

Subsequent Development of Epithelial Ovarian Cancer After Ovarian Surgery for Benign Ovarian Tumor: A Population-Based Cohort Study

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Purpose: The goal of the current study is to determine the risk of subsequent development of epithelial ovarian cancer (EOC) in women after ovarian surgery for benign ovarian tumors.

Patients and Methods: We conducted the nationwide population-based historic cohort study using the National Health Insurance Research Database (NHIRD) of Taiwan. Eleven thousand six hundred twenty women who underwent ovarian surgery for ovarian benign diseases were analyzed. The collected data included age, types of ovarian surgery, medical history by Charlson comorbidity index (CCI), infertility (yes/no), pelvic inflammatory disease (PID) (yes/no), tubal ligation (yes/no), total/subtotal hysterectomy (TH/STH) (yes/no), and endometrioma (yes/no). We used the Kaplan–Meier method and the Log-rank test to evaluate the risk factors. Cox proportional hazard methods were used to evaluate risk factors for the subsequent development of EOC. Multivariate analysis using Cox stepwise forward regression was conducted for the covariate selected in univariate analysis. Hazard ratio (HR) and 95% confidence interval (CI) were calculated using the Wald test.

Results: Subsequent EOC incidence rate (IR, incidence per 10,000 person-years) of women after ovarian surgery for benign ovarian tumors was 2.98. Separating into four groups based on different age, IR of EOC was 1.57 (<30 years), 4.71 (30–39 years), 3.59 (40–49 years) and 0.94 (≥50 years), respectively. Univariate and multivariate analyses identified only high level of CCI (≥2 or more) as an independent risk factor for subsequent development of EOC in women after ovarian surgery for benign ovarian tumors (HR 59.17, 95% CI 7.50–466.80 in women with CCI level of 2 and HR 190.68, 95% CI 24.33–2494.19, in women with CCI level ≥3, respectively).

Conclusion: Our results, if confirmed, suggest that women with other comorbidities (CCI) should be well informed that they may have a higher risk of subsequent development of EOC when ovarian surgery is planned even though the final pathology showed a benign ovarian tumor.

Keywords: benign ovarian tumor, cohort study, epidemiology, epithelial ovarian cancer, ovarian surgery, risk

Introduction

Worldwide, epithelial ovarian cancer (EOC) is the most common cause of gynecological cancer death because of silent development and an advanced-stage at diagnosis.^{1–4} Treatment requires expert multidisciplinary care, including optimal definite cytoreductive surgery before/after (interval surgery) multiagent chemotherapy plus various kinds of targeted therapy, such as poly(ADP-ribose) polymerase

inhibitors (PARP inhibitors), angiogenesis inhibitors (AIs), immune checkpoint inhibitors, and so on.^{5–11} Strides have been made to improve either progression-free survival or overall survival.^{5–11} However, the outcome of EOC remains unsatisfactory with substantial debilitation to patients and the health care system. Given the non-specific symptoms and aggressive natural history of EOC, and of most importance, the lack of established or effective screening test, the identification of risk factors, which have consistently been linked to EOC and additional risk-reductive strategies, are very important.^{12–24}

Many factors are reported to have a correlation with the development of EOC.^{12–45} For example, endometriosis has long been shown to be risky of the development of EOC.^{25–34} Several studies have specifically addressed the higher risk of EOC in patients with a history or a diagnosis of endometriosis. Similar to the design from many population-based cohort studies,^{46–50} the majority of the study enrolled the relatively “healthy” women as the reference (standardized incidence rate [SIR]: standardized incidence per 10,000 person-years) for comparison, but the risk calculation is still varied greatly.^{35–45} In the real world, these “healthy” women might not receive any kinds of gynecological surgery in their life, such as tubal surgery, ovarian surgery, uterine surgery, including total/subtotal hysterectomy (TH/STH). However, some of these surgical procedures, such as bilateral salpingo-oophorectomy (BSO), bilateral oophorectomy (BO), TH and STH have long been shown to decrease the risk of the development EOC after surgery.^{12,17,20,23,39} In addition, only a few studies have assessed EOC risk related to prior ovarian surgery.^{51–56} Therefore, we conducted a large population-based cohort study to evaluate the risk of subsequent development of EOC in women after ovarian surgery for benign ovarian tumors.

