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Relationships of Uterine and Ovarian Tumors to Pre-Existing Chronic Conditions

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Abstract

Background—Several chronic diseases have been hypothesized to affect the risk of subsequent gynecologic malignancies, possibly through shared hormonal mechanisms.

Methods—Using record linkage techniques, we assessed the relationships between hospital and outpatient admissions for gallbladder disease, diabetes, hypertension, thyroid diseases, and obesity and the subsequent development of uterine and ovarian cancers in Denmark between 1978-1998. Based on a subsample of more than 99,000 women, including 1,398 uterine and 2,491 ovarian cancers, we derived relative risks (RRs) and 95% confidence intervals (CIs) associated with overall and histology-specific cancer risks after adjustment for age, calendar time and reproductive characteristics.

Results—Uterine cancers were related to previous diagnoses of thyroid diseases (RR=1.52, 95% CI 1.17-1.98) and obesity (2.05, 1.40-3.00). Associations with diabetes were confounded by obesity, but there were some elevations in risk for subjects diagnosed with obesity prior to age 45 (RRs 1.66-1.79). Although the “usual types” of endometrial cancer largely accounted for the observed associations, there was some evidence that uterine sarcomas (n=137) were related to prior diagnoses of thyroid diseases (2.78, 1.41-5.50). In contrast, ovarian cancers were not strongly related to most documented chronic diseases. Serous carcinomas were associated with gallbladder diseases of short durations, but detection bias or misdiagnosis probably accounts for this association. An association of obesity and endometrioid ovarian was not identified.

Conclusions—Uterine cancers, including sarcomas, appear to be influenced by selected chronic diseases. Further attention should focus on possible biologic mechanisms underlying observed associations with thyroid diseases and obesity.

Keywords

uterine cancer; ovarian cancer; chronic diseases; risk

Introduction

Epidemiologic studies have suggested that several common diseases and conditions that either produce or reflect hormonal disturbances are associated with the development of gynecologic

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malignancies. However, results between studies have not been entirely consistent. Given the alarming increases in obesity, diabetes, and other chronic disorders in developing nations, it is important to understand these associations.

Diabetes has been of particular interest with respect to the risk of endometrial cancer, given increased risks observed in cohort (1-4) as well as case-control (5-13) investigations. Although concern has been expressed that this association reflects confounding by obesity, an established risk factor for endometrial cancer (13), a number of investigations have shown that diabetes persists as an independent risk factor after adjustment for body size (1;5-7;10;11). However, the influence of age at onset, type of diabetes (i.e., insulin-dependent vs. non-insulin dependent) (2;4;10;13) and length of follow-up on this risk association is not understood.

Similarly, some (6;14-16) but not all (5;13;17) studies have suggested potential links between hypertension or gallbladder disease and endometrial cancer. A number of these investigations were unable to account for other established risk factors, including obesity. Further, most of these relied on patient reports of prior conditions rather than on medically validated diagnoses, which could have resulted in biased estimates of risk (18;19).

Relationships of prior medical conditions to the risk of ovarian cancer have received less attention. Although studies have suggested links with several gynecologic conditions, including endometriosis and pelvic inflammatory diseases (20), less is known about relationships with various chronic diseases. Hypertension has been suggested as a potential risk factor (11;21-23), with at least one investigation suggesting that the association may be specific for endometrioid ovarian cancers (23). A relationship with hyperthyroidism in a recent case-control investigation was interpreted as support for a role of inflammatory processes in ovarian carcinogenesis (24). Inflammation, along with hormonal alterations, has also prompted interest in the effects of obesity on ovarian cancer risk, with some (25-28) but not all (22) investigations providing support for an association.

In a record linkage study in Denmark, we had the opportunity to assess the risk associations between pre-existing common chronic diseases as documented in hospitalization records and subsequent diagnoses of uterine and ovarian cancers. A major strength of the study was its large size, which enabled an assessment of whether distinctive histologic subtypes might show different relationships with medical histories, as has been observed for several other risk factors for both uterine (29;30) and ovarian (31-37) cancers.

