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Incidence and Factors Associated with Synchronous Ovarian and Endometrial Cancer: A Population-Based Case-Control Study

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Abstract

Objective—To estimate the incidence of synchronous endometrial cancer (EC) and ovarian cancer (OC) in the female population, among all women with EC, and in women under 50 years of age with EC, and to identify factors associated with synchronous EC/OC.

Methods—All cases of synchronous EC/OC and EC diagnosed in women residing in Olmsted County, Minnesota between 1/1/1945 and 12/31/2008 were identified. Incidence was estimated using the population denominator from decennial census data, corrected for hysterectomy prevalence. A case-control study using 15 identified cases (EC/OC) and 45 controls (EC alone) was performed.

Results—The incidence of synchronous EC/OC and EC (age-adjusted to the 2000 US female total and corrected for hysterectomy prevalence) in 1945–2008 was 0.88 and 30.3 per 100,000 person-years, respectively. Among women under 50 years of age, the corrected incidence of EC/OC and EC was 0.51 and 5.1 per 100,000 person-years, respectively. Among all women with EC, 3.1% had a synchronous OC compared to 9.4% of women under 50 years of age with EC. Patients with synchronous EC/OC were more likely than those with EC alone to present with a pelvic mass (57.1% vs. 8.9%, $p < 0.001$). Patients with EC alone were more likely to have used oral contraceptive pills (OCPs) than synchronous EC/OC cases (22.7% vs 0%; Odds ratio, 0.10; 95% CI, < 0.01 –0.87).

Conclusion—Although the incidence of synchronous EC/OC in the general population is lower than previously reported, nearly 1 in 10 women diagnosed with EC under 50 years of age will have a synchronous OC.

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The authors declare that there are no conflicts of interest.

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Keywords

Synchronous cancers; endometrial cancer; ovarian cancer

Introduction

Approximately 10% of women with ovarian cancer (OC) may have a synchronous endometrial cancer (EC), and 5% of women with EC may harbor a simultaneous OC [1–3]. In women under the age of 50 with EC, the incidence of synchronous OC has been reported to be up to 19%, and as high as 25% in women aged 24–45 years [1, 4]. Population-based studies in women diagnosed with OC have suggested that the incidence of synchronous EC/OC is less than 3% [5, 6]. However, the reported incidence of synchronous OC in the setting of an EC diagnosis has been subject to referral bias in many investigations and remains a topic of debate [1].

Consistent pathologic criteria are crucial in distinguishing between synchronous and metastatic disease and determining the accurate incidence of this phenomenon. Histologic criteria for the diagnosis of synchronous EC/OC were originally proposed by Scully et al, and updated by Ulbright and Roth [1, 7, 8]. They defined the most contemporary diagnosis of synchronous EC/OC, which requires the absence of multinodular ovarian pattern (major criterion) or two or more of the following minor criteria: absent deep myometrial invasion, unilateral ovarian involvement, absent lymphovascular invasion, lack of tubal lumen involvement, and an enlarged ovary (>5cm) [1, 7–10].

It has been previously reported that synchronous EC/OC cases are more prevalent in younger (median age 41–52 years), obese, premenopausal and nulliparous women [1, 7, 8, 10–12]. Synchronous EC/OC has also been linked to hyperestrogenic conditions (chronic anovulation, polycystic ovarian syndrome (PCOS), obesity, estrogen producing ovarian tumors, or unopposed estrogen replacement therapy) similar to those linked to type I EC [13, 14]. Family history of Lynch II syndrome has also been described in association with synchronous EC/OC [15].

The possibility of concurrent OC in the setting of an EC diagnosis is of particular clinical relevance for young women wishing to preserve fertility. Based on current estimates, up to 1 in 5 young women with EC could have a concomitant OC, suggesting ovarian assessment or removal may be prudent [1]. However, such reported incidences of synchronous EC/OC in young women may be overestimated as a result of referral bias. If this is indeed the case, fertility preservation through either medical management of low grade EC or ovarian retention at the time of hysterectomy for EC may be options with lower risk than currently estimated.