Patients and Methods

The Taiwanese National Health Insurance (NHI) program was founded in 1995, which enrolled more than 99% of the inhabitants living in Taiwan, and as of December 2010, it covered more than 99% of the population and contracted with almost all medical centers, hospitals, and clinics in Taiwan.^{46–50} This program also includes all inpatient and outpatient medical benefit claims.^{57–62} The National Health Research Institute (NHRI) cooperates with the Bureau of NHI to establish an NHI Research Database (NHIRD) in 2000, and guards the privacy and confidentiality of all beneficiaries and provides health insurance data to

researchers who have obtained ethical approval.^{25,40,41,57} The Longitudinal Health Insurance Database in 2000 (LHID 2000) contains all the original enrollment and claims data of 1 million beneficiaries, randomly sampled from the beneficiaries of the NHIRD during the period 1996 and 2000. The data of the sampled subjects in the LHID 2000 are representative of all beneficiaries, including age, sex, insurance cost, details of medical orders, procedures, and medical diagnoses with codes based on the International Classification of Diseases, Ninth Revision, Clinical Modifications (ICD9-CM).^{25,40,41,63} The identification of all patients in the LHID is encrypted and protects the privacy of patients. The NHRI provides access to the database for analysis.

This study was a retrospective population-based cohort study, containing a total of 322,534 women aged ≥ 20 years of age. This study was based in part on data from the Taiwan National Health Insurance Research Database provided by the National Health Insurance Administration, Ministry of Health and Welfare and managed by National Health Research Institutes. According to the written operating procedures, Good Clinical Practice (GCP), and the applicable regulatory requirements, this study project was approved by the Institutional Review Board of Taipei Veterans General Hospital (IRB-TPEVGH No. 2019-07-039BC), and the board is organized under and operates according to International Conference on Harmonisation (ICH/WHO GCP) and the applicable laws and regulation. In addition, the study was carried out in accordance with the principles to the Declaration of Helsinki. The requirement of patient-informed consent was waived, since the identification of the study subjects in the database has been erased before we obtained the data.

Women treated with first ovarian surgery were included. However, women with a history of ovarian cancer before this enrollment and without any visit to obstetricians or gynecologists during the study period were excluded. To increase the identification validity of women with ovarian surgery in the administrative data set, only women with surgery-confirmed diagnosis of benign ovarian tumors during the period between January 1, 2000, and December 31, 2010, were included. A total of 11,620 patients were enrolled in the current study (Figure 1).

EOC was initially detected using inpatients with a surgico-pathological diagnosis and validated using the major disease files (ICD-9-CM 183.0 from Registry for Catastrophic Illness Patients). The histological types were

