Opportunistic Salpingectomy at the Time of Laparoscopic Cholecystectomy for Ovarian Cancer Prevention

A Cost-effectiveness Analysis

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Objective: To perform a cost-effectiveness analysis to examine the utility and effectiveness of OS performed at the time of elective cholecystectomy [laparoscopic cholecystectomy (LAP-CHOL)].

Summary Background Data: OS has been adopted as a strategy to reduce the risk of ovarian cancer in women undergoing hysterectomy and tubal sterilization, although the procedure is rarely performed as a risk reducing strategy during other abdominopelvic procedures.

Methods: A decision model was created to examine women 40, 50, and 60 years of age undergoing LAP-CHOL with or without OS. The lifetime risk of ovarian cancer was assumed to be 1.17%, 1.09%, and 0.92% for women age 40, 50, and 60 years, respectively. OS was estimated to provide a 65% reduction in the risk of ovarian cancer and to require 30 additional minutes of operative time. We estimated the cost, quality-adjusted life-years, ovarian cancer cases and deaths prevented with OS.

Results: The additional cost of OS at LAP-CHOL ranged from $1898 to 1978. In a cohort of 5000 women, OS reduced the number of ovarian cancer cases by 39, 36, and 30 cases and deaths by 12, 14, and 16 in the age 40–, 50–, and 60-year-old cohorts, respectively. OS during LAP-CHOL was cost-effective, with incremental cost-effectiveness ratio of $11,162 to 26,463 in the 3 age models. In a probabilistic sensitivity analysis, incremental cost-effectiveness ratio for OS were less than $100,000 per quality-adjusted life-years in 90.5% or more of 1000 simulations.

Conclusions: OS at the time of LAP-CHOL may be a cost-effective strategy to prevent ovarian cancer among average risk women.

Keywords: cost-effectiveness, laparoscopic cholecystectomy, opportunistic salpingectomy, ovarian cancer prevention

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In 2021, ovarian cancer remains the deadliest gynecologic malignancy in the United States.[1] It is estimated that, 21,410 women will be diagnosed with ovarian cancer and 13,770 women will die from the disease. Nearly 1 in 80 women develop ovarian cancer during their lifetime.[2] Women with ovarian cancer typically present with metastatic disease as there is no effective screening test, and the population-level overall survival rate is less than 50% at 5 years after diagnosis (48.6%).[2–4] Therefore, prevention is considered a useful strategy to reduce the number of deaths from ovarian cancer.[4–6]

Mounting evidence has suggested that ovarian cancer, particularly high-grade serous ovarian cancer which is the most common histologic type, originates from the distal fallopian tube.[7–10] The cells of the superficial lining in the distal fallopian tube are transformed into malignant cells and subsequently spread to the adjacent ovary, the so called serous tubal intraepithelial carcinoma (STIC) hypothesis. This STIC hypothesis was proposed in the early-2000s and is now widely accepted.[7–11] This new theory of pathogenesis gave rise to the concept of surgical prevention through removal of the fallopian tubes, referred to as opportunistic salpingectomy (OS).[5,6,12,13] Several population-based, epidemiological studies have shown that OS is associated with a 49% to 77% reduction in the risk of ovarian cancer.[14–16] Multiple analytic models have found that OS for low-risk women undergoing gynecologic surgery is a cost-effective strategy for reducing the risk of ovarian cancer,[17–20] and the procedure has been rapidly adopted in recent years for women undergoing hysterectomy and tubal sterilization.[21–23]

Despite the benefits of OS, the procedure is rarely performed as a risk reducing strategy at the time of nongynecologic abdominopelvic procedures. In the U.S., nearly 168,000 women undergo laparoscopic cholecystectomy (LAP-CHOL) every year, and this procedure may represent a "window-of-opportunity" to offer OS for ovarian cancer prevention. Our objective was to assess the cost effectiveness of OS performed at the time of LAP-CHOL.