Materials and Methods

Ascertainment of cases and identification of calendar-period and age-matched cohort

As described in more detail elsewhere (38), we defined cases as female residents of Denmark born after 1936 who were identified through the Danish Cancer Registry as having been diagnosed between January 1, 1978 and December 31, 1998 with incident uterine cancer (ICD-O 182.0, behavior code /3) (n=1,398) or ovarian cancer (ICD-O 183.0, behavior code /3) (n=2,491). Using a two-stage sampling technique, we randomly selected from the Central Population Register (CPR) 99,812 women also born after 1936 who resided in Denmark at study entry (January 1, 1978). During the first stage, a simple random sample of women was selected from the CPR on the basis of birth year and the 9th digit of the CPR number. At the second stage, the selection of women into the subsample was further narrowed according to the birth years of all breast, ovarian and uterine 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 and borderline ovarian tumor cases considered elsewhere. Specifically, four women per case were selected for each birth year between 1937 and 1951, and six women per case 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 uterine and ovarian cancers constituted the study cohort.

Identification of benign diseases and exposures within entire 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 (39). Using these data, various diseases, including gallbladder disease (ICD-8 574; ICD-10 DK80), diabetes mellitus (ICD-8 249-250; ICD-10 DE10-DE14, DH36.0, DO24.0-DO24.3), hypertension (ICD-8 400-404; ICD-10 DI10-DI15), any thyroid disorder (ICD-8 240-246; ICD-10 DE00-DE07), and obesity (ICD-8 277.99; ICD-10 DE66), was identified. Thyroid disease was further subdivided into goiter (ICD-8 240-241; ICD-10 E04), hyperthyroidism (ICD-8 242; ICD-10 E05), hypothyroidism (ICD-8 243-244; ICD-10 E00-E03), thyroiditis (ICD-8 245; ICD-10 E06), and other thyroid diseases (ICD-8 246; ICD-10 E07). For women with more than one record of any of the selected diagnoses, the earliest date of hospital contact was chosen as the date of diagnosis. For a given hospital visit, both the primary and all secondary diagnoses were considered. 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 re-linked to the files of the CPR to determine the number of children borne by each woman.

Analysis

Women within the population subsample who were no longer at risk for ovarian or uterine cancers at study entry, either because they had undergone hysterectomy (n=385) or bilateral oophorectomy (n=41) or had been diagnosed with uterine (n=7) or ovarian (n=31) cancer prior to January 1, 1978 were excluded as appropriate. Cohort members were considered as having a medical condition if the date of diagnosis occurred prior to 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. Potential differences in risk were examined according to ages at diagnosis of each condition (<35, 35-44, ≥45 years) as well as the duration 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 intervals 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), which ever occurred first.

Using SUDAAN Release 8.0 (Research Triangle Institute, Research Triangle Park, NC), relative risks (RR) and 95% confidence intervals (CI) for uterine and ovarian cancers related to each medical condition of interest were estimated by weighted Cox regression, with the hazard rate modeled as a function of age to ensure that the estimation was based on comparisons of individuals of the same ages. Following the stratified sampling design of this study, a weighting scheme was implemented to estimate risk based on the entire female population of Denmark. Cases were assigned a weight of one, given that all eligible cases were selected, and non-cases 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 9th CPR digit. Therefore, birth

years prior to 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 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 uterine or ovarian cancers were defined as cases in analyses pertaining to their specific cancer(s), but as non-cases in analyses pertaining to the other cancer studied.

Stratified analyses were also conducted to assess whether cancer risk associated with each medical condition differed by tumor histology. Uterine cancers were grouped into four categories: 1) common indolent types, including adenocarcinoma NOS, papillary adenocarcinoma, endometrioid carcinoma, mucinous adenocarcinoma, adenocarcinoma with squamous metaplasia (n=1,178); 2) sarcoma, including leiomyosarcoma, endometrial stromal sarcoma, sarcoma NOS, epithelioid leiomyosarcoma, adenosarcoma, rhabdomyosarcoma (n=137); 3) carcinosarcoma (n=19); and 4) aggressive types, including clear cell adenocarcinoma and serous carcinoma (n=18). Ovarian carcinomas were grouped into six categories: 1) serous (n=932); 2) mucinous (n=344); 3) endometrioid (n=300); 4) germ cell (n=126); 5) clear cell (n=123); and 6) carcinosarcoma (n=19). Tumors that could not be classified into any of these histologic groups were omitted from these analyses. There were 46 uterine cancers and 647 ovarian cancers that could not be classified into an analysis category.

