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# Risk-Reducing Salpingectomy: Let Us Be Opportunistic

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## Abstract

As 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, the impact of bilateral salpingectomy could extend to *BRCA1* and *BRCA2* mutation carriers, high-risk non-carriers, and average-risk women. We 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.

### Keywords

Ovarian cancer; High-grade serous carcinoma; Fallopian tubes; Salpingectomy; Ovarian function

## 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 this disease, and 14,240 will die of it.[1,2] The majority of cases of EOC present at an advanced stage, which accounts for the high mortality rate. This is likely due to early peritoneal dissemination and an absence of symptoms in early-stage disease. While serum CA125 and pelvic ultrasound have been evaluated as potential strategies for early detection, at this time 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

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in the *BRCA1* or *BRCA2* genes, which confer up to a 40% lifetime risk of developing EOC.[4] The prevalence of these germline mutations has been estimated to be 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 repairs genes (*MLH1, MSH2, MSH6* and *PMS2)* were identified in 0.4% of participants and mutations in other EOC-associated genes, *BRIP1*, *PALB2, RAD51C, RAD51D,* and *BARD1*, in 3.3%. [7]

As 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 is strong data supporting this approach, which has been demonstrated to result in a 75–96% 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, 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 the age of 40, or when childbearing is complete[14]; however management can be tailored to an individual patient's mutation, personal and family history. However, less is known about the optimal timing in women with moderate penetrance genes, or those whose risk is based on family history alone.

Recent data point to the fimbriated end of the fallopian tube as the origin of the majority of high-grade serous ovarian cancers. It is therefore 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- 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?

We will address these questions 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 *TP53* mutations, *BRCA* mutations, and other defects in homologous recombination.[15] Early theories about the origin of EOC stem 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 two 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--have provided some of the most robust evidence for the tubal hypothesis.[20] Additionally, 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 non-functional p53; this is referred to as a "p53 signature", and is commonly found 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 found more frequently in patients with a genetic predisposition to ovarian cancer, but also in non-mutation carriers with high-grade serous ovarian carcinoma (50–75%).[24–31] In the recently published National Ovarian Cancer Prevention and Early Detection Study (GOG-0199), led by the Gynecologic Oncology Group, occult invasive or serous tubal intraepithelial ovarian/tubal/peritoneal neoplasms were detected in 25 (2.6%) of 966 patients (*BRCA* mutation carriers and high-risk non-carriers) who underwent RRSO.[32] In a subgroup analysis, 4.6%, 3.5% and 0.5% occult neoplasms were detected in patients who were known *BRCA1, BRCA2* mutation carriers, and high-risk non-carriers at the time of RRSO, respectively.[32]

Interestingly, tubal precursor lesions are not always found 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 could also be explained by a carcinogenic "field effect". Thus, it may be 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 hormonal 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 20–40% 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 carcinoma[39]; this may shed light on the mechanism of protection.

A meta-analysis including 30 studies of BTL noted a 30% risk reduction in the development of any ovarian cancers, with a subset analysis finding a stronger reduction rate (54%) in association with endometrioid compared to serous tumors.[35] A pooled analysis of 13 population-based case-control studies involving a large number 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 suggests 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 found that the adjusted risk of EOC was decreased by 64% after excisional tubal sterilization methods compared to those with non-excisional methods of without sterilization.[40]

In 2015, using the Swedish Nationwide Healthcare Registry, Falconer et al published the results of a population-based study of patients undergoing gynecologic surgery for benign conditions.[41] Women with previous gynecologic surgery for benign indications including tubal ligation (sterilization, salpingectomy, bilateral salpingo-oophorectomy [BSO], hysterectomy; n = 251,465) were compared with the unexposed population (n = 5,449,119). There was a significantly lower risk of ovarian cancer among women with previous salpingectomy (HR = 0.65, 95% CI = 0.52 to 0.81)--even unilateral salpingectomy--compared with the unexposed population. Statistically significant risk reductions were observed among women with previous hysterectomy (HR = 0.79, 95% CI = 0.70 to 0.88), sterilization (HR = 0.72, 95% CI = 0.64 to 0.81), and hysterectomy with BSO (HR = 0.06, 95% CI = 0.03 to 0.12).[41] While 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 multicentre randomized controlled trial of the impact of opportunistic salpingectomy during laparoscopic hysterectomy published by Song et al in 2016 showed that while AMH levels were significantly decreased from preoperative levels in both groups, however there was no significant difference between the salpingectomy and no salpingectomy groups.[44] Morelli et al analyzed serum Anti-Müllerian Hormone (AMH), Follicle Stimulating Hormone (FSH), and Estradiol (E2) in 79 patients who underwent hysterectomy, with or without bilateral salpingectomy, for benign uterine disease. They found no significant differences in ovarian function after surgery, and no significant differences in perioperative morbidity between the two groups.[45] A similar study by Findley et al compared 30 premenopausal women undergoing laparoscopic hysterectomy with ovarian preservation for benign indications, 15 of whom had concurrent salpingectomy. AMH levels were not significantly different at baseline, 4–6 weeks after surgery, and 3 months postoperatively in women with salpingectomy versus no salpingectomy.[46] No

