

Research Paper

# Opportunistic salpingectomy at benign gynecological surgery for reducing ovarian cancer risk: a 10-year single centre experience from China and a literature review

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## Abstract

Current evidences indicate that the fallopian tube plays a major role in the pathogenesis of epithelial ovarian cancer (EOC). Salpingectomy represents a novel and potentially effective risk-reducing option. In this study, there were 1822 patients diagnosed and treated for EOC or primary peritoneal cancer (PPC) at Department of Gynecologic Oncology, Tianjin Medical University Cancer Institute and Hospital from January 1, 2007 to April 30, 2017. Among them, 198 patients with a history of gynecological surgery because of benign diseases were enrolled to analyze further. Using 1:2 case-control study, we found that the incidence of EOC was significantly decreased in the population with salpingectomy, compared to women with fallopian tube reserved ( $P < 0.05$ ). At the same period, there were 4339 patients receiving opportunistic salpingectomy in our centre because of benign gynecological diseases. The results showed the rate of bilateral salpingectomy was annually increased from 2007 to 2017 (22.02% to 60.22%), which showed approximately threefold increase in a decade. In general, factors affecting the rate of salpingectomy included age, child number, menopause or not, marital status, educational status, income status, and with or without family history of tumor. Therefore, based on ten years experiences from our centre, it is recommended that physician should discuss with appropriate patients to perform opportunistic bilateral salpingectomy at the time of receiving benign gynecological surgery for preventing ovarian cancer. Moreover, the prospective, large scale and multi-centre studies to evaluate the safety and efficacy of salpingectomy as a preventive strategy for ovarian cancer warrant to conduct in the future.

Key words: fallopian tubes; ovarian cancer; salpingectomy; risk reduction

## Introduction

Epithelial ovarian cancer (EOC) was the leading killer among women with gynecologic cancers. In 2017, there were 22,440 estimated new diagnoses of ovarian cancer and 14,080 deaths from the disease <sup>1</sup>. Nonspecific symptoms in early stage of disease and a lack of effective screening methods are the main reasons why more than 70% of cases are diagnosed in

FIGO stage III or IV <sup>2</sup>. Despite the progress in therapy the mortality rate remains high with a five-year overall of only 20-40% for advanced disease <sup>3</sup>. Studies reported that approximately 95% of ovarian cancers are of epithelial origin and the high-grade serous caner (HGSC) represents 75% of EOC and accounts for the majority of deaths <sup>4, 5</sup>. Recently, collective

literature indicated precursor lesions of HGSC originated in the fallopian tube not from ovary<sup>6</sup>. The initial evidence for the fallopian origin of ovarian cancer came from the studies of prophylactic salpingo-oophorectomy in women bearing BRCA mutations<sup>7</sup>. Detailed examination of fallopian specimens revealed dysplastic lesions, later designated as serous tubal intraepithelial carcinoma (STIC) located in the fimbrial end<sup>8</sup>.

At present, a viewpoint is generally understood that the junction of the fallopian tube epithelium with the ovarian mesothelium might be a potential site of ovarian carcinogenesis, similar to the uterine, cervical, gastroesophageal or anorectal junctions<sup>9, 10</sup>. Thus, removal of the fallopian tubes at the time of pelvic or abdominal surgery for a benign condition (i.e. opportunistic salpingectomy) appeared as an attractive option for primary prevention of HGSC<sup>3, 11</sup>.

In this study, we aimed to analyze and explore the data of 1822 cases with EOC or primary peritoneal cancer (PPC) and 4339 cases with receiving salpingectomy on account of benign gynecological diseases from 2007 to 2017 in our centre in order to provide our experiences about the development and influence factors of salpingectomy. Additionally, we systematically reviewed the studies of opportunistic salpingectomy for ovarian cancer prevention.

## Material and methods

### Ethics statement

Institutional review board approval was obtained for this study, and informed patient consent was waived owing to the retrospective nature of the study.

### Study population

Since January 1, 2007 until April 30, 2017, there were 1822 patients diagnosed and treated for EOC or PPC at Department of Gynecologic Oncology, Tianjin Medical University Cancer Institute and Hospital. The clinical data, including age, height, weight, menstrual history, child number, history of gynecologic surgery, gynecologic surgery types, histologic subtype, and FIGO stage, were extracted from available the patients' medical records (Table 1). Among them, 198 patients had a history of gynecological surgery because of benign diseases.