Results

The characteristics of the cancer cases and the comparison subjects to whom they were compared are shown in Table 1. Given the focus on women born in 1936 or later, the average ages at cancer diagnosis were relatively young, being 49.7 years (SD=6.5) for the uterine cancer cases and 44.2 years (9.8) for the ovarian cancer cases (data not shown). The cancer patients were generally older (i.e., born in earlier birth years) than the non-cases. Cases also tended more often to be nulliparous and fewer were multiparous. There were less marked differences between the parous cancer cases and the non-cancer cases according to ages at first birth.

Table 2 shows the relationship of various chronic diseases to the risk of developing uterine cancers. Although we had a sizeable number of patients with uterine cancer, the proportions with specific diseases recorded in their prior medical records were limited, ranging from a low of 1.6% for diabetes to a high of 4.2% for thyroid diseases. Diagnoses of gallbladder disease or hypertension were not associated with altered risks of uterine cancer. Although initially significant, the association with diabetes became non-significant after adjustment for obesity diagnoses (RR=1.39, 95% CI 0.89-2.16). Significant associations persisted for diagnoses of obesity (2.05, 1.40-3.00) and thyroid diseases (1.52, 1.17-1.98), with no specific type of thyroid disease being more strongly linked to risk than others (data not shown).

When more specific information was examined regarding time since and age at first diagnoses, higher risks were also observed for thyroid diseases that were longstanding diagnoses and obesity that was diagnosed at younger ages. This analysis also provided some evidence for a possible elevation in uterine cancer risk associated with diagnoses of diabetes that occurred prior to age 45, although neither the risks of 1.66 (0.61-4.55) for those diagnosed prior to 35 years or of 1.79 (0.98-3.29) for those diagnosed at 35-44 years were statistically significant.

Relationships were further examined according to the types of uterine cancers that patients developed (Table 3). The majority of the uterine tumors were common indolent types, which continued to show significantly elevated risks associated with thyroid diseases and obesity. A smaller proportion of subjects developed uterine sarcomas (n=137). Despite limited power for evaluating chronic disease associations, we observed a significantly elevated risk of sarcomas

related to a prior diagnosis of thyroid diseases (RR=2.78, 95% CI 1.41-5.50), based on 9 exposed cases. Four of these were noted as goiter (2.20, 0.86-5.64) and the remainder as hyperthyroidism (3.96, 1.39-11.33). Hypertension was related to a non-significant elevation in the risk of sarcomas (2.69, 0.98-7.41, although the increased risk was restricted to patients with short follow-up periods, possibly reflecting diagnostic biases. Relationships of sarcomas with other diseases were difficult to interpret given small numbers of affected women (3 or fewer).

We also examined diseases related to the development of ovarian cancers (Table 4). None of the chronic diseases examined was significantly related to risk, although gallbladder diseases and obesity were associated with very minimal and non-significant increases (respective RRs of 1.27 and 1.14). Specific types of thyroid diseases also were not important predictors of subsequent ovarian cancer risk. When we examined trends according to follow-up time and ages at first diagnosis, there was generally no indication that risks were strongly influenced by these factors. A notable exception was a significantly elevated ovarian cancer risk associated with gallbladder disease of short duration (<1 year) (RR=2.55, 95% CI 1.37-4.76).

When associations were further examined according to histology of the ovarian cancers (Table 5), a significantly increased risk of serous cancers was observed among patients with a history of gallbladder disease (RR=1.57, 95% CI 1.04-2.39). Patients with short follow-up times (<1 year) were at highest risk (3.91, 1.75-8.74). A diagnosis of obesity was somewhat more strongly related to endometrioid (1.37) and clear cell (1.71) cancer, although these risks were based on very few exposed cases (4 and 2, respectively).

Discussion

This investigation had several strengths, including a population-based sample of a large number of study subjects, which enabled examination of tumor-specific relationships with a variety of different chronic diseases. Furthermore, we utilized documented information on prior diagnoses of diseases, rather than self reports, which have been used in the majority of studies assessing chronic disease effects on gynecologic malignancies.

