# Risk of Epithelial Ovarian Cancer in Relation to Benign Ovarian Conditions and Ovarian Surgery

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Abstract

**Objective**: Some forms of ovarian neoplasms may be preventable through the removal of precursor lesions. We assessed risk associated with a prior diagnosis of, and ovarian surgery following, ovarian cysts and endometriosis, with a focus on characterizing risk among tumor subgroups.

**Methods**: Information was collected during in-person interviews with 812 women with ovarian cancer diagnosed in western Washington State from 2002-2005 and 1,313 population-based controls. Logistic regression was used to calculate odds ratios (ORs) and 95% confidence intervals (CIs).

**Results**: The risk of a borderline mucinous ovarian tumor associated with a history of an ovarian cyst was increased (OR=1.7, 95% CI 1.0-2.8) but did not vary notably according to receipt of subsequent ovarian surgery. While risk of invasive epithelial ovarian cancer was slightly increased among women with a cyst who had no subsequent ovarian surgery, it was reduced when a cyst diagnosis was followed by surgery (OR= 0.6, 95% CI 0.4-0.9). This reduction in risk was most evident for serous invasive tumors. Women with a history of endometriosis had a three-fold increased risk of endometrioid and clear cell invasive tumors, with a lesser risk increase among women who underwent subsequent ovarian surgery.

**Conclusions**: Our results suggest differences in the relation of ovarian cysts and endometriosis with risk of specific subtypes of ovarian cancer, as well as the possibility that ovarian surgery in women with these conditions may lower the risk of invasive disease.

Key Words: ovarian cancer, ovarian cysts, endometriosis, epidemiology

## Introduction

The genesis of epithelial ovarian cancer is poorly understood, and may vary by tumor subtype. Among mucinous tumors, patterns of risk factors and somatic genetic alterations across benign, borderline and invasive subtypes are generally consistent with an adenoma-to-carcinoma developmental sequence, and it has therefore been hypothesized that mucinous tumors may be particularly amenable to risk reduction through the removal of benign precursors [1]. Some evidence suggests that borderline, and possibly low-grade invasive, serous tumors may similarly progress from their benign counterparts [2, 3]; thus, such a mechanism for risk reduction may extend to these tumors. Endometrioid and clear cell ovarian tumors, which are predominantly invasive, may arise from foci of endometriosis [3, 4], and so may also be amenable to reducing risk through the removal of ovarian endometrioma.

The most common ovarian cancer subtype, high-grade invasive serous disease, has long been posited to arise from the ovarian surface epithelium (possibly preferentially from epithelial cells within inclusion cysts) in the absence of a morphologically identifiable precursor [2, 5]. Recently, the fimbrial end of the fallopian tube has been proposed as an alternative site of origin for these tumors [6, 7], and some evidence of molecular precursors located in ovarian or fimbrial mucosal epithelium has emerged [8, 9]. Owing to their relatively undifferentiated histologic appearance, a substantial proportion of invasive tumors are not readily classified into any of the preceding histologic categories but are commonly believed to share a pathogenetic pathway with invasive serous tumors [5, 10, 11].

If some types of ovarian cancers are more likely than others to arise from benign precursors, then the influence of surgical removal of ovarian tissue on risk may vary by tumor subtype. In a population-based case-control study of epithelial ovarian cancer conducted in Washington State, we assessed the risk of ovarian cancer associated with a prior diagnosis of ovarian cysts or endometriosis, and with ovarian surgery, with a focus on characterizing risk among tumor subgroups jointly classified according to the degree of invasiveness and histology.

## Materials and Methods

The study population and methods have been described [12]. Female residents of a thirteen-county area of western Washington State, 35-74 years of age, diagnosed with a primary invasive or borderline epithelial ovarian tumor from 2002 through 2005 were identified through a population-based registry that is part of the Surveillance, Epidemiology, and End Results program of the US National Cancer Institute. Of 1,058 eligible women identified, 812 (76.6%) were interviewed; of the interviewed cases, 595 had invasive disease. Tumors were coded by registry staff according to the third edition of the International Classification of Diseases for Oncology (ICD-O) [13], and these codes were grouped according to guidelines of the World Health Organization [14] into the histologic subgroups of serous (n=452), mucinous (n=112), endometrioid (n=104), clear cell (n=35), and other epithelial tumors (n=109). In the latter group, the most common histologic types were adenocarcinoma, not otherwise specified (NOS, n=34), mixed cell adenocarcinoma (n=33), and carcinoma, NOS (n=16).