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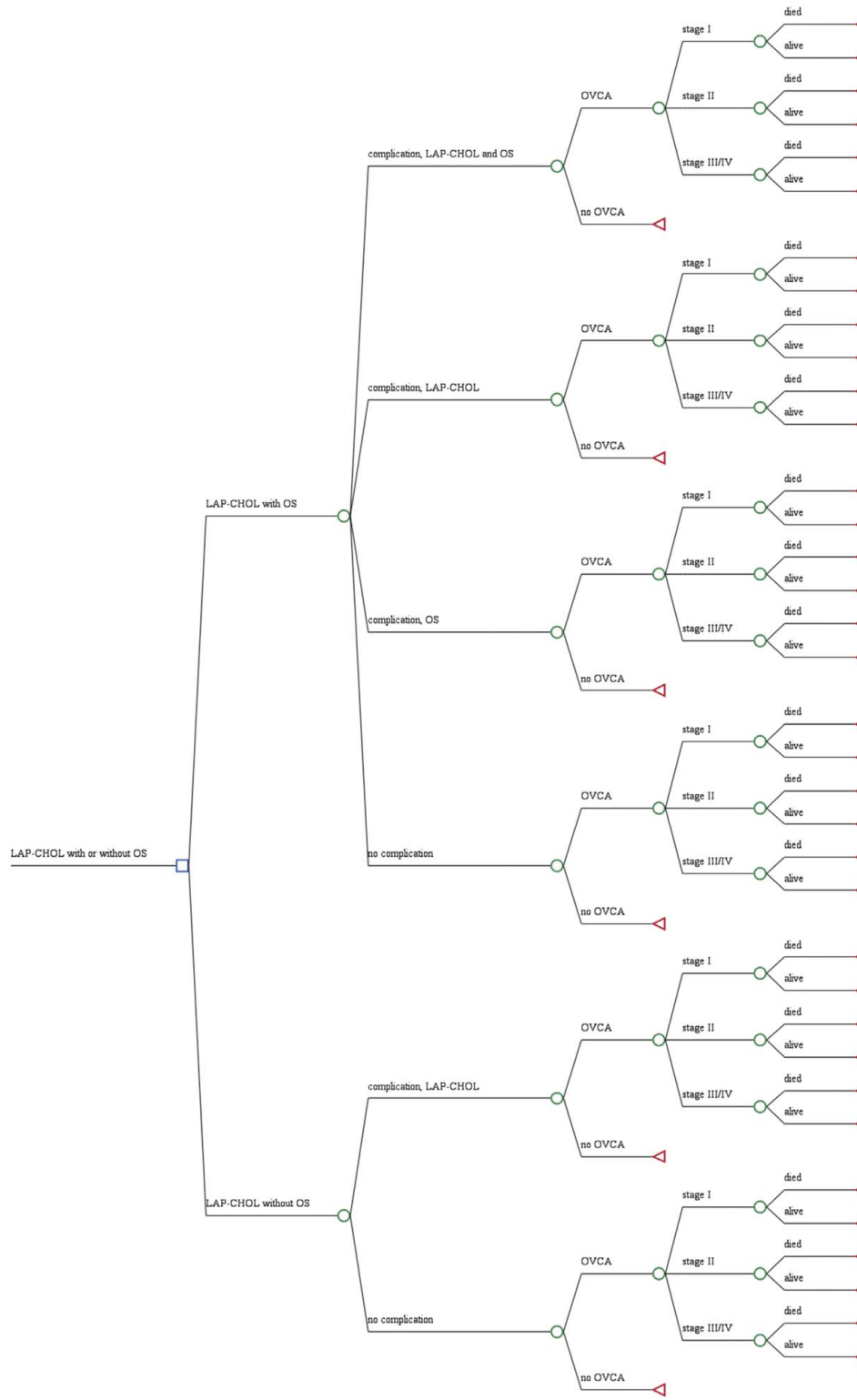

FIGURE 1. A decision model for opportunistic salpingectomy during laparoscopic cholecystectomy. Decision model was created to evaluate the cost-effectiveness of OS at time of LAP-CHOL. LAP-CHOL and OS complications were assumed to be independent events. LAP-CHOL indicates laparoscopic cholecystectomy; OS, opportunistic salpingectomy; OVCA, ovarian cancer.