This study, however, highlighted the difficulties in assessing the extent to which chronic diseases might predispose to the development of gynecologic malignancies. Although we had information on nearly 1,400 uterine cancers and 2,500 ovarian cancers, the proportion of women with prior documented diagnoses of specific diseases (e.g., diabetes, hypertension) was quite small. This to some extent reflects that our population was truncated and focused on younger patients. We were thus limited in assessing relationships, particularly for rarer tumor subtypes. Nonetheless, some of the associations that we observed are of interest in possibly identifying women who should be more carefully monitored for development of gynecologic cancers.

Obesity is a well recognized risk factor for endometrial cancers (13;17;40-42), and it was thus of interest that we confirmed that women with a specific medical diagnosis of obesity also were at an increased risk. The order of magnitude that we observed—a 2-fold elevation in risk—was somewhat less than what has been observed in most other epidemiologic investigations that have probably relied on less severe definitions of obesity (our data concentrated on hospitalizations for obesity). However, in several epidemiologic studies, a linear relationship of risk has not been observed with various indices of body mass, with elevated risks primarily observed for morbidly obese women (5;13). One investigation, however, has provided evidence for more gradual increases in risk (17). These discrepancies may relate to either varying definitions in obesity or to when in life obesity is considered. In the current study, there was little evidence of any variation in risks by follow-up time, suggesting that persistent

obesity may be a more important predictor of risk than recent changes, in line with other observations (42-44). This notion was also supported by our finding of the highest uterine cancer risks being associated with younger ages of obesity diagnoses.

Although several previous investigations have found that diabetics are at an increased risk of developing uterine cancer, the relationship has not been consistently observed. Contradictory results may reflect that some studies were not able to fully account for confounding effects of obesity, an established risk factor for both diabetes and uterine cancer. Although we initially observed a significant link between diabetes and uterine cancer risk, the relationship became non-significant after we adjusted for obesity diagnoses. Thus, our results emphasize the importance of fully accounting for obesity in assessing the independent effects of diabetes. It may also be important to assess the interactive effects of both diagnoses, given that several studies have noted particular elevations in risk for heavy, diabetic women (11;12).

Given that the two subtypes of diabetes (type 1 and type 2) have very different metabolic and hormonal characteristics, clues as to the mechanisms involved in the association between diabetes and endometrial cancer might be gleaned from assessing differences in risks. Although we could not distinguish between different types of diabetes, two previous studies have suggested higher risks among women with type 1 diabetes (2;13), while other investigations have suggested the opposite (7;10). Another study, which focused only on patients diagnosed under the age of 30 years (as a proxy for type 1 diabetes), noted a significant association with endometrial cancer risk (4), somewhat in line with our finding of the highest risks of uterine cancer among patients whose diabetes was diagnosed prior to 45 years of age.

While type 1 diabetes is characterized by the cessation of insulin biosynthesis due to the autoimmune destruction of insulin-producing pancreatic beta cells, type 2 relates more to impaired insulin release and/or decreased hepatic and extrahepatic insulin sensitivities. Thus, it has been proposed that if hyperinsulinemia is the critical link between diabetes and endometrial cancer that type 2 forms should be more strongly related to risk. Our results would not seem to support such a notion, suggesting that attention focus on other possible mechanisms. Insulin can stimulate androgen synthesis in the ovarian stroma, decrease levels of serum hormone binding globulin and increase levels of free estradiol premenopausally and estrone postmenopausally (45). Insulin-like growth factors (IGF) could also be involved, although studies which have measured IGF and their associated binding proteins have provided inconsistent relationships (46-52). Given the current contradictions regarding effects of different types of diabetes on endometrial cancer risk, additional studies which can distinguish between the subtypes and explore underlying mechanisms are needed.

