A NATIONWIDE COHORT STUDY ON THE RISK OF NON-GYNAECOLOGICAL CANCERS IN WOMEN WITH SURGICALLY VERIFIED ENDOMETRIOSIS

Short title: Endometriosis & Cancer

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Abbreviations:

SIR – standardized incidence ratio

95%CI – 95% confidence interval

FHDR – Finnish Hospital Discharge Register

Category: Cancer epidemiology

Novelty and Impact – "What's New"

The incidence of thyroid cancer was 40% and of basal cell carcinoma 20% increased in women with surgically verified endometriosis. Conversely, the incidence of oropharyngeal cancer was 40%, and of pancreatic cancers 20% decreased. In women with ovarian endometriosis, risk of rectal cancer was also increased.

ABSTRACT

We assessed the association of surgically verified endometriosis and risk of non-gynaecological cancers according to the type of endometriosis (i.e. ovarian, peritoneal, and deep infiltrating endometriosis). All diagnoses of endometriosis combined with relevant procedural codes were identified from the Finnish Hospital Discharge Register 1987-2012. Non-gynaecological cancers diagnosed after the endometriosis diagnosis were obtained from the Finnish Cancer Registry. The cohort of 49,933 women with surgically verified endometriosis and the sub-cohorts of ovarian (n=23,210), peritoneal (n=20,187), and deep infiltrating (n=2,372) endometriosis were analysed separately. The endometriosis cohort contributed 838,685 person-years of follow-up and the Finnish female population served as the reference cohort. The standardized incidence ratio (SIR) and 95% confidence interval (95%CI) was calculated for each cancer separately. The follow-up ended at emigration, death or on the 31st of December 2014. The non-gynaecological cancer risk was not increased among women with endometriosis (SIR 1.03, 95%CI 0.98-1.08). Endometriosis was associated with an increased risk of thyroid cancer in the entire cohort (SIR 1.43, 95%CI 1.23-1.64) and in the sub-cohorts of ovarian and peritoneal endometriosis. We found a decreased risk of mouth and pharynx cancer (SIR 0.60, 95%CI 0.41-0.80), and of pancreatic cancer (SIR 0.76, 95%CI 0.58-0.96). The incidence of basal cell carcinoma was elevated in the entire cohort (SIR 1.18, 95%CI 1.10-1.25) and in the sub-cohorts of ovarian and peritoneal endometriosis. In conclusion, women with surgically verified endometriosis have an altered risk of only few non-gynaecological cancers.

INTRODUCTION

Endometriosis is a common chronic inflammatory disease of the female pelvis affecting about 10% of reproductive age women. [1] Typical symptoms include dysmenorrhea, chronic pelvic pain, and subfertility. Long-term medical treatment and surgical procedures are often needed for the treatment of pain and/or infertility. [2] The aethio-pathogenesis is complex and the three different subtypes of endometriosis, i.e. ovarian, peritoneal, and deep infiltrating endometriosis, might evolve through somewhat different pathogenetic mechanisms. [3]

Cancer and endometriosis share many similar features, thus their associations have been studied intensively during recent years. [4-6] Ovarian cancer, especially clear cell and endometrioid histology, has been associated with endometriosis. [7-12] The risk of cancer of the uterine cervix has shown to be decreased and the results on the risk of the cancers of uterine corpus or breast vary. [7, 9] Of the non-gynaecological cancers, melanoma of the skin, non-Hodgkin-lymphoma, brain, endocrine, thyroid, and kidney cancers have been associated with endometriosis in previous studies. [9]

The aim of this study was to assess the risk of non-gynaecological cancers in women with surgically verified endometriosis and especially in the sub-cohorts of ovarian, peritoneal, and deep infiltrating endometriosis.

MATERIALS AND METHODS

We obtained approval from the ethics committee of the Hospital District of Helsinki and Uusimaa (238/13/03/03/2013) before the initiation of this study. Permission was also obtained from the National Institute for Health and Welfare (THL/546/5.05.00/2014), the Population Register Center (D1794/410/14), and Statistics Finland (Dnro TK53-547-14) for the data and the linkages.