In this study, we used the Rochester Epidemiology Project (REP), a valuable tool already utilized in evaluating the population-based incidence of a multitude of medical conditions [16, 17]. Previously, McDonald et al, and Beard et al conducted population-based incidence and case-control studies of EC, also using the REP, that spanned the dates January 1, 1945 to December 31, 1974 and January 1, 1975 to December 31, 1991, respectively [18, 19]. We expanded these 2 prior studies to estimate the incidence of EC and EC/OC within the female population and within women under 50 years of age. In addition, we performed a REP-based case-control study to evaluate the factors associated with the occurrence of synchronous EC/OC compared to EC alone.

Materials and Methods

Rochester Epidemiology Project

The REP is a research infrastructure (R01 AG034676), which captures health care information for virtually all individuals who have been residents of Olmsted County, Minnesota between 1966 and the present. Between 1966 and 2008, 486,564 individuals and their respective 1,145,856 medical records were included in the REP [17]. These records are linked and indexed; individuals with specific diseases may be identified through retrieval of records with pertinent diagnostic codes [16].

This study was approved by the Mayo Clinic and Olmsted Medical Center Institutional Review Boards (IRBs).

Incidence Study

The previous REP studies by McDonald et al and Beard et al were used to identify all patients with EC, including synchronous EC and epithelial OC cases, diagnosed between January 1, 1945 and December 31, 1991 [18, 19]. Germ cell tumors and granulosa cell tumors were excluded. All EC and synchronous EC/OC cases diagnosed in Olmsted County between January 1, 1992 and December 31, 2008 were identified through retrieval of records assigned International Classification of Diseases (ICD)-9 codes 182.0 or 182.8 or Hospital International Classification of Diseases Adapted (HICDA) codes 01820110, 01821110, 01829110, 01790261, and 34101110. Among those retrieved, the pathology reports were manually reviewed to confirm the diagnosis.

Synchronous EC/OCs were originally diagnosed using criteria contemporary at the time of each patient's diagnosis. Seventeen potential synchronous EC/OC cases underwent pathology review by a single gynecologic pathologist (GLK) to confirm the diagnosis based on current diagnostic criteria. Those deemed to be metastatic EC were excluded from the synchronous EC/OC cohort.

Case-Control Study

A case-control study was performed in order to evaluate the factors associated with synchronous EC/OC. In order to increase the precision of the estimates particularly due to the rarity of the disease, 3 controls with EC alone were randomly selected from Olmsted County residents diagnosed with EC in the same year (or up to within ± 4 years) that the case was diagnosed with synchronous EC/OC (defined as the "index date"). Controls were also matched on year of birth (± 6 years). All controls with EC alone and cases of EC/OC diagnosed in Olmsted County between January 1, 1945 and December 31, 1991 had previously undergone pathology review by a single gynecologic pathologist (GLK) [18, 19]. Additional controls and cases identified between January 1, 1992 and December 31, 2008 underwent pathology review by the same pathologist (GLK) at the time of this study.

Medical records were abstracted for medical and reproductive data, including race, body mass index (BMI), gravidity and parity, oral contraceptive pills (OCPs) and other hormone use, medical comorbidities including those associated with excess estrogen production (obesity, PCOS, infertility), endometriosis, age at menarche and menopause, cancer histologies, grades, and stages, vital status, and date of death or last follow-up. Where records were incomplete, the values for desired factors were flagged as unknown and these values were ignored in the final analysis.

Statistical Analysis

For the estimation of the incidence of EC and synchronous EC/OC, both overall and for women under 50 years of age, the rates were calculated with the assumption that the entire female population of Olmsted County was considered to be at risk. The numerator was the number of persons meeting the incidence criteria and diagnosed during 1945–2008 and the denominator was obtained from the decennial census data for 1945–2008 with linear interpolation between census years. Additional incidence calculations correcting for the prevalence of hysterectomy were performed using estimates of the proportion of females with intact uteri by age and calendar year from the National Health Survey and methods outlined in the report's appendix [20]. These estimates were extrapolated for subsequent years using hysterectomy rates reported for 1990 and 2000 [21]. Rates were age-adjusted to the population structure of U.S. female whites in 2000. Ninety-five percent confidence intervals (95% CIs) for the rates were calculated assuming a Poisson error distribution.

Separate stratified exact conditional logistic regression models were fit to evaluate the association between each factor and case/control status, thereby taking into account the matching between the cases and controls. Exact methods were utilized given the small sample size and low prevalence of some of the risk factors. The odds ratio (OR) and corresponding 95% confidence interval (CI) for usage of OCPs was estimated from the model; the odds ratio is a median unbiased estimate since the prevalence was zero among the EC/OC cases. All calculated p-values were two-sided and p-values less than 0.05 were considered statistically significant. Statistical analyses were performed using the SAS version 9.2 software package (SAS Institute, Inc.; Cary, NC).