Controls were selected by random digit dialing [15] using stratified sampling in five-year age categories, one-year calendar intervals and two county strata in a 2:1 ratio to women with

invasive epithelial ovarian cancer. For 14,561 (82.0%) of the 17,768 telephone numbers belonging to a residence, we determined whether an eligible (i.e., age- and county-eligible and, if so, with at least one ovary and no prior history of ovarian cancer) woman resided there. Of the 1,561 eligible women identified, 1,313 were interviewed (84.1%).

The study was approved by the Institutional Review Board of the Fred Hutchinson Cancer Research Center, and all women provided signed informed consent before participating. Information was obtained during an in-person interview, pertained to the period of time before diagnosis (for cases) or before an assigned, comparable reference date (for controls), and included demographic and lifestyle characteristics, family history of cancer, and menstrual, reproductive, and contraceptive history. Women were asked whether they had ever been diagnosed with an ovarian cyst or endometriosis, and, if so, the age at which the condition was first diagnosed. In a separate section of the interview, women were asked to report all ovarian surgeries prior to diagnosis or reference date, and the month and year in which these surgeries occurred. Women who reported a prior ovarian surgery were asked to report the amount of tissue removed as: part of one or both ovaries; cyst resection; or unilateral oophorectomy.

To reduce the possibility that any increase in risk associated with the diagnosis of a benign gynecologic condition might reflect the identification of such a condition consequent to the presence or symptoms of a borderline or invasive ovarian tumor that had not yet been identified, we excluded from our analyses of the respective variables women whose ovarian cysts (10 controls and 19 cases) or endometriosis (3 controls and 4 cases) were diagnosed during the year before the diagnosis/reference date. Also, we excluded (from the respective analyses) women

who reported ovarian surgery for a benign condition during this time frame (1 control and 3 cases). (One case reported all three of these exposures within the last year, and so was excluded from all analyses.) Lastly, we excluded five case women who were classified by the tumor registry as having primary ovarian cancer, but who reported having had a bilateral oophorectomy prior to cancer diagnosis; for most of these women, pathology reports noted the cancer as arising in an ovarian remnant. Because the length of time in which an ovarian tumor may be present, but not clinically detectable, is unknown, we also conducted analyses that assessed risk among women whose diagnosis of an ovarian cyst or endometriosis and subsequent ovarian surgery was at least 5 years before the diagnosis/reference date.

Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated using unconditional logistic regression. Polytomous logistic regression was used for analyses that separated case women according to the degree of invasiveness and/or histologic type of the tumor. For borderline tumors, we assessed risks of both mucinous and serous histologic types; other types of borderline tumors occurred too infrequently to allow separate analysis. Histologic types of invasive ovarian cancers were grouped as serous, mucinous, endometrioid / clear cell, and "other" for analysis; however, because only a small number of mucinous invasive tumors occurred (n=23), we present only selected results for this subtype.

Data analyses were conducted using STATA statistical software (version 10.0; STATA Corporation, College Station, TX). The analyses were adjusted for the frequency matching variables of age, year of diagnosis/reference date, and county of residence as well as duration of hormonal contraception and number of full-term births. Other characteristics examined as

potentially confounding the associations of interest included: race/ethnicity; cigarette smoking; education; age at menarche; body weight and body mass index (BMI), assessed both at age 30 years and five years before the reference date; tubal ligation; hysterectomy; use of hormone replacement therapy; family history of breast and/or ovarian cancer; personal history of breast cancer; and history of infertility. Additional adjustment for these characteristics did not result in a meaningful change in odds ratios.