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TABLE 1. Baseline Probabilities, Costs and Utility Values

Description				Reference
Age (yr)	40	50	60	
Laparoscopic Cholecystectomy (LAP-CHOL)				
Procedure cost ($)	6503	6503	6503	24
Complication incidence	2.1%	2.1%	2.1%	Supplemental Digital Content Table S1, http://links.lww.com/SLA/D651
Complication cost ($)	11,574	11,574	11,574	Supplemental Digital Content Table S1, http://links.lww.com/SLA/D651
Opportunistic Salpingectomy (OS)				
Cost, transvaginal ultrasound ($)	125	125	125	CPT 76830[33]
Cost, gynecologic counseling visit ($)	166	166	166	CPT 99204[33]
Procedure cost ($)	797	797	797	CPT 58700[33]
Operating room time (min)	30	30	30	
OR cost [per min, ($)]	39	39	39	31
Complication incidence	1.1%	1.1%	1.1%	34
Complication cost ($)	1162	1162	1162	34
Ovarian cancer risk reduction	65%	65%	65%	14
Cost, two 5-mm trocars ($)	35	35	35	49
Cost, uterine manipulator ($)	70	70	70	49
Cost, electrosurgical device (LigaSure) ($)	462	462	462	49
Cost, specimen retrieval bag ($)	53	53	53	49
Cost, pathology testing ($)	42	42	42	CPT 88304 (level III)
Ovarian Cancer				
Lifetime risk	1.17%	1.09%	0.92%	35
Stage I distribution	48.7%	34.4%	24.6%	Supplemental Digital Content Table S2, http://links.lww.com/SLA/D651
Stage II distribution	10.5%	12.2%	9.9%	Supplemental Digital Content Table S2, http://links.lww.com/SLA/D651
Stage III-IV distribution	40.8%	53.3%	65.5%	Supplemental Digital Content Table S2, http://links.lww.com/SLA/D651
Stage I mortality rate	8.1%	14.6%	17.4%	Supplemental Digital Content Table S2, http://links.lww.com/SLA/D651
Stage II mortality rate	15.9%	26.4%	32.9%	Supplemental Digital Content Table S2, http://links.lww.com/SLA/D651
Stage III-IV mortality rate	62.4%	61.6%	67.0%	Supplemental Digital Content Table S2, http://links.lww.com/SLA/D651
Cost, first year ($)	93,321	93,321	93,321	19
Cost, annual ($)	9176	9176	9176	19
Cost, last year ($)	110,294	110,294	110,294	19
Utility				
Complications, disutility	–0.11	–0.11	–0.11	50
Ovarian cancer, stage I	0.81	0.81	0.81	20
Ovarian cancer, stage II	0.64	0.64	0.64	20
Ovarian cancer, stage III-IV	0.55	0.55	0.55	20
Surgery	0.30	0.30	0.30	38
Lost Wages				
Hourly wage ($)	14	14	14	39
Weekly wage ($)	641	641	641	40
Time lost, preoperative gyn visit* (h)	4	4	4	
Time lost, OVCA last year (h)	485.3	485.3	485.3	41
Expected life years	42.6	33.4	24.7	Per 2017 estimates[37]

Cost values are rounded to dollar point.
*Transvaginal ultrasonography and preoperative counseling visit.
CPT indicates current procedural terminology; LAP-CHOL, laparoscopic cholecystectomy; OS, opportunistic salpingectomy; OVCA, ovarian cancer.

METHODS

Model Overview

We developed a decision analytic model to simulate the sequelae of OS performed at the time of LAP-CHOL (Fig. 1). The primary outcome was the incremental cost effectiveness of OS. As women who undergo LAP-CHOL are most commonly middle aged,[24,25] and age is a well-known risk factor for ovarian cancer,[2–4] 3 age groups were examined in the base case model: 40, 50, and 60years. Cohorts of 10,000 women with a 1:1 allocation to OS (n = 5000 for LAP-CHOL without OS vs n = 5000 for LAP-CHOL with OS) were examined. The model was created in TreeAge Pro (Healthcare, version 2021, Williamstown, MA).

