Review Article

Risk-Reducing Salpingectomy: Let Us Be Opportunistic

Kara C. Long Roche, MD; Nadeem R. Abu-Rustum, MD; Mlica Nourmoussavi, MD; and Oliver Zivanovic, MD

Because there is no screening test for ovarian cancer, effective prevention strategies may be the best way to reduce the mortality of this most lethal gynecologic malignancy. Increasing evidence supports the hypothesis that the fallopian tube is the site of origin for the vast majority of high-grade serous carcinomas. Our growing understanding of the pathogenesis of this disease offers a rare opportunity to explore new preventive measures, such as bilateral salpingectomy, which may provide great benefit without compromising ovarian function. If the tubal paradigm is accurate, then the impact of bilateral salpingectomy could extend to *BRCA1* and *BRCA2* mutation carriers, high-risk noncarriers, and average-risk women. The authors present a review of the literature on the role of risk-reducing salpingectomy in all women and in high-risk groups, with a focus on morbidity, ovarian function, potential clinical applicability, and epidemiological considerations. ***Cancer* 2017;123:1714-20.** *© 2017 American Cancer Society.*

KEYWORDS: fallopian tubes, high-grade serous carcinoma, ovarian cancer, ovarian function, salpingectomy.

INTRODUCTION

Epithelial ovarian cancer (EOC) is the leading cause of death from gynecologic malignancy in the United States, where, in 2016, an estimated 22,280 women will be diagnosed with the disease, and 14,240 will die of it.[1,2] The majority of patients with EOC present at an advanced stage, which accounts for the high mortality rate. This is likely because of early peritoneal dissemination and an absence of symptoms in early stage disease. Although serum cancer antigen 125 (CA 125) and pelvic ultrasound have been evaluated as potential strategies for early detection, currently there is no effective screening test.[3]

Risk factors for the development of EOC include age, menopausal status, reproductive history, and, most significantly, family history. Hereditary breast and ovarian cancer (HBOC) syndrome is an inherited condition characterized by an increased lifetime risk for developing breast cancer and EOC. The majority of individuals with HBOC have a mutation in breast cancer gene 1 (*BRCA1*) or *BRCA2* that confers up to a 40% lifetime risk of developing EOC.[4] It has been estimated that the prevalence of these germline mutations is as high as 1 in 400.[5,6] Other mutations have also been implicated in the pathogenesis of EOC; in a recent study of 347 women with ovarian cancer published by Norquist et al, mutations in Lynch-associated mismatch-repair genes (mutL homolog 1 [*MLH1*], mutS homolog 2 [*MSH2*], *MSH6*, and PMS 1 homolog 2 [*PMS2*]) were identified in 0.4% of participants; and mutations in other EOC-associated genes, including BRCA1-interacting protein C-terminal helicase 1 (*BRIP1*), partner and localizer of BRCA2 (*PALB2*), RAD51 homolog C (*RAD51C*), *RAD51D*, and BRCA-associated ring domain 1 (*BARD1*), were identified in 3.3% of participants.[7]

Because there is no effective screening test, removal of the ovaries and fallopian tubes—also known as risk-reducing salpingo-oophorectomy (RRSO)—is recommended for prevention in high-risk women. There are strong data supporting this approach, which has been demonstrated to result in a 75% to 96% decrease in ovarian cancer risk and a 50% decrease in breast cancer risk in *BRCA* mutation carriers,[8,9] with recent data suggesting that the majority of that impact is in *BRCA2* mutation carriers.[10] However, RRSO results in surgical menopause, which has a significant impact on cardiovascular health and osteoporotic health, as well as quality of life (hot flashes, vaginal dryness, dyspareunia, and changes in sexual function and body image).[11-13] It is challenging to determine the optimal time frame in which women will achieve the greatest benefit from RRSO. In women with *BRCA* mutations, RRSO is generally recommended by age 40 years, or when childbearing is complete[14]; however, management can be tailored to an individual patient's mutation, or personal and family history. However, less is known about the optimal timing for women with moderate penetrance genes or those whose risk is based on family history alone.