## Results

Characteristics of cases and controls have previously been described [12, 16]. Approximately 90% of cases and controls were non-Hispanic white women. Consistent with most prior epidemiologic studies of ovarian cancer, cases were less likely than controls to have given birth, and reported a lesser extent of exposure to hormonal forms of contraception. Both a family history of ovarian cancer and a personal history of breast cancer were more commonly reported by cases than controls.

Unilateral oophorectomy was the most common type of ovarian surgery reported among both cases and controls (Table 1). The remaining ovarian surgeries were reported as excision of a cyst or of a partial ovary, and were grouped for analysis. When the diagnosis of a prior ovarian cyst and/or endometriosis was not considered in the analysis, the overall risk of developing a borderline tumor was slightly increased among women who had had prior ovarian surgery (OR=1.4; 95% CI 0.9-2.2). The strength of this association did not differ by the extent of surgery (i.e., unilateral oophorectomy versus other ovarian surgery; Table 1), and reflected a doubling in risk of borderline mucinous tumors, with no alteration in risk noted for borderline

serous tumors (Table 2). In contrast, prior ovarian surgery was associated with a 30% reduction in risk (95% CI 0.5-1.1) of invasive ovarian cancer (all types combined; Table 1) in analyses that did not incorporate diagnosis of cysts or endometriosis. A reduction in risk associated with prior ovarian surgery was noted for each histologic grouping of invasive ovarian cancers, although these results were imprecise (Table 3; only two women who developed an invasive mucinous ovarian cancer had undergone ovarian surgery (OR=0.9; data not shown)).

A self-reported history of having had an ovarian cyst (diagnosed by a physician) was associated with a small increase in risk of developing a borderline ovarian tumor (OR=1.3, 95% CI 0.9-1.8) and did not vary notably according to whether a woman reported ovarian surgery after her cyst diagnosis (Table 1). In analyses that separated tumors by both histology and invasiveness, the risk of borderline mucinous tumors was elevated among women with a prior ovarian cyst (OR=1.7, 95% CI 1.0-2.8), while risk of borderline serous tumors was not. The risk of a mucinous borderline tumor was, if anything, slightly higher in women who underwent ovarian surgery (Table 2).

A history of a prior ovarian cyst (in analyses that did not account for subsequent ovarian surgery) was not associated with risk of invasive epithelial ovarian cancer (OR for all histologic types combined =1.0, 95% CI 0.7-1.3; Table 1). However, this association appeared to differ according to the receipt of ovarian surgery. While the risk of invasive disease was marginally increased among women who had been diagnosed with a cyst and had no subsequent ovarian surgery, it was reduced when a cyst diagnosis was followed by surgery (OR= 0.6, 95% CI 0.4-0.9, relative to women with no history of a cyst). The reduction in risk associated with surgery

following cyst diagnosis was most evident for serous invasive tumors (Table 3) and remained present in analyses that considered only surgeries that occurred at least five years before the reference date, as well as when women with low-grade serous tumors were excluded (data not shown). Results for "other" histologic types of invasive disease (i.e., those that were not serous, mucinous, endometrioid, or clear cell) resembled those for serous tumors (Table 3). Only four invasive mucinous tumors occurred among women with a prior history of ovarian cysts (OR=0.9; data not shown). The types of ovarian surgery reported by women with ovarian cysts were fairly similar among cases and controls.

Among women who reported having been diagnosed with endometriosis, we observed no association with risk of developing a borderline tumor (Table 1). There was a suggestion that risk of invasive epithelial ovarian cancer associated with a prior diagnosis of endometriosis varied according to subsequent ovarian surgery; relative to women with no history of endometriosis, the OR was 1.6 (95% CI 1.1-2.3) among women with endometriosis and no surgery, while it was 1.2 (95% CI 0.5-2.5) among women with surgery (Table 1). Also, among women with endometriosis who underwent subsequent ovarian surgery, a larger proportion of controls (85%) than cases (60%) reported a unilateral oophorectomy. Among women with endometriosis who had undergone a unilateral oophorectomy, the OR was 0.8 (95% CI 0.3-2.1), whereas it was 3.3 (95% CI 0.7-15.3) among women with this condition who reported a lesser extent of ovarian surgery (i.e., cystectomy or partial oophorectomy; data not shown).