Results

Incidence of EC/OC

A total of 488 ECs, which included 15 cases of synchronous EC/OCs, were diagnosed in Olmsted County, Minnesota between January 1, 1945 and December 31, 2008. The incidence of EC alone and synchronous EC/OC (age-adjusted to the 2000 US female total) during the study period was 20.2 (95% CI, 18.5 – 22.0) and 0.61 (95% CI, 0.30–0.92) per 100,000 person-years, respectively (Table 1 and Table 2, respectively). The incidence corrected for hysterectomy prevalence was 30.3 (95% CI, 27.6 – 33.0) and 0.88 (95% CI, 0.43 – 1.33) per 100,000 person years, respectively. Among all women diagnosed with EC, 3.1% were synchronous EC/OC.

During the study period, 74 cases of EC were diagnosed in women under the age of 50, with a corrected incidence of 5.1 (95% CI, 3.9 – 6.3) per 100,000 person-years. Within this cohort of younger women, there were 7 cases of synchronous EC/OC, with a corrected incidence in the Olmsted County female population of 0.51 (95% CI, 0.13 – 0.88) per 100,000 person years. Thus, among women younger than age 50 with EC, 9.4% were synchronous EC/OC.

The fifteen cases of synchronous EC/OC were spread across the study period; 1 in 1945–1954, 3 in 1955–1964, 1 in 1965–1974, 2 in 1975–1984, 4 in 1985–1994, 3 in 1995–2004, and 1 in 2005–2008. Given the increase in the Olmsted County female population over the years, the incidence of EC/OC has essentially remained stable over time.

Case-Control Study

Demographic and clinical characteristics of patients diagnosed with synchronous EC/OC are shown in Table 3. Among the 15 synchronous EC/OC cases, 7 (46.7%) were under 50 years of age. Only 2 (13.3%) cases of EC/OC were diagnosed under the age of 45. One of these

patients (case 6, Table 3) was 39 years of age and was diagnosed with breast cancer 24 years after her EC/OC diagnosis. A genetic etiology was not identified. The other patient (case 10, Table 3) was 44 years old, and had a personal history of breast cancer diagnosed 4 years prior to her EC/OC diagnosis. She was ultimately diagnosed with Lynch II syndrome. Although family history did not differ significantly between cases and control, (51% vs. 60%, $p=0.69$), 2 synchronous EC/OC cases had a first-degree relative with OC, and 2 other cases had a family history of Lynch II syndrome. None of the EC alone controls had a family history of Lynch II syndrome or BRCA1/2.

There were no significant differences in race, BMI, parity, or age of menopause between synchronous EC/OC cases and age-matched EC only controls (Table 4). While there was no difference in the proportion with endometriosis, infertility, PCOS, hormone replacement therapy, or history of dysfunctional uterine bleeding between EC/OC cases and controls, women with EC alone were more likely to have used oral contraceptive pills (OCPs) compared to women with EC/OC (22.7% vs. 0%; $p=0.035$; Table 4). Specifically, OCP use was associated with a lower likelihood of synchronous EC/OC (OR, 0.10; 95% CI, < 0.01–0.87).

Patients with synchronous EC/OC were more likely to present with a pelvic mass than EC alone (57.1% vs. 8.9%, $p<0.001$, Table 5). Among pre-diagnosis comorbidities, there was a higher proportion of hypertension in patients with synchronous EC/OC compared to controls (55.6% vs. 20%; $p=0.020$). There was no difference in the rate of other comorbidities including smoking, hyperlipidemia, and diabetes mellitus between EC/OCs and EC alone (data not shown).

Patients with EC/OC had stage I and grade 1 or 2 EC in 14/15 (93.3%), while 37/45 (82.2%) of controls were diagnosed with stage I EC and 88.9% of those were grade 1 or 2. EC in both cases and controls was more often of endometrioid histology than other histologies. Among EC/OC cases, 14 (93.3%) were endometrioid EC and 1 (6.7%) was papillary serous. Among controls, 40 (88.9%) were endometrioid, 2 (4.4%) were papillary serous and 3 (6.7%) were other histologies. Most EC/OC cases had stage I OC (11/15; 73.3%) and 10/15 (66.7%) had concurrent endometrioid OC and EC histology.

