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ORIGINAL ARTICLE

Cancer risk after hospital discharge diagnosis of benign ovarian cysts and endometriosis

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Background. The aim was to evaluate whether patients with benign ovarian cysts, functional ovarian cysts, or endometriosis have an increased risk of developing gynecologic cancer.
Methods. The Swedish Hospital Discharge Register was used to identify a cohort of women discharged from hospital with the diagnoses of ovarian cyst ($n = 42\,217$), functional ovarian cyst ($n = 17\,998$), or endometriosis ($n = 28\,163$). To each case, three controls were matched. The National Swedish Cancer Register matched all incident cancers diagnosed among cases and controls. From the Fertility Register, the date of birth of children born to the cases and controls were obtained.
Results. Women with endometriosis had an increased risk for ovarian cancer (OR 1.34; 95% CI 1.03–1.75), but no association was found between ovarian cysts or functional cysts and ovarian malignancy, including all ages. Young women (15–29 years old) discharged from hospital for ovarian cysts and functional cysts showed an increased risk of developing ovarian cancer later in life (OR 2.2; 95% CI 1.3–3.9 and OR 1.8; 95% CI 1.5–2.0), as well as women with ovarian cysts who had undergone ovarian cyst resection or unilateral oophorectomy (OR 8.8; 95% CI 5.2–15). The risk of developing ovarian cancer was inversely related to parity. Mean age at diagnosis was significantly lower in all three study groups.
Conclusion. In this study women with endometriosis and young women who had undergone surgery with removal of an ovarian cyst had an increased risk of developing ovarian cancer.

Key words: epidemiology; ovarian cancer; ovarian neoplasm

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Ovarian cancer is the sixth most frequent cancer among Swedish women and the fourth leading cause of death in cancer among women aged 45–64 years (1). As a result of unspecific and mostly mild symptoms, two-thirds of the patients are already in an advanced stage of the disease (FigO stages III and IV) at the time of diagnosis, facing a poor prognosis (2). The life-time risk for ovarian cancer in Swedish women is 1.5%, which is comparable to that of the rest of the Western industrial world. Thus, one woman out of 70 will develop the disease (3). The life-time risk ranges from 0.6% in women without a family history of ovarian cancer, at least three term pregnancies, and a minimum of 4 years of oral contraceptive use, to 3.4% in nulliparous women not having used oral contraceptives. Even though the majority of ovarian cancers are sporadic, the greatest risk factor is a family history of the disease (4).

The significance of benign ovarian cysts and their relation to ovarian cancer is unclear. Primary ovarian cancer is supposed to arise from the

mesothelial surface cells of the ovary or its inclusion cysts. It has been shown that a higher rate of surgery for ovarian cysts is not associated with an earlier diagnosis of ovarian cancer (5,6). Furthermore, abnormal morphological changes have been found in macroscopically normal ovaries in asymptomatic women undergoing surgery for hereditary reasons (7). On the other hand, weak epidemiological data suggest a malignant potential in certain benign ovarian tumors (8). Endometriosis and endometriomas have been found to be associated with an increased risk of developing ovarian cancer (9). Also, dysplasia and transition from benign to malignant epithelium have been found in ovarian cystadenocarcinomas (10–12), indicating that ovarian cysts may be precursors of ovarian cancer.

Another question is whether women having had a benign or functional cyst have an altered risk of developing ovarian cancer. The aim of this case–control study was to evaluate whether patients with benign ovarian cysts, functional ovarian cysts, or endometriosis have an increased risk of developing gynecologic cancer, especially ovarian cancer.

Materials and methods

Data from The Swedish Hospital Discharge Registry (The National Board of Health and Welfare) were used to identify a cohort of women born in Sweden before 1970. All were discharged from hospital during the period 1969–96 with the diagnoses of ovarian cyst, functional ovarian cyst, or endometriosis. The unique personal identification number, assigned to each resident in Sweden, was used. The Swedish Hospital Discharge Registry started in 1969. At that time it covered 60% of the Swedish population, in 1978 75%, and in 1983 85%. Since 1987, all patients discharged from hospitals in Sweden are included. The register contains information about surgical procedures and up to eight discharge diagnoses, coded according to the International Classification of Diseases (ICD-8 1969–86 and ICD-9 1987–96). The diagnostic codes used in the present study were ovarian cyst, including benign or unknown ovarian tumor (220.0–9 benign tumor in ovary; 620.2 unspecified cyst in ovary; 235.99, 236.2 unknown ovarian tumor), functional ovarian cyst/Corpus luteum (615.2 and 620.0–1), and endometriosis (625.3 and 617.0–9). To each case three controls, with the same date of birth, were matched using the Swedish Population Register, Statistics Sweden, which includes all persons living in Sweden. Codes from The Swedish Hospital Discharge Registry for surgical procedures and dates of operations were linked to the cases and controls. Data from the National Swedish Cancer Register, founded in 1958, matched all incident cancers diagnosed among cases and controls up to December 31, 1997. The Cancer Registry has coded malignant neoplasms according to the ICD-7 classification during the entire period of the study. The Fertility Register, also kept by Statistics Sweden, contains information on all children born to Swedish women. From the Fertility Registry, the dates of birth of children born to the cases and controls were obtained. Women having changed their personal identification number were excluded ($n = 122$). The cases were then given a file number and the controls a corresponding control number in order to unidentify the database. This database was used in the statistical analyses. In order to avoid misclassification of benign cysts or undiagnosed malignancy at the time of hospital discharge, 1 year was allowed to elapse before any diagnosis of malignancy was accepted in the studied population.