A history of endometriosis was most clearly associated with risk of endometrioid and clear cell types of invasive disease; the risk in the combined group of women with either of these tumor

types was nearly tripled (Table 3). Also, in this group, the increased risk associated with not having had ovarian surgery was somewhat more pronounced. The ORs were 3.2 (95% CI 1.9-5.6) and 1.6 (95% CI 0.4-5.7) among such women who did not or did undergo ovarian surgery, respectively, relative to women with no history of endometriosis (Table 3). However, the small number of cases in this tumor subgroup who had had ovarian surgery limited the precision of these results.

## Discussion

Strengths of the current study include its population-based design and relatively large size; nevertheless, some subgroup analyses were limited by sample size. Also, similar to most other studies that have assessed the relation of ovarian cysts with risk of ovarian cancer, the interpretation of our results is limited by the absence of information on the types of ovarian abnormalities that occurred, as well as the specific reason that ovarian surgery was performed. It is likely that a range of conditions (e.g., physiologic follicular and corpus luteum cysts; endometrioid and dermoid cysts; and benign serous and mucinous tumors) may have been reported as ovarian cysts. The majority of functional ovarian cysts are thought to resolve within 60-90 days; functional cysts that do not resolve within this time frame, as well as other types of ovarian cysts, are more likely to be treated surgically. The size of a cyst and the age and menopausal status of an affected woman may also influence the likelihood of surgical treatment.

We cannot discount the possibility of incomplete or differential recall by cases and controls, nor can we exclude the possibility that characteristics associated with willingness to participate in the study could have resulted in a non-representative sample of cases or controls. However, recall

bias is unlikely to account for differences in risk across tumor subgroups. While differing response proportions across histologic types could influence our results if the exposures examined were linked to our ability to interview cases [16], our response proportions were broadly similar and relatively high for women with borderline (80.6%) and invasive (75.4%) tumors. Also, response proportions were similar (ranging from 77% for mucinous invasive to 88% for endometrioid invasive disease) for all disease subtypes except those grouped as "other invasive" (largely undifferentiated) tumors, among whom we interviewed only 53% of eligible women. Thus, any bias relating to differential participation according to tumor type, if present, might be expected to most strongly influence findings in this latter subgroup.

The exclusion of women whose diagnosis of a benign gynecologic condition or ovarian surgery occurred within the year before the diagnosis/reference date was done to reduce possible bias resulting from 1) symptoms of an existing, as-yet undiagnosed, cancer leading to these diagnoses or surgery or 2) increased or early detection of an asymptomatic tumor during evaluation or treatment for a benign condition. The potential for such a bias to have otherwise influenced our findings is suggested by the larger proportion of cases than controls who reported a cyst diagnosis in that interval. However, an additional potential bias must also be considered: relative to women without a history of a pelvic condition and/ or surgery (in whom no ovarian evaluation is performed), women who undergo ovarian evaluation with no cancer identified will be less likely to be diagnosed with ovarian cancer for some time period. This sort of "healthy screenee" bias [17] would be expected to lead to spuriously low estimates of ovarian cancer risk associated with the diagnosis and/or treatment of some pelvic conditions, at least temporarily. Cognizant of this, we performed analyses focusing on cancer risk associated with ovarian surgeries performed

at least five years earlier, for by five years it is anticipated that little or no such bias should remain.

Only a few studies have assessed ovarian cancer risk in relation to prior ovarian surgery [18-20], and none of these provide data regarding risk of disease subtypes or the possible indication for surgery. In a record linkage study in Canada, the risk of invasive or borderline ovarian cancer among 18,375 women who had undergone unilateral oophorectomy was substantially increased early in the follow-up period (6 months to <2 years after surgery; observed/expected cancers = 3.8, $p<0.001$), with no association observed from 2 to more than 10 years after surgery. In two other reports, however, unilateral oophorectomy was associated with 40% and 80% reductions in risk of ovarian cancer [19, 20]. These disparate results, together with the results of the current study, suggest that the indication for surgery-- as well as differences in risk according to tumor subtype-- should be considered in studies that examine the influence of ovarian surgery on cancer risk.