Effects of hypertension have also been of interest with respect to uterine malignancies, with a number of studies reporting positive associations (6;15;16;44;53-61). Our results, however, did not in general support a link between the two diseases. Deciphering the relationship is complex, given that it has usually been difficult to distinguish effects of the underlying condition from associated therapies. Our study faced similar difficulties, and we could not determine how the severity affected subsequent cancer risks. A further complication was the need to consider confounding effects of obesity. Although in several studies, hypertension persisted as an independent risk factor after adjustment for obesity and other risk factors (6; 11;16;56), in other studies the relationship disappeared (5;13;17) or the association with hypertension was strongest in obese women (12;13;15). This led one investigator (12) to hypothesize that a metabolic syndrome involving obesity, hypertension and insulin resistance may contribute to endometrial carcinogenesis.

Thyroid diseases, one of the more commonly diagnosed conditions among our study subjects, appeared related to a slight increase in uterine cancer risk. Although some findings related to

this disease were based on small numbers, it was noteworthy that patients with long-standing diagnoses were at a significantly elevated risk and that the association was strongest for uterine sarcomas, particularly when diagnoses of goiter or hyperthyroidism were considered. Our findings require confirmation but are of interest given that thyroid diseases are associated with a variety of alterations in steroid hormones (62). Specific attention may be warranted with respect to sarcomas, given that their etiology remains poorly understood (63;64).

Ovarian cancer has been less well investigated with respect to histories of select medical conditions (22;65). Although a recent study suggested a relationship with hyperthyroidism (24), we failed to observe any relationship with this or any other type of thyroid disease. Although several studies have suggested modestly elevated risks of ovarian cancer related to obesity (25-28), we failed to confirm this association. This may have reflected our dependence on hospital or recent diagnoses. Thus, we were unable to assess observations of others that obesity during adolescence may be the strongest predictor of ovarian cancer risk (25-27), particularly for premenopausal onset diseases (27).

Obesity was of particular interest with respect to histologic subtypes of ovarian cancer, given suggestions from other studies of a more pronounced effect for endometrioid ovarian tumors (26;31). Although stronger effects might be anticipated given that these tumors resemble endometrial cancers, which have been extensively related to obesity (13), we failed to confirm this. Although there may have been some misclassification of histologies, it was of interest that in separate analyses we observed distinctive relationships of endometriosis with clear cell and endometrioid tumors using data from this same linked registry study (38). Thus, our failure to observe a specific association of obesity with endometrioid tumors may reflect our dependence on hospital diagnoses of obesity or low power for detecting an association.

The only other chronic disease that appeared to show any relationship with ovarian cancer was gallbladder disease, with the association strongest for serous ovarian cancers. However, the fact that the highest risks were restricted to patients with very short intervals of follow-up suggests either effects of detection bias or misdiagnosis given that ovarian cancer patients often demonstrate non-specific abdominal symptoms prior to disease detection (66).

Although our investigation had a number of strengths, there were some notable limitations. This included the absence of a standardized histopathologic review of all cases. Further, information on prior diseases primarily derived from inpatient records, since outpatient diagnoses were available only for the latter years of the study and some diseases may have been misclassified. If non-differential (affecting both cases and controls), any misclassification would have tended to underestimate the effects of the chronic diseases on the risk of uterine and ovarian cancer. Furthermore, although we had information on time intervals since an initial diagnosis of one of the chronic diseases of interest, the follow-up in most cases was relatively short (6-9 years, depending on the analyses pursued). Finally, we had only limited information on important risk factors for gynecologic cancers, possibly preventing us from accounting for important confounding effects.

The study, however, provides unique data regarding the effects of a variety of chronic diseases on the subsequent development of gynecologic malignancies. Using record linkage approaches and information derived from medical records, we confirmed previous findings from studies based on patient recall of a general absence of association of most chronic diseases with the risk of ovarian cancer. In contrast, uterine cancers did show some distinctive relationships, particularly in relation to thyroid disorders and obesity, and possibly diabetes diagnosed at younger ages. Additional studies are needed to address which parameters of these diseases predispose to subsequent cancer risk, including whether specific shared hormonal alterations are involved.

