0	33.2	29.0
1947-1951	15.1	17.6	18.1	17.6	12.0	17.6
1952-1956	9.0	12.8	12.5	12.8	5.0	12.8
1957-1961	5.4	5.9	11.2	5.9	1.2	5.9
1962 or later	7.5	4.0	13.5	4.0	0.9	4.0
Parity* (%)						
0	22.2	10.8	27.2	10.8	18.4	10.8
1	18.2	16.0	19.1	16.0	17.7	16.0
2	38.3	45.5	33.1	45.5	41.7	45.5
3	16.0	20.8	15.7	20.8	16.1	20.8
≥4	5.3	6.8	4.9	6.8	6.1	6.8
Mean (SD)	1.7 (1.2)	2.0 (1.1)	1.5 (1.2)	2.0 (1.1)	1.8 (1.2)	2.0 (1.1)
Age at first birth (%)						
<20	14.9	15.7	17.4	15.7	14.1	15.6
20-24	36.5	42.7	34.8	42.7	41.7	42.7
25-29	19.9	22.8	15.4	22.8	19.9	22.8
≥30	6.6	8.0	5.2	8.0	5.9	8.0
Mean (SD)	23.3 (4.3)	23.4 (4.3)	22.8 (4.3)	23.4 (4.3)	23.2 (4.2)	23.4 (4.3)

*Determined at time of diagnosis for cases and time of censoring for controls.

Table 2. Relationship of endometriosis to risk of ovarian and uterine tumors, Medical Conditions Linked Registry Study, Denmark

	Ovarian cancers		Borderline ovarian tumors		Uterine cancers	
	n	RR* (95% CI)	*n*	RR (95% CI)	*n*	RR (95% CI)
Endometriosis						
No	2,441	1.00 (Reference)	848	1.00 (Reference)	1,389	1.00 (Reference)
Yes	50	1.69 (1.27-2.25)	12	1.22 (0.69-2.17)	9	1.23 (0.63-2.38)
<1 y	5	3.01 (1.25-7.25)	5	7.51 (3.10-18.18)	5	13.97 (5.76-33.93)
1-4 y	14	1.95 (1.15-3.31)	2	0.75 (0.19-3.01)	1	0.71 (0.10-5.07)
≥5 y	31	1.49 (1.04-2.14)	5	0.77 (0.32-1.86)	3	0.54 (0.17-1.68)
Uterine leiomyomas						
No	2,319	1.00 (Reference)	797	1.00 (Reference)	1,297	1.00 (Reference)
Yes	172	1.36 (1.16-1.60)	63	1.84 (1.41-2.40)	101	3.63 (2.94-4.47)
<1 y	50	5.31 (4.00-7.06)	32	11.17 (7.80-16.01)	53	18.48 (13.99-24.41)
1-4 y	34	0.91 (0.65-1.28)	13	1.21 (0.70-2.11)	24	2.90 (1.93-4.36)
≥5 y	88	1.10 (0.88-1.36)	18	0.85 (0.53-1.36)	24	1.43 (0.95-2.15)

*RRs adjusted for calendar time (per 5 years), parity (no, yes), number of births (continuous), and age at first birth (per 5 years) as time-dependent variables (with age used as a time metric in the regression models). Additional adjustment for obesity, tubal ligation, hysterectomy (for ovarian analysis), unilateral oophorectomy, and bilateral oophorectomy (for uterine analysis) did not result in substantial changes in the risk estimates.

preceded their diagnosis of cancer by <1 year were at highest risk for both carcinomas and sarcomas. However, for sarcomas, significant risks persisted among those with both 1 to 4 years (RR, 20.80; 95% CI, 11.32-38.22) and ≥5 years (RR, 5.70; 95% CI, 2.27-14.32) of follow-up. In contrast, the risk of carcinomas associated with long-term follow-up was not elevated (RR, 1.19; 95% CI, 0.74-1.90).

Discussion

Using record linkage and a cohort approach to analyze population-based data, we showed that women with endometriosis or leiomyomas are at significantly increased risk for the future diagnosis of carcinomas of the ovary and endometrium and uterine sarcomas. Risks were generally greater for women diagnosed with endometriosis or leiomyomas within the year preceding the diagnosis of cancer, suggesting that detection bias (i.e., increased gynecologic monitoring after the benign diagnosis) may explain several of the observed associations. However, persistent and specific associations of endometriosis with ovarian endometrioid and clear cell carcinomas, but not other histologic types of ovarian carcinomas, add to the evidence that endometriosis in some women may represent a precursor of ovarian carcinoma.