Overall, 8 (53.3%) patients with EC/OC were still alive at the time of this study (median follow-up, 18.4 years) (Table 3). No patients with synchronous EC/OC died of their EC, while 5 patients with EC/OC died of OC (3 within 3 years and 2 over 20 years later after recurrent OC).

Discussion

While the incidence of synchronous OC in women diagnosed with EC has been reported to be up to 19% in women under 50 years of age and as high as 25% in women aged 24–45 years [1, 4], in the current study, we found that the proportion of women under 50 years of age with EC that had concomitant OC was only 9.4%. When considering women of any age diagnosed with EC and adjusting for hysterectomy, the rate in our population was slightly higher than previous SEER data, which estimated an overall age adjusted incidence of EC of 23.9 per 100,000 women years [22]. Yet, the 3.1% overall incidence of a synchronous OC among EC patients in Olmsted County is lower than that reported in previous studies. Taken together, these findings suggest that previous incidence reports may have been overestimates.

The rates of EC have been gradually rising over the last 2 decades, possibly secondary to the growing obesity epidemic [24]. Beard et al showed that in Olmsted County, Minnesota, the incidence of EC slightly increased between 1964–1975 and 1975–1991 [19]. In this study,

despite the large time span in which synchronous EC/OC was diagnosed and the increase in EC rates over time, the incidence of synchronous EC/OC remained low and stable over the study time period. This suggests that obesity, although an independent risk factor for EC, may not contribute to the incidence of synchronous EC/OC. Furthermore, the effect of changes in population demographics over the 65 year study period does not appear to have significantly impacted the incidence of synchronous EC/OC.

In this case-control study, while endometriosis was not significantly higher in EC/OC patients compared to those with EC alone, we were limited by the small numbers of cases. Among the 15 EC/OCs, none of the 5 with non-endometrioid OCs had concomitant endometriosis. This observation is consistent with previous studies indicating a relationship only between the presence of endometriosis and development of a synchronous endometrioid OC [10, 24, 25, 26]. We observed that 66.7% of synchronous cancers had concurrent endometrioid histology in both primaries, and that 33.3% were also associated with endometriosis. Similar to our study, others have demonstrated that up to 70% of synchronous EC/OCs have endometrioid histology in both primaries with endometriosis identified in 30% of cases [1, 10, 25]. Unopposed estrogen has been suggested to be an important contributor to the malignant transformation of endometriosis seen in 0.7–1.0% of patients with endometriosis [26]. Compared to those without known endometriosis, the risk of OC is four-fold higher in the presence of endometriosis with both endometrioid and clear cell histologies described [27].

Several studies have described the occurrence of EC in the setting of unopposed estrogen use as well as the protective effect of combined estrogen and progesterone use [18, 19, 28, 29]. As we observed a significantly lower rate of synchronous EC/OC among OCP users, perhaps the protective benefits of OCPs in EC are also protective against synchronous EC/OC. The mechanism for this deserves further exploration. OCPs have not only been shown to protect against EC, but are also utilized as chemoprevention in those at risk of OC [30, 31]. It is possible that in the setting of endometriosis-related OC risk, the use of OCPs protects against excess estrogen and blocks its stimulatory effect. This finding merits further study in larger populations with higher EC/OC prevalence.

Considering nearly 1 in 10 women under the age of 50 diagnosed with EC may also harbor a synchronous OC, patients must be counseled on the risks of non-standard therapy. However, it is imperative to consider that in developed countries, increasing postponement of child-bearing until later in life has led to increased rates of pregnancy in women between 35–49 years of age [32]. The OCs diagnosed in conjunction with EC are often early stage and have an excellent prognosis [33–35]. This would support the option of cautious fertility preservation in select young patients with EC. Both hormonal therapy of grade 1 EC and ovarian preservation carry a risk of missing an occult ovarian cancer [4, 36, 37], and a delay in OC diagnosis could impact cancer-specific survival. Patients confirmed to have synchronous EC/OC must be aware about the guarded prognosis of their disease, as a risk of OC recurrence exists, and the mortality rate due to OC in our cohort was 33%. Ruling out the absence of adnexal disease prior to fertility-preserving therapy through either imaging or even a diagnostic laparoscopy, may reassure both patient and provider.