The cohort of surgically verified endometriosis was identified from the Finnish Hospital Discharge Register (FHDR) from 1987 to 2012. All endometriosis-associated diagnoses with relevant concomitant surgical codes were used. Index day was the day of discharge from the hospital following the first endometriosis related surgery. FHDR includes both main and subsidiary diagnoses, records from the public and private sectors, and also a record of day-surgeries from 1994 forward. The formation of the cohort as well as the quality assessment of the endometriosis diagnosis of the FHDR records has been described previously. [13]

The endometriosis cohort was divided into sub-cohorts according to the site of endometriosis using the diagnostic codes assigned at the index surgery. During 1987-1995, the 9th version of International Classification of Diseases and related Health Conditions (ICD) and in 1996-2012 the 10th version was used. The main sub-cohorts were determined as ovarian endometriosis (ovary ICD-9/ICD-10: 6171A/N80.1), peritoneal endometriosis (tubes 6172A/N80.2, peritoneum 6173A/N80.3, retrouterine 6173B), and deep infiltrating endometriosis (rectovaginal 6174A/N80.4, intestine 6175A/N80.5, bladder N80.80, sacrouterine ligament N80.81). The diagnoses not included in the abovementioned sub-

cohorts were mixed endometriosis (concomitant ovarian and deep infiltrating endometriosis) and other endometriosis (cicatrix cutis 6176A/N80.6, other specified 6178X/N80.8, N80.89, other unspecified 6179X/N80.9). The categories of ovarian, deep infiltrating, and mixed endometriosis were also permitted to include secondary diagnoses of peritoneal endometriosis and/or other endometriosis. The sub-cohort of peritoneal endometriosis could also include secondary diagnoses of other endometriosis but not ovarian, deep infiltrating, nor mixed endometriosis. The FHDR records, with adenomyosis as a single diagnosis, were excluded due to absence of histological verification.

The Finnish Cancer Registry maintains a register of all diagnosed cancers in Finland from 1953 forward and includes additional information on personal identity code, the dates of cancer diagnoses, and topography and morphology codes of the malignancies. [14] The personal identity code has been available for every citizen from the late 1960s onwards enabling reliable registry linkages. The endometriosis cohort was linked to the Cancer Registry to assess information on all incident cancers. The follow-up started on the index day and ended either on the day of emigration, death, or December 31st, 2014. The data on emigrations and deaths were retrieved from the Finnish Population Register Centre.

STATISTICAL ANALYSES

Person-years of follow-up were calculated by five-year age categories and calendar periods, and by time since the index day (<0.5, 0.5-4.9, 5-9.9, ≥10 years). The standardized incidence ratio (SIR) was calculated as the ratio between the observed and the expected number of

cancers in each stratum. The expected number was defined by multiplying the accumulated person-years of follow-up in each stratum by cancer incidence rate in the corresponding Finnish female population. The 95% confidence intervals (95%CI) for the SIR were based on the assumption that the number of observed cases followed a Poisson distribution.

RESULTS

Table 1 describes the endometriosis cohort by age groups at index day, and by person-years at the follow-up. The median age of the women in the endometriosis cohort was 36.4 years at baseline. There were altogether 838,685 person-years of follow-up and the median follow-up time was 16.8 years.

The SIRs of all site and non-gynaecological cancers with their 95%CI and numbers of observed and expected specific cancer cases are shown in Table 2. Altogether 3,619 cancers of were observed in the entire endometriosis cohort. Of these, 1,716 non-gynaecological cancers were observed and 1,672 expected. Table 3 shows the cancer risks according to the sub-cohorts of endometriosis.

The incidence of the cancers of mouth and pharynx was significantly lower in the entire endometriosis cohort (SIR 0.60, 95%CI 0.41-0.85) and in the sub-cohort of ovarian endometriosis, than in the general female population. The incidence of pancreatic cancer was also decreased in the entire endometriosis cohort (SIR 0.76, 95%CI 0.58-0.96) (Tables 2 and 3).