For statistical analysis the Mantel-Haenszel procedure was applied for the determination of odds ratio (OR) and the 95% confidence intervals (CI) after stratifications as specified (13).

Results

Risk of developing gynecologic cancer

There was no change in the risk of developing ovarian cancer having had an ovarian cyst or functional ovarian cyst, while women with endometriosis had an increased risk for ovarian malignancy (Table I). It was not possible to determine precisely the ovarian status on the basis of the operation code for hysterectomy. Therefore, women who had undergone hysterectomy with or without oophorectomy were excluded, but there were only minor changes in the results after the exclusion of these women. No change in breast cancer risk was found. A decreased risk of developing endometrial cancer was found in women with ovarian cysts and endometriosis. Women with endometriosis also had a decreased risk for cervical cancer. Women with endometriosis showed an even more pronounced risk of developing ovarian cancer more than 10 years after diagnosis (OR 1.46, 95% CI 1.01–2.11).

There was no change in total cancer risk (all types of invasive malignancies) after having had an ovarian cyst, OR 0.99 (95% CI 0.85–1.14) or a functional ovarian cyst, OR 0.90 (95% CI 0.69–1.19), whereas women with endometriosis had an increased overall risk for malignancy, OR 1.15 (95% CI 1.00–1.32).

Risk of developing ovarian cancer related to previous ovarian surgery

When analyzing women having undergone ovarian cyst resection and/or unilateral oophorectomy separately, the risk for subsequent ovarian cancer was almost nine-fold higher, OR 8.8 (95% CI 5.2–14.8), as opposed to those who were not treated surgically, OR 0.48 (95% CI 0.35–0.66). Among women who later developed ovarian cancer ($n = 367$), nine women had been registered with the surgical code for bilateral oophorectomy at least 1 year before the cancer diagnosis (cases $n = 2$ and controls $n = 7$). This may be because of misclassification (using code for bilateral instead of the code for unilateral oophorectomy) or the

Table I. Odds ratio for gynecologic cancers in women with hospital discharge diagnoses, ovarian cyst, functional cyst or endometriosis

	Ovarian cyst				Functional cyst				Endometriosis			
Cancer type	OR	95% CI	Case *n*	Control *n*	OR	95% CI	Case *n*	Control *n*	OR	95% CI	Case *n*	Control *n*
Ovary	0.86	0.67–1.10	78	280	1.24	0.81–1.89	31	72	1.34	1.03–1.75*	81	181
Breast	1.07	0.98–1.18	586	1680	1.00	0.85–1.18	189	569	1.10	0.98–1.23	427	71165
Endometrium	0.66	0.51–0.86*	66	308	0.66	0.39–1.12	17	77	0.58	0.42–0.81*	39	211
Cervix	0.78	0.58–1.04	55	217	1.30	0.90–1.90	39	90	0.57	0.37–0.90*	23	120
No cancer			40406	124542			17461	52539			26969	81073

*95% confidence intervals excluded 1.0
Only cancer diagnoses more than 1 year since the primary hospital discharge diagnoses are included.
Women with surgery as bilateral oophorectomy and hysterectomy with or without bilateral oophorectomy are excluded.
Stratification is performed for women's age and the number of children born by the women before and after the primary hospital discharge diagnosis.

fact that the ovarian cancer had started as a peritoneal cancer.

Risk of developing ovarian cancer in relation to age of previous ovarian cyst

The youngest age group (10–29 years old) with an ovarian cyst or a functional cyst, treated or not treated, showed an increased risk of developing ovarian cancer (Table II). A decreased risk for ovarian cancer was observed in women aged older than 50 years discharged from hospitals with the diagnosis of ovarian cyst. Young women with endometriosis showed an even higher increased risk of developing ovarian cancer compared with the total age group.