A major strength of this study is the utilization of the population-based case-control design using the REP. This type of study design, by focusing on a defined population, and by capturing virtually all health care delivered to this population, avoids the potential referral bias that is common to studies which focus only on patients treated at a single institution. In addition, the length of information available through the linked medical records makes it possible to examine exposures that may have occurred decades prior to the onset of the disease. Pathology specimens included in the study have been reviewed by a single

pathologist with extensive experience in gynecologic pathology, which limited diagnostic ambiguities. Our study also has limitations. The rare nature of EC/OC and our small numbers restricted our ability to provide solid associations between the disease and EC cases alone. Larger numbers may certainly yield a wider range of associations. Nevertheless, we were able to identify an important association between OCP use and lower rates of EC/OC.

Despite being a relatively rare phenomenon, a synchronous EC/OC is encountered in nearly 1 in 10 endometrial cancer patients under the age of 50. For the gynecologic oncologist, as well as other providers involved in the care of patients with EC/OC, defining the risk of OC in the setting of diagnosed EC is crucial in women considering fertility-preserving cancer treatments. Molecular analyses of ECs and OCs in women diagnosed with synchronous cancer may further our understanding of the risk factors for this phenomenon and better define the effect of obesity and other comorbidities on this disease.

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Highlights

- The incidence of synchronous endometrial and ovarian cancer in Olmsted County is found to be smaller than that reported in other studies.
- Women with endometrial cancer under the age of 50 may have a 1 in 10 risk of developing a synchronous ovarian cancer
- Oral contraceptive pills may be protective of synchronous endometrial and ovarian cancer development; however, larger studies are needed to investigate this further.

Table 1

Incidence of endometrial cancer among Olmsted County, Minnesota women, 1945–2008, uncorrected and corrected for the estimated prevalence of hysterectomy.

Age-group (years)	No. of cases	Uncorrected rate *	Corrected rate
0–14	0	0	0
15–34	6	0.6	0.7
35–44	27	6.5	7.8
45–54	105	33.3	47.3
55–64	146	64.0	98.1
65–74	109	65.6	100.1
75	95	59.0	94.3
Total	488	20.2 [†]	30.3 [†]

* Age-specific incidence rate per 100,000 person-years.

** Age-specific incidence rate per 100,000 person-years, corrected for the population not at risk by virtue of prior hysterectomy.

[†] Incidence per 100,000 person-years directly age-adjusted to the (total) population structure of the United States in 2000.

Table 2

Incidence of synchronous endometrial and ovarian cancer among Olmsted County, Minnesota women, 1945–2008, uncorrected and corrected for the estimated prevalence of hysterectomy and bilateral salpingo-oophorectomy.

Age-group (years)	No. of cases	Uncorrected rate *	Corrected rate
0–14	0	0	0
15–34	0	0	0
35–44	2	0.49	0.58
45–54	6	1.90	2.70
55–64	4	1.75	2.69
65–74	3	1.81	2.76
75	0	0	0
Total	15	0.61 †	0.88

* Age-specific incidence rate per 100,000 person-years.

** Age-specific incidence rate per 100,000 person-years, corrected for the population not at risk by virtue of prior hysterectomy.

† Incidence per 100,000 person-years directly age-adjusted to the (total) population structure of the United States in 2000.

Table 3
Demographic and clinical characteristics of synchronous endometrial and ovarian cancer cases