Prior studies that have assessed whether women with a history of benign ovarian cysts might be at altered risk of ovarian cancer provide inconsistent results and, for the most part, do not provide data for histology-specific risks and/or risks among women with and without subsequent ovarian surgery. Thus, direct comparisons to the current study are limited. A large, pooled analysis of case-control studies [21] included only those cysts identified as a cause of infertility, and reported an overall increased risk of ovarian cancer (OR=1.9, 95% CI 0.8-4.5), with a nearly 4-fold elevation in risk of serous borderline tumors. In contrast, ORs of 0.7 and 1.3, both with wide confidence bounds, were reported for the association of ovarian cysts and invasive

epithelial ovarian cancer in other case-control studies [22, 23]. In one of these [23], subanalyses examined the relative frequency of a benign ovarian cyst identified during a histopathologic review of the malignant lesion. Mucinous [relative risk (RR) =12.9, 95% CI 4.2-39.7] and, to a lesser extent, endometrioid tumors were categorized as more often arising from a benign cyst than were serous tumors. In a Swedish record linkage study, Borgfeldt [24] reported ORs for ovarian cancer of 0.9 (95% CI 0.7-1.1) and 1.2 (95% CI 0.8-1.9) among women with a hospital discharge diagnosis of a benign ovarian cyst/tumor and functional cysts, respectively, with no information on histology of the ovarian cancer; in contrast to the current study, women who underwent ovarian surgery were at a substantially increased risk (OR=8.8, 95% CI 5.2-14.8), again with no information on the histology of the malignant tumor. Crayford et al [25] assessed the impact of removal of persistent benign cysts in a cohort of asymptomatic volunteers whose cysts were identified via ultrasonography, and reported no decrease in the proportion of expected deaths from ovarian cancer relative to other cancers during follow-up. However, this comparison did not allow examination of risk of ovarian cancer (overall or by histologic type) independently associated with such asymptomatic cysts and/or their removal; also, a large proportion of women who underwent surgical investigation for a cyst had both ovaries removed.

Prior studies assessing the impact of endometriosis are rather consistent in their finding of a moderately increased risk of invasive epithelial ovarian cancer, with no increase in risk of borderline tumors [4, 24, 26]; however, the influence of ovarian surgery on cancer risk among women with endometriosis has not been assessed. Studies addressing risk in histologic subgroups also have observed consistently that the association is attributable to an increased risk of endometrioid and clear cell tumors [26, 27], and histopathologic examinations of ovarian

tumors provide evidence of a tendency for endometriosis to be present at a higher frequency among women with endometrioid and clear cell ovarian tumors than among women with other ovarian tumor subtypes [28]. Results of both Swedish [29] and Japanese [27] cohort studies suggest that the association of ovarian cancer risk and endometriosis may be greatest among women whose endometriosis is present on the ovaries. The results of the current study are thus consistent with prior studies and further raise the possibility (albeit with limited precision) that ovarian surgery in women with a diagnosis of endometriosis may lower subsequent cancer risk, relative to women with endometriosis who do not undergo ovarian surgery. Because, in the current study, we have no data regarding the location (i.e., ovarian or other) of endometriosis among women with this diagnosis, our results may 1) underestimate the association of ovarian cancer risk associated with the occurrence of ovarian endometriosis and 2) underestimate the extent to which ovarian surgery may lower risk among women with ovarian endometriosis.

We observed a moderate increase in risk of developing a borderline mucinous tumor among women with a prior ovarian cyst, consistent with the possibility that some benign ovarian abnormalities may serve as precursors of this tumor type. However, risk of this subtype was, if anything, further increased among women who reported ovarian surgery after their cyst diagnosis. These results contrast with a recent hypothesis that removal of benign precursor lesions may preferentially reduce risk of mucinous tumors [1]. It is possible that benign ovarian abnormalities may serve as risk markers, rather than precursors, of subsequent borderline mucinous tumors; or that benign precursors of borderline mucinous tumors, if they exist, may tend to occur in multiple locations or to reoccur.