The eligible control women were collected from the database of our center. They received operation and were followed up more than 20 years until April 30, 2017, and had at least one intact ovary and fallopian tube. The controls (n=389) had no history of ovarian cancer and were frequency matched to cases (2:1 ratio). Remarkably, there were not statistically different significances between the EOC group and

the control group on age, body mass index (BMI), child number, and menopause status when choosing matched control cases (Table 2).

**Table 1.** Clinical characteristics of EOC and PPC patients

Characteristic	N (%)
<b>Age(mean±SD), y</b>	52.59±9.2, 52
<52	566
≥52	1256
<b>Body mass index (kg/m<sup>2</sup>)</b>	25.29±3.52
<b>Child number</b>	
0	203 (11.14)
1-2	960 (52.69)
>2	659 (36.17)
<b>Menopause</b>	
yes	1302 (71.46)
No	520 (28.54)
<b>With history of gynecologic surgery</b>	<b>198 (10.87)</b>
<b>Gynecologic surgery types</b>	
Hysterectomy	65 (32.93)
USO	48 (24.24)
Hysterectomy and USO	36 (18.18)
Hysterectomy and bilateral salpingectomy	24 (12.12)
BSO	14 (7.07)
Hysterectomy and BSO	11 (5.56)
<b>Without history of gynecologic surgery</b>	1624 (89.13)
<b>Histology</b>	
Serous	1292 (70.91)
Mucinous	194 (10.65)
Endometrioid	235 (12.90)
Clear cell	87 (4.77)
Other*	14 (0.77)
<b>FIGO Stage (2009)</b>	
I–II	529 (29.03)
III–IV	1293 (70.97)

EOC =Epithelial ovarian cancer; PPC= Primary peritoneal cancer; BSO=bilateral salpingoophorectomy; USO=unilateral salpingoophorectomy; \*Other subtypes= for example Brenner and squamous cell tumors

**Table 2.** Characteristics of epithelial ovarian cancer cases and based controls

Characteristic	EOC =198 Cases (N, %)	Control =389 Cases (N, %)
<b>Age(mean±SD), y</b>	52.31±12.4	52.32±12.7
<52	86 (43.4)	168 (43.2)
≥52	112 (56.6)	221 (56.8)
<b>Body mass index (kg/m<sup>2</sup>)</b>	25.47±5.5	25.32±6.2
<b>Child number</b>		
0	17 (8.6)	33 (8.5)
1-2	121 (61.1)	237 (60.9)
>2	60 (30.3)	119 (30.6)
<b>Menopause</b>		
yes	109 (55.1)	214 (55.0)
No	89 (44.9)	175 (45.0)
<b>Salpingectomy</b>		
Yes	133 (67.2)	304 (78.1)
No	65 (32.8)	85 (21.9)

At the same period, there were 7404 patients receiving operation therapy in our centre owing to benign gynecological diseases. Among them, 4339 patients received unilateral or bilateral opportunistic salpingectomy because of benign gynecological

diseases. The clinical information of these women, including age, height, weight, menstrual history, child number, marital status, economic status, family history of tumor, detailed clinical diagnosis, surgical route, operation time, and so on were extracted to analyze further (Table 3).

