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# **Further evidence that endometriosis is related to tubal and ovarian cancers: a study of 271,444 inpatient women**

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## **Highlights**

- The rate of tubal cancer is higher in women with pelvic endometriosis [adjusted odds ratio (OR) 2.80, 95% confidence interval (CI) 1.84–4.27] and women with adenomyosis (adjusted OR 4.88, 95% CI 3.66–6.50) compared with women without these conditions.
- Similar associations were found between ovarian cancer and pelvic endometriosis and between ovarian cancer and adenomyosis.

## ABSTRACT

*Objective:* To evaluate associations between endometriosis and tubal and ovarian cancers in a large population-based study.

*Methods:* The Health Care Cost and Utilization Project – National Inpatient Sample databases from 2005 to 2014 were used in this study. Data on patients with a diagnosis of tubal or ovarian cancer and endometriosis (overall and subtypes including adenomyosis and pelvic endometriosis) using International Classification of Diseases, Ninth Edition, Clinical Modification codes were extracted. Logistic regression analysis was performed to evaluate associations between tubal and ovarian cancers and endometriosis. Adjustment was made for age, race, median income level, payment plan, hospital location and obesity.

*Results:* Of 38,800,139 women aged >18 years who were hospitalized between 2005 and 2014, 271,444 women with adenomyosis and/or pelvic endometriosis, 4289 women with tubal cancer and 133,253 women with ovarian cancer were identified. The rate of tubal cancer was three-fold higher in women with endometriosis compared with women without endometriosis (0.03% vs 0.01%). The odds ratio (OR) adjusted for age, race, obesity, income and insurance type was 4.02 [95% confidence interval (CI) 3.17–5.11;  $p<0.01$ ]. The rate of tubal cancer was higher in women with adenomyosis (0.04% vs 0.01%; adjusted OR 4.88, 95% CI 3.66–6.50;  $p<0.01$ ) and women with pelvic endometriosis (0.02% vs 0.01%; adjusted OR 2.80, 95% CI 1.84–4.27;  $p<0.01$ ) compared with women without these conditions. Similar associations were found between ovarian cancer and pelvic endometriosis and ovarian cancer and adenomyosis.

*Conclusion:* Both pelvic endometriosis and adenomyosis are strongly associated with tubal and ovarian cancers.

*Keywords:*

Endometriosis

Adenomyosis

Tubal cancer

Ovarian cancer

HCUP-NIS database

## **1. Introduction**

Endometriosis is defined as the presence of endometrial glands and/or stroma outside the uterine cavity. It is estimated that approximately 10% of premenopausal women have endometriosis [1]. In symptomatic women with pelvic pain or infertility, the prevalence of endometriosis is between 35% and 50% [2,3]. As some women with endometriosis are asymptomatic, the exact prevalence is unknown. The pathogenesis of endometriosis remains unclear; some authors believe that endometriotic cells originate from the uterus, while others have implicated other tissues including stem cells [4,5]. Genetic, endocrine and environmental factors may also be involved [6].

The association between pelvic endometriosis and ovarian cancer has been reported previously, with most authors reporting an association [7–13] with clear cell, low-grade serous and endometrioid ovarian cancers [odds ratios (OR) ranged from 2 to 3] [11,14–17]. No association was found with mucinous or high-grade serous and borderline tumours [11,14]. However, in two large cohorts, the authors could not find any relationship between endometriosis and ovarian cancer [18,19]. The number of women with endometriosis in those studies may have been too low to reach the statistical power needed to demonstrate an association. Tubal cancer is less common, and to the best of the authors' knowledge, the association between tubal cancer and endometriosis has not been explored to date.

The aim of this study was to evaluate associations between endometriosis and tubal and ovarian cancers in a large population-based study.