In contrast, history of a prior ovarian cyst was associated with only a modestly increased risk of invasive ovarian cancer, and among women with cysts and subsequent surgery, risk was reduced; this pattern was most evident for serous invasive tumors. While this common subtype of ovarian cancer has often been stated to arise "de novo", indicating a rapid progression in the absence of an identifiable precursor, evidence is accumulating to support the existence of a precursor (possibly only detectable at the molecular level), either in the ovarian [8] or distal tubal [9] epithelium. Conceivably, such precursors may occur more commonly among women with some types of benign ovarian abnormalities, and may further be removed during the course of subsequent ovarian surgery. While our results require replication, they suggest differences in the relation of ovarian cysts and endometriosis with risk of specific subtypes of epithelial ovarian cancer, as well as the possibility that ovarian surgery after diagnosis of these conditions may reduce risk of invasive disease.

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**Table 1. Risk of epithelial ovarian cancer in relation to gynecologic diagnoses and ovarian surgery overall and among women with borderline and invasive tumors**

| | Controls | Borderline tumors | | Invasive tumors | | All tumors | |
|---|---|---|---|---|---|---|---|
| | (*n*=1313)[a] | Cases (*n*=215)[a] | OR[b] (95% CI) | Cases (*n*=591)[a] | OR[b] (95% CI) | Cases (*n*=806)[a] | OR[b] (95% CI) |
| **Ever had ovarian surgery**[c] | | | | | | | |
| **No** | 1182 | 189 | 1.0 (ref) | 544 | 1.0 (ref) | 733 | 1.0 (ref) |
| **Yes** | 125 | 25 | 1.4 (0.9-2.2) | 43 | 0.7 (0.5-1.1) | 68 | 0.9 (0.6-1.2) |
| **Unilateral oophorectomy** | 75 | 14 | 1.4 (0.8-2.6) | 28 | 0.8 (0.5-1.2) | 42 | 0.9 (0.6-1.4) |
| **Other type of ovarian surgery** | 50 | 11 | 1.4 (0.7-2.7) | 15 | 0.6 ((0.4-1.2) | 26 | 0.8 (0.5-1.4) |
| **Had ovarian surgery at least 5 years before diagnosis/reference date:** | 114 | 24 | 1.5 (0.9-2.5) | 41 | 0.8 (0.5-1.1) | 65 | 0.9 (0.7-1.3) |
| **Ever diagnosed with ovarian cyst**[c] | | | | | | | |
| **No** | 1071 | 160 | 1.0 (ref) | 481 | 1.0 (ref) | 641 | 1.0 (ref) |
| **Yes** | 219 | 47 | 1.3 (0.9-1.8) | 94 | 1.0 (0.7-1.3) | 141 | 1.1 (0.8-1.3) |
| **Ovarian surgery after cyst**[c] | | | | | | | |
| **No** | 121 | 29 | 1.3 (0.8-2.1) | 67 | 1.3 (0.9-1.8) | 96 | 1.3 (1.0-1.8) |
| **Yes** | 95 | 18 | 1.2 (0.7-2.1) | 25 | 0.6 (0.4-0.9) | 43 | 0.7 (0.5-1.1) |
| **Had ovarian surgery at least 5 years before diagnosis/reference date:** | 86 | 17 | 1.3 (0.8-2.3) | 23 | 0.6 (0.4-0.9) | 40 | 0.8 (0.5-1.1) |
| **Ever diagnosed with endometriosis**[c] | | | | | | | |
| **No** | 1199 | 195 | 1.0 (ref) | 521 | 1.0 (ref) | 716 | 1.0 (ref) |
| **Yes** | 94 | 17 | 0.9 (0.5-1.6) | 64 | 1.5 (1.1-2.1) | 81 | 1.3 (1.0-1.8) |
| **Ovarian surgery after endometriosis**[c] | | | | | | | |
| **No** | 73 | 12 | 0.8 (0.4-1.6) | 53 | 1.6 (1.1-2.3) | 65 | 1.4 (1.0-2.0) |
| **Yes** | 20 | 4 | 0.9 (0.3-2.8) | 10 | 1.2 (0.5-2.5) | 14 | 1.1 (0.5-2.2) |
| **Had ovarian surgery at least 5 years before diagnosis/reference date:** | 16 | 4 | 1.2 (0.4-3.8) | 9 | 1.3 (0.6-3.0) | 13 | 1.3 (0.6-2.7) |