Case	Age at EC/ OC diagnosis	BMI	Parity	Presentation	Endometriosis	OC Histology	EC Histology	EC Stage [†] /Grade [‡]	OC Stage [†] /Grade [‡]	Status and time to last follow-up or death
1	46	43.7	0	Abdominal pain, pelvic mass	Yes	Endometrioid	Endometrioid	IB/2	IA/2	Alive without disease, 9.9 years
2	49	29.7	2	Vaginal bleeding	No	Serous borderline	Endometrioid	IA/1	IA/1	Alive without disease, 16.1 years
3	45	44.1	1	Abdominal pain, pelvic mass	No	Serous	Endometrioid	IA/1	IC/1	Alive without disease, 2.2 years
4	56	23	1	Vaginal bleeding, abnormal pap smear	No	Serous	Serous	II/3	IV/3	Died of OC, 1.8 years
5	73	26.2	0	Vaginal bleeding, pelvic mass	Yes	Borderline Mucinous	Endometrioid	IA/1	IA/1	Alive without disease, 5.2 years
6	39	18.9	0	Vaginal bleeding, abdominal pain	Yes	Endometrioid	Endometrioid	IA/1	IB/1	Died of metastatic breast cancer (without disease), 40.5 years
7	46	22.5	1	Vaginal bleeding	Yes	Endometrioid	Endometrioid	IA/1	IA/1	Alive without disease, 43.7 years
8	57	26.8	4	Vaginal bleeding	No	Endometrioid	Endometrioid	IB/1	IC/2	Died of recurrent OC, 20.3 years
9	50	31.8	3	Vaginal bleeding, pelvic pain, pelvic mass	No	Endometrioid	Endometrioid	IA/1	IA/2	Died of recurrent OC, 21.8 years
10	44	29.4	0	Vaginal bleeding		Endometrioid	Endometrioid	IA/1	IC/1	Alive without disease, 21.4 years
11	73	38.8	1	Pelvic mass	No	Serous	Endometrioid	IA/1	IV/2	Died of cardiac failure with partially resected OC, 6 days
12	73	39.6	4	Vaginal bleeding, pelvic mass	No	Endometrioid	Endometrioid	IB/2	IC/2	Died of pneumonia following myocardial infarct (without disease), 10.9 years
13	58	34.7	0	Vaginal bleeding, pelvic mass, anemia	No	Endometrioid	Endometrioid	IA/1	IA/2	Alive without disease, 28.6 years
14	64	36.3	4	Abdominal pain, pelvic mass	NoT	Endometrioid	Endometrioid	IA/2	IV/3	Died of OC, 2.6 years
15	46	21.9	2	Vaginal bleeding	Yes	Endometrioid	Endometrioid	IA/1	IIIB/1	Alive without disease, 20.6 years

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OC= ovarian cancer

EC= endometrial cancer

‡ Grading is based of singly gynecology pathologist (GLK) review

‡ Stage based contemporary FIGO staging criteria at time of diagnosis

Table 4

Demographic characteristics and gynecologic history of cases (EC/OC) and controls (EC alone)

Demographic and Gynecologic History	EC/OC (n= 15)	EC Alone (n= 45)	P- Value [†]
Age at cancer diagnosis (years)	55.1 (11.4) 39.5–73.7	56.2 (10.1) 39.6–75.8	0.25
Caucasian race	15 (100)	45(100)	--
BMI at cancer diagnosis (kg/m ²)	31.2 (8.1) (18.9–44.1)	29.8 (7.8) (19.3 –52.4)	0.56
Nulliparity	5 (33.3)	16 (36.4)	>0.99
Age at menopause (years)	48.8 (5.4) 39.0–57.0	49.4 (6.2) 37.0–72.0	0.38
Combined oral contraceptives use (any duration)	0/15 (0)	10/44 (22.7)	0.035
Endometriosis	5/15 (33.3)	6/41 (14.6)	0.25
Infertility	2/13 (15.4)	4/41 (9.8)	0.93
Polycystic ovarian syndrome	0/12 (0)	2/35 (5.7)	0.67
Hormone replacement therapy use	2 (13.3)	8 (17.8)	>0.99
History of dysfunctional uterine bleeding	7/14 (50)	32/43 (74.4)	0.15

[†] P-values are based on fitting a separate stratified exact conditional logistic regression model for each factor.

* Values reported as frequency (percentage) or mean (SD) and range.

Table 5

Presenting symptoms and signs of cases (EC/OC) vs. controls (EC alone)

Presenting symptoms and signs	EC/OC (n= 15)	EC Alone (n= 45)	P- Value [†]
Vaginal bleeding	11 (73.3)	39 (86.7)	0.44
Abdominal/pelvic pain	5/14 (35.7)	10 (22.2)	0.61
Pelvic mass	8/14 (57.1)	4 (8.9)	< 0.001
Pulmonary symptoms	2 (13)	0	0.032
Endometrial cells on pap smear	1 (6.7)	7 (15.6)	0.63

[†] P-values are based on fitting a separate stratified exact conditional logistic regression model for each factor.

* Values reported as frequency (percentage) or mean (SD) and range.