Fig.1 Flow-Chart

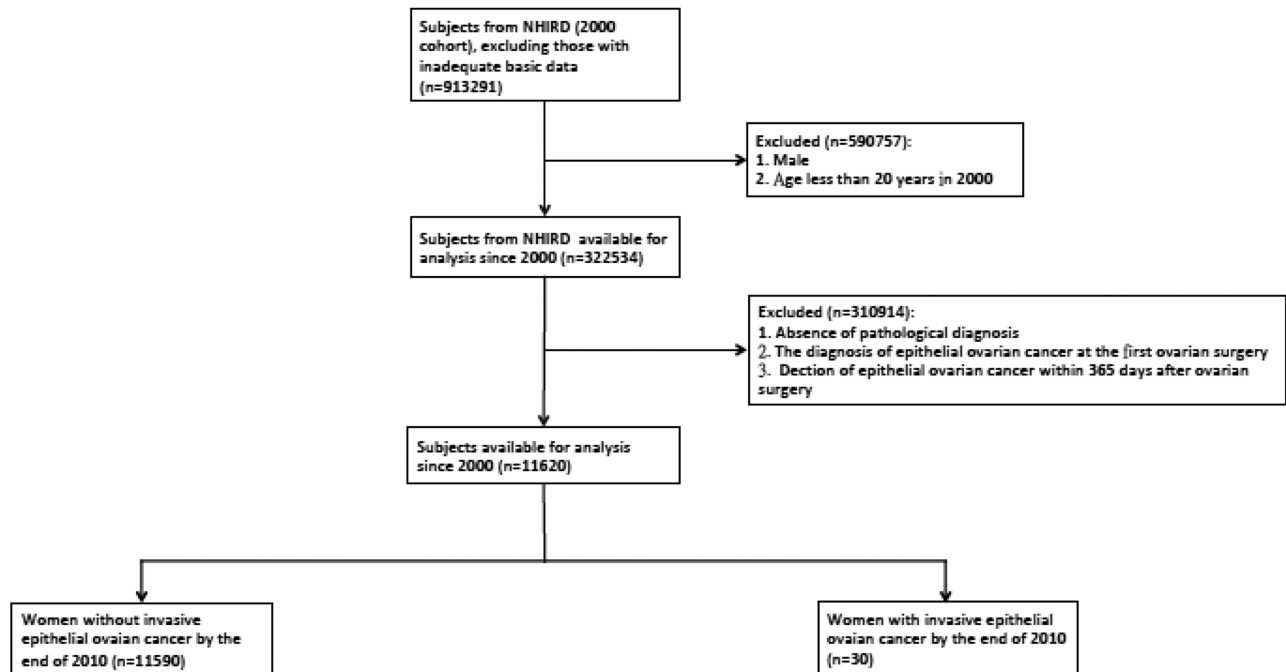


Figure 1 Flowchart of the current cohort study.

according to the World Health Organization Classification of Tumors.^{41,64,65} The included histological types were serous (8441/3, 8460/3, 8461/3), mucinous (8470/2, 8470/3, 8471/3, 8480/3, 8482/3), endometrioid (8380/3, 8382/3, 8383/3), clear cell (8310/3, 8313/3), malignant Brenner (9000/3), undifferentiated (8020/3, 8021/3), and carcinosarcoma (8950/3, 8980/3, 8981/3). Since EOC can be diagnosed at the first ovarian surgery as well as synchronous benign ovarian tumors and uterine/cervical malignancy can be incidentally found, to clarify the subsequent risk of developing EOC in women after ovarian surgery, we excluded patients with the diagnosis of EOC at the first ovarian surgery and furthermore excluded women with a diagnosis of EOC within 365 days after her first ovarian surgery.

We used following ICD-9 CM codes (65.xx) to enrolled patients who underwent ovarian surgery, and for example, ICD-9 CM codes 65.01, 65.09, 65.31 or 65.39 were for unilateral oophorectomy (UO). The other detailed ICD-9 CM codes are shown in [supplement 1](#). In addition, to verify the role of tubal ligation, and total/subtotal hysterectomy on the subsequent development of EOC, these ICD-9 CM codes, including 68.3, 68.4, 68.5, 68.6, 68.7, 68.8 and 68.9 as well as 66.32 and 66.39 were used to identify these types of surgery.

To analyze the role of age in women after ovarian surgery for benign ovarian diseases on the subsequently developing EOC, we used 4 age groups (those <30, 30–39, 40–39, and ≥50 years) to perform the age stratification analyses.

Statistical Analysis

Starting from the cohort index date, the study subjects were followed until the occurrence of hospitalization with EOC (ICD-9-CM 183.0) or death, whichever came first, or at the end of the study (December 31, 2010) if no EOC or death. The incidence rate of EOC was calculated every 10,000 person-years (IR, incidence per 10,000 person-years). Cases lost during the follow-up and those with subsequent development of EOC at the end of the follow-up period were considered censored observations. Survival curves were generated using the Kaplan–Meier method, and the differences between survival curves were calculated using the Log-rank test. Cox proportional hazard methods were used to evaluate prognostic factors for survival. Multivariate analysis using Cox stepwise forward regression was conducted for the covariate selected in univariate analysis. Hazard ratio (HR) and 95% confidence interval (CI) were calculated using the Wald test. A P value <0.05 was considered to be statistically significant. All statistical analyses were

conducted with SAS version 9.3 (SAS Institute, Cary, NC) and Stata Statistical Software, version 12.0 (Stata Corporation, College Station, TX).

Results

Among the total of 11,620 subjects, 30 subjects developed invasive EOC between 2001 and 2010 (Figures 1 and 2).

The subtypes of invasive EOC included serous type (n=11, 36.7%), endometrioid type (n=7, 23.3%), clear cell type (n=6, 20.0%), mucinous type (n=5, 16.7%), and mixed type (n=1, 3.3%). The total person-years of follow-up were 100 815 person-years. The EOC IR of women treated with ovarian surgery for benign ovarian tumors was 2.98 per 10,000 person-years. Characteristics at baseline are shown in Table 1.