An increased incidence of thyroid cancer was seen in the entire cohort (SIR 1.43, 95%CI 1.23-1.64). This excess was highest in the peritoneal sub-cohort and was especially seen for thyroid cancer with papillary histology (Tables 2 and 3).

Endometriosis in general, and specifically ovarian and peritoneal endometriosis, was also associated with an increased incidence of basal cell carcinoma of the skin (Tables 2 and 3).

DISCUSSION

Women with surgically verified endometriosis did not differ from the general female population in the overall cancer risk, or in the overall risk of non-gynaecological cancers. The risk of cancers of the mouth and pharynx, and pancreas was decreased, while the risk of thyroid cancer was increased. This increased risk was seen in the sub-cohort of ovarian and peritoneal endometriosis and concerned thyroid cancer with papillary histology. We also found an increased incidence of basal cell carcinoma in the entire cohort, and in the sub-cohorts of ovarian and peritoneal endometriosis.

A strength of our study is the large, population-based cohort, which comprises almost 840,000 person-years of follow-up. The Finnish cancer and hospitalization registers are known for their completeness and high quality. [14-16] Many of the previous studies assessing the cancer risk in women with endometriosis included self-reported endometriosis or inpatients with and without surgical verification. [17-20] The present cohort consists of only

women with surgically verified endometriosis, most of whom had been significantly symptomatic. In addition, the surgical treatments provided to our cohort might have modified in part the endometriosis associated cancer risk. This must be kept in mind when comparing the different studies. Moreover, our results should be generalized only for women with surgically verified endometriosis.

To our knowledge only one previous study has assessed the risks of non-gynaecological cancers according to the location of endometriosis. [17] A weakness of our study is that the sub-cohort of deep infiltrating endometriosis remains small (n=2,372), and the follow-up times of this sub-cohort are shorter than the others as the diagnostic criteria for this type of endometriosis were first established in the mid-1990s. [3]

We could not account for potential cancer-related risk factors, such as body mass index, tobacco smoking, and alcohol consumption, which may have confounded our results. Of the various life-style factors associated with cancer risks, body mass index has been reported to be lower in endometriosis patients than in the general population. [21-23] Due to this, the SIR estimates of cancers that are associated with obesity may be slightly too low. The results are inconsistent of whether women suffering from endometriosis use alcohol or smoke more than general population. [24, 25] However, the incidence of lung cancer was not decreased in the present endometriosis cohort, which may suggest similar smoking habits as those of the general population.

As a novel finding, we found a 40% decreased risk of mouth and pharynx carcinomas. This was seen in the entire cohort and in the sub-cohort of ovarian endometriosis. The risk factors

for these cancers include tobacco smoking, heavy alcohol consumption, and human papilloma virus (HPV) infections. [26] HPV infections have been connected especially to cancers of tonsils, hypo-pharynx, and the base of tongue in men. [27-30] In a previous study based on the same Finnish endometriosis cohort, a decreased risk of squamous cell carcinoma and precancerous lesions of the uterine cervix were found. [31] As both of these conditions are strongly related to HPV infections, we speculate that women with endometriosis might be less exposed to HPV infections than other Finnish women. Alternatively, there might be more complex alterations in the immune response associated with both endometriosis and HPV-related diseases.

The incidence of pancreatic cancer was about one-fifth lower in the entire endometriosis cohort than in the general population. The known risk factors for pancreatic cancer are tobacco smoking, heavy alcohol consumption, previous pancreatitis, diabetes, high body mass index, and pancreatic cancer with relatives. [32,33] Experimental studies have shown that estrogen inhibits growth in the pancreatic cancer cells. [34] Moreover, the use of estrogen -only and any hormone replacement therapy has been associated with a decreased risk of pancreatic cancer. [35, 36] Thus the reason for this lowered risk of pancreatic cancer in women with surgically verified endometriosis might be related both to the life-style factors and hormonal treatments used to control the endometriosis symptoms.