[a] Numbers in column may not sum to total due to missing values.
[b] Adjusted for age, calendar year of diagnosis/reference date, county of residence, number of full term births, and duration of hormonal contraception.
[c] For relevant analyses, excludes women with cysts or endometriosis diagnosed within the year before reference, as well as those whose ovarian surgery occurred within the year before the reference date.

**Table 2. Risk of borderline epithelial ovarian cancer in relation to gynecologic diagnoses and ovarian surgery, by histologic type**

| | Controls | Borderline mucinous tumors | | Borderline serous tumors | |
|---|---|---|---|---|---|
| | (*n*=1313)[a] | Cases (*n*=89)[a] | OR[b] (95% CI) | Cases (*n*=116)[a] | OR[b] (95% CI) |
| **Ever had ovarian surgery**[c] | | | | | |
| **No** | 1182 | 74 | 1.0 (ref) | 106 | 1.0 (ref) |
| **Yes** | 125 | 15 | 2.0 (1.1-3.7) | 9 | 0.9 (0.4-1.8) |
| **Unilateral oophorectomy** | 75 | 8 | 1.9 (0.9-4.2) | 6 | 1.0 (0.4-2.4) |
| **Other type of ovarian surgery** | 50 | 7 | 2.2 (0.9-5.3) | 3 | 0.7 (0.2-2.3) |
| **Had ovarian surgery at least 5 years before diagnosis/reference date:** | | | | | |
| | 114 | 15 | 2.3 (1.2-4.3) | 8 | 0.9 (0.4-1.9) |
| **Ever diagnosed with ovarian cyst**[c] | | | | | |
| **No** | 1071 | 62 | 1.0 (ref) | 90 | 1.0 (ref) |
| **Yes** | 219 | 24 | 1.7 (1.0-2.8) | 21 | 1.0 (0.6-1.6) |
| **Ovarian surgery after cyst**[c] | | | | | |
| **No** | 121 | 13 | 1.7 (0.9-3.2) | 15 | 1.2 (0.7-2.2) |
| **Yes** | 95 | 11 | 1.8 (0.9-3.6) | 6 | 0.7 (0.3-1.7) |
| **Had ovarian surgery at least 5 years before diagnosis/reference date:** | | | | | |
| | 86 | 11 | 2.1 (1.0-4.2) | 5 | 0.7 (0.3-1.8) |
| **Ever diagnosed with endometriosis**[c] | | | | | |
| **No** | 1199 | 80 | 1.0 (ref) | 106 | 1.0 (ref) |
| **Yes** | 94 | 6 | 0.9 (0.4-2.2) | 10 | 0.9 (0.5-2.0) |
| **Ovarian surgery after endometriosis**[c] | | | | | |
| **No** | 73 | 3 | 0.7 (0.2-2.2) | 8 | 1.0 (0.4-2.3) |
| **Yes** | 20 | 3 | 1.6 (0.4-5.8) | 1 | 0.4 (0.1-3.3) |
| **Had ovarian surgery at least 5 years before diagnosis/reference date:** | | | | | |
| | 16 | 3 | 2.2 (0.6-8.1) | 1 | 0.6 (0.1-4.5) |

[a] Numbers in column may not sum to total due to missing values.
[b] Adjusted for age, calendar year of diagnosis/reference date, county of residence, number of full term births, and duration of hormonal contraception.
[c] For relevant analyses, excludes women with cysts or endometriosis diagnosed within the year before reference, as well as those whose ovarian surgery occurred within the year before the reference date.