Corresponding author: Oliver Zivanovic, MD, Gynecology Service, Department of Surgery, Memorial Sloan Kettering Cancer Center, 1275 York Avenue, New York, NY 10065; Fax: (212) 717-3214; zivanovo@mskcc.org

Gynecology Service, Department of Surgery, Memorial Sloan Kettering Cancer Center, New York, New York

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TABLE 1. Precursor Lesions of High-Grade Serous Epithelial Ovarian, Fallopian Tube, and Peritoneal Carcinomas

Precancerous Lesions	Immunohistochemical Profile
p53 Signature	No morphologic phenotype, p53+++ and Ki67 < 10%
Proliferating p53 signature	No morphologic phenotype, p53+++ and Ki67 > 10%
STIC	Atypical serous epithelium, p53+++ and Ki67+++, PAX2, γH2AX+, Laminin γ1
SCOUT	Proliferation of Bcl2-positive secretory cells with loss of *PAX2*

Abbreviations: Bcl-2, B-cell lymphoma 2; γH2AX+, positive for 1 of several genes encoding for histone H2A; p53, tumor protein 53; PAX2, paired box gene 2; SCOUT, secretory cell overgrowth; STIC, serous tubal intraepithelial carcinoma.

Recent data point to the fimbriated end of the fallopian tube as the origin of the majority of high-grade serous ovarian cancers. Therefore, it is reasonable to consider incorporating salpingectomy—removal of the entire fallopian tube with conservation of the ovaries, which may provide protection against disease without the morbidity of premature menopause—into the modern prevention paradigm for EOC. However, important questions remain about the efficacy, potential impact on ovarian function, and most appropriate allocation of this strategy in average-risk and high-risk women: 1) What are the risks and benefits of salpingectomy? 2) What is the role of salpingectomy in high-risk women? 3) When should we consider salpingectomy in average-risk women? These questions are addressed here.

THE TUBAL PARADIGM

High-grade serous carcinomas account for 70% of all ovarian cancers. These are the most common, and among the most lethal, of ovarian malignancies. High-grade serous ovarian cancers often present at an advanced stage and are associated with tumor protein 53 (*TP53*) mutations, *BRCA* mutations, and other defects in homologous recombination.[15] Early theories about the origin of EOC stemmed from epidemiologic studies associating incessant ovulation with the development of malignancy.[16-18] However, the growing use of RRSO in the high-risk population, in addition to improvements in pathologic assessment over the past 2 decades, has given pathologists an opportunity to detect occult, invasive or intraepithelial neoplasms,[19] furthering our understanding of the pathogenesis of EOC (Table 1). The identification of occult, invasive disease in the fallopian tube and serous tubal intraepithelial carcinoma (STIC)—now understood to be a precursor lesion to high-grade serous carcinoma—has provided some of the most robust evidence for the tubal hypothesis.[20] In addition, molecular markers and gene expression profiles of high-grade serous carcinoma support a tubal origin, with lineage continuity of specific *TP53* mutations between high-grade serous carcinoma and the accompanying STIC lesion. *TP53* mutations result in an abundance of nonfunctional p53; this is referred to as a "p53 signature," and is commonly identified adjacent to STIC lesions.[21-23]

With a meticulous examination of the fallopian tube using the Sectioning and Extensively Examining the Fimbriated end (SEE-FIM) protocol,[19] STICs and invasive tubal carcinomas were identified more frequently in patients with a genetic predisposition to ovarian cancer, but also in nonmutation carriers with high-grade serous ovarian carcinoma (range, 50%-75%).[24-31] In the recently published National Ovarian Cancer Prevention and Early Detection Study (Gynecologic Oncology Group (GOG)-0199), led by the GOG, occult, invasive, or serous tubal intraepithelial ovarian/tubal/peritoneal neoplasms were detected in 25 of 966 patients (2.6%; *BRCA* mutation carriers and high-risk noncarriers) who underwent RRSO.[32] In a subgroup analysis, 4.6%, 3.5%, and 0.5% of occult neoplasms were detected in patients who were known *BRCA1* mutation carriers, *BRCA2* mutation carriers, and high-risk noncarriers at the time of RRSO, respectively.[32]