**Table 3.** Clinical characteristics of 4339 patients with benign disease and salpingectomy

Characteristic	N=4339 (%)
<b>Age(mean±SD, median), y</b>	55.1±7.82, 55
<55	1068 (24.61)
≥55	3271 (75.39)
<b>Body mass index (kg/m<sup>2</sup>)</b>	24.18±3.78
<b>Child number</b>	
0	384 (8.85)
1-2	2287 (52.71)
>2	1668 (38.44)
<b>Menopause</b>	
yes	3318 (76.47)
No	1021 (23.53)
<b>Marital status</b>	
Unmarried	857 (19.75)
Married	3482 (80.25)
<b>Educational status</b>	
Middle school or less	998 (23.00)
High school	2998 (69.09)
College or more	1341 (30.91)
<b>Income status</b>	
Low	898 (20.70)
Median	2392 (55.13)
High	1049 (24.17)
<b>Family history of tumor</b>	
Yes	2819 (64.97)
No	1520 (35.03)
<b>Family history of ovarian or breast cancer</b>	
Yes	411 (9.47)
No	3928 (90.53)
<b>Salpingectomy</b>	
Unilateral	1321 (30.44)
Bilateral	3018 (69.56)
<b>Clinical diagnosis</b>	
Benign ovarian tumor	521 (12.01)
Adenomyosis/endometriosis	937 (21.59)
Leiomyoma	2429 (55.98)
Pyosalpinx/salpingitis	265 (6.11)
Others	187 (4.31)
<b>Surgical route</b>	
Abdominal hysterectomy (AH)	3471 (80.00)
Laparoscopic hysterectomy (LH)	868 (20.00)
<b>Operation time (mean±SD), min</b>	30±20

## Statistical analysis

Continuous data and frequency data were analyzed by Fisher's exact test and the chi-square test. Description of categorical variables was used as rate (%) and description of continuous variables were expressed as mean ± standard deviation (SD). Logistic regression analysis was used to estimate ORs and 95% CIs for developing ovarian cancer in association with salpingectomy. Two-sided P-values were considered statistically significant at P≤0.05. Statistical

analysis was performed using SPSS software passage for Windows (version 20.0; SPSS Inc., Chicago, IL, USA).

## Results

### Salpingectomy reducing the risk of EOC

We identified 1822 patients with a diagnosis of EOC or PPC from 2007 to 2017 in our centre. Extracting the data of past medical history, we found there were 198 patients with a history of gynecological surgery because of benign diseases. Among them, 65 cases had the history of hysterectomy (33%); 48 cases had the history of receiving unilateral salpingoophorectomy (USO) therapy (24%); 36 cases had history of receiving hysterectomy and USO (18%); 24 cases had operation history of receiving hysterectomy and bilateral salpingectomy (12%); 14 cases had history of bilateral salpingoophorectomy (BSO) therapy (7%); 11 cases had history of receiving hysterectomy and BSO (6%) (Figure 1). Then, by using of conditional logistic regression statistical analysis, salpingectomy reduced overall EOC risk in the age-adjusted model (OR=1.750; 95% CI=1.194-2.564; P=0.004). Similarly, in multivariate models, including age, child number, and menopause status, women who had salpingectomy had a lower risk of ovarian cancer compared to women without receiving salpingectomy (OR=2.080; 95% CI=1.340-3.227; P=0.001). Thus, the incidence of EOC was significantly decreased in the population with salpingectomy, compared to women with fallopian tube reserved according to population control-base analysis.

### Rate of salpingectomy increasing annually from 2007 to 2017

In 2007, 336 women with benign gynecological disease received operation therapy in our centre and there 74 cases were performed by bilateral salpingectomy among them. Surprisingly, there already 112 patients with benign gynecological disease received bilateral salpingectomy among 186 operation cases in our centre from January to April in 2007. We found the overall rate of bilateral salpingectomy was gradually increased in our centre from 2007 to 2017 (from 22.02% to 60.22%), which showed approximately threefold increase in a decade (Table 4, Figure 2).

### Factors affecting the rate of salpingectomy in our centre

There were 7404 patients receiving operation therapy owing to benign gynecological diseases in our centre from 2007 to 2017. Among them, 4339 patients received unilateral or bilateral opportunistic salpingectomy because of benign gynecological