Base Case Model Parameters

All women in the study were assumed to undergo cholecys-tectomy via a laparoscopic approach (Table 1). The incidence and costs of complications of LAP-CHOL were estimated by query of a hospital-based, administrative data source

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(Supplemental Digital Content Table S1, http://links.lww.com/SLA/D651).[26] International Classification of Disease-9 code 51.23, International Classification of Disease-10 codes 0FB44ZZ, 0FT44ZZ, and current procedural terminology (CPT) codes 47562, 47563, and 47564 were used to identify LAP-CHOL cases. We estimated the probability of complications and additional costs associated with a biliary duct injury or severe, Clavian IV, perioperative complications (including sepsis, myocardial infarction, pulmonary embolism, cardiac arrest, or shock) compared to patients without a complication.[27–29] The baseline cost of LAP-CHOL was estimated as $6503 based on prior work.[24] The complication rate was estimated as 2.1% and the cost of a complication from LAP-CHOL was estimated as $11,574.

In the base case, OS performed at the time of LAP-CHOL was estimated to provide a 65% relative reduction in the lifetime risk of ovarian cancer, based on prior studies.[14–16] The additional surgical time required for OS was estimated as 30 minutes based on our best plausible estimates. A prior study reported the median time of 13 minutes to perform OS and we accounted for possible reduced efficiency such as turnover time for a second surgical team.[30] We assumed that the same staff supports the second surgical team. Operating room costs were estimated as $39 per minute, resulting in $1170 of operating room costs for OS.[31] The additional cost for medical equipment for OS at LAP-CHOL was estimated as $620 (Table 1), based on the assumption that (i) the periumbilical endoscopic port for LAP-CHOL would be used for OS, (ii) 2 additional trocars would be placed in the lower abdomen as the operative ports for LAP-CHOL are generally placed in upper abdomen,[32] (iii) an electrosurgical device will be utilized to remove the fallopian tubes as a monopolar hook is typically used for LAP-CHOL, and (iv) specimen retrieval will occur through use of a specimen collection bag. Additionally, cost of an intrauterine manipulator was included to facilitate exposure. Physician reimbursement for OS was estimated as $797 based on the Centers for Medicare and Medicaid Services Physician Fee Schedule for CPT code 58700.[33] The cost of pathologic analysis of the fallopian tube was estimated as $42 for CPT code 88304. The additional cost for preoperative evaluation and counseling by a gynecologic surgeon was estimated as $291 to include a transvaginal ultrasonogram to evaluate adnexal structure [$125 (CPT code 76830)], and an outpatient office visit for 45 to 59 minutes [$166 (CPT code 99204)] (Table 1). The incidence and cost of complications associated with OS were estimated as 1.1% and $1162, respectively, based on data from a prior study.[34]

The lifetime risk, stage distribution, and stage-specific mortality of ovarian cancer were estimated based on patient age at the time of LAP-CHOL (40, 50, and 60 years). Specifically, the lifetime risk of ovarian cancer after LAP-CHOL was estimated as 1.17%, 1.09%, and 0.92% for women 40–, 50–, and 60–year of age based on data from the National Cancer Institute's Surveillance, Epidemiology, and End Results database.[35] The Surveillance, Epidemiology, and End Results database was used to estimate the cancer stage distribution which was categorized as stage I, II, and III–IV disease, and the 5–year all-cause mortality rates were estimated based on cancer stage in each age cohort.[36] The model used a lifetime time horizon and 5–year all-cause mortality for cancer patients. Ovarian cancer patients who were alive were assumed to incur the cost offirst year cancer treatment; whereas cancer patients who died were assumed to incur the costs of the first year, 3 years of subsequent treatment, and the last year of treatment. Ovarian cancer treatment costs were estimated at $93,321 for the first year, $9176 per year thereafter, and $110,294 in the last year of life.[19] Life expectancy was based on the 2017 US national statistics (42.6 years for age 40, 33.4 years for age 50, and 24.7 years for age 60).[37]

Quality of Life and Utilities

Expected survival was multiplied by health state utility values reflecting quality of life associated with all possible health outcomes.

The utility of the surgical period was assumed to be 0.30 for 30 days.[38] If the patients had complications, then a disutility of –0.11 was applied over the same period of time. Patients who did not have cancer were assumed to be in perfect health with a utility of 1.0 after surgery. Ovarian cancer patients who did not die of disease were assumed to have the stage-specific utility until the end of the first year, and then returned to normal health; whereas women who died of cancer were assumed to have 3 years with the stage-specific utility after the first year.