differences in operative time or estimated blood loss were found.[44–46] Data also suggests that even when a wide excision is taken to completely excise all fallopian tube tissue, salpingectomy does not negatively impact ovarian reserve or perioperative morbidity.[47] While laboratory measurements such as 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. This 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: ~16 minutes more for hysterectomy with bilateral salpingectomy versus without salpingectomy, and 10 minutes more for bilateral salpingectomy versus tubal ligation. Despite this, no differences were seen in 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 towards ovarian conservation, with recent data suggesting that over 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 following hysterectomy. 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, using a modeled analysis designed to determine cost effectiveness of opportunistic salpingectomy as a cancer prevention strategy during hysterectomy for benign conditions or sterilization.[50] Salpingectomy with hysterectomy at age 45 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 having hysterectomy at any time prior to age 50. The model predicted a 38.1% reduction in ovarian cancer cases with the addition of salpingectomy, with a number needed to treat (NNT) of 273. If a BSO was performed instead of salpingectomy, it would prevent 238 cases of ovarian cancer but incur an additional 934 deaths from premature menopause (without HRT). Salpingectomy, when performed 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. In order for this to remain true, salpingectomy had to provide a relative 25% increase in risk reduction over tubal ligation. As well, 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 cases with the use of salpingectomy versus tubal ligation. This translates into a NNT 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, rates of salpingectomy for sterilization increased from 0.4% to 33.3%, and salpingectomy during hysterectomy with ovarian conservation increased from 5% to 35%, over a 3-year period. Despite the additional procedure, these cases were not associated with an increased rate of complications or readmissions.[48] Similar trends have also been reported in the United States. A recent publication from a large, community-based healthcare system demonstrates that between 2011 to 2014, the rates 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 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] 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

As 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 demonstrate a 75–96% decrease in ovarian cancer risk, as well as a marked reduction in breast cancer risk and all-cause mortality.[8,9,54–56] While RRSO is generally recommended by age 40[14,57], the proportion of women actually undergoing RRSO is estimated to be only 60–70%. This is likely due to concerns about the impact of premature menopause.[58] As previously noted, premature menopause is associated with increased cardiovascular, osteoporotic, and overall mortality risks, as well as 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* mutations carriers, highlights the potential need for different approaches to each. Although a previous study reported that RRSO conferred rates of risk reduction of 85% and 72%, respectively, among *BRCA1* and *BRCA2* mutation carriers[54], a recent meta-analysis of three prospective studies suggests 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 supports that RRSO confers significant protection against premenopausal breast cancer in women with a *BRCA2* mutation; however this protection was not seen in women carrying a *BRCA1* mutation.[10]

Not only may the impact of RRSO be different between the two groups; the age at which RRSO should be performed is also different. Finch et al reported that the highest incidence of ovarian cancer among *BRCA*1 mutation carriers was between 50–59 years; among *BRCA*2 mutation carriers, the highest incidence was a decade later (60–69 years).[61] As women with *BRCA*1 mutation are at risk for an earlier onset of cancer, it is recommended that RRSO is considered at age 35 and complete no later than age 40. [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, 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 identification of a STIC lesion or occult high-grade serous carcinoma. In collaboration with Facing Our Risk of Cancer Empowered (FORCE), an on-line patient survey was performed to determine if *BRCA* mutation carriers would be interested in an ISDO study. The survey showed 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 to RRSO.[64] In a separate poll of 173 cancer geneticists, genetic counselors, and gynecologic oncologists in the UK, 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. They concluded that RRSO was the dominant strategy overall, as 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 followed by delayed oophorectomy at age 50 conferred the highest quality-adjusted life expectancy. The impact was even stronger in *BRCA1* compared to *BRCA2* mutation carriers.[63]

While 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 as it is still unclear what proportion of EOC is tubal in origin. The need for two separate operations increases surgical risks and may lead to decreased acceptance of and decreased compliance with completion of delayed oophorectomy. Additionally, when compared to 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 prior to 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, currently underway, is a two-arm, non-randomized, multi-center clinical trial comparing changes in female 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 to 50, and must have a deleterious germline mutation in BRCA1/2 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 wellbeing, onset and severity of vasomotor symptoms (hot flashes and night sweats), complication rates, number of malignancies, and quality of life measures between the two arms. As the first multi-site trial of ISDO in the US, 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; these women are therefore candidates for surgical risk reduction. While 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 such as this may maximize prevention while minimizing its negative impact on patients' quality of life.

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**Table 1**

Precursor lesions of high-grade serous epithelial ovarian, fallopian tube, and peritoneal carcinomas

| Pre-cancerous 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, yH2AX+, Laminin y1 |
| SCOUT | Proliferation of Bcl2-positive secretory cells with loss of PAX2 |

STIC, serous tubal intraepithelial carcinoma

SCOUT, secretory cell overgrowth