Thyroid cancer has been linked to female sex hormones as it occurs predominantly in women. Moreover, unbalanced estrogen metabolism and alterations in potentially carcinogenic estrogen-DNA adducts have been shown in women with thyroid cancer. [37] Thus estrogen may be a risk factor for both thyroid cancer and endometriosis. Yet an association of thyroid cancer with exogenous hormonal treatments has not been shown. [38] Thyroid cancer

has been associated with endometriosis in two earlier Swedish register-based studies (SIRs 1.3-4.7). [17, 19] The third, latest Swedish register-based study and a large cohort study from the United States showed no association. [39,40] We found an 40-50% excess risk in the sub-groups of ovarian, and peritoneal endometriosis. A Swedish study also assessed the risks according to the location of endometriosis (ovary, pelvis, and uterus) and found no association with thyroid cancer in the entire cohort but increased association with uterine endometriosis, i.e., adenomyosis. [17] We excluded the diagnosis of uterine endometriosis as unreliable in the absence of histological data. Additional risk factors for thyroid cancer include ionizing radiation, especially in childhood, and inherited factors. [41,42] Our endometriosis cohort represents equally all of Finland and therefore factors related to place of residence, such as fallouts from the nuclear testing in the 1960s or the smaller fallout after the Chernobyl accident, should not bias our results. [43]

Unlike the previous studies, [9, 43] we found a slightly increased incidence of basal cell carcinoma in the entire cohort and in the sub-cohorts of ovarian and peritoneal endometriosis. [9,44] We speculate that this increase might in part be due to increased surveillance as endometriosis patients are likely to attend health care more often in comparison to the general public.

There are case reports describing cancers located in the abdominal cavity near the endometriotic foci. [45,46] We found 61 cases of rectum and recto-sigmoid cancer in women with ovarian endometriosis, versus 46 cases expected. Moreover, among women with deep infiltrating endometriosis there were four cases of ill-defined cancer versus one case expected. Both of these associations might be incidental, but they may also result from malignant transformation of ovarian or deep infiltrating endometriosis.

In conclusion, the risk of oral, pharyngeal, and pancreatic cancer was decreased, but in contrast, increased incidence of thyroid cancer and basal cell carcinoma was seen. The independent effects of altered life-style factors and possible surveillance bias related to frequent contacts with health care could not be quantified but might be significant. The overall risk of non-gynaecological cancer in women with surgically verified endometriosis was similar to that in the Finnish female population.

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Table 1. Number of women (n) with surgically verified endometriosis, by age at the procedure and type of endometriosis. Numbers of person-years given by age at follow-up.

Age (years)	Type of endometriosis							
	All		Ovarian		Peritoneal		Deep infiltrating	
	n	Person years	n	Person years	n	Person years	n	Person years
10-19	525	676	121	154	343	446	24	34
20-29	12,685	51,212	4,888	18,268	5,835	25,326	839	3,286
30-39	18,027	186,115	7,896	74,168	7,673	86,189	865	10,111
40-49	15,286	263,145	8,249	117,459	5,374	117,878	514	8,362
50-59	2,985	220,562	1,800	109,863	850	91,023	109	4,993
≥60	425	116,975	256	62,810	112	44,574	21	2,150
Total	49,933	838,685	23,210	382,721	20,187	365,436	2,372	28,936

Table 2. Observed (Obs) and expected (Exp) numbers of cancer cases, standardized incidence ratios (SIR) and 95% confidence intervals (95%CI) of cancers among women with endometriosis, by site.