## **2. Materials and methods**

The Health Care Cost and Utilization Project – National Inpatient Sample (HCUP-NIS) databases from 2005 to 2014 [20] were used. This database is composed of national inpatient hospital discharge data that accounts for >96% discharge data from community hospitals in the USA. Data on patients with ovarian and tubal cancers using International Classification of Diseases, Ninth

Edition, Clinical Modification (ICD-9-CM) codes 183.0 (malignant neoplasm of ovary) and 183.2 (malignant neoplasm of fallopian tube) were extracted. Other adnexal cancers [malignant neoplasm of broad ligament of uterus, of parametrium, of round ligament of uterus and of other specified or unspecified site (ICD-9-CM codes 183.3, 183.4, 183.5, 183.8 and 183.9, respectively)] were excluded. This database has a cross-sectional design, and data are available for one calendar year for each woman. Endometriosis of the uterus (adenomyosis) and pelvic endometriosis (including ovarian, tubal, pelvic peritoneum, intestine and unspecified endometriosis) were evaluated separately. Next, data on women with adenomyosis (ICD-9-CM code 617.0) and pelvic endometriosis [ICD-9-CM codes 617.8 and 617.9 (unspecified endometriosis), 617.1 (ovarian endometriosis), 617.2 (fallopian tube endometriosis), 617.3 (pelvic peritoneum endometriosis), 617.4 (rectovaginal septum and vaginal endometriosis) and 617.5 (intestine endometriosis)] were extracted separately. These codes for endometriosis have been used in previous published studies [21]. The flow chart for selection of the study population is shown in Fig. 1.

**<insert Figure 1 near here>**

Sociodemographic characteristics of women with and without tubal or ovarian cancers, and women with and without endometriosis were compared separately. In addition, genetic susceptibility for breast and ovarian cancers (ICD-9-CM codes v84.01 and v84.02) were compared between women with and without endometriosis.

Chi-squared test was used to compare categorical variables, and Mann–Whitney test was used to compare continuous variables. Multi-variate logistic regression analysis was performed to evaluate associations between tubal and ovarian cancers and pelvic endometriosis (overall and subtypes) and adenomyosis. Variables that were significant on univariate analysis were included

in the multi-variate regression model. Given the large study size,  $p < 0.01$  was considered to indicate statistical significance to further eliminate significance by chance. The analysis was performed using STATA Version 16 (StataCorp, College Station, TX, USA). In agreement with the Tri-Council Policy statement (2010), this study was exempt from institutional review board approval as it was based solely on anonymous publicly available data.

### 3. Results

Of 38,800,139 women aged >18 years who were hospitalized between 2005 and 2014, 271,444 women had adenomyosis and/or pelvic endometriosis. Concomitant adenomyosis and pelvic endometriosis was found in 8% of cases (21,623/271,444 women). In total, 4288 women with tubal cancer and 133,253 women with ovarian cancer were identified. Six hundred and seventy-three women had both ovarian and tubal cancers.

The baseline sociodemographic characteristics of women with and without tubal cancer, as well as women with tubal cancer with and without endometriosis are shown in Tables 1 and 2. For ovarian cancer, baseline sociodemographic characteristics of women are shown in Tables S1 and S2 (see online supplementary material). The rate of tubal cancer in women with endometriosis was three times higher than in women without endometriosis (0.03% vs 0.01% respectively). The OR adjusted for age, obesity, race, income and insurance type was 4.02 [95% confidence interval (CI) 3.17–5.11;  $p < 0.01$ ]. A similar association was found between tubal cancer and adenomyosis (0.04% vs 0.01%; adjusted OR 4.88, 95% CI 3.66–6.50;  $p < 0.01$ ) and tubal cancer and pelvic endometriosis (0.02% vs 0.01%; adjusted OR 2.80, 95% CI 1.84–4.27;  $p < 0.01$ ). Tubal cancer was significantly associated with the location of endometriosis (Table 3), and the strongest association was found between tubal cancer and rectovaginal endometriosis (adjusted OR 11.99, 95% CI 1.69–85.3;  $p < 0.01$ ). Higher rates of ovarian cancer were found in women with pelvic endometriosis compared with women without pelvic endometriosis (0.71% vs 0.34%,



respectively; adjusted OR 2.61, 95% CI 2.41–2.82;  $p<0.01$ ), and in women with adenomyosis compared with women without adenomyosis (0.67% vs 0.35%; adjusted OR 2.18, 95% CI 2.02–2.35;  $p<0.01$ ) (Table 4).