Early evidence reported in support of a causal connection between endometriosis and ovarian cancer included the clinical co-occurrence of cancer and endometriosis in the same ovary and recognition of apparent continuity of the lesions on pathologic examination (25). Recently, case-control (13, 14) and cohort (15-17) studies have found that women with endometriosis have RRs for ovarian cancer in the range of 1.7 to 1.9. Although common risk factors have been identified for endometriosis and ovarian cancer, most notably nulliparity (26), a biological relationship is suggested based on clinicopathologic studies that have linked endometriosis to ovarian clear cell and endometrioid carcinomas as opposed to other histologies. In a review of the available literature, the prevalence of concomitant endometriosis and epithelial ovarian cancer was calculated as being 4.5%, 1.4%, 35.9%, and 19.0% for serous, mucinous, clear cell, and endometrioid ovarian cancer, respectively (26). Importantly, these studies often found strong pathologic evidence for the direct development of clear cell and endometrioid carcinomas from endometriosis, whereas this was lacking for cases in which endometriosis and serous or mucinous cancer were found in the same patients, suggesting that the latter may have represented a chance association.

The specific etiologic association between endometrioid and clear cell carcinoma and endometriosis is supported indirectly by previous studies regarding the pathogenesis of endometriosis. Studies suggest that transtubal exfoliation of endometrial tissue with implantation in the ovary is a probable mechanism that explains the development of ovarian endometriosis (27).

Table 3. Relationship of endometriosis and leiomyomas to risk of invasive ovarian cancers by histology, Medical Conditions Linked Registry Study, Denmark

	Serous (*n* = 932)		Mucinous (*n* = 344)		Endometrioid (*n* = 300)		Clear cell (*n* = 123)	
	n	RR* (95% CI)	*n*	RR (95% CI)	*n*	RR (95% CI)	*n*	RR (95% CI)
Endometriosis								
No	918	1.00 (Reference)	340	1.00 (Reference)	287	1.00 (Reference)	118	1.00 (Reference)
Yes	14	1.20 (0.70-2.04)	4	1.01 (0.38-2.71)	13	3.37 (1.92-5.91)	5	3.03 (1.23-7.44)
<1 y	0		1	4.00 (0.56-28.66)	2	10.25 (2.56-41.06)	0	
1-4 y	4	1.47 (0.55-3.94)	2	1.94 (0.48-7.80)	4	0.43 (0.08-2.36)	1	2.64 (0.36-19.35)
≥5 y	10	1.20 (0.64-2.24)	1	0.37 (0.05-2.65)	7	2.53 (1.19-5.38)	4	3.37 (1.24-9.14)
Uterine leiomyomas								
No	870	1.00 (Reference)	327	1.00 (Reference)	273	1.00 (Reference)	114	1.00 (Reference)
Yes	62	1.22 (0.94-1.59)	17	1.08 (0.65-1.78)	27	1.57 (1.05-2.34)	9	1.20 (0.61-2.36)
<1 y	24	6.22 (4.38-10.00)	5	3.93 (1.61-9.59)	7	5.54 (2.60-11.82)	2	3.70 (0.91-15.06)
1-4 y	10	0.69 (0.37-1.28)	4	0.82 (0.31-2.22)	6	1.19 (0.53-2.67)	0	
≥5 y	28	0.85 (0.58-1.25)	8	0.82 (0.40-1.68)	14	1.28 (0.74-2.19)	7	1.47 (0.68-3.18)

*RRs adjusted for calendar time (per 5 years), parity (no, yes), number of births (continuous), and age at first birth (per 5 years) as time-dependent variables (with age used as a time metric in the regression models). Additional adjustment for obesity, tubal ligation, hysterectomy (for ovarian analysis), unilateral oophorectomy, and bilateral oophorectomy (for uterine analysis) did not result in substantial changes in the risk estimates.

Table 4. Relationship of endometriosis and leiomyomas to risk of borderline ovarian tumors by histology, Medical Conditions Linked Registry Study, Denmark

	Serous (n = 363)		Mucinous (n = 391)	
	n	RR* (95% CI)	n	RR (95% CI)
Endometriosis				
No	357	1.00 (Reference)	386	1.00 (Reference)
Yes	6	1.46 (0.65-3.29)	5	1.12 (0.46-2.71)
<1 y	3	10.19 (3.25-31.95)	1	3.33 (0.47-23.42)
1-4 y	0		2	1.65 (0.41-6.65)
≥5 y	3	1.12 (0.36-3.51)	2	0.67 (0.17-2.71)
Uterine leiomyomas				
No	328	1.00 (Reference)	374	1.00 (Reference)
Yes	35	2.59 (1.80-3.72)	17	1.05 (0.64-1.72)
<1 y	19	16.31 (10.14-26.26)	5	3.69 (1.53-8.93)
1-4 y	7	1.62 (0.76-3.46)	6	1.19 (0.53-2.68)
≥5 y	9	1.08 (0.55-2.10)	6	0.61 (0.27-1.36)

*RRs adjusted for calendar time (per 5 years), parity (no, yes), number of births (continuous), and age at first birth (per 5 years) as time-dependent variables (with age used as a time metric in the regression models). Additional adjustment for obesity, tubal ligation, hysterectomy (for ovarian analysis), unilateral oophorectomy, and bilateral oophorectomy (for uterine analysis) did not result in substantial changes in the risk estimates.