The U.S Department of Labor Bureau of Statistics data were used to define the median cost of lost wages per hour or per week for women.[39,40] All women were assumed to have lost wages during the perioperative period for 30 days after surgery. Women who underwent OS were assumed to have lost wages for 1 gynecologic consultation (counseling and transvaginal ultrasound). Women who died of cancer were assumed to have time-related cost in the last year of life estimated from reported patient time lost.[41] Costs and quality-adjusted life-years (QALYs) were discounted at a rate of 3% annually. All costs were inflation-adjusted to 2017 U.S. dollars.

TABLE 2. Cost–Effectiveness of Opportunistic Salpingectomy at the Time of Laparoscopic Cholecystectomy in the Base Case Analysis

Characteristic No.	LAP-CHOL Without OS n = 5000	LAP–CHOL With OS n = 5000
40 yr of age		
Cost	$54,557,402	$63,507,411
Incremental cost		$8,950,009
Incremental per patient cost		$1929
Ovarian cancer cases	59	20
Ovarian cancer death	18	6
QALYs	211824.01	212625.86
Incremental effectiveness		801.86
ICER		$11,162
50 yr of age		
Cost	$54,277,439	$63,651,814
Incremental cost		$9,374,375
Incremental per patient cost		$1898
Ovarian cancer cases	55	19
Ovarian cancer death	22	8
QALYs	166024.65	166612.57
Incremental effectiveness		587.91
ICER		$15,945
60 yr of age		
Cost	$53,479,789	$63,516,253
Incremental cost		$10,036,464
Incremental per patient cost		$1978
Ovarian cancer cases	46	16
Ovarian cancer death	24	8
QALYs	122737.63	123116.89
Incremental effectiveness		379.26
ICER		$26,463

ICER indicates increment cost-effectiveness ratio; LAP-CHOL, laparoscopic cholecystectomy; OS, opportunistic salpingectomy; OVCA, ovarian cancer; QALYs, quality adjusted life-years.

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The primary outcome was the incremental cost-effectiveness ratio (ICER), estimated as the difference in incremental cost between the 2 strategies divided by the incremental effectiveness, measured in QALYs. The model was estimated from a societal perspective with a willingness-to-pay (WTP) threshold of $100,000 in the United States.[42] Secondary outcomes included the number of ovarian cancer cases and deaths.

Sensitivity Analyses

To examine the robustness of the results, we performed 1–way, 2–way, and probabilistic sensitivity analyses. In 1–way sensitivity analyses, we varied the ovarian cancer risk reduction associated with OS (50%, 25%, and 10%), operative room cost per minute (10%, 25%, and 50% increase from base case), surgical time (15, 45, and 60 minutes), complication rate (2.5% and 5.0%), and cost (25% and 50% increase from base case) related to OS.

In 2–way sensitivity analyses, we varied operating room time and cost, and varied ovarian cancer risk reduction and operating room time simultaneously. To further assess the uncertainty around the outcomes, we performed probabilistic sensitivity analyses using Monte Carlo simulations of 1000 trials to sample from the plausible distributions of multiple parameter estimates (Supplemental Digital Content Table S2, http://links.lww.com/SLA/D651) and reported the results as an incremental cost-effectiveness scatterplot. This study followed the Consolidated Health Economic Evaluation Reporting Standards statement to outline the study for decision analytical model.[43]

RESULTS

In the base case, the incremental cost per patient of OS at the time of LAP-CHOL was $1929, $1898, and $1978 for women age 40, 50, and 60 years of age at the time of surgery, respectively. OS at the time of LAP-CHOL reduced the number of ovarian cancer cases by 39, 36, and 30 cases per 5000 women in the 40–, 50–, and 60-year-old cohorts, respectively. This resulted in a reduction in ovarian cancer deaths of 12, 14, and 16 in the age 40–, 50–, and 60-year-old cohorts, respectively.