<insert Tables 1–4 near here>

In an additional analysis, the genetic susceptibility of women with adnexal cancer to malignant neoplasms of the breast/ovary was evaluated. The distribution was found to be comparable between women with and without endometriosis [0.05 vs 0.15%, respectively, in women with ovarian cancer ( $p=0.26$ ) and 0.76% vs 0%, respectively, in women with tubal cancer ( $p=0.40$ )].

#### **4. Discussion**

The results of this study demonstrated a strong association between endometriosis and tubal cancer, with an adjusted OR of 2.80 for pelvic endometriosis and 4.88 for adenomyosis. Strong associations were also found between ovarian cancer and pelvic endometriosis (adjusted OR 2.61) and between ovarian cancer and adenomyosis (adjusted OR 2.18). To the best of the authors' knowledge, the latter association has not been reported previously.

Previous case–control studies and cohort studies have suggested an association between ovarian cancer and endometriosis [11,22,23]. This association was compelling with an OR ranging from 2 to 3 depending on the histological subtype of the ovarian cancer [11]. Wentzensen et al. found an association between endometriosis and endometrioid and clear cell carcinoma [13], and Pearce et al. reported higher risk of low-grade serous carcinoma in women with endometriosis [11]. The present results show that endometriosis is related to both ovarian and tubal cancers. However, the use of HCUP-NIS data did not enable the authors to evaluate the histological

subtype of adnexal malignancy. This database does not provide histopathological diagnoses. In most cases, endometriosis is diagnosed by laparoscopy or laparotomy with or without histopathological confirmation. Nevertheless, the ICD-9 codes used for endometriosis have been validated [21].

There is increasing evidence that ovarian cancer, mainly serous carcinoma, originates from the secretory cells of the Fallopian tubes. However, the pathophysiology of malignancy in women with endometriosis is unclear. It has been postulated that it is related to genetic mutations or altered micro-environments [24], mediated by excess oestrogen or a progesterone deficit [25], or by local inflammation and alterations in the inflammatory process [25]. Different pathways to carcinogenesis are also possible. Murakami et al. found endometriosis-associated ovarian cancer in clinically detectable endometrial cysts [26]. Ovarian and tubal cancers in women with endometriosis seem to manifest a couple of years earlier than in women without endometriosis. This differs from high-grade serous carcinoma which is often found in later stages of life. It appears that ovarian and tubal cancers in women with endometriosis are less aggressive.

Genetic susceptibility to breast and ovarian cancers was found to be comparable between women with and without endometriosis. The small number of genetically susceptible subjects in the endometriosis group could be explained by the fact that histopathology of ovarian cancer in women with endometriosis is mainly endometrioid and clear cell, in contrast to serous adenocarcinoma which is most common in BRCA carriers.

There are similarities between endometriosis and adenomyosis where ectopic endometrium is found in both conditions. In an immunochemistry study, the authors found lower intensities of cytokeratin in adenomyosis and endometrioma than in eutopic endometrium [27]. They postulated that the ectopic endometrium may have a lower degree of differentiation regardless of the site. In another study involving 12,447 women with adenomyosis, the authors reported that they were at

higher risk of endometrial and thyroid cancers. They also found that women with endometriosis were at increased risk of endometrial and ovarian cancers [28].

The present study found significant associations between endometriosis and both tubal and ovarian cancers. A strong association was found between rectovaginal endometriosis and tubal cancer, but not between rectovaginal endometriosis and ovarian cancer. This may be because rectovaginal endometriosis is confined in a closed space, preventing the spread of endometriotic cells. This needs further investigation.

Limitations of this study include the use of an administrative database with a cross-sectional nature and inaccessibility to evaluate the type of adnexal malignancy. The lack of pathological confirmation is the main weakness, and it is known that it can be difficult to differentiate between tubal and ovarian cancers. However, it was assumed that these cases would be mainly coded as ovarian cancer, and thus the population coded as tubal cancer was likely to be diagnosed correctly. Some published studies have shown that ICD codes had high sensitivity compared with histological documentation for breast, lung and colorectal malignancies [29–31]. Some clinical confounding factors may have been missed by using this database. However, in terms of strengths of this study, a large database of women with endometriosis in different locations was used, and ovarian and tubal cancers were evaluated separately.