Risk of developing ovarian cancer in relation to number of children

There was almost no difference in risk figures according to the number of children born after the diagnosis, whereas the number of children before diagnosis of ovarian cyst, functional cyst or endometriosis was of importance (Table III). The ovarian cancer risk was significantly increased in nulliparous with functional cysts or endometriosis. In women with an ovarian cyst diagnosis, the cancer risk also decreased with parity. The overall tendency was decreasing ovarian cancer risk with increasing number of children born in all three studied groups.

Mean age at ovarian cancer diagnosis

The mean age for ovarian cancer was significantly lower in the women discharged from hospital for ovarian cyst (47.6 years, SEM 1.27; $n = 80$) vs. the control group (54.1 years, SEM 0.56; $n = 287$) ($p < 0.001$); for the women discharged from hospital for functional cyst (40.7 years, SEM 1.70; $n = 31$) vs. the control group (49.1 years, SEM 1.12; $n = 72$) ($p < 0.02$); and also for the women discharged from hospital with endometriosis (49.0 years, SEM 0.91; $n = 90$) vs. the control group (51.6 years, SEM 0.60; $n = 183$) ($p < 0.001$). Even when the youngest women below 30, respectively, 35 years of age with ovarian cancer were excluded in the calculations, the mean age for ovarian cancer was significantly lower in the women treated for ovarian cysts, functional cysts or endometriosis as compared with their respective control group ($p < 0.05$ for all six comparisons).

Table II. Odds ratio for ovarian cancer diagnosis related to woman's age more than 1 year since the woman's first hospital discharge with diagnoses of ovarian cyst, functional cyst, and endometriosis

	Ovarian cyst		Functional cyst		Endometriosis	
Age (years)	OR	CI 95%	OR	CI 95%	OR	CI 95%
10–29	2.23	1.29–3.86*	1.76	1.50–2.00*	3.52	1.56–7.95*
30–49	0.83	0.60–1.16	0.86	0.46–1.52	1.26	0.50–3.16
50+	0.44	0.25–0.77*	–	–	0.98	0.42–2.31

*95% confidence intervals excluded 1.0
–: strata missing cases or controls.
Women with surgery as bilateral oophorectomy and hysterectomy with or without bilateral oophorectomy are excluded.
Stratification is performed for the number of children born by the women before and after the primary hospital discharge diagnosis.

Table III. Odds ratio for ovarian cancer diagnosis from the first hospital discharge diagnoses of ovarian cyst, functional cyst, or endometriosis related to the number of children given birth to before and after diagnosis

Number of children		Ovarian cyst		Functional ovarian cyst		Endometriosis	
before diagnosis	after diagnosis	OR	CI 95%	OR	CI 95%	OR	CI 95%
0	0–16	1.50	0.97–2.31	2.28	1.18–4.37*	1.89	1.19–3.01*
1–3	0–16	0.70	0.51–0.95*	1.21	0.88–1.66	1.21	0.88–1.66
4–5	0–16	0.21	0.03–1.35	1.01	0.19–5.29	1.27	0.24–6.63
0	0	1.43	0.87–2.32	2.47	1.15–5.30*	1.87	1.15–3.06*
1–3	0	0.68	0.49–0.95*	1.04	0.55–1.94	1.16	0.84–1.61
4–5	0	0.21	0.03–1.05	1.01	0.19–5.29	1.27	0.24–6.63

*95% confidence intervals excluded 1.0.
Only cancer diagnoses more than 1 year since the primary hospital discharge diagnoses are included.
Gynecologic surgical procedures are not considered.

Discussion

In this case–control study we found no association in the total material between the hospital discharge diagnosis of an ovarian or functional cyst and later development of ovarian cancer. However, there was a significantly increased risk for ovarian cancer in young women discharged from hospital for an ovarian or functional ovarian cyst, especially if they were childless. Endometriosis was associated with an overall increased risk of developing cancer (all types of invasive malignancies included). Young age and nulliparity increased the risk. Women with unilateral oophorectomy or ovarian cyst resection showed an increased ovarian cancer risk later as compared with those with ovarian cysts in whom no surgery was performed. In addition, the mean ages at diagnosis of ovarian cancer were significantly lower in the cases as compared with the control groups.

There are several limitations to these data. Primarily, one may speculate over the generalization of results on patients hospitalized for ovarian cysts/benign tumors, functional cysts, or endometriosis. Women hospitalized for an adnexal lesion probably had persisting and/or symptomatic adnexal lesions. Also, there may by an increased risk for dysplasia in a long-standing cystic lesion especially if epithelial cells increase in number by mitosis as the cyst grows. Further, in women without histopathological verification, functional cysts might have been misclassified as ovarian cysts and vice versa. When the reliability of the registers was tested, the Swedish Hospital Discharge Registry was found to have a misclassification rate of 7% (14). The reliability of the surgical codes was found to be good (15). One percent of the codes are missing and 5% are erroneous. As for the National Swedish Cancer Registry, approximately 98% of the diagnoses are being morphologically verified (3). The missing cancer diagnoses are very few when compared with the National Death Certificate Register in Sweden (3). A quality study of the Fertility Register has also been performed lately showing good accuracy (personal communication, Statistics Sweden). The discrepancy between the Fertility Register and the Swedish Population Register was 5–8% in the 1930s and 1940s, 2–4% in the 1950s and 1960s, and less than 1% since 1967. Nevertheless, the missing codes and the errors in the registers should be proportional in the case and control groups, minimizing the importance of the errors.