OS at the time of LAP-CHOL resulted in an increase in QALYs per 5000 cases of 801.86 for the 40–year cohort, 587.91 for the 50–year cohort, and 379.26 for the 60–year cohort (Table 2). The ICER for OS at the time of LAP–CHOL was $11,162 per QALY for the 40-year-old cohort, $15,945 per QALY for the 50-year-old cohort, and $26,463 per QALY for the age 60-year-old cohort, respectively. OS was cost-effective for all 3 age strata at a WTP threshold of $100,000.

In a 1–way sensitivity analysis for the 50–year cohort (Supplemental Digital Content Table S3, http://links.lww.com/SLA/D651), when ovarian cancer risk reduction associated with OS was reduced to 25%, the ICER increased to $73,080 per QALY. OS at time of LAP-CHOL was no longer cost-effective when the ovarian cancer risk reduction associated was 15% or lower (ICER $129,946 per QALY). When the operating room cost per minute was increased by 50% or surgical time was increased to 60 minutes, OS at the time of LAP-CHOL remained cost-effective (ICER $27,141 and $33,508, respectively, per QALY). Similarly, OS at the time of LAPCHOL remained cost-effective when the complication rate of OS was increased to 5.0% (ICER $21,351 per QALY), or when the OSrelated complication cost was increased by 50% (ICER $20,845 per QALY). Similar results were observed in the 40- and 60-year-old cohorts (Supplemental Digital Content Tables S4–5, http://links.lww.com/SLA/D651).

In 2–way sensitivity analyses among 50-year-old women (Supplemental Digital Content Table S6, http://links.lww.com/SLA/D651), OS at the time of LAP-CHOL was cost-effective over the range of plausible values of operating room cost and surgical time. When varying ovarian cancer risk reduction and

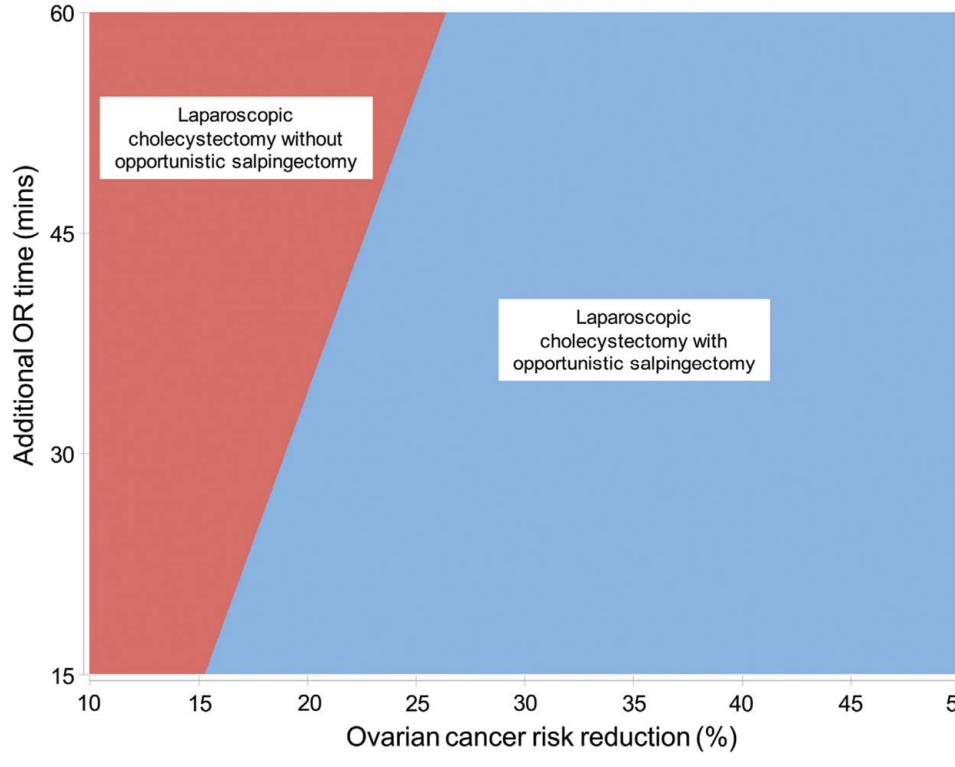

FIGURE 2. Two-way sensitivity analysis of ovarian cancer risk reduction and additional operating time among women 50 years of age. Ovarian cancer risk reduction with OS varied from 10% to 50% (X-axis). Additional operating time for salpingectomy at LAP-CHOL varied from 15 to 60 minutes (Y-axis). The meta data is shown in Supplemental Digital Content Table S2, http://links.lww.com/SLA/D651.