In term of the age on the risk of development of EOC in women after ovarian surgery for ovarian benign diseases, our results indicate that IR of EOC is consistently higher when age ranged between 30 and 39 years (IR of EOC 4.71), as well as between 40 and 49 years (IR of EOC 3.59) compared with that (IR of EOC 1.57) of the youngest group (women <30 years). It is interesting to find that women aged ≥ 50 years had a lower IR of EOC (0.94 per 10,000 person-years) (Table 2).

Univariate analysis showed that only higher Charlson comorbidity index (CCI) was associated with an increasing risk for subsequent development of EOC in women after

ovarian surgery for benign ovarian diseases (Table 3). As expected, TH or STH was associated with a decreased risk of subsequent development of EOC after ovarian surgery for benign ovarian diseases (Table 3). Multivariate analysis further confirmed that only higher CCI (≥ 2) was an important and independent risk factor associated with a significantly increased risk of subsequent development of EOC (Table 4). By contrast, hysterectomy (total or subtotal) or total removal of the ovary (BSO or BO) was not associated with the risk of subsequent development of EOC (Table 4).

Discussion

The impact of ovarian surgery for benign ovarian tumors on the subsequent risk of the developing EOC has seldom been evaluated.^{51–55} In this population-based cohort study using linked administrative data, we found that the EOC IR of women after ovarian surgery for benign ovarian tumor was 2.98 per 10,000 person-years, which is higher than EOC SIR of women (ranging from 0.5 to 1.0 per 10,000 person-years) in the general population in Taiwan,^{25,27,40,41,64–75} suggesting that ovarian surgery for any histology types of benign ovarian tumors might indeed be associated with increased subsequent development of EOC. We supposed a 3-fold to 6-fold increase if we used the EOC SIR as a reference from the general population.^{25,27,40,41,65–77}

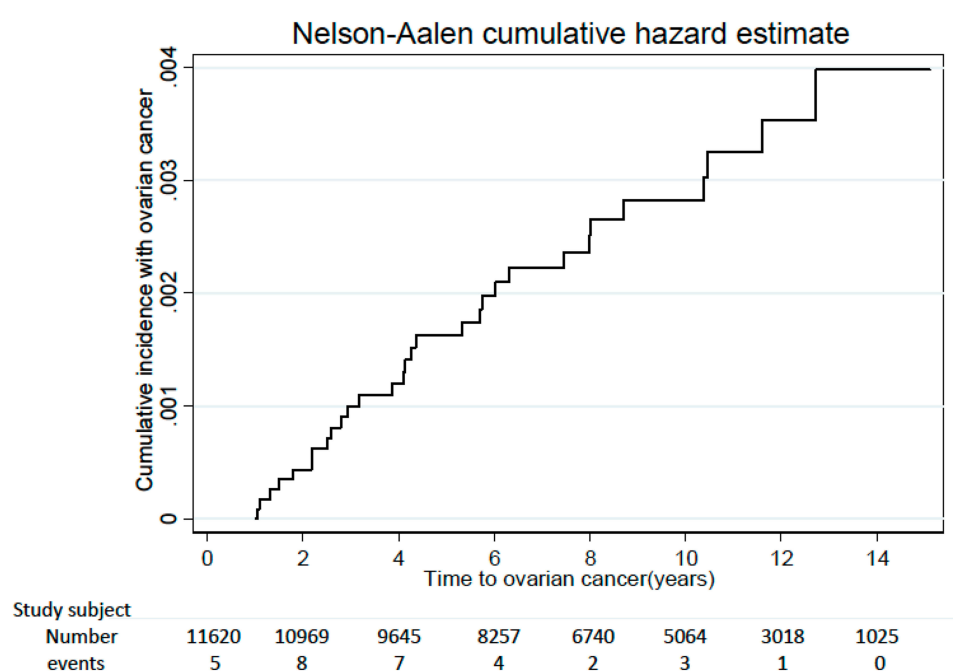


Figure 2 Accumulation number of patients developing EOC during this cohort period.