It is noteworthy that tubal precursor lesions are not always identified in patients with high-grade serous ovarian carcinomas. This may be a result of sampling error or tumor overgrowth; however, the synchronous diagnosis of STIC in the fallopian tube and high-grade serous ovarian carcinoma suggests a pathogenic correlation. This finding may also be explained by a carcinogenic "field effect." Thus, it is possible that not all high-grade serous EOCs arise in the fallopian tube, and that alternative pathways of carcinogenesis exist. The role of the ovary in the pathogenesis of EOC, specifically the impact of hormone milieu and ovulatory events, is not yet well understood, and will be a crucial component in the quest to understand the pathogenesis of the disease.

LESSONS FROM BILATERAL TUBAL LIGATION AND OTHER INTERVENTIONS

The association between bilateral tubal ligation (BTL) and a decreased risk of ovarian cancer is well established,

resulting in an overall 20% to 40% lower rate of EOC in women after BTL.[33-38] The impact of BTL appears to be greatest on endometriosis-associated histologies, such as clear cell and endometrioid carcinomas,[39] and this may shed light on the mechanism of protection.

A meta-analysis that included 30 studies of BTL noted a 30% risk reduction in the development of any ovarian cancers, and a subset analysis revealed a stronger reduction rate (54%) in association with endometrioid compared with serous tumors.[35] A pooled analysis of 13 population-based case-control studies involving large numbers of patients reported a 29% decreased risk of any ovarian cancer in patients who had undergone tubal sterilization. The protective effect was again most significant in the setting of clear cell and endometrioid histologies (up to 50% reduction), supporting the theory that tubal occlusion may prevent carcinomas related to ascending cells.[36] Tubal ligation does not appear to confer the same degree of protection against the more common serous carcinomas, which are now believed to originate in the distal fallopian tube fimbria. However, data suggest that excisional tubal sterilization may confer a greater degree of protection than tubal ligation. A population-based, nested case-control study published in 2014 compared 194 cases with 388 controls, and revealed that the adjusted risk of EOC was decreased by 64% after excisional tubal sterilization methods compared with the reduction achieved using nonexcisional methods or without sterilization.[40]

In 2015, using the Swedish Nationwide Healthcare Registry, Falconer et al published the results from a population-based study of patients who underwent gynecologic surgery for benign conditions.[41] Women who underwent previous gynecologic surgeries for benign indications, including tubal ligation (sterilization, salpingectomy, bilateral salpingo-oophorectomy [BSO], hysterectomy; n = 251,465) were compared with an unexposed population (n = 5449,119). There was a significantly lower risk of ovarian cancer among women who underwent previous salpingectomy (hazard ratio [HR], 0.65; 95% confidence interval [CI], 0.52-0.81)—even unilateral salpingectomy—compared with the unexposed population. Statistically significant risk reductions were observed among women who previously underwent hysterectomy (HR, 0.79; 95% CI, 0.70-0.88), sterilization (HR, 0.72; 95% CI, 0.64-0.81), and hysterectomy with BSO (HR, 0.06; 95% CI, 0.03-0.12).[41] Although these data support the role of the fallopian tube in the pathogenesis of EOC and suggest that salpingectomy may be an effective risk-reducing strategy in the general population, it is important to note that hysterectomy with BSO conferred the greatest degree of protection in this cohort.

SALPINGECTOMY: IS IT SAFE?