diseases, compared with 3065 cases without salpingectomy. The detailed data of clinical characteristics about these two groups patients was analyzed by chi-square test and listed in table 5. In age subgroup analysis, the rate of salpingectomy of patients with  $\geq 55$  years was significantly higher than that of the subgroup with  $< 55$  years (75% vs 25% and 20% vs 80%,  $P < 0.001$ ). In menstrual status subgroups analysis, the rate of salpingectomy in menopause women population was higher than that in premenopausal women obviously (76% vs 24% and 29% vs 71%,  $P < 0.001$ ). In marital status subgroups analysis, the results indicated the married women population preferred to receive salpingectomy operation comparing with the unmarried women (80% vs 20% and 72% vs 20%,  $P < 0.001$ ). We also found that the rate of salpingectomy in patients with better educational population was apparently high, compared to the patient with middle school or less educational status (31%+46%=77% vs 23% and 31%+40%=71 vs 29%,  $P < 0.001$ ). Additionally, it was easier for patients with better economic status to choose salpingectomy, compared to the patient with low income status (24%+55%=79% vs 21%, and 21%+51%=72% vs 28%,  $P < 0.001$ ). Moreover, the rate of salpingectomy in women with one child or more was significantly higher than that in women without child (53%+38%=91% vs 9% and 15%+51%=66% vs 34%,  $P < 0.001$ ). Furthermore, the rate of salpingectomy in patients with family history of tumor was higher than that in patients without family history of tumor (65% vs 35% and 34% vs 66%,  $P < 0.001$ ). In general, factors affecting the rate of salpingectomy included age, child number, menopause or not, marital status,

educational status, income status, and with or without family history of tumor (table 5).

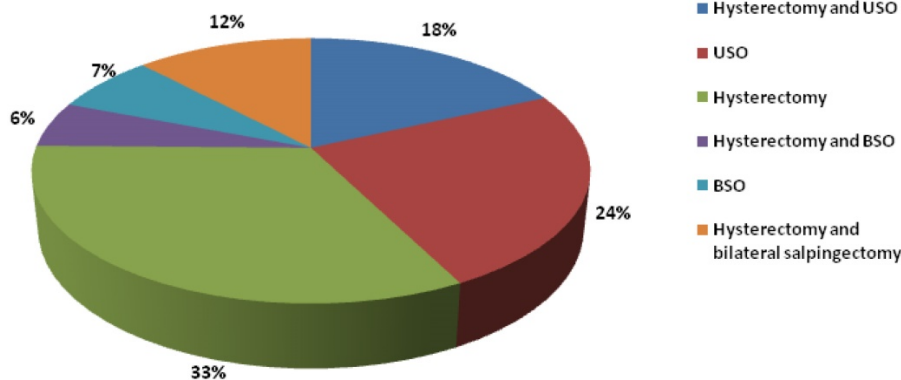
**Table 4.** The Rate of Bilateral Salpingectomy in our centre from 2007 to 2017

Year	Bilateral salpingectomy Cases (n)	Benign diseases operation cases (n)	The rate of bilateral salpingectomy (%)
2007	74	336	22.02
2008	132	471	28.03
2009	218	703	31.01
2010	263	751	35.02
2011	286	785	36.43
2012	307	682	45.01
2013	352	721	48.82
2014	386	743	51.95
2015	411	758	54.22
2016	477	799	59.70
2017	112	186	60.22
Total	3018	6935	

### Discussion

As we known, ovarian cancer is a heterogeneous disease that can be divided into three main types: sex cord stromal tumors, germ cell tumors, and EOC<sup>12</sup>. EOC accounts for the vast majority of ovarian cancers and consists of different subtypes, including HGSC, low-grade serous, mucinous, endometrioid, clear cell, and so on. The various histotypes differ in epidemiology, etiology, and treatment. HGSC is the most common and aggressive subtype of EOC, which accounts for 75% of cases<sup>9</sup>. Molecular and genetic data indicate that HGSC of the ovary may have a similar origin to HGSC of the fallopian tube and peritoneum, and therefore, it has been suggested that all the three be described collectively as HGSC<sup>13</sup>.

Recently, accumulative literature demonstrated the fallopian tube was the original site of EOC and the initial evidence was considered from the studies of prophylactic salpingoophorectomy in women bearing BRCA mutations<sup>14-16</sup>. Carefully examination of fallopian specimens revealed dysplastic lesions, later designated as STIC located in the fimbrial end<sup>17</sup>. With emphasis, the precursor lesions have never been found in the ovarian epithelium. There is additional evidence supporting the concept of the fallopian origin of ovarian HGSC that the gene expression profile of HGSC is closely related to fallopian tube epithelium rather than to the ovarian surface epithelium<sup>9</sup>. Moreover, in a