Table 1 Baseline Characteristics of the Study Subjects (Follow-Up Period Was 100 815 Person-Years)

Variables	Number (n=11,620)	%
Development of epithelial ovarian cancer		
Yes	30	0.26
No	11,590	99.74
Socioeconomic status		
≥40,000	1273	10.96
20,000–39,999	2874	24.73
<20,000	4649	40.01
Others	2824	24.30
Work		
Yes	10,318	88.80
No	1302	11.20
Urbanization		
Urban	3802	32.72
Suburban	5357	46.10
Rural	2461	21.18
Total/subtotal hysterectomy		
Yes	4329	37.25
No	7291	62.75
Ovarian surgery		
Partial oophorectomy	7596	65.37
UO/USO ± partial oophorectomy	979	8.43
BSO/BO	3045	26.20
Repeated ovary surgery		
Yes	717	6.17
No	10,903	93.83
Tubal ligation		
Yes	142	1.22
No	11,478	98.78
Pelvic inflammatory disease		
Yes	8909	76.67
No	2711	23.33
Infertility		
Yes	1168	10.05
No	10,452	89.95
Cardiovascular disease		
Yes	1168	10.05
No	10,452	89.95
Diabetes mellitus		
Yes	1365	11.75
No	10,255	88.25
Chronic liver disease		
Yes	361	3.11
No	11,259	96.89
Surgery confirmed ovarian endometrioma		
Yes	4408	37.93
No	7212	62.07

(Continued)

Table 1 (Continued).

Variables	Number (n=11,620)	%
Rheumatic disease		
Yes	531	4.57
No	11,089	95.43
Charlson comorbidity index		
0	5749	49.48
1	2391	20.58
2	1488	12.81
≥3	1992	17.14

Abbreviations: BSO/BO, bilateral salpingo-oophorectomy/bilateral oophorectomy; USO/UO, unilateral salpingo-oophorectomy/unilateral oophorectomy.

In Kreiger et al's study, there was no reduction of the development of subsequent EOC in women after UO, and in addition, the risk is statistically significantly increased early in the follow-up periods, with odds ratio (OR) ranging from 1.12 to 3.83.⁵¹ However, with increasing length of follow-up, the OR declined toward unity with OR ranging from 1.31 in the follow-up period between 2 years and 5 years to 0.90 in the follow-up period of more than 10 years.⁵¹ The following Chiaffarino's report also supports this concept that there was no protective role for subsequent development of EOC in women who have been treated with UO/USO (OR: 0.60, 95% CI 0.3–1.4) after adjustment of additional terms for education, parity, oral pill use, and family history of ovarian and breast cancer in first-degree relatives.⁵² However, not all data supported the increased risk of subsequent EOC in women after ovarian surgery. Earlier studies from Annegers et al in 1979 and Beard et al in 2000 showed the conflicted results, and both studies supported the protective role of oophorectomy in the reduction of subsequently developing EOC.^{53,54} In 2013, Melin et al suggested that radical ovarian surgery for endometriosis, including UO as well as complete resection of all visible endometriosis, is protective against later development of EOC,⁴³ although the potentially increasing risk of morbidity during the surgery should be reminded.^{78–97}

In addition, clinicians might have consensus that sometimes it is hard to totally eradicate all visible or invisible lesions, including ovarian tissues, especially when the certain situations exist, such as deep infiltration endometriosis, severe adhesion between ovary and surrounding pelvic tissue or organs, which will make a total removal of ovary difficult (remnant ovarian syndrome).^{102–105} Moreover, these disparate results suggest that the different histology types of benign ovarian tumors should be considered in studies that

Table 2 The Incidence Rate of Epithelial Ovarian Cancer in Women Treated with Ovarian Surgery for Benign Ovarian Diseases Based on the Different Age Status