A primary concern about routine salpingectomy is the potential effect on ovarian function, including its impact on the timing of menopause. Evidence suggests that women with a prior hysterectomy experience menopause earlier than those without hysterectomy,[42,43] raising concerns about the additional impact of salpingectomy on ovarian perfusion. Many studies have sought to quantify the impact of salpingectomy on ovarian function, with reassuring results. A multicenter, randomized, controlled trial of the impact of opportunistic salpingectomy during laparoscopic hysterectomy, published by Song et al in 2016, demonstrated that, although anti-Mullerian hormone (AMH) levels were significantly decreased from preoperative levels in both groups, there was no significant difference between the salpingectomy and no-salpingectomy groups.[44] Morelli et al analyzed levels of serum AMH, follicle-stimulating hormone, and estradiol (E2) in 79 patients who underwent hysterectomy with or without bilateral salpingectomy for benign uterine disease. Those investigators observed no significant differences in ovarian function after surgery and no significant differences in perioperative morbidity between the 2 groups.[45] A similar study by Findley et al compared 30 premenopausal women who underwent laparoscopic hysterectomy with ovarian preservation for benign indications, 15 of whom underwent concurrent salpingectomy. AMH levels were not significantly different at baseline, 4 to 6 weeks after surgery, and 3 months postoperatively in women who underwent salpingectomy versus no salpingectomy.[46] No differences in operative time or estimated blood loss were reported.[44-46] The data also suggested that, even when a wide excision is undertaken in order to completely excise all fallopian tube tissue, salpingectomy does not negatively impact ovarian reserve or perioperative morbidity.[47] Although laboratory measurements like AMH provide reproducible, objective data, further investigation is warranted using more clinically relevant endpoints, such as the timing and severity of menopausal symptoms.

A recently published cohort study from the Ovarian Cancer Research Program of British Columbia (OVCARE) evaluated the perioperative safety outcomes of 49,931 women who underwent hysterectomy with and without bilateral salpingectomy or BSO. That cohort also included women who underwent surgical sterilization by means of bilateral salpingectomy or tubal ligation. A bilateral salpingectomy was associated with a minimal increase in operative

time (approximately 16 minutes more for hysterectomy with bilateral salpingectomy vs without salpingectomy, and 10 minutes more for bilateral salpingectomy vs tubal ligation). Despite this finding, no differences were observed in the risks of hospital readmission, blood transfusions, or length of hospital stay.[48]

OPPORTUNISTIC SALPINGECTOMY: PREVENTION IN THE GENERAL POPULATION

Compelling evidence has shifted common practice toward ovarian conservation, with recent data suggesting that >50% of women who undergo hysterectomy for a benign indication will have their ovaries left in situ.[48,49] Historically, there was little consensus regarding the practice of salpingectomy, and many women were left with the complete adnexa in situ after hysterectomy. However, as the tubal hypothesis emerged, so did the question of salpingectomy in average-risk women as a means of risk reduction.

Kwon et al recently investigated this issue, using a modeled analysis designed to determine the cost effectiveness of opportunistic salpingectomy as a cancer-prevention strategy during hysterectomy for benign conditions or sterilization.[50] Salpingectomy with hysterectomy at age 45 years was less costly and more effective (longer life expectancy gain for women who would have died prematurely from ovarian cancer) than hysterectomy alone or hysterectomy with BSO. This held true for women who underwent hysterectomy at any time before age 50 years. The model predicted a 38.1% reduction in ovarian cancer diagnoses with the addition of salpingectomy, with a number needed to treat of 273. BSO instead of salpingectomy would prevent 238 diagnoses of ovarian cancer but would incur an additional 934 deaths from premature menopause (without hormone-replacement therapy). Salpingectomy instead of tubal ligation was slightly more costly but more effective, with an incremental cost-effectiveness ratio of $27,278 per year of life gained. For this to remain true, salpingectomy had to provide a relative 25% increase in risk reduction over tubal ligation. In addition, the cost of salpingectomy could not exceed that of tubal ligation by more than $1000. According to the authors' model, there is a relative 29.2% risk reduction in ovarian cancer diagnoses with the use of salpingectomy versus tubal ligation. This translates into a number needed to treat of 366.[50]