Data also suggest that tubal ligations are protective against ovarian endometrioid and clear cell carcinomas but do not alter risk for other histologic tumor types (28). Interestingly, all histologic types of ovarian carcinomas (including endometrioid and clear cell) have been similarly directly associated with nulliparity and high socioeconomic status and inversely associated with oral contraceptive use.

The preponderance of endometrioid and clear cell tumors may provide clues as to the process by which endometriosis progresses to malignancy. Several studies have shown atypical endometriosis to precede clear cell or endometrioid ovarian cancers (6, 8, 29-31), suggesting that these forms of endometriosis may act as precancerous lesions similar to the connection between atypical endometrial hyperplasias and endometrial cancers. Alterations in tumor suppressor (e.g., *PTEN* and *p53*; refs. 5, 32-35), DNA repair (e.g., *hMLH1*; ref. 36), and progesterone receptor promoter (37) genes have been suggested to be involved. Endometriotic cysts have been found to have loss of heterozygosity and partial deletions of chromosomes 9p, 11q, and 22q (32). Additional mechanisms may include clonality and high rates of aneuploidy (38) and K-*ras* mutations (39, 40).

Our study also attempted to evaluate relationships of endometriosis with borderline ovarian tumors, of interest given previous findings of concurrent endometriosis and borderline ovarian tumors (11, 41-44). We were limited in our ability to evaluate associations given small numbers of subjects. The only elevations that we observed were among women with endometriosis of short durations. This suggests an effect of detection bias, especially because borderline tumors are often diagnosed among symptomatic patients (45).

The study also provided an opportunity to evaluate the relationship of endometriosis to the risk of uterine tumors. The relationship with uterine sarcomas was of particular interest, given findings that tumors with a malignant stromal component, such as sarcomas, carcinosarcomas, and adenosarcomas, have been associated with extraovarian endometriosis (4, 46-48). Our results, however, showed that increases in risk were restricted to tumors (either carcinomas or sarcomas) diagnosed within the first year of follow-up, suggesting detection bias rather than a true etiologic relationship.

Although uterine leiomyomas are extremely common, there has been only limited investigation of their relationship to subsequent cancer risk. Several clinical studies have detected uterine malignancies among women undergoing hysterectomies for leiomyomas. The rate seems to be quite low, probably <1% (20, 22, 49), with the highest rates observed among older women (49). Few studies have attempted to assess relationships over time. The largest study, a case-control study of 399 patients with endometrial cancer diagnosed between ages 20 and 54 years, found a RR of 3 for a self-reported history of a myoma (23). Further circumstantial evidence for the link is found in the common risk factors for leiomyomas and uterine sarcomas, with both diseases showing increased risks associated with African American race (50, 51), obesity (50-53), nulliparity (50, 54), and estrogen use (50, 53). The majority of these findings support a hormonal etiology of both disorders.

In our study, we found that a history of leiomyomas seemed to predispose to both common indolent uterine cancers and sarcomas. The risk for sarcomas was substantially elevated, exceeding a 24-fold increased risk. Clinically, uterine leiomyomas have been linked with sarcomas, but they have been thought to be an extremely rare outcome even among patients with rapidly growing leiomyomas (19). Although we found that the risk was still significantly elevated even after 5 years of follow-up, the highest risk was observed for subjects with shorter follow-up periods. Given this, we are hesitant to evoke causality, especially given evidence that uterine sarcomas can be difficult to diagnose preoperatively (55). Importantly, it has been found that carcinosarcomas can be detected preoperatively but that leiomyosarcomas and endometrial stromal sarcomas are often diagnosed as benign. Without further information on the distinctive types of sarcomas in our study, it is difficult to exclude the possibility that some of the previous diagnoses of leiomyomas may have been undiagnosed sarcomas. Alternatively, because criteria for the diagnosis of cellular leiomyoma and mitotically active leiomyoma may not have been well recognized during early follow-up, some cases diagnosed previously as low-grade leiomyosarcomas might be reclassified as benign leiomyomas using more updated criteria. The very strong connection that we observed and the fact that risks persisted over extended follow-up time would tend to support some common origins, although it is not possible to decipher whether there is an etiologic relationship or whether leiomyomas merely represent one aspect of a multicentric disease with sarcomas.