	Age < 30 Years	Age 30–39 Years	Age 40–49 Years	Age ≥ 50 Years	P*
	n = 1883	n = 3484	n = 3565	n = 2688	
Number of patients with EOC	3	14	11	2	
Incidence per 10,000 person-years	1.57	4.71	3.59	0.94	
Crude HR (95% CI)	1.00 (Reference)	2.986 (0.858–10.398)	2.277 (0.635–8.169)	0.593 (0.099–3.551)	0.0850
P**		0.0857	0.2066	0.5668	
Adjusted HR ¹ (95% CI)	1.00 (Reference)	2.998 (0.858–10.470)	2.415 (0.639–9.128)	0.610 (0.091–4.069)	0.0964
P**		0.0853	0.1938	0.6095	
Adjusted HR ² (95% CI)	1.00 (Reference)	1.347 (0.374–4.849)	0.468 (0.117–1.882)	0.052 (0.008–0.348)	0.0002***
P**		0.6489	0.2851	0.0023**	
Adjusted HR ³ (95% CI)	1.00 (Reference)	3.312 (0.950–11.542)	4.029 (1.079–15.047)	1.298 (0.186–9.065)	0.1072
P**		0.0601	0.0382*	0.7924	
Adjusted HR ⁴ (95% CI)	1.00 (Reference)	3.251 (0.931–11.352)	4.062 (1.051–15.707)	1.200 (0.157–9.160)	0.0990
P**		0.0646	0.0422*	0.8605	
Adjusted HR ⁵ (95% CI)	1.00 (Reference)	1.540 (0.431–5.504)	1.076 (0.265–4.364)	0.142 (0.020–1.013)	0.0326*
P**		0.5064	0.9182	0.0515	

Notes: IR: incidence rate (incidence per 10,000 person-years); EOC: invasive epithelial ovarian cancer; HR: hazard ratio; 95% CI: 95% confidence interval; P*: comparison among all groups. P**: comparison between study group and reference group (age <30 years). Adjusted HR¹: adjustment for pelvic inflammatory disease, infertility status, cardiovascular disease, diabetes mellitus, chronic liver disease, and rheumatic disease. Adjusted HR²: adjusted for pelvic inflammatory disease, infertility, and Charlson comorbidity index (CCI). Adjusted HR³: adjustment for total/subtotal hysterectomy, unilateral oophorectomy, unilateral salpingo-oophorectomy, bilateral oophorectomy, bilateral salpingo-oophorectomy, tubal ligation. Adjusted HR⁴: adjustment for conditions of HR¹ and HR³. Adjusted HR⁵: adjustment for conditions of HR² and HR³. * P < 0.05, ** P < 0.01, *** P < 0.001.

examine the influence on EOC risk.⁸⁰ As shown above, our results indicated that the initial procedure of ovarian surgery may not be associated with the decreased risk of subsequent development of EOC, even though BO or BSO was performed at the initial surgery.

Although it is hard to explain the aforementioned finding, one presumption is about the mysterious etiology of EOC.^{98–101} Conventionally, according to the histology, it is easy to classify EOC as serous, endometrioid, clear cell, mucinous, and other subtypes, which is also supported by some experts, such as Dr. Prat who further separated serous into high grade and low grade based on distinct histological features and molecular genetics.¹⁰¹ However, for a convenient way of conceptualizing different mechanisms of tumorigenesis, the dualistic classification of EOC into “type I” and “type II” is often and popularly applied in the research setting, although it may conflict with recent molecular insights of the etiology of EOC.⁹⁸ The best example is the endometriosis-associated EOC (clear cell and endometrioid), which is traditionally classified as “type I”, it is absence of assuming an indolent course or type I genetic profile.⁷⁷

In the current study, the distribution of histology types of EOC in women after ovarian surgery for benign ovarian tumor seemed to be similar to the data of the national

population-based registry in Taiwan,⁶⁵ wherein the former was compared with the latter with data showing 36.7% versus 41.4% in serous type, 20.0% versus 24.5% in mucinous type, 23.3% versus 17.5% in endometrioid type, 20% versus 13.7% in clear cell type and 3.3% versus 2.9% in others, respectively, suggesting that the subjects in the current study can be considered as part of the general population with minimal selection bias in Taiwan.

One important finding in the current study is the identification of high level of CCI (CCI=2) as an important factor associated with a near 60-fold increase in risk of subsequent development of EOC compared to women without CCI or lower CCI (CCI=1) (HR 59.17, 95% CI 7.50–466.80), which was near 200-fold increase compared to those in women with no or lower CCI (CCI=1). It suggests that when we deal with women with benign ovarian tumors who plan to undergo ovarian surgery, we should inform the subsequent risk of EOC development for those patients with higher CCI. In fact, CCI is the most used score to measure comorbidity, which is applied to a health care administrative database, and can predict relative mortality adequately.^{106–110} It is well known patients with higher CCI have a higher risk of surgery and/or anesthesia-associated morbidity and mortality. The current study in Danish found that patients with surgery