Many are now advocating that opportunistic salpingectomy become the standard of care during surgery for benign gynecologic conditions. The OVCARE group reported that, after an educational initiative supporting salpingectomy was launched among gynecologists, the rate of salpingectomy for sterilization increased from 0.4% to 33.3%, and the rate of salpingectomy during hysterectomy with ovarian conservation increased from 5% to 35% over a 3-year period. Despite the additional procedure, there was no associated increase in the rate of complications or readmissions.[48] Similar trends have also been reported in the United States. A recent publication from a large, community-based health care system demonstrated that, between 2011 to 2014, the rate of salpingectomy at the time of hysterectomy rose from 14.7% to 72.7%.[51]

These reports are comparable to those focusing on other cancer-prevention strategies, and provide strong evidence that opportunistic salpingectomy is safe and does not incur additional risks. In addition to guidelines released by the Society of Obstetricians and Gynaecologists of Canada and the Royal Australian and New Zealand College of Obstetricians and Gynaecologists, both the American College of Obstetricians and Gynecologists and the Society of Gynecologic Oncology now recommend that salpingectomy be considered at the time of surgical sterilization or hysterectomy for benign disease.[52,53] Thus, as salpingectomy becomes more prevalent in the benign gynecology community, it is crucial to continue to investigate its safety and efficacy; future studies should aim to determine the rate of preinvasive disease in the fallopian tubes of average-risk women, as well as the potential sequelae of leaving the ovaries in situ.

THE ROLE OF SALPINGECTOMY IN HIGH-RISK WOMEN

Because there is no effective screening test for EOC, the standard of care in high-risk women is RRSO. Multiple prospective and retrospective studies evaluating RRSO in *BRCA* mutation carriers have demonstrated a 75% to 96% decrease in ovarian cancer risk, as well as a marked reduction in breast cancer risk and all-cause mortality.[8,9,54-56] Although RRSO is generally recommended by age 40 years,[14,57] it is estimated that the proportion of women actually undergoing RRSO is only 60% to 70%. This is likely because of concerns about the impact of premature menopause.[58] Premature menopause, as noted above, is associated with increased cardiovascular, osteoporotic, and overall mortality risks and a potentially deleterious impact on quality of life.[12,59]

The exact benefits and optimal timing of intervention in distinct high-risk groups remain a source of active debate. Differences in the efficacy of risk-reducing

treatment for *BRCA1* versus *BRCA2* mutation carriers highlight the potential need for different approaches to each. Although a previous study reported that RRSO conferred rates of risk reduction of 85% and 72% among *BRCA1* and *BRCA2* mutation carriers,[54] respectively, a recent meta-analysis of 3 prospective studies suggested that most of the benefits of RRSO are derived by *BRCA1* mutation carriers. However, this may be explained by the lower absolute numbers of *BRCA2* mutation-associated gynecologic cancers.[60] With regard to the impact on breast cancer risk, recently published data from the Hereditary Breast Cancer Clinical Study Group support the finding that RRSO confers significant protection against premenopausal breast cancer in women with *BRCA2* mutations; however, this protection was not observed in women with *BRCA1* mutations.[10]

Not only may the impact of RRSO be different between the 2 groups, but the age at which women should undergo RRSO is also different. Finch et al reported that the highest incidence of ovarian cancer among *BRCA*1 mutation carriers was between ages 50 and 59 years; among *BRCA*2 mutation carriers, the highest incidence was a decade later (range, 60-69 years).[61] Because women with *BRCA*1 mutations are at risk for an earlier onset of cancer, it is recommended that RRSO be considered at age 35 years and completed no later than age 40 years.[57]