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Table 1

Distribution of Demographic and Reproductive Characteristics of Uterine and Ovarian Cancer Cases and Non-Cases, Linked Medical Conditions Study, Denmark

	Uterine Cancer Analysis		Ovarian Cancer Analysis	
	Cases (n=1,398)	Non-Cases (n=99,172)	Cases (n=2,491)	Non-Cases (n=99,421)
Birth year				
1937-41	47.4%	30.7%	34.1%	30.7%
1942-46	33.2%	29.0%	28.9%	29.0%
1947-51	12.0%	17.6%	15.1%	17.6%
1952-56	5.0%	12.8%	9.0%	12.8%
1957-61	1.2%	5.9%	5.4%	5.9%
1962 or later	0.9%	4.0%	7.5%	4.0%
Parity				
0	18.4%	10.9%	22.2%	10.8%
1	17.7%	16.0%	18.2%	16.0%
2	41.7%	45.5%	38.3%	45.5%
3	16.1%	20.8%	16.0%	20.8%
≥4	6.1%	6.9%	5.3%	6.8%
Mean (SD)	1.8(1.2)	2.0(1.1)	1.7(1.2)	2.0(1.1)
Age at first birth				
<20	14.1%	15.6%	14.9%	15.7%
20-24	41.7%	42.7%	36.5%	42.7%
25-29	19.9%	22.8%	19.9%	22.8%
≥30	5.9%	8.0%	6.6%	8.0%
Mean(SD)	23.2(4.2)	23.4(4.3)	23.3(4.3)	23.4(4.3)

Table 2
Risk of Uterine Cancer by Various Chronic Diseases, Medical Conditions Linked Registry Study

	Gallbladder Disease		Diabetes		Hypertension		Thyroid Disease		Obesity	
	No. of cases	RR (95% CI) ¹	No. of cases	RR (95% CI) ²	No. of cases	RR (95% CI) ¹	No. of cases	RR (95% CI) ¹	No. of cases	RR (95% CI) ¹
Ever diagnosed	1371	1.00	1376	1.00	1375	1.00	1339	1.00	1370	1.00
No	27	1.11 (0.76-1.64)	22	1.39 (0.89-2.16)	23	1.13 (0.75-1.72)	59	1.52 (1.17-1.98)	28	2.05 (1.40-3.00)
Yes										
Time since first diagnosis										
<1 year	1	0.40 (0.06-2.88)	4	2.57 (0.96-6.85)	5	1.89 (0.78-4.55)	4	1.35 (0.51-3.61)	2	2.16 (0.54-8.66)
1-4 years	6	0.79 (0.35-1.76)	8	1.69 (0.82-3.48)	6	0.81 (0.36-1.82)	15	1.51 (0.90-2.51)	8	2.48 (1.23-5.00)
≥5 years	20	1.42 (0.91-2.22)	10	1.05 (0.55-1.98)	12	1.17 (0.66-2.08)	40	1.55 (1.13-2.13)	18	1.89 (1.18-3.03)
Age at first diagnosis										
<35	2	0.72 (0.18-2.90)	4	1.66 (0.61-4.55)	2	1.64 (0.40-6.70)	8	1.60 (0.79-3.24)	8	3.14 (1.55-6.37)
35-44	8	0.81 (0.40-1.62)	11	1.79 (0.98-3.29)	10	1.37 (0.73-2.57)	27	1.40 (0.95-2.06)	13	1.99 (1.14-3.47)
≥45	17	1.48 (0.91-2.40)	7	0.95 (0.44-2.06)	11	0.93 (0.51-1.70)	24	1.66 (1.10-2.50)	7	1.53 (0.72-3.25)

¹ Adjusted for age, calendar time (per 5 years), parity (no, yes), number of births, age at first birth (per 5 year) as time-dependent variables.

² Adjusted for above variables, as well as hospitalizations for obesity.

Risk of Different Subtypes of Uterine Cancer by Various Chronic Diseases, Medical Conditions Linked Registry Study

Table 3

	Gallbladder Disease		Diabetes		Hypertension		Thyroid Disease		Obesity	
	No. of cases	RR (95% CI) ^I	No. of cases	RR (95% CI) ²	No. of cases	RR (95% CI) ^I	No. of Cases	RR (95% CI) ^I	No. of Cases	RR (95% CI) ^I
Common Indolent Types (n=1,178)	23	1.11 (0.73-1.68)	19	1.36 (0.85-2.19)	19	1.07 (0.68-1.69)	48	1.44 (1.07-1.92)	25	2.16 (1.44-3.23)
Sarcomas (n=137)	2	0.94 (0.24-3.78)	2	1.50 (0.32-7.10)	4	2.69 (0.98-7.41)	9	2.78 (1.41-5.50)	3	2.30 (0.74-7.17)

^I Adjusted for age, calendar time (per 5 years), parity (no, yes), number of births, age at first birth (per 5 years) as time-dependent variables.