**Table 3. Risk of invasive epithelial ovarian cancer in relation to gynecologic diagnoses and ovarian surgery, by histologic type of tumor**

| | Controls | Serous invasive tumors | | Endometrioid and clear cell invasive tumors | | Other invasive, excluding mucinous | |
|---|---|---|---|---|---|---|---|
| | (*n*=1313)[a] | Cases (*n*=332)[a] | OR[b] (95% CI) | Cases (*n*=133)[a] | OR[b] (95% CI) | Cases (*n*=103)[a] | OR[b] (95% CI) |
| **Ever had ovarian surgery**[c] | | | | | | | |
| **No** | 1182 | 304 | 1.0 (ref) | 121 | 1.0 (ref) | 98 | 1.0 (ref) |
| **Yes** | 125 | 26 | 0.8 (0.5-1.2) | 10 | 0.8 (0.4-1.6) | 5 | 0.5 (0.2-1.3) |
| **Unilateral oophorectomy** | 75 | 17 | 0.8 (0.5-1.4) | 6 | 0.8 (0.3-2.0) | 3 | 0.5 (0.2-1.6) |
| **Other type of ovarian surgery** | 50 | 9 | 0.7 (0.3-1.4) | 4 | 0.7 (0.3-2.2) | 2 | 0.5 (0.1-2.1) |
| **Had ovarian surgery at least 5 years before diagnosis/reference date:** | | | | | | | |
| | 114 | 26 | 0.8 (0.5-1.3) | 9 | 0.8 (0.4-1.6) | 4 | 0.4 (0.2-1.2) |
| **Ever diagnosed with ovarian cyst**[c] | | | | | | | |
| **No** | 1071 | 284 | 1.0 (ref) | 94 | 1.0 (ref) | 84 | 1.0 (ref) |
| **Yes** | 219 | 45 | 0.8 (0.6-1.1) | 30 | 1.5 (0.9-2.4) | 15 | 0.9 (0.5-1.6) |
| **Ovarian surgery after cyst**[c] | | | | | | | |
| **No** | 121 | 33 | 1.1 (0.7-1.7) | 20 | 1.9 (1.1-3.2) | 11 | 1.2 (0.6-2.3) |
| **Yes** | 95 | 11 | 0.4 (0.2-0.8) | 9 | 1.0 (0.5-2.1) | 4 | 0.5 (0.2-1.5) |
| **Had ovarian surgery at least 5 years before diagnosis/reference date:** | | | | | | | |
| | 86 | 11 | 0.5 (0.2-0.9) | 8 | 1.0 (0.4-2.1) | 3 | 0.5 (0.1-1.5) |
| **Ever diagnosed with endometriosis**[c] | | | | | | | |
| **No** | 1199 | 298 | 1.0 (ref) | 105 | 1.0 (ref) | 96 | 1.0 (ref) |
| **Yes** | 94 | 31 | 1.3 (0.9-2.1) | 26 | 2.8 (1.7-4.7) | 7 | 0.9 (0.4-2.0) |
| **Ovarian surgery after endometriosis**[c] | | | | | | | |
| **No** | 73 | 24 | 1.3 (0.8-2.2) | 23 | 3.2 (1.9-5.6) | 6 | 0.9 (0.4-2.3) |
| **Yes** | 20 | 6 | 1.3 (0.5-3.2) | 3 | 1.6 (0.4-5.7) | 1 | 0.7 (0.1-5.1) |
| **Had ovarian surgery at least 5 years before diagnosis/reference date:** | | | | | | | |
| | 16 | 6 | 1.5 (0.6-3.9) | 2 | 1.5 (0.3-6.7) | 1 | 0.8 (0.1-6.5) |

[a] Numbers in column may not sum to total due to missing values.
[b] Adjusted for age, calendar year of diagnosis/reference date, county of residence, number of full term births, and duration of hormonal contraception.
[c] For relevant analyses, excludes women with cysts or endometriosis diagnosed within the year before reference, as well as those whose ovarian surgery occurred within the year before the reference date.