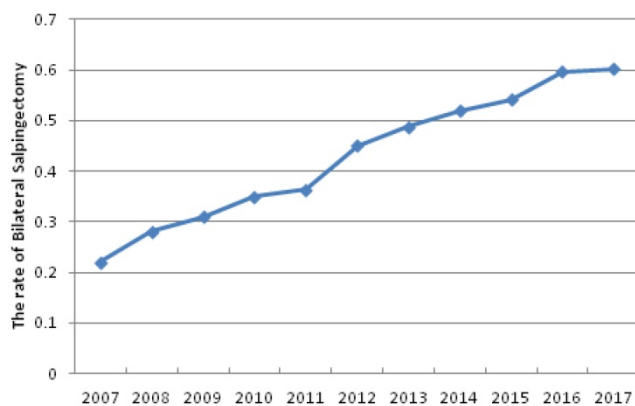


**Figure 1.** There were 198 patients with a history of gynecological surgery because of benign diseases in our centre. Among them, 65 cases had the history of hysterectomy (33%); 48 cases had the history of receiving unilateral salpingoophorectomy (USO) therapy (24%); 36 cases had history of receiving hysterectomy and USO (18%); 24 cases had operation history of receiving hysterectomy and bilateral salpingectomy (12%); 14 cases had history of bilateral salpingoophorectomy (BSO) therapy (7%); 11 cases had history of receiving hysterectomy and BSO (6%).

mouse model, Kim and his colleagues showed that the removal of the fallopian tubes, but not removal of the ovaries, prevents HGSC formation<sup>18</sup>. Therefore, opportunistic bilateral salpingectomy (OBS) (also called prophylactic salpingectomy and risk-reducing salpingectomy) at the time of pelvic or abdominal surgery for a benign condition has been recommended by several associations and experts<sup>19-26</sup> (Table 6).

**Table 5.** Factors affecting the rate of salpingectomy in our centre

Characteristic	N=7404		P
	With salpingectomy N=4339 (%)	Without salpingectomy N=3065 (%)	
<b>Age(mean±SD, median), y</b>	55.1±7.82, 55		<0.001
<55	1068 (25)	2452(80)	
≥55	3271 (75)	613 (20)	
<b>Body mass index (kg/m<sup>2</sup>)</b>	24.18±3.78		
<b>Child number</b>			<0.001
0	384 (9)	1046(34)	
1-2	2287 (53)	1571(51)	
>2	1668 (38)	448(15)	
<b>Menopause</b>			<0.001
yes	3318 (76)	878(29)	
No	1021 (24)	2187(71)	
<b>Marital status</b>			<0.001
Unmarried	857 (20)	844(28)	
Married	3482 (80)	2221(72)	
<b>Educational status</b>			<0.001
Middle school or less	998 (23)	889(29)	
High school	1998 (46)	1226(40)	
College or more	1343 (31)	950(31)	
<b>Income status</b>			<0.001
Low	898 (21)	850(28)	
Median	2392 (55)	1575(51)	
High	1049 (24)	640(21)	
<b>Family history of tumor</b>			<0.001
Yes	2819 (65)	1034(34)	
No	1520 (35)	2031(66)	



**Figure 2.** The overall rate of bilateral salpingectomy was gradually increased in our centre from 2007 to 2017 (from 22.02% to 60.22%), which showed approximately threefold increase in a decade.