² Adjusted for above variables, as well as hospitalizations for obesity.

Table 4
Risk of Ovarian Cancer by Various Chronic Diseases, Medical Conditions Linked Registry Study

	Gallbladder Disease		Diabetes		Hypertension		Thyroid Disease		Obesity	
	No. of cases	RR (95% CI) ^I	No. of cases	RR (95% CI) ^I	No. of cases	RR (95% CI) ^I	No. of Cases	RR (95% CI) ^I	No. of Cases	RR (95% CI) ^I
Ever diagnosed	2444	1.00	2477	1.00	2464	1.00	2435	1.00	2465	1.00
No	47	1.27 (0.95-1.71)	14	0.69 (0.40-1.17)	27	0.93 (0.64-1.37)	56	0.94 (0.72-1.23)	26	1.14 (0.77-1.69)
Yes										
Time since first diagnosis										
<1 year	10	2.55 (1.37-4.76)	3	1.56 (0.50-4.81)	2	0.52 (0.13-2.10)	3	0.62 (0.20-1.92)	1	0.62 (0.09-4.41)
1-4 years	16	1.32 (0.81-2.17)	2	0.34 (0.08-1.35)	7	0.66 (0.31-1.39)	15	0.91 (0.55-1.52)	5	0.87 (0.36-2.00)
≥5 years	21	1.00 (0.65-1.55)	9	0.72 (0.37-1.39)	18	1.24 (0.78-1.99)	38	0.99 (0.71-1.36)	20	1.30 (0.83-2.03)
Age at first diagnosis										
<35	7	0.90 (0.42-1.90)	4	0.67 (0.25-1.80)	1	0.30 (0.04-2.13)	15	1.16 (0.69-1.94)	9	1.29 (0.66-2.51)
35-44	22	1.43 (0.93-2.19)	8	1.06 (0.53-2.14)	16	1.37 (0.83-2.26)	33	1.12 (0.79-1.58)	13	1.28 (0.73-2.22)
≥45	18	1.32 (0.82-2.10)	2	0.29 (0.07-1.17)	10	0.72 (0.38-1.34)	8	0.46 (0.23-0.92)	4	0.71 (0.26-1.90)

^I Adjusted for age, calendar time (per 5 years), maternal status, parity, number of births, age at first birth (per 5 years) as time-dependent variables.

Risk of Different Subtypes of Ovarian Cancer by Various Chronic Diseases, Medical Conditions Linked Registry Study

Table 5

	Gallbladder Disease		Diabetes		Hypertension		Thyroid Disease		Obesity	
	No. of cases	RR (95% CI) [/]	No. of cases	RR (95% CI) [/]	No. of cases	RR [/] (95 % CI)	No. of Cases	RR (95% CI) [/]	No. of Cases	RR (95% CI) [/]
Serous (n=932)	23	1.57 (1.04-2.39)	5	0.62 (0.26-1.51)	8	0.69 (0.34-1.39)	20	0.84 (0.54-1.32)	11	1.23 (0.68-2.24)
Mucinous (n=344)	5	0.98 (0.40-2.41)	1	0.37 (0.05-2.67)	0	---	8	1.02 (0.50-2.07)	4	1.26 (0.47-3.37)
Endometrioid (n=300)	6	1.28 (0.57-2.87)	2	0.74 (0.18-2.99)	5	1.31 (0.54-3.18)	7	0.90 (0.42-1.90)	4	1.37 (0.51-3.66)
Clear Cell (n=123)	1	0.51 (0.07-3.68)	3	1.69 (0.85-8.58)	3	1.90 (0.59-6.08)	3	0.93 (0.30-2.92)	2	1.71 (0.42-6.97)

[/] Adjusted for age, calendar time (per 5 years), parity (no, yes), number of births, age at first birth (per 5 years) as time-dependent variables.