Table 3 Univariate Cox Regression Analysis

Characteristics	Number of Patients		
	11,620	Hazard Ratio (95% Confidence Interval)	P
Endometrioma			
No	7212	1 (Reference)	
Yes	4408	1.714 (0.838–3.507)	0.1403
Age			
≤39	5367	1 (Reference)	
>39	6253	0.716 (0.348–1.475)	0.3654
Total /subtotal hysterectomy			
No	7291	1 (Reference)	
Yes	4329	0.252 (0.088–0.722)	0.0103*
Ovarian surgery			
BSO/BO	3045	1 (Reference)	0.2753
UO/USO ± partial oophorectomy	979	3.047 (0.546–16.988)	0.2038
Partial oophorectomy	7596	2.253 (0.782–6.494)	0.1327
Tubal ligation			
No	11,478	1 (Reference)	
Yes	142	0	0.9847
Pelvic inflammatory disease			
No	2711	1 (Reference)	
Yes	8909	0.942 (0.404–2.195)	0.8892
Infertility			
No	10,452	1 (Reference)	
Yes	1168	1.805 (0.691–4.715)	0.2282
Cardiovascular disease			
No	10,452	1 (Reference)	
Yes	1168	0.584 (0.139–2.452)	0.4626
Diabetes mellitus			
No	10,255	1 (Reference)	
Yes	1365	1.086 (0.379–3.112)	0.8781
Chronic liver disease			
No	11,259	1 (Reference)	
Yes	361	0	0.9843
Rheumatic disease			
No	11,089	1 (Reference)	
Yes	531	1.423 (0.339–5.972)	0.6302
Charlson comorbidity index			
0	5749	1 (Reference)	0.0017**
1	2391	0	0.9880
2	1488	37.531 (4.804–293.193)	0.0005***
≥3	1992	53.484 (7.160–399.531)	0.0001***

Notes: *P < 0.05, **P < 0.01, ***P < 0.001.

Abbreviations: BSO/BO, bilateral salpingo-oophorectomy/bilateral oophorectomy; USO/UO, unilateral salpingo-oophorectomy/unilateral oophorectomy.

for hip fracture in a high level of CCI (≥3) had a significantly higher risk of reoperation (HR 2.36, 95% CI 1.19–4.69).^{1,19} Our results also found that patients with

a high level of CCI indeed have a statistically significantly higher risk of subsequent development of EOC after ovarian surgery for benign ovarian tumors. Therefore, if the

Table 4 Multivariate Cox Regression Analysis

Characteristics	Number of Patients		
	11,620	Hazard Ratio (95% Confidence Interval)	P
Endometrioma			
No	7212	1 (Reference)	
Yes	4408	1.007 (0.445–2.278)	0.9866
Age			
≤39	5367	1 (Reference)	
>39	6253	0.880 (0.346–2.235)	0.7873
Total/subtotal hysterectomy			
No	7291	1 (Reference)	
Yes	4329	0.362 (0.081–1.614)	0.1826
Ovarian surgery			
BSO/BO	3045	1 (Reference)	
UO/USO ± partial oophorectomy	979	2.122 (0.304–14.824)	0.4482
Partial oophorectomy	7596	0.883 (0.195–3.998)	0.8722
Tubal ligation			
No	11,478		
Yes	142		
Pelvic inflammatory disease			
No	2711	1 (Reference)	
Yes	8909	0.760 (0.301–1.920)	0.5622
Infertility			
No	10,452	1 (Reference)	
Yes	1168	1.387 (0.478–4.025)	0.5469
Charlson comorbidity index			
0	5749	1 (Reference)	0.0017**
1	2391	0	0.9882
2	1488	59.165 (7.499–466.804)	0.0001***
≥3	1992	190.679 (24.333–1494.186)	<0.0001***

Notes: **P < 0.01, ***P < 0.001.