Cancer site	ICD-10	Obs	Exp	SIR	95%CI
All sites	C00-96, D32-33, D41-43, D45-47, D76	3619	3695	0.98	0.95-1.01
Breast	C50	1555	1575	0.99	0.94-1.03
Gynaecological cancers	C51-C58	348	447.5	0.78	0.70-0.86
All sites, excluding breast cancer and gynaecological cancers	C00-C49, C59-96, D32-33, D41-43, D45-47, D76	1716	1672	1.03	0.98-1.08
Mouth and pharynx	C00-14	31	51.2	0.60	0.41-0.85
Lip	C00	0	3.0	0.00	0.00-1.21
Tongue	C02	7	12.5	0.56	0.23-1.15
Mouth, other	C03-06	7	14.3	0.49	0.20-1.00
Salivary glands	C07-08	8	8.2	0.97	0.42-1.91
Pharynx	C01, C09-14	9	13.2	0.68	0.31-1.29
Digestive organs	C15-26	447	469.9	0.95	0.87-1.04
Oesophagus	C15	7	12.9	0.54	0.22-1.12
Stomach	C16	62	59.9	1.03	0.79-1.32
Small intestine	C17	16	12.1	1.32	0.76-2.14
Colon	C18	148	156.2	0.95	0.80-1.10
Rectum, rectosigmoid	C19-20	103	90.2	1.14	0.93-1.37
Liver	C22	20	22.4	0.89	0.54-1.37
Gallbladder, bile ducts	C23-24	18	22.3	0.81	0.48-1.27
Pancreas	C25	62	82.1	0.76	0.58-0.96
Other digestive organs	C26	4	4.6	0.88	0.24-2.24
Respiratory organs	C30-39	155	169.2	0.92	0.78-1.06
Nose, sinuses	C30-31	4	3.9	1.04	0.28-2.65
Larynx, epiglottis	C32	2	4.0	0.51	0.06-1.82
Lung, trachea	C33-34	145	158.8	0.91	0.77-1.06
Mediastinum, pleura	C38	0	1.1	0.00	0.00-3.40

Bone	C40-41	6	4.7	1.29	0.47-2.80
Melanoma of skin	C43	156	151.5	1.03	0.87-1.19
Skin, non-melanoma	C44	62	57.4	1.08	0.83-1.38
Mesothelioma	C45	6	3.8	1.57	0.58-3.41
Kaposi sarcoma	C46	0	0.3	0.00	0.00-14.2
Autonomic nervous system	C47	0	0.9	0.00	0.00-4.34
Soft tissues	C48-49	27	26.0	1.04	0.69-1.51
Urinary organs	C64-68	116	116.3	1.00	0.82-1.18
Kidney	C64	80	76.5	1.05	0.83-1.30
Bladder and urinary tract	C65-68	36	39.7	0.91	0.63-1.25
Eye	C69	8	6.4	1.25	0.54-2.46
Brain, central nervous system	C70-72, D32-33, D42-43	207	188.6	1.10	0.95-1.25
Thyroid gland	C73	179	125.4	1.43	1.23-1.64
Papillary histology		152	105.7	1.44	1.22-1.67
Other histology		27	19.7	1.37	0.90-1.99
Other endocrine glands	C74-75	2	4.04	0.49	0.06-1.78
Ill-defined, unknown	C76, C80	45	46.1	0.98	0.71-1.30
Lymphoid and hematopoietic tissue	C81-96, D45-47, D76	269	250.7	1.07	0.95-1.20
Hodgkin lymphoma	C81	10	15.1	0.66	0.32-1.21
Non-Hodgkin lymphoma	C82-86, C96, D76	135	127.0	1.06	0.89-1.25
Myeloma and other plasma cell tumors	C90	35	31.0	1.13	0.79-1.56
Leukaemia	C91-95	62	52.5	1.18	0.91-1.51
Not included above					
Basal cell carcinoma of the skin	C44	904	767.7	1.18	1.10-1.25

Table 3. Observed (Obs) numbers of cancer cases, standardized incidence ratios (SIR) and 95% confidence intervals (95%CI) of cancers among women with endometriosis, by type of endometriosis and cancer site.