The observation that nulliparity increases the risk of ovarian cancer is in accordance with earlier reports, where multiparas have a 40–60% risk reduction (16–19). Infertile women, unsuccessfully treated with hormones have a higher risk of developing ovarian cancer, especially after long-term use (20,21). However, women successfully treated did not have an increased risk (20). The possible reason for this increased risk was ovarian dysfunction and not the hormonal treatment. In addition, another interesting hypothesis has been proposed to explain the reduced risk of ovarian cancer in parous women: namely that pregnancy hormones or other immunological changes during pregnancy may clear the ovaries from cells that have undergone malignant transformation (18).

As for endometriosis, our results are in accordance with an earlier report based on discharge diagnoses where cases were compared with the standardized incidence ratio of ovarian cancer but parity was not considered (9). Other reports have also suggested a histological transformation of benign endometriosis to early epithelial ovarian cancer (22,23). There are several theories concerning the development of endometriosis. One theory is that endometriosis arises from metaplasia of the coelomic epithelium, another that endometrial cells regurgitate through the fallopian tubes at menstruation and implant on pelvic structures. Deficiency in the

immunological system has also been considered to contribute to the development of endometriosis. Local inflammatory response at the endometriotic implantations initiates proteolytic systems which are involved in carcinogenesis (24). Chronic inflammation and/or a deficient immunological response to endometriosis may contribute to the increased risk of developing ovarian cancer in patients suffering from endometriosis (25).

In the present study, women with ovarian cyst resection or unilateral oophorectomy for benign causes had a highly increased risk of later developing ovarian cancer. This may be because of premalignant dysplasia in the contra-lateral ovary or misclassified borderline tumors which may have had unrecognized peritoneal implants. Histo-pathological changes have been found in macroscopically normal ovaries in women operated on because of a strong family history (7,26). In ovarian cancer stage Ia, microscopic changes are found in up to 7% of the contra-lateral ovary (27), which may indicate that ovarian cancer is a multifocal disease. This emphasizes the importance of a thorough examination of the whole abdominal cavity, both at laparoscopic and open surgery, for ovarian cysts and also peritoneal washing and biopsies of the peritoneum. Whether benign macroscopic changes, except endometriosis, precede ovarian cancer is unclear. Our finding may indicate that this is the case. Several studies have been performed to verify whether an inclusion cyst in the other ovary is more common in ovarian cancer patients, but studies are inconclusive (5,7,26,28,29). Another explanation may be that the surgical trauma itself starts the process toward dysplasia and malignancy, as the removal of a cyst traumatizes the ovarian-surface epithelium. The healing process entails increased cell division activity and inflammation with activation of proteolytic enzymes similar to those in cancer invasion and metastases (24,25). In addition, inflammatory cytokines activating nitric oxide have shown to cause DNA damage and inhibit DNA repair proteins (30). Thus after ovarian surgery, as well as in endometriosis, an inflammatory response may be the key to carcinogenesis.

Cases were significantly younger when receiving the diagnosis of ovarian cancer as compared with women in the control groups. In families with a hereditary risk for ovarian cancer, the median age at diagnosis is significantly lower than the median age of women without a history of familiar ovarian cancer (31). However, only approximately 5–10% of all ovarian cancer is considered to be caused by inherited mutations, which is why the differences in mean age at ovarian cancer diagnosis can not be fully explained by hereditary factors.

In the present study women with endometriosis had a decreased risk of developing endometrial and cervical cancer. Treatment of endometriosis often includes synthetic progestin, gonadotropin-releasing hormone analogs, or combined oral contraceptives known to reduce the risk of endometrial hyperplasia and cancer (32,33). The reduced risk of cervical cancer may be the result of intensified screening and treatment of premalignant lesions of the cervix in the group of women with endometriosis, as they may have contacted their gynecologist more frequently.

In conclusion, this hospital registry study indicates an increased risk for ovarian cancer in women suffering from endometriosis and young women treated for ovarian cysts, especially if the cyst is removed. This latter association encourages expectant monitoring in young women with asymptomatic cysts if malignancy is not suspected. The tentative biological explanations such as the inflammatory response after surgery or endometriosis-mediating carcinogenesis needs to be proven.

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