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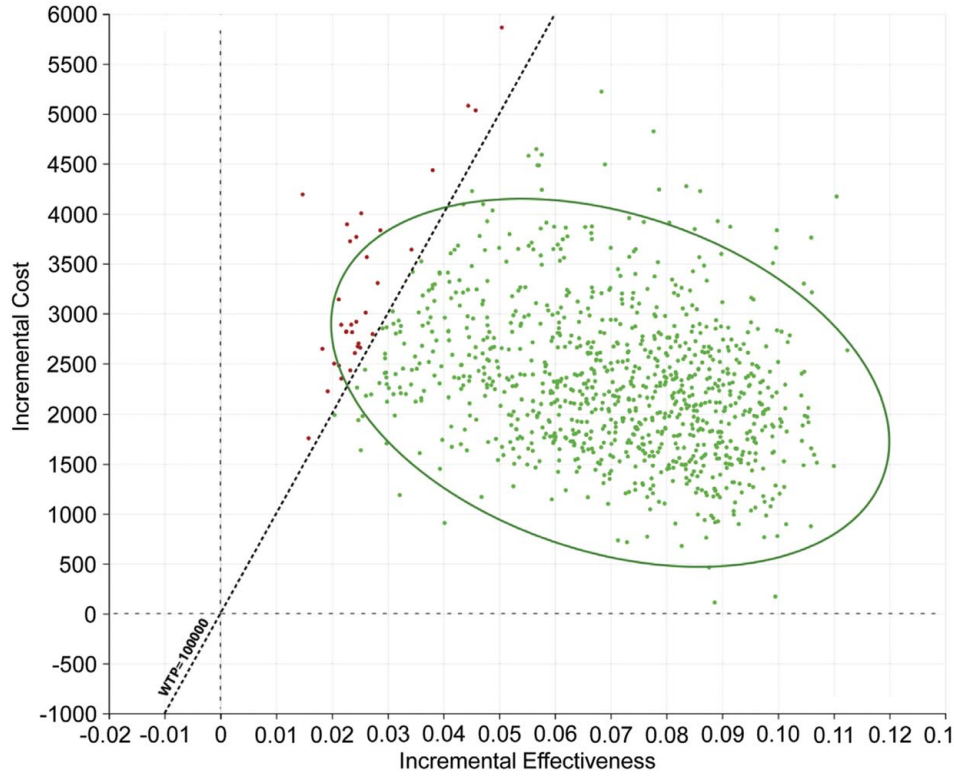

FIGURE 3. Probabilistic sensitivity analysis among women 50 years of age. Incremental cost-effectiveness comparing OS to no OS through the Monte Carlo simulation (n = 1000). OS indicates opportunistic salpingectomy.

surgical time simultaneously, OS was less cost-effective (ICER $102,259 per QALY) when the ovarian cancer risk reduction was 15% and the surgical time was 15 minutes or longer (Fig. 2 and Supplemental Digital Content Table S6, http://links.lww.com/SLA/D651). The results among the age 40- and 60-year cohorts were similar (Supplemental Digital Content Figs. S1–2, http://links.lww.com/SLA/D652 and Supplemental Digital Content Tables S7–8, http://links.lww.com/SLA/D651).

In a probabilistic sensitivity analysis among the 50-year-old cohort ((Fig. 3), OS at the time of LAP-CHOL was cost-effective in 96.7% of the 1000 Monte Carlo simulations (cost-effective for OS in 96.7%, and dominant in 0.0%). The ICER exceeded the WTP threshold of $100,000 in 3.3% of simulations. The results were largely unchanged among the age 40-year-old cohort (97.1%); in the age 60-year-old cohort, OS at LAP-CHOL remained cost effective in >90% of simulations (90.5%) (Supplemental Digital Content Figs. S3–4, http://links.lww.com/SLA/D652).