Cancer site	Type of endometriosis								
	Ovarian (n=23,210)			Peritoneal (n=20,187)			Deep infiltrating (n=2,372)		
	Obs	SIR	95%CI	Obs	SIR	95%CI	Obs	SIR	95%CI
All sites	1812	0.99	0.95-1.03	1479	0.97	0.92-1.02	86	0.92	0.74-1.14
Breast	754	0.97	0.91-1.04	661	1.01	0.93-1.08	38	0.96	0.68-1.32
Gynaecological cancers	193	0.87	0.75-0.99	129	0.70	0.59-0.83	9	0.81	0.37-1.53
All sites, excluding breast cancer and gynaecological cancers	865	0.99	0.93-1.06	689	1.01	0.93-1.09	39	0.92	0.65-1.26
Mouth and pharynx	14	0.55	0.30-0.92	14	0.67	0.36-1.11	2	1.52	0.18-5.48
Digestive organs	244	1.02	0.90-1.15	168	0.89	0.76-1.02	10	0.93	0.45-1.71
Stomach	32	1.06	0.73-1.49	25	1.02	0.66-1.50	3	2.22	0.46-6.47
Small intestine	10	1.66	0.80-3.05	3	0.61	0.12-1.76	1	3.33	0.08-18.57
Colon	80	1.01	0.80-1.26	59	0.94	0.71-1.20	2	0.54	0.07-1.94
Rectum, rectosigmoid	61	1.34	1.02-1.71	34	0.93	0.65-1.30	2	0.95	0.11-3.41
Liver	11	0.95	0.48-1.70	6	0.67	0.25-1.46	2	4.10	0.50-14.80
Gallbladder, bile ducts	7	0.60	0.24-1.24	10	1.14	0.55-2.09	0	0.00	0.00-8.14
Pancreas	35	0.82	0.57-1.14	23	0.71	0.45-1.06	0	0.00	0.00-2.10
Respiratory organs	89	1.03	0.82-1.26	57	0.84	0.64-1.09	1	0.27	0.01-1.52
Lung, trachea	81	0.99	0.79-1.23	55	0.87	0.65-1.12	1	0.29	0.01-1.64
Melanoma of skin	68	0.94	0.73-1.19	64	1.01	0.78-1.28	5	1.04	0.34-2.42
Skin, non-melanoma	41	1.38	0.99-1.87	17	0.75	0.44-1.20	1	0.78	0.02-4.33
Soft tissues	13	1.02	0.54-1.74	13	1.21	0.64-2.07	0	0.00	0.00-5.47
Urinary organs	55	0.93	0.70-1.20	49	1.05	0.78-1.38	2	0.77	0.09-2.78
Kidney	36	0.93	0.65-1.28	35	1.14	0.79-1.57	2	1.15	0.14-4.13

Bladder and urinary tract	19	0.93	0.56-1.44	14	0.89	0.49-1.48	0	0.00	0.00-4.34
Eye	6	1.89	0.69-4.10	2	0.75	0.09-2.72	0	0.00	0.00-26.29
Brain, central nervous system	86	0.95	0.76-1.17	93	1.17	0.95-1.43	7	1.31	0.53-2.70
Thyroid gland	80	1.37	1.09-1.70	81	1.50	1.19-1.86	4	0.97	0.26-2.48
Papillary histology	67	1.37	1.06-1.74	70	1.53	1.19-1.93	4	1.15	0.31-2.94
Other histology	13	1.38	0.73-2.36	11	1.34	0.67-2.40	0	0.00	0.00-5.59
Lymphoid and hematopoietic tissue	140	1.12	0.94-1.31	113	1.10	0.91-1.31	3	0.47	0.10-1.37
Hodgkin lymphoma	4	0.60	0.16-1.54	5	0.76	0.25-1.76	0	0.00	0.00-5.61
Non-Hodgkin lymphoma	75	1.18	0.93-1.48	56	1.08	0.82-1.40	1	0.32	0.01-1.80
Myeloma and other plasma cell tumors	23	1.44	0.91-2.16	11	0.89	0.44-1.59	1	1.52	0.04-8.46
Leukaemia	29	1.12	0.75-1.60	26	1.21	0.79-1.76	1	0.74	0.02-4.13
Ill-defined, unknown	23	0.97	0.62-1.45	11	0.60	0.30-1.07	4	3.91	1.06-10.00
Not included above									
Basal cell carcinoma of the skin	445	1.15	1.05-1.26	369	1.19	1.07-1.31	25	1.33	0.86-1.96