Abbreviations: BSO/BO, bilateral salpingo-oophorectomy/bilateral oophorectomy; USO/UO, unilateral salpingo-oophorectomy/unilateral oophorectomy.

future fertility is not required anymore, the need for additional total/subtotal hysterectomy plus oophorectomy and/or salpingectomy or salpingo-oophorectomy could be discussed to weigh the ratio of risk and benefit.^{79–97}

In the current study, however, adding total/subtotal hysterectomy to the benign ovarian surgery was not associated with a risk reduction on the subsequent development of EOC after ovarian surgery. This finding argued against a long-term belief that hysterectomy with/without oophorectomy can protect against EOC effectively,^{51–55} but supported the results obtained from studies challenging aforementioned long-held belief, including a recent population-based record-linkage study by Dixon-Suen et al¹² and a recent meta-analysis by Wang et al.⁸¹ Dr. Dixon-

Suen et al showed that hysterectomy alone was not associated with risk of EOC overall (HR 0.98, 95 CI 0.85–1.11) or with the risk of most common serous subtype (HR 1.05, 95% CI 0.89–1.23), suggesting that substantial alteration of EOC risk can not be achieved by hysterectomy with ovarian conservation for most women.¹²

Finally, we evaluated the relationship between age and EOC risk, considering age as an important factor for the development of EOC.^{12,13,20,23,24,40,41} Different from our previous studies,^{40,41} EOC IR remained consistent in women aged between 30 and 50 years (Table 2). EOC IR in the younger population (age <30 years) and elder population (age ≥50 years) was low. It can be explained by the relatively conservative surgery in women during reproductive age due

to fertility need. By contrast, when peri-/post-menopausal women need ovarian surgery, the procedure of TH/STH and BSO could always be taken into consideration despite the benign nature.

The strength of the current study includes a large population-based cohort study, Asian population, Chinese population, enrolled subjects who have been treated with ovarian surgery for benign ovarian tumor (definite operation procedure), chronic medical illness (CCI), and infertility or pelvic inflammatory disease.

However, there are some limitations. First, except endometrioma, other subtypes of benign ovarian tumors were not further stratified. Second, the specific reason (indication) for ovarian surgery was not available. For example, the torsion of the ovary as an emergency might be an indication of ovarian surgery, but the relevant information was not available in the database. However, our data were obtained from the Taiwanese NHI program, of which the data could not be included if no pathology was performed. In addition, we also exclude those who do not have a pathology report, which has been shown in Figure 1. Third, the size of the cyst has not been included. Fourth, only a small number of EOC developed during the follow-up period, limiting the precision of our risk estimates in the study. However, this limitation might be due to the low incidence rate of this targeted disease (EOC). Additionally, compared with previous studies with a large sample size, only 10 cases of EOC occurred during the 10-year follow-up period.⁹⁶ In the Japanese study, during the follow-up period, only 4 cases developed subsequent EOC after ovarian surgery.⁵⁶ Recently, Murakami et al summarized 32 published articles to monitor the risk of EOC from ovarian endometrial cysts and only identified 79 cases.²⁶ The relatively long interval between enrollment in the cohort and the diagnosis of an EOC, along with the exclusion of those subjects with a diagnosis of invasive EOC within 365 days after ovarian surgery for benign ovarian tumors, suggest that the observed increase in risk was not the preexisting tumors themselves. Finally, we had neither profile of gene (for example, BRCA status) nor the data of parity, and also did not have information about the detailed of infertility and other surgery or medication history, such as oral contraceptive, hormone therapy in the database, all of which are associated with the increased or decreased risk of development of EOC.^{111–115} In Taiwan, the examination of BRCA status is not covered by insurance of the Taiwan Bureau of National Health Insurance and Ministry of Health and Welfare. There are many current clinical

studies showing better outcomes in EOC patients with BRCA1/BRCA2 mutants after maintenance therapy of PARP inhibitors.^{6–9,116}

The lack of cost-effective screening method and unavoidable worst prognosis while EOC is diagnosed remind us of the consideration of using prevention strategy to decrease the occurrence of EOC. Identification of risk factors for the development of EOC can further augment the effects to decrease EOC-related morbidity and/or mortality. In the current study, we disclosed women with higher comorbidity ($CCI \geq 2$) disease undergoing ovarian surgery for benign ovarian tumors indeed have a higher risk of subsequent development of EOC. Based on the aforementioned findings, we commend that risk/benefit ratio should be balanced carefully, because this increased risk not only relies on how well we help with prevention of subsequent development of EOC, but also depends on how accurately we protect patients from the danger of a false-positive result (benign ovarian tumors-associated overtreatment and following morbidity and mortality).

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Author Contributions

All authors contributed to data analysis, drafting and revising the article, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

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