In conclusion, pelvic endometriosis and adenomyosis are strongly associated with both tubal and ovarian cancers.

### **Conflict of interest**

None declared.

### **Funding**

None.

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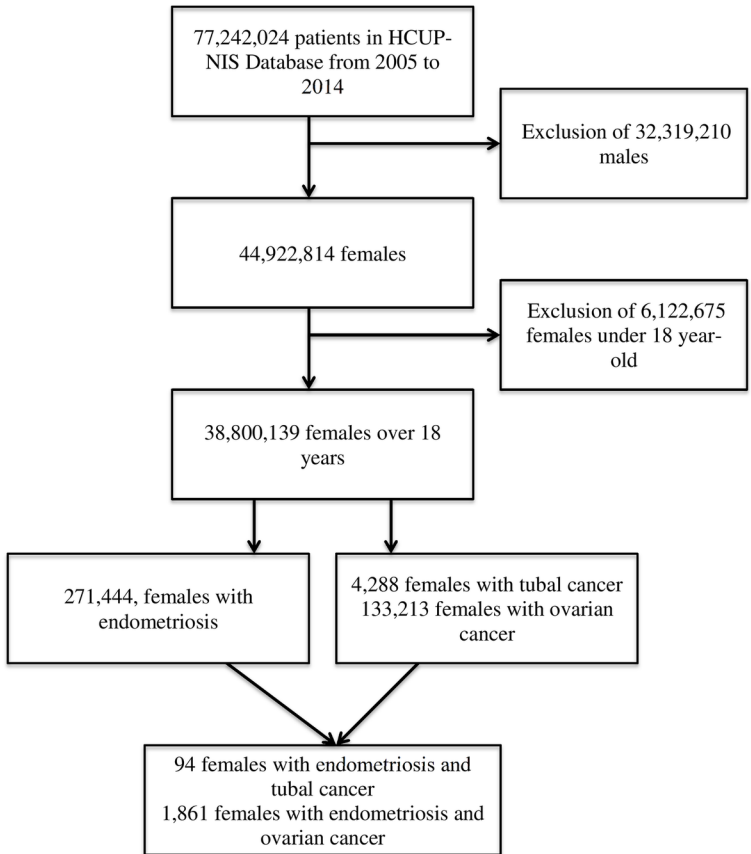
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**Fig. 1.** Flow chart of women included in the study.

**Figure 1.** Flow chart of included women in the study.





**Table 1**

Demographic and clinical characteristics of women with and without tubal cancer who were hospitalized in the USA between 2005 and 2014.

Characteristics	No tubal cancer ( <i>n</i> =38,795,501)	Tubal cancer ( <i>n</i> =4288)	<i>p</i> -value
Age in years, median (IQR)	56 (33–75)	65 (57–72)	<0.01
Race			
White	67.3%	82.0%	<0.01
Other	32.7%	18.0%	
Median income quartiles (US\$)			
First quartile (1–25,000)	29.2%	19.3%	<0.01
Second quartile (25,000–35,000)	26.1%	22.3%	
Third quartile (35,000–45,000)	23.8%	27.1%	
Fourth quartile (≥45,000)	20.8%	31.3%	
Urban	82.9%	84.6%	0.14
Insurance type			
Medicare	42.7%	48.8%	<0.01
Medicaid	18.4%	5.6%	
Private	31.7%	41.2%	
Other	7.2%	4.4%	
Obesity	9.8%	6.5%	<0.01
Endometriosis	0.7%	2.2%	<0.01

IQR, interquartile range

**Table 2**

Demographic and clinical characteristics of women with tubal cancer, with or without endometriosis, who were hospitalized in the USA between 2005 and 2014.