**Table 6.** Chronological Statements of Gynecological Boards on Opportunistic Salpingectomy

Year	Associations or Experts	Recommendation
2011	Canadian gynecological group <sup>19</sup>	Consider surgical removal of fallopian tubes at the time of hysterectomy, even when ovaries were conserved Replace tubal ligation with excision bilateral salpingectomy for the purpose of permanent contraception Refer all patients with HGSC for hereditary cancer counseling and genetic testing for BRCA1/2 mutations
2011	Royal Australian and new Zealand college of obstetricians and gynecologists <sup>18</sup>	Doctors should discuss the risks and benefits of bilateral salpingectomy with patients undergoing by hysterectomy for benign disease
2013	Society of Gynecologic Oncology (SGO) <sup>21,22</sup>	For women at average risk of ovarian cancer, risk-reducing salpingectomy should also be discussed and considered with patients at the time of abdominal or pelvic surgery, hysterectomy or in lieu of tubal ligation
2013	Committee on gynecologic practice <sup>22</sup>	Prophylactic salpingectomy may offer clinicians the opportunity to prevent ovarian cancer in their patients. Randomized controlled trials are needed to support the validity of this approach to reduce the incidence of ovarian cancer
2014	Royal college of Obstetricians and Gynecologist <sup>25</sup>	Women who are not at high risk for BRCA mutation and have completed their families should be carefully considered for prophylactic removal of the fallopian tubes with conservation of ovaries at the time of gynecological or other intraabdominal surgery
2015	American college of obstetricians and gynecologists (ACOG) <sup>20</sup>	Women at population-level risk of ovarian cancer who are undergoing ovary-sparing hysterectomy for benign indications should be offered bilateral salpingectomy to reduce their risk of ovarian cancer
2015	Commission Ovary of the AGO <sup>24</sup>	During preoperative counseling prior to hysterectomy, all patients should be informed about the potential beneficial impact of opportunistic salpingectomy and the associated risks
2016	American cancer of association <sup>23</sup>	Opportunistic salpingectomy to patients as an opportunistic procedure during benign hysterectomies and as an alternative to bilateral tubal ligation for sterilization procedures

Meanwhile, we summarized and analyzed the rate of salpingectomy for the benign gynecologic condition in our centre from 2007 to 2017. The results revealed that the overall rate of bilateral salpingectomy was annually increased in from 22.02% to 60.22%, approaching threefold increase in a decade. Moreover, factors affecting people determined to perform salpingectomy or not included age, child number, menopause or not, marital status, educational status, income status, and with or without family history of tumor, in fact, which involved the perceptions of public and gynecologists about prophylactic salpingectomy for preventing ovarian cancer in China. In Korea, towards to general population, the questionnaires were distributed to 100 healthy female volunteers. Questionnaire for this survey included questions on demographics, medical history, knowledge of and belief about risk-reducing

salpingectomy (RRS), and barrier to its application. Among 100 respondents, 71% did not realize the seriousness of ovarian cancer, 79% were unaware of the fact that salpinx was the origin of ovarian cancer, and 87% stated that they had never heard of RRS as a preventive method for ovarian cancer. The authors suggested physicians should discuss RRS with patients and consider this procedure at the time of abdominal or pelvic surgery<sup>29</sup>. Correspondingly, in order to examine Italian obstetrician-gynecologists' knowledge, a survey was conducted to gather their opinions about prophylactic bilateral salpingectomy (PBS) for the prevention of ovarian cancer and assess current clinical practice and willingness to incorporate salpingectomy into surgical interventions (benign indications). A total of 479 surveys were returned. At least 80% respondents reported performing PBS during hysterectomy for benign indications, chiefly with the intent of ovarian cancer risk reduction and decreasing the risk of reoperation and subsequent tubal pathologies. PBS as a prophylactic measure to reduce the incidence of ovarian cancer is a well-known strategy among the Italian gynecologists interviewed. Finally, the author suggested wider educational initiatives should be undertaken to increase the implementation of salpingectomy in Italy<sup>30</sup>.

However, there are limitations of our study. Firstly, our study just is a retrospective summarization of the patients' literature of our centre, there is a great need for prospective and large scale studies to evaluate the safety and efficacy of salpingectomy as a preventive strategy for ovarian cancer. Secondly, considering our results from a single centre, the multi-centre study should be taken in order to provide more information of opportunistic salpingectomy from general population in China. Additionally, our study based on 10 years experiences and absence long period follow-up for estimate the validity of decreasing morbidity of ovarian cancer, even for prediction of survival and prognosis for these new EOC cases. Thus, the longer follow up and summarization of these enrolled patients should be performed in the future.

Conclusively, the incidence of EOC was significantly decreased in the population with salpingectomy in our centre, compared to women with fallopian tube reserved. Furthermore, the overall rate of bilateral salpingectomy was annually increased from 2007 to 2017, which effected by several factors, including age, child number, menopause or not, marital status, educational status, economic status, and with or without family history of tumor. Therefore, based on comprehensive assessment, it is recommended that appropriate patients should be

discussed to perform applicable opportunist bilateral salpingectomy at the time of receiving benign gynecological surgery for preventing ovarian cancer.

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## Competing Interests

The authors have declared that no competing interest exists.

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