DISCUSSION

These data suggest that under a wide range of assumptions regarding benefit, cost, and complications, OS at the time of LAP-CHOL may be a cost-effective strategy to reduce the incidence and mortality of ovarian cancer. These findings apply to average risk women who are 40 to 60 years of age at the time of surgery.

Most prior studies have evaluated OS at the time of gynecologic procedures, with few addressing the possible benefit of OS during other elective and semi-elective abdominal procedures. A prospective study of OS at the time of LAP-CHOL performed in 6 centers in Austria reported that the OS was successfully performed in 93% of women. OS added an additional 13 minutes of surgical time and there were no OS-related complications reported postoper-atively. Within the cohort, 1 patient was diagnosed with a STIC.[30] A decision analysis of OS at the time of non-gynecologic laparoscopic procedures including cholecystectomy, appendectomy, colectomy, and herniorrhaphy also reported a reduction in mortality from ovarian cancer.[44] Our analysis suggests that OS in conjunction with LAP-CHOL is cost effective under a wide range of feasible parameters, even if operative times are longer than reported or if the risk reduction for ovarian cancer is lower than previously reported.

Not unexpectedly, our estimates suggest that the magnitude of ovarian cancer risk reduction associated with OS at the time of LAP–CHOL is greater is younger women.[45] Somewhat paradoxically however, the reduction in ovarian cancer mortality was greater in older women, likely as a result of more advanced stage disease with higher mortality occurring in older women.[3] Regardless, these findings suggest that OS at the time of LAP-CHOL is potentially useful across a wide spectrum of ages.

Although OS during LAP-CHOL may theoretically be associated with a reduced burden of ovarian cancer, the feasibility of such a strategy remains largely untested. A number of potential logistical challenges require further exploration. First, patients would need to have preoperative counseling and a review of their family history. This would likely require extra referral and potentially delay surgical scheduling. Similarly, OS and LAP-CHOL will need to be coordinated between a general surgeon and gynecologic surgeon again potentially prolonging the time to surgical scheduling. Third, even under the best-case scenario, OS will increase operating room times which is likely to be unpopular among general surgeons. Finally, data on patient perceptions and attitudes surrounding OS at the time of cholecystectomy are limited. A survey of women who were scheduled to have elective LAP-CHOL reported that 85% considered OS at the time of LAP-CHOL as a good idea.[46]

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A window-of-opportunity surgical approach for cancer risk reduction has the potential to have a substantial impact at the population level. In the United States, nearly 20 million individuals are estimated to have gallstones and approximately 300,000 chole–cystectomies are performed annually.[47,48] The majority of patients are female (62.4%) and undergo laparoscopic surgery (90%). This implies that more than 165,000 women will have LAP-CHOL annually. Thus, OS at LAP-CHOL could potentially reduce the incidence of ovarian cancer by approximately 1000 cases per year if 80% of women undergoing LAP-CHOL received OS.

We recognize a number of important limitations. First, our findings are dependent on the parameter estimates chosen. To limit bias, we performed a comprehensive literature review and included a wide range of sensitivity analyses to ensure the robustness of our findings. Second, we were unable to explicitly model patient characteristics such as known relevant genetic mutations, family history of ovarian cancer, and other risk factors for ovarian cancer. Similarly, we were unable to include surgical history and other technical factors that may impact the ease with which OS is performed. Third, our model included estimates for LAP-CHOL, and these findings may differ for either a robotic-assisted or open procedure. However, a 2019 analysis reported that only 2% of cholecystectomies were performed with robotic assistance.[24] Lastly, our model did not include differences in histologic subtypes of ovarian cancer. Despite these limitations, our findings were robust across a wide range of parameter values and assumptions.

In sum, our analysis suggests that OS at the time of LAP-CHOL may be a cost-effective strategy to prevent ovarian cancer among average-risk women. Given the sizable number of women who undergo LAP-CHOL annually, OS has the potential to result in a substantial reduction in the burden of ovarian cancer. Further study to explore patient and provider attitudes and preferences and pilot testing of the feasibility of OS in combination with LAP-CHOL are warranted.

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