Characteristics	Tubal cancer without endometriosis ( <i>n</i> =4194)	Tubal cancer with endometriosis ( <i>n</i> =94)	<i>p</i> -value
Age in years, median (IQR)	65 (57–72)	58 (52–68.3)	<0.01
Race			
White	82.1%	79.3%	0.51
Other	17.9%	20.7%	
Median income quartiles (US\$)			
First quartile (1-25,000)	19.5%	10.3%	0.09
Second quartile (25,000-35,000)	22.3%	20.5%	
Third quartile (35,000-45,000)	27.1%	26.9%	
Fourth quartile (≥45,000)	31.1%	42.3%	
Urban	84.6%	86.7%	0.83
Insurance type			
Medicare	49.3%	28.7%	<0.01
Medicaid	5.6%	3.2%	
Private	49.7%	60.6%	
Other	4.4%	7.5%	
Genetic susceptibility to malignant neoplasm of breast/ovary	0.76%	0.0%	0.40
Obesity	6.5%	5.3%	0.65

IQR, interquartile range.

**Table 3**

Risk of tubal cancer depending on endometriosis.

	Tubal cancer <i>n</i> =4288	Unadjusted OR (95% CI) <i>p</i> -value	Adjusted <sup>a</sup> OR (95% CI) <i>p</i> -value
Overall endometriosis			
No	0.01%	3.18 (2.59–3.91)	4.02 (3.17–5.11)
Yes	0.03%	<0.01	<0.01
Adenomyosis			
No	0.01%	3.92 (3.06–5.01)	4.88 (3.66–6.50)
Yes	0.04%	<0.01	<0.01
Pelvic endometriosis			
No	0.01%	2.24 (1.56–3.20)	2.80 (1.84–4.27)
Yes	0.02%	<0.01	<0.01
Ovarian endometriosis			
No	0.01%	2.29 (1.33–3.94)	3.54 (2.01–6.25)
Yes	0.03%	<0.01	<0.01
Tubal endometriosis			
No	0.01%	6.38 (3.04–13.39)	10.38 (4.94–21.82)
Yes	0.07%	<0.01	<0.01
Pelvic peritoneum endometriosis			
No	0.01%	2.17 (1.23–3.83)	2.52 (1.26–5.06)
Yes	0.02%	<0.01	<0.01
Rectovaginal endometriosis			
No	0.01%	7.87 (1.11–55.79)	11.99 (1.69–85.3)
Yes	0.09%	0.04	0.01
Intestine endometriosis			
No	0.01%	4.42 (1.42–13.71)	4.53 (1.13–18.12)
Yes	0.05%	0.01	0.03

OR, odds ratio; CI, confidence interval.

<sup>a</sup>Adjusted on age, race, obesity, income quartile and insurance type.

**Table 4**

Risk of ovarian cancer depending on endometriosis.

	Ovarian cancer <i>n</i> =133,213	Unadjusted OR (95% CI) <i>p</i> -value	Adjusted <sup>a</sup> OR (95% CI) <i>p</i> -value
Overall endometriosis			
No	0.34%	2.02 (1.93–2.11)	2.39 (2.26–2.52)
Yes	0.68%	<0.01	<0.01
Adenomyosis			
No	0.35%	1.98 (1.86–2.11)	2.18 (2.02–2.35)
Yes	0.71%	<0.01	<0.01
Pelvic endometriosis			
No	0.34%	2.05 (1.92–2.19)	2.61 (2.41–2.82)
Yes	0.70%	<0.01	<0.01
Ovarian endometriosis			
No	0.34%	2.86 (2.61–3.12)	3.50 (3.15–3.88)
Yes	0.67%	<0.01	<0.01
Tubal endometriosis			
No	0.34%	3.10 (2.56–3.75)	3.69 (2.94–4.64)
Yes	1.05%	<0.01	<0.01
Pelvic peritoneum endometriosis			
No	0.34%	1.84 (1.65–2.05)	2.36 (2.08–2.69)
Yes	0.63%	<0.01	<0.01
Rectovaginal endometriosis			
No	0.34%	1.52 (0.68–3.38)	1.19 (0.38–3.69)
Yes	0.52%	0.31	0.77
Intestine endometriosis			
No	0.34%	4.26 (3.46–5.26)	4.99 (3.91–6.37)
Yes	1.44%	<0.01	<0.01

OR, odds ratio; CI, confidence interval.

<sup>a</sup>Adjusted on age, obesity, race, income quartile and insurance type.