Several previous investigations have focused on associations between benign gynecologic diseases and gynecologic cancers, but the majority of these have been clinically based and often

Table 5. Relationship of endometriosis and uterine leiomyomas to risk of uterine cancer by histology, Medical Conditions Linked Registry Study, Denmark

	Common indolent types (n = 1,178)		Sarcomas (n = 137)	
	n	RR* (95% CI)	n	RR (95% CI)
Endometriosis				
No	1171	1.00 (Reference)	135	1.00 (Reference)
Yes	7	1.14 (0.54-2.42)	2	2.72 (0.66-11.12)
<1 y	3	10.95 (3.51-34.20)	2	39.07 (9.43-161.80)
1-4 y	1	0.90 (0.13-6.43)	0	
≥5 y	3	0.63 (0.20-1.98)	0	
Uterine leiomyomas				
No	1118	1.00 (Reference)	97	1.00 (Reference)
Yes	60	2.42 (1.86-3.16)	40	24.83 (16.65-37.02)
<1 y	29	11.77 (8.12-17.06)	24	112.59 (70.23-179.24)
1-4 y	13	1.81 (1.04-3.13)	11	20.80 (11.32-38.22)
≥5 y	18	1.19 (0.74-1.90)	5	5.70 (2.27-14.32)

*RRs adjusted for calendar time (per 5 years), parity (no, yes), number of births (continuous), and age at first birth (per 5 years) as time-dependent variables (with age used as a time metric in the regression models). Additional adjustment for obesity, tubal ligation, hysterectomy (for ovarian analysis), unilateral oophorectomy, and bilateral oophorectomy (for uterine analysis) did not result in substantial changes in the risk estimates.

limited to the concurrent presence of endometriosis or leiomyomas and cancer among women undergoing hysterectomies. Our investigation had several strengths for evaluating the relationships of endometriosis and leiomyomas to subsequent cancer risk. This included the fact that diagnoses were not dependent on patient recall and that the relationships were evaluated over time, allowing assessment of latency effects. In addition, it was possible to link diagnoses against complete ascertainment of subsequent cancers and to assess effects of gynecologic diseases after consideration of effects of reproductive predictors of risk. Furthermore, given the large size of the patient population, it was possible to evaluate not only relationships with overall cancer risks but also according to histologies of the tumors that developed.

Although our study had several strengths, there were also some notable limitations. This included the underascertainment of endometriosis and uterine leiomyomas among the underlying population either because of missing information in the Hospital Discharge Register (56) or because of our dependence on using information related to inpatient evaluations. This could have resulted in a focus on women with the most severe disorders, which may have resulted in an overestimation of the extent of association between the benign conditions and subsequent cancer risk. The absence of information on how the conditions were diagnosed also hindered our ability to assess effects of detection bias. Furthermore, women undergoing hysterectomies or bilateral oophorectomies as treatment for their benign conditions would have been censored from selected analyses, limiting our ability to assess long-term effects. Patients whose conditions were first ascertained at the time of these operations would also not have been considered in our analyses for subsequent cancer risk. In addition, because we had to rely on cancer registry diagnoses of cancer rather than on more precise reviews, we may have had some misclassification. However, this should have been a generalized effect and not one that would have affected observed associations with prior medical histories. An additional limitation was that women were not followed past the age of 60 years, precluding the generalization of these associations to the development of cancers at older ages. Finally, many of the results were based on small numbers, necessitating cautious interpretations.

In summary, this study provided insights into the effects of benign gynecologic diseases on the risks of subsequent cancers. Supporting previous research, we found that endometriosis seemed to predispose to the subsequent development of ovarian cancers. This effect seemed restricted to endometrioid and clear cell tumors, with some evidence of increasing risks with follow-up time, with risks for clear cell tumors exceeding 3 for those with $\geq$5 years of follow-up. Although not well investigated in previous epidemiologic investigations, our data seemed to indicate that patients with uterine leiomyomas experience an increased risk of subsequent uterine malignancies. Particularly high risks were noted for uterine sarcomas, although our data did not allow us to determine whether the relationship is etiologic, a result of shared risk factors, or a reflection of imprecise diagnoses of the initial leiomyomas. Given growing interest in the nonsurgical management of leiomyomas (57, 58), further investigations are needed to assess whether these tumors predispose to sarcomas. Studies that directly address the effects of detection bias and misclassification of leiomyomas will be essential to advancing our understanding of the relationships. Investigations that focus on biomarkers in tissue samples may also provide insights regarding possible carcinogenic processes.

Acknowledgments

We thank Emily Steplowski (Information Management Services) and Gloria Gridley (National Cancer Institute) for their assistance with data management and technical support.

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