Interval salpingectomy with delayed oophorectomy (ISDO) has been proposed as an alternative strategy to traditional RRSO in the management of high-risk women.[62,63] During the interval salpingectomy portion of this strategy, the fallopian tube, including the entire fimbriated end, must be excised and processed using the SEE-FIM technique. In addition to the expected (although unquantified) reduction in ovarian cancer risk, ISDO would also provide an opportunity for clinical inspection of the peritoneal cavity as well as early pathologic evaluation of the fallopian tubes, which might facilitate the identification of a STIC lesion or occult, high-grade, serous carcinoma. In collaboration with Facing Our Risk of Cancer Empowered, an online patient survey was performed to determine whether *BRCA* mutation carriers would be interested in an ISDO study. The survey indicated that 34% of eligible high-risk women (n = 204) were "definitely interested," even if the delay in oophorectomy resulted in an increase in cancer risk compared with RRSO.[64] In a separate poll of 173 cancer geneticists, genetic counselors, and gynecologic oncologists in the United Kingdom, 71% agreed with the tubal hypothesis, 77% supported ISDO within a clinical trial setting, and 60% agreed to offer it to high-risk women who declined RRSO.[65]

In 2013, Kwon et al published a modeled analysis (including a quality-adjusted analysis) on the long-term outcomes and cost effectiveness of ISDO in high-risk groups. The authors concluded that RRSO was the dominant strategy overall, because it was the least costly and most effective with respect to overall life expectancy. However, when factoring in quality-adjusted life years, salpingectomy at age 40 years followed by delayed oophorectomy at age 50 years conferred the highest quality-adjusted life expectancy. The impact was even stronger in *BRCA1* mutation carriers compared with *BRCA2* mutation carriers.[63]

Although ISDO may hold the promise of benefit with minimal risk, there are significant concerns regarding its application in high-risk women. The degree of protection is unknown, especially because it is still unclear what proportion of EOC is tubal in origin. The need for 2 separate operations increases surgical risks and may lead to decreased acceptance of and compliance with the completion of delayed oophorectomy. In addition, compared with RRSO, bilateral salpingectomy will almost certainly not confer any breast cancer risk reduction in women with HBOC.[66] Given the proven benefit of RRSO in women at elevated risk, the risks of deviating from this strategy must be carefully considered and evaluated before incorporating ISDO into practice.

There is a great need for prospective studies evaluating the safety and efficacy of ISDO as a preventive strategy. The Women Choosing Surgical Prevention (WISP) trial, which is currently underway, is a 2-arm, nonrandomized, multicenter clinical trial comparing changes in sexual function and quality of life between high-risk, premenopausal women undergoing ISDO versus RRSO. Patients on this trial must be premenopausal, between the ages of 30 and 50 years, and must have a deleterious germline mutation in *BRCA1*/*BRCA2* or in any of the other 9 ovarian cancer genes that provide an actionable level of risk, including the Lynch syndrome genes *MLH1, MSH2, MSH6*, and *PMS2*, as well as *BRIP1, PALB2, RAD51C, RAD51D*, and *BARD1*. High-risk women who are eligible for this trial will be counseled and given their choice of study arm: ISDO or RRSO. The study will compare psychosocial well-being, onset and severity of vasomotor symptoms (hot flashes and night sweats), complication rates, number of malignancies, and quality-of-life measures between the 2 arms. As the first multisite trial of ISDO in the United States, this study will provide important information on the uptake, completion, and

comparison of vasomotor and sexual dysfunction in patients undergoing ISDO versus RRSO.[67]

CONCLUSIONS

Current evidence indicates that the fallopian tube plays a major role in the pathogenesis of EOC. Salpingectomy represents a novel and potentially effective risk-reducing option. In the general population, it is now standard practice to offer salpingectomy for sterilization and to remove the fallopian tubes at the time of hysterectomy with ovarian conservation. As adoption of these procedures increases, the rate of ovarian cancer in the general population should decrease over time. The role of salpingectomy in high-risk women is still a source of debate. As genetic testing becomes more accessible, greater numbers of women are being identified as having an inherited predisposition to EOC; therefore, these women are candidates for surgical risk reduction. Although ISDO holds promise as a risk-reducing strategy for those with inherited risk, many unanswered questions remain. Prospective research is crucial to the safe incorporation of ISDO into routine practice. Going forward, the hope is that strategies like this may maximize prevention while minimizing its negative impact on patients' quality of life.

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